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Review article

Protective role of stem cells in POI: Current status and mechanism of action, a review article

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ABSTRACT

Premature ovarian insufficiency (POI) has far-reaching consequences on women's life quality. Due to the lack of full recognition of the etiology and complexity of this disease, there is no appropriate treatment for infected patients. Recently, stem cell therapy has attracted the attention of regenerative medicine scholars and offered promising outcomes for POI patients. Several kinds of stem cells, such as embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSCs) have been used for the treatment of ovarian diseases. However, their potential protective mechanisms are still unknown. Undoubtedly, a better understanding of the therapeutic molecular and cellular mechanisms of stem cells will address uncover strategies to increase their clinical application for multiple disorders such as POI. This paper describes a detailed account of the potential properties of different types of stem cells and provides a comprehensive review of their protective mechanisms, particularly MSC, in POI disorder. In addition, ongoing challenges and several strategies to improve the efficacy of MSC in clinical use are addressed. Therefore, this review will provide proof-of-concept for further clinical application of stem cells in POI.

1. Introduction

Premature ovarian insufficiency (POI), formerly referred to as premature ovarian failure (POF), is defined as amenorrhea due to the loss of ovarian function before 40 years of age [1,2]. Women with POI suffer from hypoestrogenism, hypergonadotropism, primary or secondary amenorrhea, and infertility [3]. Due to our immature understanding of POI pathogenesis mechanisms, there is still no effective treatment for these patients. The management of POI is palliative and includes hormone replacement therapy (HRT), psychosocial support, diet and exercise, donor oocyte, and cell therapy. Although these strategies can improve women's quality of life,

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they cannot restore ovarian function or ovulation [4]. HRT, as a routine treatment for POI, is associated with an increased risk of cancer, venous thromboembolism, heart attacks, and failure to restore normal ovarian function [5]. The use of corticosteroids in POI of autoimmune origin is controversial and ineffective [6]. Preterm delivery, ethical considerations, and immune intolerance between mother and fetus are other problems related to oocyte donation as a current treatment option for POI patients [5]. Therefore, an effective therapy for POI is highly warranted.

Given the unique characteristics of stem cells, clinical trials are ongoing to develop new therapeutic approaches for POI. Among various cell types that have been used so far, mesenchymal stem cells (MSCs), a multipotent non-hematopoietic subset of stem cells, are considered as a great promise for a new therapeutic approach for these patients due to their rich tissue sources, multilineage differentiation capacity, easy *in vitro* amplification, and unique immunobiological properties [7]. Although MSCs have proven effective in a variety of degenerative illnesses, their molecular mechanisms of effectiveness in reproductive diseases are not well-understood and need to be clarified before being used in clinical settings [8–10]. A series of studies have reported the therapeutic effects of MSCs in animal models and POI patients [11,12]. While these studies are in the first stages of development and more future research is required. Undoubtedly, expanding our understanding of the MSC mechanism governing in POI disorder would be important to detect new target opportunities for these patients [12]. Accordingly, the present paper first reviews several kinds of stem cells and their therapeutic potential in clinical practice. Then, we describe the comprehensive therapeutic mechanisms, the possible opportunities and challenges of MSC therapies, in POI treatment. We also describe several strategies for the better application of MSCs in cell therapy to provide the basis for future studies on the applications of MSCs in clinical settings.

2. Method

2.1. Search strategy

In order to access the relevant data, an online literature search was performed on Web of Science, PubMed, Google Scholar, and, Scopus databases, and studies related to stem cell therapy in POI disease were analyzed using the following terms and phrases: (“Premature ovarian insufficiency” OR “POI” OR “Premature ovarian failure” OR “POF” OR “early menopause”) AND (“Cell therapy” OR “stem cell” OR “Mesenchymal stem cell” OR “MSC” OR “Embryonic stem cells (ESCs)” OR “Induced pluripotent stem cells (iPSC)”) AND “Inflammation” AND “Apoptosis” “Angiogenesis” AND “Stress oxidative” AND “Folliculogenesis” AND “Autophagy” AND “Fibrosis”. All searches were conducted by two reviewers, separately.

2.2. Inclusion and exclusion criteria

All published articles (including observational, interventional, animal studies, narrative reviews, cross-sectional, and cohort designs) were eligible to be included in this systematic review), regardless of their language, were searched and reviewed. All references were entered into EndNote software. After removing the duplicates, the full text of all selected papers were reviewed and all irrelevant papers and studies with no exact data were excluded. Moreover, we collected studies with following inclusion criteria: all the pathognomonic features of POI in experimental models of systemic & ovary injuries; MSCs; therapeutic mechanism of MSC, and folliculogenesis, hormone regulatory, anti-oxidant, anti-inflammation, anti-apoptotic, angiogenesis and anti-fibrotic as the outcome. Finally, the overall results were subjected to discussion in which the possible mechanisms of stem cells on POI and the feasibility of their clinical usage were explained and a conclusion was finally drawn.

3. POI pathogenesis features

3.1. Impaired folliculogenesis and hormone dysregulation

Although the exact mechanism of the POI pathogenesis is unclear, a decrease in the number of ovarian follicles and a dearth of hormone secretion are among the most commonly suggested mechanisms [13]. POI is characterized by early termination of ovarian function, blockage of folliculogenesis, and exhaustion of the resting primordial follicle pool [14,15]. The folliculogenesis is a complex process regulated with multiple signaling pathways and cross-talk between the oocyte and surrounding somatic cells. During the reproductive lifespan of an adult woman, primordial follicles develop into primary, secondary, and antral stage follicle [7]. But, only few follicles are selected for ovulation and the majority of primordial follicles are lost by apoptosis [16]. Thus, the pool of primordial follicles is a determinant factor for fertility and reproductive health [17]. As mentioned, increased rate of follicle apoptosis and the reduced peak of follicle number, are hallmarks of POI [18]. However, the complete absence of primordial follicles is not seen in the POI women and some follicles remain in the ovary of these patients [19]. Therefore, activation of these dormant follicles can be considered as a promising therapeutic approach [19]. For this purpose, identifying the involved pathologic mechanisms in this process can be considered as new therapeutic targets. Multiple mechanisms are involved in POI development, including ovarian inflammation, fibrosis, granulosa cell (GC) apoptosis, insufficient autophagy and excessive oxidative stress which will be discussed below [20].

3.2. Oxidative stress

Alterations in immunological parameters and oxidative stress are considered as two major pathologic factors [21]. Despite the significant role of oxidative stress in ovulation and luteinization, the gradual accumulation and high level of oxidative damage can

induce infertility by detrimental effects on oocyte and granulosa cells' microenvironment and induce follicular atresia, ovarian inflammation, and mitochondrial DNA (mtDNA)-related disorders [22]. Oxidative stress is involved in several reproductive disorders including polycystic ovary syndrome (PCOS), endometriosis, and POI [22]. POI is also characterized by decreased antioxidant levels and increased oxidative stress in cumulus cells, oocytes and ovaries, and oxidative stress levels are correlated with worse outcomes [23]. Recently, gene set enrichment analysis (GSEA) using both Hallmark and KEGG gene sets in POI patients showed that POI is associated with inhibition of pathways related to oxidative phosphorylation, DNA damage repair and mitochondrial function, such as PI3K/AKT/mTOR pathways, and early and late estrogen response pathways [24].

Mitochondria as an important source of intracellular reactive oxygen species (ROS), are more sensitive to oxidative stress. Due to the poor DNA repair system, mtDNA has a much higher mutation rate than nuclear DNA [25]. These mutations are directly related to the development of some clinical diseases such as diabetes, cardiomyopathy, and neurodegenerative disease [25,26]. Oocytes have more mtDNA copies than other cells, thus abnormal levels of ROS cause mtDNA damage and produce more free radicals in these cells [22]. High levels of ROS lead to low ATP production, which can *per se* accelerate ovarian germ cell apoptosis, oogenesis impairment, low oocyte count, and finally contribute to POI (Fig. 1) [22,27]. A recent study reported that much lower levels of mtDNA were seen in patients with POI [22,25]. Therefore, anti-oxidative therapies or strategies to modify mitochondrial dysfunction may be an attractive therapeutic intervention for its management [21,26].

3.3. Inflammation

Chronic inflammation is a major factor involved in the pathogenesis of POI. Inflammation is related to folliculogenesis and its dysregulation contributes to impaired oocyte quality and POI disease [28]. Increased expression of inflammatory indices in patients with POI, such as the neutrophil to lymphocyte ratio (NLR), oxidative stress index and increased expression of proinflammatory cytokines and transcription factors (e.g NF-κB) indicate their involvement in POI pathogenesis [21]. Estrogens are involved in immune processes by inhibiting many pro-inflammatory pathways; therefore, low levels of estrogen in POI patients shift the immune response to the inflammation state [29]. In addition, the pathological inflammation of POI is caused by an imbalance between the inflammatory and anti-inflammatory network that is characterized by reduced anti-inflammatory factors and elevated proinflammatory cytokines [20].

3.4. Autophagy

Autophagy is an extremely complex process for the removal of various cellular constituents such as proteins and organelles to

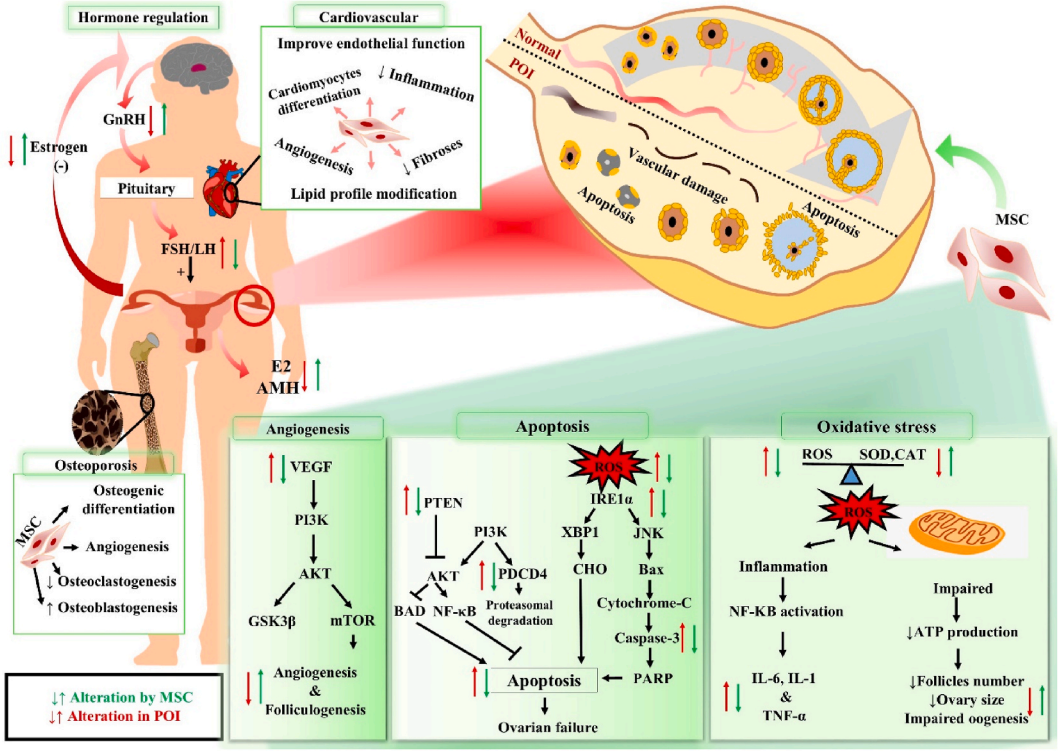

Fig. 1. The mechanism actions of stem cell therapy for the treatment of Premature ovarian insufficiency (POI) patients.

modulate various physiological and pathological events [30]. It functions in many physiological processes, under both intracellular and extracellular stress such as hypoxia, nutrient starvation, endoplasmic reticulum (ER) stress, infection, and inflammatory signals [30]. The role of autophagy in pregnancy-related complications remains to be explored [31]. It is also reported that autophagy regulation is involved in healthy pregnancy from pre-implantation to embryo survival [31]. In addition to the important role in reproduction, autophagy may also play dual-pro-survival or pro-atresia roles with regard to follicles [32]. It is well known that deregulated autophagy is a pathological mechanism involved in endometriosis and uterine fibroids, common reproductive disorders that impose a serious burden for public health systems [33]. It has been shown that impaired autophagy promotes the onset of POI [34]. Due to autophagy-dependent regulation of GCs differentiation, decreased autophagy levels are considered as a pathologic mechanism, resulting indefective differentiation of GCs and impaired E2 synthesis in POI patients [35]. The microarray analysis showed the significantly reduced of autophagy-related factors (ATG5, BECN1, SIRT1, TRIM13, VMP1, WDR45, Lc3 and Beclin1) in women affected by POI [36,37]. Therefore, inhibition of follicle atresia through the regulation of autophagy can retain the germ cells in the ovary and enhance female reproductive capacity [38]. Accordingly, regulating autophagy seems to be a promising strategy to overcome these pregnancy-related complications [39].

3.5. Angiogenesis

Angiogenesis is a biological phenomenon playing a key role in physiological and pathological conditions and is essential for follicular development and maturation [40]. The normalities of the capillary network and vascular supply have important role in the selection and ovulation of the dominant follicle and this network damaging can contribute to inhibition of follicular development and disruption of ovarian endocrine function [40]. Among several factors involved in the regulation of autophagy, vascular endothelial growth factor (VEGF) perform critical functions. The low expression of ovarian tissue VEGF protein in POI models, demonstrated the importance role of angiogenesis in follicle development [40]. It seems that increased vascularization in the ovaries helps to increase blood supply and accelerates the healing process of POI [41].

3.6. Apoptosis

Apoptosis, as a regulatory process, has an important role in the maintenance of healthy follicles. However, apoptosis is also considered one of the most important pathogenesis mechanisms of POI [42]. Accelerated follicle loss, as a main pathogenic reason for POI, occurs through the inability to manage follicular selection and follicle apoptosis [43]. Based on the physiological environment and follicular development of the ovary, the occurrence of apoptosis has special regulatory factors and patterns. The impaired protective role of estrogen and progesterone against apoptosis in POI patients can justify this abnormality [44]. Oxidative stress is considered as an important contributing factor in triggering ovarian apoptosis [45]. Excess ROS can induce apoptosis through mitochondrial dysfunction, recruitment of a series of caspase cascades, pro-inflammatory cytokine activation and via increasing phosphorylation of c-Jun N-terminal kinases (JNKs) and P53 pathways [46].

4. Cell therapy

Stem cells are unspecialized cells characterized by unique potentials, such as long-term cell division, self-renewal properties, and differentiation into multiple lineages. They are subdivided into three distinct categories, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and adult stem cells (ASCs) [47]. hESCs are the only stem cells with unlimited property to differentiate into any cell type, but some ethical and technical issues limit their widespread implementation [48,49]. In an attempt to overcome hESCs-associated limitations, strategies such as the differentiation of adult somatic cells into pluripotent stem cells using the transcription factors Oct4, Sox2, Klf4, and, Myc have been investigated [49]. hiPSCs closely resemble hESCs in morphology, pluripotency, self-renewal, and gene expression, while having no ethical limitations [50,51]. Nevertheless, the risk of post-transplant teratoma formation, tumorigenesis, and uncontrolled integration of vectors into the host cell's genome have currently limited their clinical applications [51]. Adult stem cells (ASCs) are multipotent non-embryonic stem cells that are found in the area of various adult organisms entitled "stem cell niche" which provides a specific microenvironment, where stem cells receive stimuli that determine their fate [52]. Among adult stem cells, MSCs have proved to be a promising tool in the development of therapeutic strategies, due to their unique properties [53]. International Society for Cellular Therapy (ISCT) has defined MSCs as multipotent stromal cells with self-renewal properties, often regarded as plastic-adherent cells in standard culture conditions and characterized by a capacity to differentiate into multiple cell lineages [54–56]. Homing and migration to damaged tissue sites using chemokines, adhesion molecules, and matrix metalloproteinases (MMPs) are important therapeutic properties of MSCs. After migration, MSCs involve in tissue regeneration through producing large amounts of growth factors and can inhibit cell apoptosis, promote tissue regeneration, and display powerful immunomodulatory effects [56].

MSCs are harvested from various autologous and allogeneic sources and, unlike ESCs or iPSCs, are well-tolerated with no ethical concerns; however, their proliferation abilities are limited [57,58]. Moreover, the risk of post-transplant malignancy, which is common in the case of ESCs and iPSCs, is not seen in MSCs transplantation. MSCs can be isolated from a variety of sources which we will explain further. The most commonly MSCs used for the treatment of POI are bone marrow mesenchymal stem cells (BM-MSCs), adipose mesenchymal stem cells (AD-MSCs), umbilical cord mesenchymal stem cells (UC-MSCs), placental mesenchymal stem cells (PMSCs), amniotic mesenchymal stem cells (AMSCs) and menstrual stem cells (MenSCs) [59].

In this paper, therapeutic mechanisms of different types of stem cells in POI treatment are reviewed (Table 1), and related ongoing

Table 1
Preclinical studies of MSCs in POI.

Stem cell	Dosage	Delivery method	Year	Research Outcome	Mechanism	Ref
BM-MSC -EV	125 μg dissolved in 100 μL PBS	IV	2020	↑ E2 and AMH ↓ FSH ↑ basal and sinus follicles number Inhibit GC apoptosis	GC apoptosis inhibition through Exosomal mir-144 by targeting PTEN-PI3K/AKT	[202]
BM-MSC	2×10^6	IV	2021	↑ FSH and E2 Restores fertility ↑ Ovarian follicle pool ↓ Ovarian apoptosis ↑ Granulosa cells proliferation and secondary follicle development	Control of apoptosis, proliferation, and differentiation of ovarian follicles through TGF-β, Wnt/β-catenin, and Hippo pathways Recovered the folliculogenesis process through upregulation of FOXO1, GDF-9, and Fst genes and by Aoptosis inhibition by Bax/Bcl-2, caspase 3	[71]
BM-MSC –EV	150 μg dissolved in 100 μL PBS	IV	2021	↓ FSH and LH ↑AMH and E2 ↓ GC apoptosis	Ovarian function improvement and GC apoptosis reduction through Exosomal MiR-644-5p targeting p53	[204]
AD-MSC	1×10^6	IP		↑ Primordial follicles number ↓ Atretic follicles number ↑ AMH ↓ Follicle apoptosis	The expression of Connexin43 and pnnexin1 regulation	[224]
AD-MSC-EV	1×10^6	IP	2018	↑ Follicle number ↓ GC apoptosis	GC apoptosis inhibition and GCs proliferation through upregulation of SMADs	[206]
MenSC	2×10^6	IV	2017	↑ Follicle number ↓ GC apoptosis ↑ Regeneration and ovarian function	Protective effects by secreting FGF2	[141]
MenSC	1×10^6	IV		↑ AMH, FSHR and E2	Not report	[39]
MenSC	1×10^6	IV	2019	↑ Follicle number ↓ GC apoptosis	↓ Pro-apoptotic gene expression (e.g., Bax) ↑ Anti-apoptotic gene expression (e.g., Bcl-2)	[126]
UC-MSC	1×10^6	IV	2021	↑ Ovarian size and number ↑ Primary and secondary follicles ↓ Atretic follicle ↑ E2 and ↓ FSH	Anti-apoptotic and anti-inflammatory effects through the AKT activation	[80]
UC-MSC	1×10^6	IV	2019	↑ Follicle number and ↓ atretic follicle ↑ E2 and ↓ FSH ↑IL-4 and ↓ IFN-γ and IL-2	Recovery of ovarian function and endometrial receptivity through modulation of the Th1/Th2 cytokine ratio	[114]
UC-MSC	5×10^6	IV	2019	↑ E2 and AMH Folliculogenesis recovery ↑ Pregnant rate	Ovarian function improvement through NGF/TrkA signaling pathway	[131]
UC-MSC	2×10^6	Orthotopically	2016	↑ E2 and AMH ↓ FSH ↑ Antral follicle number	The expression of TGF-β and PCNA regulation	[144]
UC-MSC	Low (0.25×10^6), medium (1×10^6) and high (4×106)	IV	2020	↑ E2 and AMH Restore estrous cycle ↓ GC apoptosis	Not reported	[95]
UC-MSC	1×10^6	IV	2022	↑ FSH and E2 ↓ Atresia follicle Inhibit T cell proliferation	Ovarian function improvement through PPAR and cholesterol metabolism pathways	[225]
UCMSC-HGF	1×10^6		2023	↓ Ovarian tissue fibrosis ↓ GC apoptosis ↑ Ovarian angiogenesis mediated by HGF over-expression	Ovarian function improvement through alleviate the ovarian angiogenesis mediated by HGF over-expression and follicle activation through KITL expression in GC	[87]
UC-MSC-EV	20 μg/mL, 150 μg	IP	2021	↑ Pregnancy rate ↑ Ovarian cell proliferation ↑ Ovarian follicles number	↑ GC proliferation cell by regulating the Hippo pathway	[73]
UC-MSC-EV	10^{12} particles	intra-ovarian	2020	↓ ROS accumulation ↑ GC prolifration	Therapeutic effect and repress ROS accumulation through target SIRT7 and its downstream target genes (PARP1, γH2AX, and XRCC6) via delivery of exosomal miR-17-5P	[207]
UC-MSC-EV	1×10^{10} particles	IP	2023	↓ FSH and ↑ E2 and AMH ↓ GC apoptosis	Ovarian microenvironment improvement through immunomodulation- and cellular viability-associated gene sets	[208]

(*continued on next page*)

Table 1 (*continued*)

Stem cell	Dosage	Delivery method	Year	Research Outcome	Mechanism	Ref
UC-MSC-EV	30 μg/ml		2022	↑ GCs estrogen secretion	miR-21 carried by hucMSCs-derived exosomes could downregulate LATS1, thereby reducing phosphorylated LOXL2 and YAP, and ultimately promoting estrogen secretion in ovarian granulosa cells.	[205]
Collagen/ UC-MSCs	2×10^5	Orthotopically	2019	↑ E2 and AMH ↓ FSH ↑ Granulosa cell proliferation ↑ Ovarian angiogenesis	Ovarian angiogenesis with the increase of CD31 expression	[210]
ESC-MSCs	1×10^6	IV	2020	↓ FSH and ↑ AMH and E2 Restore fertility Follicle development	Restore ovarian structure and function through paracrine factors such as VEGF, IGF-2 and HGF	[142]
PM-MSCs	1×10^6	IV	2019	↑ E2 and ↓ FSH and LH ↑ Folicle number ↓ Atretic follicle ↓ GC prolifration	GC apoptosis inhibition through IRE1α pathway	[130]
PM-MSCs	1×10^6	IV	2018	Improve Estrous Cycles ↓ GC apoptosis	Infammatory regulations mediated by regulation of the Th1/Th2 cytokine balance and increase Treg cells	[113]
fMSCs	1×10^6	IV	2019	↑ E2 and AMH and ↓ FSH ↑ Sinus follicle number ↓ Apoptosis	Oxidative protection and anti-apoptosis effect through MT1, JNK1, PCNA and AMPK	[85]
AMSC	5×10^5	Orthotopically	2016	↓ Apoptosis ↑ Primordial follicle number ↓ Atretic follicle number	Protect effect through exosomal miR-10a	[89]
AMSC	1×10^6	IP	2016	Improve the estrous cycle ↑ Fertility rate ↑ Primordial follicle number ↓ Atretic follicle number	Ovarian function improvement through FOXL2, GDF-9 and LIF	[83]
AMSC-EV	150 μg dissolved in 100 μL PBS	IV	2020	↑ Follicle number ↑E2 and AMH and ↓ FSH ↓ GC apoposis	Exosomal miR-320 plays a major role on ovarian function via SIRT4, ANT2, AMPK, and L-OPA1 signaling	[209]
AES	12×10^6	IV	2020	↓ Inflammation ↓ GC apoptosis ↑ Secondary and mature Follicles number ↓ Atretic follicles number	Ovarian function improvement by decrease the inflammation and inhibiting TNF-α-mediated cell apoptosis	[115]
AES	2×10^4	Orthotopically	2017	↑ Secondary and mature follicles number ↓ Atretic follicles number ↓ GC apoptosis ↑ Angiogenesis and vasoformation	The protective effect in the injured ovary through TGF-β1, GDF9, BMP15 which involve in the anti-apoptosis, regulation of follicle development and pro-angiogenesis	[84]
AEC-EV	10 μL and 100 μL	Orthotopically	2019	Maintain the primordial follicles number ↓ GC apoptosis	GC apoptosis inhibition via functional miR-1246 delivery	[136]
UC-MSC-EV	150 μg	IV	2019	↑ Ovarian primordial and preovulatory follicles number Ovarian angiogenesis induction Estrous cycle recovery	Ovarian function improvement by inducing angiogenesis via the PI3K/AKT signaling pathway and angiogenic cytokines (including VEGF, IGF, and angiogenin)	[143]
ADSC	50 μL	intra-ovarian	2019	Follicular development ↓ GC apoptosis ↑ Angiogenesis	Local ovarian microenvironment improvement through apoptosis inhibition (decrease Bax expression and increase Bcl-2 expression), and angiogenesis effect via secretion of FGF2, IGF-1, HGF, and VEGF ,	[138]
iPS	1×10^7		2016	↑ Ovarian weight ↑ E2 ↓ Atretic follicles	Not reported	[93]
iPS	1×10^3	Intra ovarian	2013	↑ E2 ↓ Vimentin and fibronectin expression in ovarian tissue ↑ Ovarian weight	Not reported	[96]
iPSC-EVs	200 μg EV produced by 5 × 106 iPSC-MSCs	IP	2023	↑ Follicle number ↑ GC proliferation ↓ GC apoptosis	Ovarian damage reduction via the ILK-PI3K/AKT	[222]

Table 2
List of registered mesenchymal stem cell (MSC)-based clinical trials for Premature ovarian insufficiency (POI).

ID	Phase	Status	Locations	Cell type	Dose	Route	Sample size	Primary outcoms	Secondary outcoms
NCT02151890	I II	Completed	Al-Azhar University	OCT4 marker measured	NA	Laparoscopic injection	n = 40	Pregnancy	NA
NCT05138367	I	Completed	Li-jun Ding, Nanjing University	UCA-PSCs or WJ-MSCs	1×10^7/400 μL	Local (injected into ovarian tissue)	n = 20	Blood perfusion in the ovary & Antral Follicle Diameter	Blood flow index in the ovaries
NCT02043743	I II	Completed	El-Rayadh Fertility Centre	BM-MSC	3-5 × 10^6/ml	Local (injected into ovarian tissue)	n = 60	↓ Serum FSH level & ↑ serum E2 and AMH	Disappearance of menopausal symptoms
NCT02644447	I II	Completed	Chinese Academy of Sciences	UC-MSC and UC-MSCs with Injectable Collagen Scaffold Transplantation	10×10^6/ml	Local (injected directly into bilateral ovaries)	n = 23	Safety and Tolerability	Number of Antral follicle development & Serum level of E2, AMH and FSH & Pregnancy rate
NCT03816852	II	Active	Sclnow Biotechnology Co., Ltd.	UC-MSCs	9×10^7/ml	IV	n = 12	Menstrual changes	Kupperman score & Follicular development & hormone level
NCT03069209	I II	Active	Stem Cells Arabia	BM-MSC	NA	IV	n = 50	Return of menstrual cycle	
NCT03877471	I	Active	Chinese Academy of Sciences	embryonic stem cell derived MSC-like cell	3 groups, with low (0.2 × 107), medium (0.5 × 107), and high dosage (1.0 × 107) of cells injection for each ovary	Local (injected into bilateral ovaries	n = 28	Not available	Pregnancy & FSH levels & Follicular function & Increase in endometrial thickness
NCT05308342	NA	Recruiting	Li-jun Ding, Nanjing University	UC-MSCs	(5×10^6) and (10×10^6) cells	Local (injected into ovarian tissue)	n = 66	Follicular development rate	Changes in blood flow index in the ovary & Clinical pregnancy rate
NCT04815213	I	Recruiting	University of Jordan	BM-MSC	20×10^6/ovary	Local (injected into ovarian tissue)	n = 10	Incidence of treatment-emergent adverse events	Hormonal profile & Ovarian changes & Endometrial changes
NCT02696889	NA	Recruiting	University of Illinois at Chicago	BM-SCs	NA	Local (injected into ovarian tissue)	n = 3	Improved diagnostic hormonal levels	Improved hormonal levels & Resumption of menses & Achievement of pregnancy
NCT00353197	NA	Recruiting	Hadassah Medical Organization	Derivation of hESC line	NA	NA	n = 80	NA	NA
NCT02603744	I II	Unknown	Royan Institute, Iran	AD-MSCs	3 groups, with (5×10^6), (10×10^6) and (15×10^6) cells	Local (injected into ovarian tissue)	n = 9	ovary mass	Hormonal profile & Number of antral follicle & Antral follicle volume & Menstruation recurrence rate & Pregnancy rate
NCT03033277	I II	Unknown	Chinese Academy of Sciences	UC-MSCs	NA	Local (injected into ovarian tissue)	n = 320	Number of mature follicle	Hormonal profile & Ovarian volume & Pregnancy rate
NCT01742533	I II	Unknown	Shenzhen Beike Bio-Technology Co., Ltd.	UC-MSCs and hCBMNC	NA	NA	n = 40	Serum Level of follicle-stimulating hormone	Uterine and Ovary characteristic & Incidence of Adverse Events and Serious Adverse Events
NCT02062931	I II	Unknown	Sayed Bakry	BM-MSC suspended in platelets rich plasma (PRP)	3-5 × 10^6/ml	Local (injected to ovarian tissues and ligaments)	n = 60	Decrease in serum FSH level & Elevation in serum E2 and AMH level	Hormonal Assessment & Clinical Disappearance of Menopausal Symptoms & Pregnancy rate

Abbreviations: I·V.: Intravenous Infusion; NA: Not Applicable.

clinical trials are also discussed (Table 2).

4.1. Potential therapeutic mechanisms of MSCs in POI

MSCs may be the missing piece of the puzzle in the management and treatment of POI patients (Figs. 1 and 2). The successful results of MSCs in animal models raised our expectations of these cells [9,12,60,61]. MSC's function can be attributed to diverse mechanisms, including self-homing, and differentiating to a certain stage. The activation of dormant cells and encourage them to re-enter the cell cycle, is another property of MSCs [62]. MSCs are able to migrate to the ovaries, and it has been shown that ovarian niche can attract different types of stem cells from various sources [8]. MSCs restore damaged cells via cell fusion and paracrine factors (such as cytokines, growth factors, and hormones), and delivering their genes and organelles (e.g., mitochondria) to damaged cells [63]. Mitochondrial transplantation as a promising therapeutic strategy is considered not only for restoration of mitochondrial damage, but also for the regulation, survival, proliferation, and differentiation of the target cells [64]. Recently, some studies have reported that mitochondrial transfer from stem cells to injured cells can be considered as a therapeutic strategy for tissue injury. Under these conditions, damaged cells are able to capture healthy mitochondria from stem cells to produce ATP, as well as to reduce the inflammatory response and apoptosis [64–66].

MSCs may restore ovarian function by regulating the compromised environment and insufficient growth factors replacement, vascular regeneration, and recovery of germ cells or follicles [8]. The various therapeutic mechanisms of MSCs in POI disease are mediated through different signaling pathways [67,68].

Ovarian development and regulatory mechanisms are complex, some signaling phatways could trigger parallel survival and cell

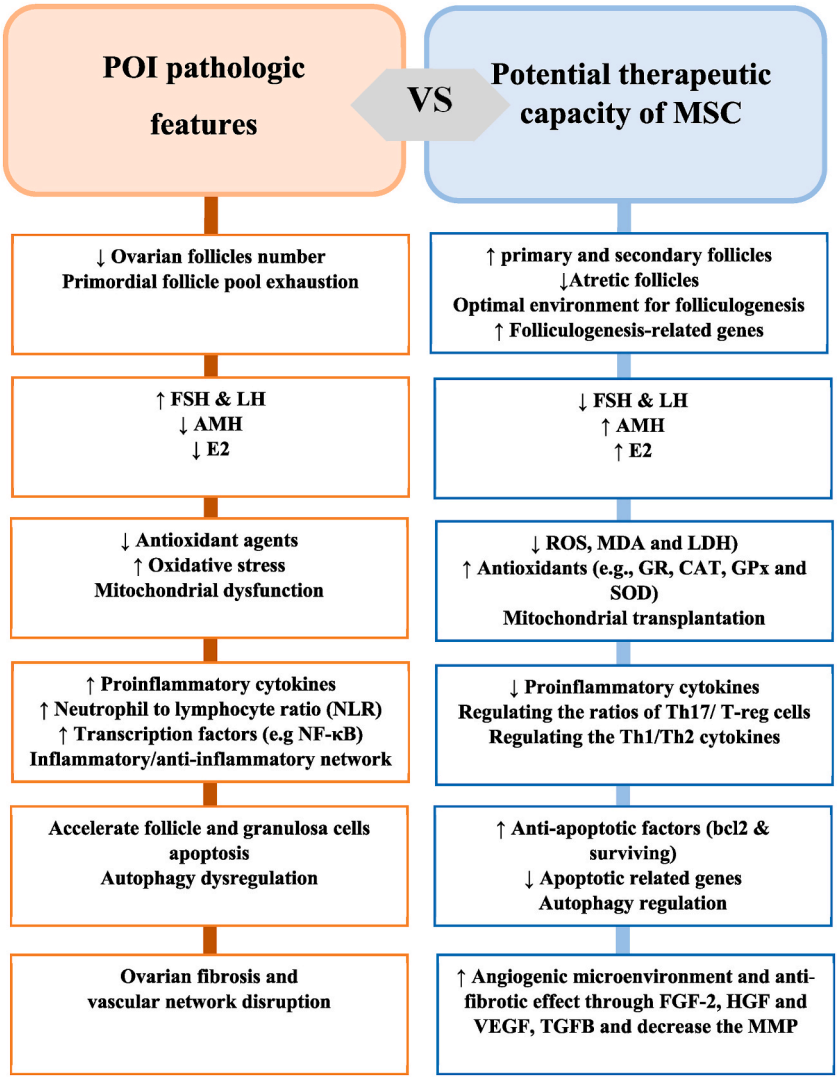

Fig. 2. Therapeutic mechanisms of MSC versus pathologic mechanisms of POI.

growth signaling pathways in follicle development. Several pathways including phosphatase and tensin homolog deleted on chromosome 10 (PTEN), mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3 kinase/protein kinase B (PI3K/Akt), have fundamental role in cellular processes such as metabolism, cell survival and apoptosis. The abnormal functional of these pathways inhibit development of primordial follicles and lead to POI [59]. Akt activation is regulated by PI3K and PTEN which ultimately leads to activation of a series of pathways including FOXO3a (regulator factor in atresia and follicle growth), P27 (maintenance of primordial follicular reserve), BCL-2 and BCL-2 associated agonist of cell death (BAD) (a cellular mitochondrialand apoptosis regulatory pathways) [59,69]. The role of Akt/FOXO and mTOR pathways in follicle activation have proved in several studies. PI3K/Akt through FOXO protein inhibits excessive depletion of primordial follicles. Attenuation of FOXO3 through PI3K/Akt leads to POI through disruption of oxidative/anti-oxidant systems balance [70].

The Hippo pathway and its downstream transcription effector, yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ), are considered as a critical factor in folliculogenesis through regulating ovarian follicle's activation and function [71]. The activation disorder of this pathway contributes to decrease survival of primordial follicles and leading to POI [72]. The role of MSCs in ovarian follicular development through these pathways has been demonstrated, and we will discuss [73–77].

4.2. Preclinical and clinical evidence supporting therapeutic effects of MSC in POI disease

4.2.1. Folliculogenesis and hormone regulatory effects

Studies have shown that MSCs such as BM-MSC and AD-MSC can restore chemotherapy-induced damage to ovaries and can induce an optimal environment for folliculogenesis [57,58,78,79]. Increasing follicle numbers with normal structure is a major therapeutic effect of MSCs [78]. MSCs can also rescue the number of primordial follicles in the injured ovaries and promote folliculogenesis [67,68]. For example, increased primary and secondary follicles and decreased atretic follicles were reported after treatment with different types of MSCs in POI models [80–82]. The potential therapeutic mechanism of hAMSCs and amniotic epithelial cells (AECs) in POI model is mediated through secretion of multiple follicular development-associated factors such as BMP19, FOXL2, growth differentiation factor-9 (GDF-9) and leukaemia inhibitory factor (LIF) in ovarian tissues that are involved in ovarian follicle growth, fertilization, and normal reproduction [83,84].

The our previouse results have also shown that fetal mesenchymal stem cells (fMSCs) inhibit follicle loss and can recover sex hormones in POI mouse model via upregulation of JNK, proliferating cell nuclear antigen (PCNA), and AMPK at the mRNA and protein levels [85]. PCNA as a major regulator of replication fidelity and DNA damage repair, is critical for cellular proliferation [85]. AMPK is a vital intracellular energy sensor that mediates the coordination of cell growth and metabolism [85]. BM-MSCs and UC-MSC can improve ovarian function and reproductive ability in radiation-associated POI models through the TGF-β, Wnt/β-catenin, and Hippo pathway [71,73]. Wnt/β-catenin as an another regulator of folliculogenesis improves granulosa cell proliferation and is involved in preantral to antral follicle maturation [71].

It was demonstrated that hUC-MSCs-secreted hepatocyte growth factor (HGF) can activate follicle activation through up-regulation of c-kit/kit ligand (KITL) (an essential component of ovarian folliculogenesis in mammals) in granulosa cells [86,87]. It was shown that PD-MSCs transplantation can restore ovarian function in ovariectomized (Ovx) rats by enhancing the expression of major folliculogenesis-related genes, such as Nanos3 (nanos homolog 3), Nobox (newborn ovary homeobox) and Lhx8 (LIM-homeobox protein 8) [88].

In addition, MSCs can lead to changes in circulating microRNAs (miRNAs) involved in the ovarian reserve. For example, suppressed expression of miR-145-5p, an essential factor involved in the primordial follicle development and transition to primary follicle has been shown after hPD-MSCs injection [17]. In addition, the exosomal delivery of miR-10a by AMSC could be useful for the preservation of follicle apoptosis [89].

Evidence suggests that treatment with MSCs, in addition to regenerating the ovarian reserve, effectively improves the hormonal profile in experimental models [13,39,90]. It is reported that the elevated levels of FSH and LH in POI experimental models, due to a lack of the feedback control of estrogen and other ovarian hormones (e.g., inhibin), can be restored by stem cells through increasing estradiol levels [91]. MSCs can ameliorate estrogen deficiency via their aromatase (CYP19) activity, which is necessary for estrogen production [92,93]. In addition, they can reduce levels of FSH and LH while inducing FSHR and AMH expression in animal models [88,94,95]. It is noteworthy that increased persistence and level of estrogen by MSCs are not associated with a risk of hypertrophy or tumor formation [92]. It is shown that hormone-sensitive ovarian epithelial (OSE)-like cells differentiated from iPSs using microRNA-17-3p (miR-17-3p), decrease vimentin expression, and induce fibronectin, E2, and ovarian weight in POI-induced mice [96].

4.2.2. Anti-oxidant effects

Evidence suggests that anti-oxidant effects of MSCs can be justified through reduction of ROS, augmenting host antioxidant defenses, immunomodulation mechanisms, mitochondrial function improvement and secretion of several factors including VEGF, HGF, and heme oxygenase-1 (HO-1) (a stress-inducible enzyme with strong antioxidant and anti-apoptotic properties), and activation of the PI3K/Akt, FOXO3a, MAPK, and Nuclear factor-erythroid 2 related factor 2 (Nrf2)-ARE pathways [97,98].

MSCs would appear to have attractive therapeutic potential through their powerful anti-oxidant and immunoregulatory effects (Figs. 1 and 2) [99]. MSCs exert multitargeted antioxidant effects on different POI models through the downregulation of ROS and oxidoreductases (e.g., malondialdehyde (MDA), lactate dehydrogenase, (LDH)) and the upregulation of antioxidants (e.g., glutathione reductase (GR), catalase (CAT), glutathione peroxidase (GPx) and superoxide dismutase (SOD)) [23,85,100,101]. For example, PD-MSCs and AD-MSC can improve ovarian function via oxidative stress reduction by altering heme oxygenase-1 and -2 (HO-1 and HO-2) protein expression and increasing antioxidants factors such as SOD1 and CAT [100–102]. The HO-1 with anti-oxidant and

anti-inflammatory properties, is involved in the ovary physiology and the secretion of gonadotropins from the pituitary gland [103]. The antioxidant effects of PD-MSC in POI model are also mediated by the secretion of EGF [90]. The EGF induces the expression of nuclear factors NRF2 and HO-1, and down-regulate the PTEN expression [104]. Studies have found that BM-MSCs impact the activity of anti-oxidant factors such as SOD and MDA and the release of insulin-like growth factor-1 (IGF-1) [105,106]. IGF-1 signaling mitigates the effects of oxidative stress.

Mitochondrial transmission to damaged cells by MSCs is a possible pathway for repairing endometrium vessels in women with POI [43]. It has already been shown that BMSCs can decrease cell apoptosis and improve cell proliferation and angiogenesis through mitochondrial transferring to injured human umbilical vein endothelial cells via tunneling nanotubes [107]. It was revealed that BM-MSCs transplantation in an age-associated ovarian hypofunction animal model can improve the quantity and quality of oocytes through enhancing mitochondrial function and attenuating cell apoptosis [108]. To our understanding, the lack of comprehensive studies regarding this therapeutic potential of MSCs in the treatment of POI demands further attention.

4.2.3. Anti-inflammatory effects

MSCs, through cell-cell contact and soluble mediators, can modulate the immune response and minimize inflammation-associated tissue damage [109]. Minimizing the detrimental effects of inflammation on the follicles and improving oocyte quality have been reported following MSC transplantation [109]. The involvement of the several pathways such PI3K/pAkt and peroxisome proliferator-activated receptor gamma (PPAR-γ) has been shown in the beneficial effects of MSC in the context of POI [80,110,111].

It was reported that the MSCs can rescue fertility in POI mouse models through an anti-inflammatory effect by downregulating expression of inflammatory factors including tumor necrosis factor-α (TNF-α), interleukin (IL)-8, IL-6, IL-1b, and interferon-γ in damaged ovaries [83,112–115]. PD-MSC transplantation in POI mice, can restore ovarian function by regulating the ratios of T-helper 17/CD8 T (Tc17) (Th17/Tc17) and Th17/regulatory T (Treg) cells, which are important in inflammatory and autoimmune diseases [116].

Autoimmune mechanisms are involved in approximately 4 %–30 % of women with POI [113]. Immunologically, the ovary is not considered a privileged organ; nevertheless, certain levels of immunologic tolerance protect the ovaries from harmful reactions, whose disruption may cause irreversible damage to the ovaries [117]. Although autoimmunity attacks mainly target cells that produce steroids in corpora lutea and pre-ovulatory follicles, in certain cases, fibrosis occurs, follicles are depleted and epithelial cells are abnormally activated [118]. MSCs can improve ovarian function by regulating immune responses [113,119]. The Treg cells are important in immune regulation and T-helper 1/T-helper 2 (Th1/Th2) cytokine balance, which is dysregulated in POI patients. The transforming growth factor β (TGF-b β) secreted by Treg has angiogenesis and matrix-remodeling properties which are essential for follicular development and antrum formation [113]. Ovarian function in POI models was recovered after MSCs transplantation through regulating the T-reg and their associated cytokines [113,120]. It was reported that MSCs upregulate the T-regs and inhibit via the PI3K/Akt signaling pathway in POI animal model [114,121].

4.2.4. Effects against autophagy

The ability of MSCs toward autophagy-enhancing or -inhibiting pathways remains unclear [122]. It is reported that HO-1 expressed in hUC-MSCs can recover ovarian function in POI mouse models via activating the JNK/Bcl-2 signal pathway-regulated autophagy [123]. The function of the JNK signal transduction pathway is a protective mechanism against xenobiotic invasions and acute oxidative damage. This pathway is also found to be associated with some molecular events in autophagy regulation through the disruption of the Bcl-2/Beclin1 complex [123]. Additionally, previous studies have shown that the hUC-MSCs improve ovarian function through inhibiting the cells apoptosis which is achieved in part through the regulation of ROS levels via the autophagy-related AMPK/mTOR pathway, two major autophagy regulators [100]. Therefore, considering the existing evidence on the link between autophagy and oxidative stress and the therapeutic mechanisms of MSCs, comprehensive studies in this field are warranted.

4.2.5. Anti-apoptotic effects

The anti-apoptotic effects of MSCs in ovarian cells have been related to the production of certain factors (.e.g, VEGF, HGF, epidermal growth factor (EGF), and IGF-1), the secretion of exosomal miRNAs, the regulation of apoptosis-related genes, including Bcl-2, Bax, Caspase3, as well as the downregulation of ROS production [9,121,124–126].

The involvement of many signaling pathways in the anti-apoptotic effects of MSCs has been reported in POI models, such as ER stress inositol-requiring enzyme 1α (IRE1α), hippo and FAK-AKT signaling pathway [107,127–129]. It is shown that IRE1α, as an ER transmembrane sensor, mediates the regulation of cell fate and is involved in granulosa cells apoptosis of POI models [130].

It was reported that NGF/TrkA signaling pathway is involved in anti-apoptosis mechanism of UC-MSC in POI model by chemotherapy [131]. The PD-MSC-secreted EGF can inhibit ROS by induction of NRF2 and HO-1, and inhibiting PTEN expression [103]. We reported that, MSCs can restore ovarian function through elevating survivin and Bcl-2 and repressing apoptotic genes (e.g., Caspase-3 and Caspase-9) expressed as a result of oxidative stress [85]. The anti-apoptotic mechanisms of AD-MSCs in chemotherapy-induced POI models are mediated through the promotion of Bcl-2 and VEGF [132].

The pleiotropic effects of MSCs are mediated by the secretion of soluble paracrine factors [133]. Exosomes, a family of nano-sized vesicles, are one of these paracrine mediators that mediate cell communication via their growth factors, bioactive cytokines, signaling lipids, mRNAs, and regulatory miRNAs [133,134]. Stem cell-derived exosomes contain miR-146a, miR-10a, and miR-1246, which target genes associated with granulosa cell apoptosis and play a role in follicle protection by regulating the rate of apoptosis [135,136]. miR-21, as a primary miRNA discovered in mammals, regulates granulosa-apoptosis and follicular development and improves ovarian structure and function [134,136]. This is achieved via targeting the tumor suppressor factors, such as programmed cell death 4

(PDCD4) and PTEN. PDCD4 and PTEN play regulatory roles in cell apoptosis [136]. Increased expression of PTEN, due to the induction of apoptosis, is involved in the pathogenesis of POI [134]. miR-21 derived-stem cells inhibit granulosa cell apoptosis through the downregulation of PTEN and PDCD4 [134].

4.2.6. Angiogenesis and anti-fibrotic effects

MSCs, as an angiogenesis regulators, create a pro-angiogenic microenvironment and support the long-lasting blood vessel networks through differentiating into endothelial cells and vascular smooth muscle or releasing pro-angiogenic factors such as VEGF, stromal cell derived factor 1 (SDF1), IGF, Monocyte chemoattractant protein-1 (MCP-1), and FGF-2 (Figs. 1 and 2) [137,138]. After binding to receptors, VEGF and IGF-1 can repair ovarian vessels, enhance follicular formation and improve the structure and function of damaged ovaries through the PI3K/Akt and GSK3β/β-catenin pathways. SDF1 is involved to MSCs differentiation to vascular endothelial cells [139].

The therapeutic effects of MSCs in different models of POI showed that decreased angiogenesis and ovarian function could be recovered after MenSC, ES-MSC, AD-MSC, and BM-MSC transplantation through their FGF-2 and VEGF factors. It is also shown that VEGF inactivation is associated with the inhibition of follicular development [140–142]. UC-MSC-derived microvesicles could restore ovarian function by inducing angiogenesis via PI3K/AKT signaling pathway activation and carrying miR-126-3p [107,143] (Fig. 1). UC-MSC can repair damaged ovarian in POI rat model through upregulate expression of TGF-β [144]. It was reported that TGF-β is involved in ovarian angiogenesis and follicular development in POI model and can inhibit follicle apoptosis [145].

Fibrosis is one of the histopathological findings of POI disease [146–148]. Ovarian fibrogenesis is caused by the production of certain factors, such as MMPs, TGF-β, and VEGF [56]. Anti-fibrotic effects are among the other expected mechanisms of MSCs that could be beneficial in POI. These cells prevent the proliferation of fibroblasts and reduce the deposition of extracellular matrix [121, 149].

It was confirmed that elevated level of TGF-β1 in ovarian tissue of POI model was diminished after BM-MSCs transplantation [71]. Reduction of granulosa cell apoptosis and interstitial ovarian fibrosis are effective mechanisms of MenSCs [127]. The anti-fibrotic effects of UC-MSC and Men-MSC in POI model are mediated through TGF-β1/Smad3 signaling pathway and secreting FGF2 factor that contributed to improve ovarian function [141, 150].

5. Effects of stem cells on long-term consequences of POI

In addition to the short-term effects of POIs, premature withdrawal of estrogen can affect various organs which are a primary target of estrogen action [151]. These effects manifest as various diseases, such as cardiovascular diseases (CVD), osteoporosis, metabolic syndrome (MetS), and cognitive impairments. CVD is the major cause of shortened life expectancy in patients with POI. Therefore, it is ideal that treatment candidate for these patients can also support these problems. Although a comprehensive study has not been conducted to investigate the therapeutic effects of MSCs on the long-term consequences of POI patients, nevertheless due to unique properties of MSCs, we suggest that in addition to their therapeutic effects on ovarian function, MSCs can be considered a suitable candidate for the mentioned long term complication treatment of these patients. In the following, we discuss our hypothesis.

Due to the effect of estrogen on cholesterol metabolism, decreasing coronary constriction and atherosclerotic plaques, low-level of estrogen in POI women can be a factor in increasing the risk of CVD in these patients [152]. MSCs are potent mediators of cardiac repair via stimulation of repair mechanisms, such as immunomodulatory effects, fibrosis inhibition, cardiac stem cell proliferation and differentiation of myocardial cells, and apoptosis resistance promotion (Figs. 1 and 2) [153–155]. Accordingly, feasibility and safety of MSC therapy in patients with heart disease have been tested in several completed and ongoing clinical trials and their results suggested that MSCs may ameliorate relevant clinical parameters in theses patients, however, the optimal MSC dose and delivery route for the treatment and the reasons for low survival rates after transplantation need to be studied [154,156]. Therefore, although no study has investigated the cadrdiovascular beneficiary of MSC in POI subjects, nevertheless, we seem that it can be considered as a future target therapy.

Osteoporosis is a systemic metabolic bone disease characterized by decreased bone quality and microstructural degeneration [157]. Studies show a direct relationship between osteoporosis and lack of estrogen in the postmenopausal period [158]. It is also shown that formation of peak bone mass (PBM) and the status of bone mineral density (BMD) are affected by hypoandrogenemia and hypoestrogenism in POI patients [158]. The mainstream treatment of osteoporosis is to stimulate osteogenesis or inhibit further bone resorption through pharmacological interventions [159]. However, such treatments cannot reverse the existing bone loss and may be associated with side effects, including osteonecrosis of the jaw, cancer, thromboembolic events, and strokes [159]. Preclinical investigations on MSC transplantation provide evidence of bone healing by osteogenic differentiation, angiogenesis induction, and coordination between bone remodeling, formation, and resorption (Fig. 1) [160,161]. Nevertheless further preclinical research is needed to clarify the long-term safety, effectiveness, and clinical applications of MSCs in osteoporosis [162].

The MetS is a complicated clinical condition and has emerged as a threatening global epidemic. Compared to normal people, individuals affected by MetS are more likely to develop diseases such as diabetes, cancer, bone loss, cardiovascular complications, and non-alcoholic fatty liver disease (NAFLD). The current medical practice cannot offer solutions for patients diagnosed with this syndrome [163]. MSCs are found to have positive impacts on multiple MetS clusters and have been shown to be safe and effective [143]. MSCs have been used to treat type 2 diabetes mellitus (T2DM) due to their potential to differentiate into β-like insulin-producing cells and secretion of bioactive cytokines that build an appropriate microenvironment for stimulating the regeneration of β-cells and inhibition of immune responses mediated by T cells [163,164]. These findings suggest that MSCs may contribute to homeostasis regulation and glucose metabolism while being actively engaged in the regulation of the immune system and regeneration/repair of

tissues [148]. It is shown that MSCs contribute to modifying abnormal lipid metabolism [164,165]. The expression of fatty acid oxidation genes is promoted, while the expression of adipogenesis genes responsible for the regulation of lipid metabolism is inhibited by MSCs, which results in improved MetS and NAFLD [165]. Although their safety and effectiveness in clinical application are still far from optimal, MSCs have attracted a great deal of scholarly attention for modifying MetS and obesity. Future studies are required to delineate the therapeutic role of MSCs in MetS patients and their safety.

6. Clinical applications of MSCs in POI patients

Based on the promising therapeutic effects of MSCs in POI animal models and some preclinical studies, numerous clinical trial investigating efficacy and safety of MSCs for ovarian insufficiency, were conducted in patients with POI [145]. The first clinical study indicated that BM-MSCs transplantation could be a promising therapy in POI women, due to their ovarian restoration phenomena [166]. Using BM-MSC, resulted in follicular regeneration, increased AMH levels and successful pregnancy in women diagnosed with POI [167]. Several other studies reported potential use of BM-MSCs in some POI patients [168,169]. A similar approach was reported in two studies in 10 and 30 women with POI, which indicated resumed menstruation and successfully pregnancy, following autologous MSCs transplantation [170,171]. Following the promising aforementioned data, similar results pertain to addressing ovarian insufficiency have been shown from other sources of stem cells, except BMSCs. For example, in a clinical study, 61 women diagnosed with POI were subjected to UC-MSCs transplantation under the guidance of vaginal ultrasound and 4 patients achieved successful pregnancy after UC-MSCs transplantation and no serious complications or side effects were observed in any of the patients [119]. Recently, novel approaches have been investigated to improve MSCs efficacy in regenerative medicine and tissue repair. A clinical analysis was designed with 2 treatment groups to compare the potential effects of transplanting UC-MSCs and collagen/UC-MSCs in women with POI. Following MSCs transplantation directly into ovaries, the improvement in ovarian function was seen in collagen/UC-MSCs group, in addition, fertility restoration in both groups suggests that MSCs transplantation could be an effective treatment in POI patients [172].

The good safety profle of MSCs have been demonstrated in different clinical applications, such as infertility. Although the limited small sample trials indicated the safty of MSCs for more than a year in POI women, but long-term safety and adverse events are limited [173]. Therefore, further comprehensive and larger clinical studies are critical to establish the standardizing the preparation and ensuring the safety of the MSCs stherapy on the reproductive system [174].

7. Optimizing MSCs for therapeutic purposes

MSCs optimization can address their limitation and improve the safety and efficacy of MSCs in clinical applications. Therefore, numerous studies have been carried out to evaluate the factors pertain to survival rates, efficacy and therapeutic potential of transplanted MSCs which will discuss in this section [145].

The therapeutic effects of MSCs depend on how they are produced and administrated [175]. This, *per se*, is influenced by the stage of the disease, dose of delivery, patient genetics, the extent of response to MSCs, and how they are produced [175]. Such variabilities make it necessary for MSCs to be tailored for the intended therapy, giving rise to the question of how MSC response can be optimized [175]. A range of MSC optimization methods are being applied which are summarized below.

7.1. Stem cells-preconditioning

The therapeutic effectiveness and survival rate of MSCs can be improved through several strategies including genetic modification and non-genetic modification techniques [176]. Genetic modification through overexpression of the optimal elements and soluble factors including chemokines, enzymes, cytokines, growth factors, microRNAs, and transcription factors, could promote homing and migration of MSCs [177]. Safety concerns regarding the use of genetically-modified MSCs are the major factor limiting their use in clinical settings. It has been argued that inflammatory and other immune responses are induced by viral expression systems, and tumourigenic risk is caused by viral integration in the genome of the host. Moreover, a deeper insight into genetically engineered MSCs is indeed a necessity to evaluate their long-term impact and potential therapeutic strategies. Thus, to promote the therapeutic applicability of MSCs, an alternative way for the development of non-genetically modified MSCs may prove highly efficient [178]. Pre-activation of MSCs helps obtain the intended results and inhibit their inactivation as they are able to identify and remember stimuli in the microenvironment.

Specific areas of tissues, known as stem cell niche, are home to stem cells. Both cellular and acellular components are present in such multidimensional environments, which offer a chance for manipulation and proliferation of cells, determination of stem cell fate, and maintenance of stem cell homeostasis. These components are cell to cell interactions, chemical factors (PH, oxygen, nutrients, ionic strength, metabolites cytokines, and chemokines), extracellular matrix (composition, structure, topology, and stiffness), and physical elements (temperature, osmotic pressure, stretch, and electrical signals) [179,180]. Therefore, physiological microenvironment simulation pre-activation can improve MSC production and their biological properties [60]. In patologic condition, the microenvironment which MSCs will be involved contains destructive factors that make the transplanted cells experience oxidative stress and apoptosis, which in turn significantly impair the therapeutic efficacy of MSCs. This has provided an incentive for researchers to improve cell properties to tolerate hostile environments and preserve their effectiveness against diseases. In this regard, as a complementary pre-activation condition of therapeutic MSCs, it is suggested that effector cells or their released active substances be applied instead of other alternatives such as bioactive compounds, cytokines, or typical proinflammatory factors [178]. This approach

can improve the efficincy of MSCs-based treatment in specific diseases [181]. Today, preconditioning of MSCs with a variety of active substances, pharmacological and biologic agents has shown promising results in different experimental diseases [182]. It was demonstrated that hypoxia preconditioning of MSCs played a positive role in maintaining MSCs pluripotency, mobilization, and homing and promoting normal embryo development [145]. For example, studies have shown that heat shock pretreatment inhibits MSC apoptosis and enhances their repair potential and anti-apoptotic effect on chemotherapy-induced POI models [183].

7.2. Improving stem cells-engraftment

MSCs therapy is found to be limited due to their post-translate engraftment into the target tissue [176]. MSC homing is dependent on their receptors and cell adhesion molecules (i.e., E-selectin glycoprotein ligand-1), and some factors such as TNF-α and HGF. However, these ligands are poorly expressed in MSC or may be affected by long-term *in vitro* culture conditions. For this reason, using different strategies such as genetic or enzymatic modifications, conjugation of specific antibodies or proteins, or the use of retroviral vectors encoding homing receptors can enhance homing efficiency of MSCs towards the desired tissue [184].

Improved MSC homing can also be achieved by the optimization of cell administration [142]. An effective cell delivery method is highly important for the transplantation of MSCs and their therapeutic efficacy as it may offer regenerative benefits with the lowest possible side effects [185]. Despite the variation between transplantation methods, previous studies investigated the therapeutic potential of intravenous (IV) and intraovarian injection and arterial injection, of MSCs in POI models, while there are only a few studies about the homing of MSCs into the ovarian [186]. A recent study has shown that stem cell distribution via ovarian injection was seen only in the ovaries and uterus. While IV transplanted stem cells were detected in different tissues such as ovaries, uterus, liver, kidneys, and lungs [186]. In comparison to intraovarian injection, the IV route provides an opportunity to deliver different concentrations of cells with more minimally invasive. However, IV injections carry a risk of embolism due to larger or insufficiently dissociated cells. Also, this route is painful and has severe adverse effects especially when organs such as the liver, heart, and brain are involved in toxicity [187,188]. Choosing the transplantation method needs further research and discussion [186].

7.3. Improving ovarian conditions

Evaluation of ovarian conditions in POI women, before stem cell transplantation, is another interesting mechanism to optimize stem cells function [189]. It should be noted that impaired ovarian condition due to aging, autoantibodies, or gonadotoxins may lead to a decreased ovarian response to transplanted MSCs [189]. So, ovaries must be improved in terms of a sufficient amount of soluble agents, proper blood flow, healthy cortex, epithelium, and neural network [189]. It seems that soluble factors and platelet-rich plasma (PRP) injection into the ovary will improve the ovarian microenvironment and subsequently stem cell function [189]. Cytoplasmic granules of platelet, including platelet-derived growth factor (PDGF), EGF, IGF-1, VEGF, liver cell growth factor, and adenosine di- and triphosphate can promote compromised ovarian microenvironment [189,190]. In POI models, soluble factors transplantation prior to stem cell injection provides a condition for proliferation and survival of stem cells in the ovarian environment and can improve the small number of follicles [43].

7.4. Use of biomaterials

Despite promising results and increasing advances in stem cell therapy, low retention and cell survival are limitations of MSCs for clinical applications [191]. The use of biomaterials, as cell carriers, has been successful in controlling the fate of transplanted cells [111]. Biomaterials, as a bioactive scaffold, are involved in the culture, differentiation, engraftment, and function of implanted cells via providing a desirable microenvironment [111]. They range from natural (e.g., extracellular matrix (ECM), collagen, fibrin, and hyaluronic) to synthetic products (e.g., polytetrafluoroethylene (PTFE)) and have been employed for MSC/exosome/secretome delivery [111]. For example, MSC transplantation using ECM, synthetic polymers and collagen scaffolds increases ovarian size, follicle growth, and granulosa cell proliferation, and improves vascular development in the POI experimental models [192,193]. The collagen scaffold via improving estrus cycles, and follicle development can promotes the pregnancy rates in POI model [194]. Due to endometrium regeneration, collagen/MSCs system can be condisered for women with endometrium disorder that have fertility demands [195]. Thus, it seems that tissue engineering in combination with MSCs can be considered as a promising therapeutic option for POI disease [145]. However, the mechanisms of action are still unclear, and safety and efficacy characteristics need further studies [111].

7.5. Use of stem cells-derived secretomes and exosomes

The potential risks for tumorigenesis and immunogenicity are other problems with stem cell therapy. These risks can be overcome by using acellular therapies, such as stem cells-derived secretomes, cytokines, and exosomes [111]. Stem cells-derived culture medium includes various soluble factors, microvesicles, and exosomes that have similar roles to stem cells, such as tissue repair, anti-inflammatory, and immune regulatory properties [196]. So, condition media from stem cells could be considered as an alternative to cell therapy [196,197]. Exosomes, as membrane biological nanoparticles, can affect cell phenotype and function by binding to cellular ligands and inducing proteins, microRNA, and long coded RNA into the target cell cytosol [198]. No risk of immune rejection and malignancy, stability, and long-term maintenance are advantages of exosomes compared to stem cells [161]. However, exosome isolation, characterization, and analysis techniques still need to be addressed [56]. Exosomes from MSC-mediated cell therapy have shown promising results in various disease models such as POI [198–201].

Exosome-encapsulated miRNAs are considered as an important mechanism of genetic exchange between cells [202]. Previous studies have shown potential therapeutic advantages of MSC-derived exosomal miRNAs for the treatment of various diseases and injuries [202,203]. It is reported that miRNAs are mediated in the pathogenesis, early diagnosis, and evaluation of the therapeutic efficacy of POI [202]. For instance, it is shown that overexpression of miR-144-5p in BM-MSCs has efficacy against the CTX-induced POI model, through the inhibition of GC apoptosis by targeting PTEN [202]. In another study, it is suggested that miR-644-5p carried by BMSC-derived exosomes had the potential to treat POI and restore ovarian function by targeting p53 of cells [204]. miR-21 carried by hucMSCs-derived exosomes could improve secretion of estrogen in GC cells through targeting of LATS1, a inhibitor factor for estrogen secretion [205]. In our previous studies, we evaluated the therapeutic potential of MSC-derived exosomes and their molecular mechanism in the POI model [136,206]. Our findings revealed that the therapeutic effect of MSCs in POI model can be mediated through delivery of exosomal miR-17-5P that targets mRNA SIRT7, a major cell regulator to metabolic and oxidative stresses [207].

Recently, it was reported that UCMSC-derived exos has a critical rol in improving the ovarian microenvironment in POI model through modulation of immune response, apoptosis, fibrosis, and metabolism [208]. RNA-seq and multifaceted bioinformatics analyses have shown differentially expressed genes (DEGs) involved in immunomodulation (e.g., Brms1 and Cpa1), fibrosis (e.g., Hmox1, Eppk1, Eva1a, Errfl1, Fgfbp1), metabolism (e.g., Ddr1, Pcdh17, Noct, Rpl30, Cbr1) and apoptosis [208]. In another study, we demonstrated that AD-MSC-derived exosom in a POI mouse model improve ovarian function through regulation of the SMA and mother against decapentaplegic (MAD)-related proteins (SMADs) signaling pathway [206]. SMADs as an intracellular components of the TGF-β signaling pathway are involved in oogenesis and proliferation of GC cells [206]. To determine the therapeutic mechanism of AMSC-derived exosomes in POI disease, we revealed that AMSC can diminish ROS levels by regulating SIRT4 and relative genes (ANT2, AMPK, and L-OPA1) through exosomal miR-320a delivering to the oocyte, hGCs, and ovaries [209]. Sirtuins (SIRT) are fundamental regulators of cellular functions, such as proliferation, metabolism, and lifespan [209]. It is suggested that hippo pathway is another involved factor in therapeutic effects of UC-MSC-derived exosome in improvement of ovarian function [73].

In addition, using collagen/UC-MSCs promoted follicles development and ovarian angiogenesis with the increased expression of CD31 [210]. CD31 and VEGF are considered as a well defined markers of prognostic angiogenic markers. These studies uncovered a new therapeutic opportunity of exosome-based therapy for POI treatment. Despite, promosing results, before clinical application of MSC-EVs, the key issues including the large-scale production, characterization, and safety profile assessments should be addressed [145].

7.6. Use of MSCs derived from induced pluripotent stem cells

One big challenge with regard to the therapeutic use of MSCs is the method used for their generation. Direct harvesting of MSCs from donors might be invasive in some cases and have some health risks [164]. On the other hand, any variation in the source of MSCs, levels of expansion, and protocols for culturing might result in the heterogeneous functionality of MSCs. Thus, therapeutic application of MSCs is bound to their large-scale expansion that preserves homogeneity and biological activities [211]. Non-invasive methods that can be used for the large-scale isolation of homogenous populations of MSCs are highly required in clinical settings [212]. For this, pluripotent stem cells (PSCs), such as ESCs and iPSCs, have been considered as potentially ideal sources [213]. The availability of abundant resources with minimum ethical concerns has extended the use of iPSCs, which can be differentiated into highly-efficient functional MSCs (iPSC-MSCs), offering an optimal source of MSC with acceptable levels of homogeneity and quality [214]. Similarly, hiPSC-derived MSCs can be easily produced from skin-derived fibroblasts and lymphocytes, and are more stable in molecular signature, differentiation, and proliferation applications than tissue-derived MSCs [215]. The high potential for therapeutic effect, regardless of the donor's age, is another advantage of hiPSCs [213]. Future investigations regarding safe hiPSC-MSCs generation will bring impressive insights into pluripotent stem cell applications in clinical trials. Recent studies investigated GMP-grade MSCs derived from iPSCs in various diseases and complications [216–218]. It seems that iPSC-MSCs may be considered as a putative cellular source for reproductive disorders. Oocyte regeneration from iPSCs has shown a revolution in reproductive medicine and can address limitation by current reproductive technologies [219]. Recently, it was shown that primordial germ cell-like cells (PGCLCs) derived from murine ES/iPS cells, can resume meiosis and follicles formation to product competent oocytes [220,221]. It was shown that transplantation of hormone-sensitive ovarian epithelial (OSE)-like cells derived from human iPS in a POI mouse model, has positive effect on ovarian function and contribute to decrease expression of vimentin and increase levels of E2 [96]. Also, it was demonstrate that OGLCs derived from iPSCs can repair damaged ovarian tissue and promote follicular development in a mouse model of POI [93]. Therapeutic effect of iPSC-MSC-EVs can bemediated through up-regulation of the integrin-linked kinase (ILK) -PI3K/AKT pathway in GC, a key mediator in cell proliferation and survival [222]. Despite of attractive results, there are several limitation in regard to ovarian somatic cells extraction and low efficacy of the iPS differentiation into mature oocytes [223].

8. Conclusions and future perspectives

POI can affect not only women's fertility but also their mental health and the function of other organs. Despite many efforts, there is no appropriate therapy to the present date. Given their low immunogenicity, easy accessibility, and the possibility of *in vitro* reproduction in large quantities, stem cells can be considered as a new promising therapeutic candidate for POI patients. Preclinical data suggest that stem cells can migrate to the injured ovary and improve ovarian function through their multiple protective mechanisms, such as anti-inflammatory, anti-oxidants, anti-apoptosis, anti-fibrosis, and angiogenesis effects. However, the exact mechanisms of stem cells in this particular disease are yet to be uncovered and there is a bottleneck that should be addressed before application in clinical settings. The function of transplanted MSCs in different levels of the physiological immune response as a normal and

inflammation state, appropriate dose and administration method, life span, and stability of immunomodulatory activity of MSCs is an essential issue that remains unanswered. Furthermore, MSCs used in combination with pharmaceutical approaches or an alternative cell type that complement characteristics of MSCs can be considered as other potential strategies. Overcoming this problem is not possible except through more clinical trials and many studies to identify new features of stem cells in POI patients.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of abbreviations

AD-MSC Adipose tissue derived-mesenchymal stem cell
AES Amniotic epithelial cells
AFSC Amniotic fluid stem cells
AMH Anti-müllerian hormone
AMPK Adenosine-monophosphate activated-protein kinase
ASCs Adult stem cells
Bcl-2 B-cell lymphoma-2
BMD Bone mineral density
BM-MSC Bone marrow-derived mesenchymal stem cells
CAT Catalase
CVD Cardiovascular diseases
ECM Extracellular matrix
EGF Epidermal growth factor
ESCs Embryonic stem cells
EVTs Extravillous trophoblasts
FAK Focal adhesion kinase
FGF-2 Fibroblast growth factor-2
FSH Follicle-stimulating hormone
GnRH Gonadotropin-releasing hormone
GR Glutathione reductase
HGF Hepatocyte growth factor
HIV Human Immunodeficiency Virus
HO-1/2 Heme oxygenase-1/2
HPV Human Papilloma Virus
HRT Hormone replacement therapy
HSV Herpes Simplex Virus
IGF-1 Insulin-like growth factor-1
iPSCs Induced pluripotent stem cells
IRE1α Inositol-requiring enzyme 1α
ISCT International Society for Cellular Therapy
JNK c-Jun NH2-terminal kinase

LDH Lactate dehydrogenase
LH Luteinizing hormone
Lhx8 LIM-homeobox protein 8
MAPK Mitogen-protein kinase
MCP-1 Monocyte chemoattractant protein-1
MDA Malondialdehyde
MenSCs Menstrual blood-derived Stem Cells
MetS Metabolic syndrome
MMPs Matrix metalloproteinases
MSCs Mesenchymal stem cells
mtDNA Mitochondrial DNA
mTOR Mammalian target of rapamycin
NAFLD Non-alcoholic fatty liver disease
Nanos3 Nanos homolog 3
NLR Neutrophil to lymphocyte ratio
Nobox Newborn ovary homeobox
NRF2 Nuclear factor erythroid 2–related factor 2
OGLCs Ovarian granulosa-like cells
Ovx Ovariectomized
PCOS Polycystic ovary syndrome
PDCD4 Programmed cell death 4
PDGF Platelet-derived growth factor
PD-MSCs Placenta-derived mesenchymal stem cells
PI3K Phosphatidylinositol 3-kinase
POI Premature ovarian insufficiency
POF Premature ovarian failure
PTEN Phosphatase and tensin homolog
ROS Reactive oxygen species
PGCLCs Primordial germ cell-like cells
PRP Platelet-rich plasma
PSCs Pluripotent stem cells
PTFE Polytetrafluoroethylene
RTIs Reproductive tract infections
SOD Superoxide dismutase
T2DM Type 2 diabetes mellitus
TGF-b β Transforming growth factor β
TNF-α: Tumor necrosis factor-α
Treg Regulatory T cell
UC-MSC Umbilical cord-derived mesenchymal stem cells
VEGF Vascular endothelial growth factor
WJ-MSCs Wharton's jelly-derived mesenchymal stem cells
XBP1 X-box binding protein 1

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