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REVIEW

Premature ovarian insufficiency: pathogenesis and therapeutic potential of mesenchymal stem cell

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Abstract

Primary ovarian insufficiency (POI) is defined as a reduction in ovarian function before the expected age of menopause. POI is known to increase the risk of cardiovascular disorders, osteoporosis, cognitive decline, and mood disorders, resulting in a reduced quality of life. Appropriate hormone replacement for premenopausal women decreases these adverse health risks and improves quality of life for women with POI, but does not prolong life expectancy. The potential etiologies of POI include chromosomal abnormalities and genetic mutations, autoimmune factors, and iatrogenic causes, including surgery, chemotherapy, and radiation therapy. A major association is suggested to exist between reproductive longevity and the DNA damage pathway response genes. DNA damage and repair in ovarian granulosa cells is strongly associated with POI. Depletion of oocytes with damaged DNA occurs through different cell death mechanisms, such as apoptosis, autophagy, and necroptosis, mediated by the phosphatase and tensin homolog (PTEN)/phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/forkhead transcription factors 3 (FOXO3) pathway. Mesenchymal stem cells (MSCs) are characterized by the ability of self-renewal and differentiation and play an important role in the regeneration of injured tissues. Transplantation of MSCs has been shown to functionally restore ovarian reserve in a POI mouse model. Recent advances in stem cell therapy are likely to be translated to new therapeutic options bringing new hope to patients with POI. The aim of this review is to summarize the pathogenic mechanisms that involve cell death and DNA damage and repair pathways and to discuss the stem cell–based therapies as potential therapeutic options for this gynecologic pathology.

Keywords Premature ovarian insufficiency · Menopause · Ovary · Hormone replacement therapy · Cell death · DNA repair · Mesenchymal stem cells

Ovarian insufficiency and menopause

Menopause is a clinically defined condition determined retrospectively after a 12-month permanent cessation of menstruation without other reasons for amenorrhea such as pregnancy, hormonal therapy, or other medical conditions [1]. Most women go through menopause between the ages of 49 and 52 years. Worldwide, a typical woman experiences menopause at an average age of 50.5 years, although differences exist between races and geographic areas [2]. Approximately 5% of women experience menopause between the ages of 40 and 45 years, and approximately 1% women enter menopause before the age of 40 years [3, 4]. This clinical syndrome defined by loss of ovarian function under the age of 40 is called premature ovarian insufficiency (POI), formerly referred to as "premature menopause" or "premature ovarian failure (POF)." About 1 in 1000 women develops POI under the age of 30, sometimes as early as the teenage years.

Menopause reflects a decline in follicular function. As estrogen decreases with great variability, women may experience the various signs and symptoms during the months or years leading up to menopause or after menopause such as irregular menstrual periods, hot flashes, night sweats, sleep

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disruption, and mood changes. In the postmenopausal state, women sometime experience vaginal dryness, vulvovaginal atrophy, lower urinary tract symptoms, thinning hair, and dry skin [5]. Among these signs and symptoms, loss of menstruation is the first or only symptom of POI, which can be preceded by irregular menstrual cycles.

In addition, POI patients develop different health risks compared to women undergoing natural menopause because they are exposed to a longer hypoestrogenic state. Given that POI occurs during childbearing ages, one of the most severe outcomes associated with POI is severely reduced fertility with low birth rates [6–8]. Women with POI also have a decreased life expectancy, largely due to cardiovascular morbidity and mortality [9–12]. Because POI leads to estrogen deficiency, patients have a higher risk of osteoporosis and bone fractures, which is known to result in worsening quality of life later in life [9, 13–18]. Women who undergo "surgical menopause" to remove both ovaries due to benign (adnexal masses and risk reducing surgery) or malignant (endometrial cancer and ovarian cancer) diseases undergo abrupt POI, if not given hormone replacement therapy, with subsequent cognitive decline as a result of Alzheimer's disease [19–21]. Often unexpected diagnosis of POI leads to psychological confusion in young women, resulting in higher rates of depression compared to their healthy controls due to reduced self-esteem and social anxiety [22].

Genetic, autoimmune, and chemo/radiation causes

The etiology of POI is known to be related to chromosome X–associated abnormalities, single genetic mutations, autoimmune factors, and iatrogenic factors, but the cause of many cases goes unidentified [7]. Genetic factors are major determinants of menopausal age in the general population and have been associated with approximately 7% of POI cases [23–25]. Chromosomal abnormalities causally related to POI are fragile X chromosome syndrome (FXS) [26–28] and Turner syndrome [29]. FXS leads to the most common cause of inherited intellectual disability, caused by a loss-of-function mutation in the *fragile X mental retardation 1* (*FMR1*) gene located on the X-chromosome, locus Xq27.3. Turner syndrome is a condition of partial or complete absence of the X chromosome, such as 45XO or 45X/46XX mosaicism in females. Notable X-linked genetic mutations associated with POI involve *growth differentiation factor-9* (*GDF-9*) and *bone morphogenetic protein-15* (*BMP-15*) [30, 31], whereas autosomal abnormalities were found in *forkhead box l2* (*FOXL2*) [32], *follicle-stimulating hormone receptor* (*FSHR*) [33], *stromal antigen 3* (*STAG3*) [34], *x-Ray repair cross complementing 2* (XRCC*2*) [35], and *minichromosome maintenance 8 homologous recombination repair factor* (*MCM8*) [36] genes. Although the cause of POI has not been clearly identified, about 10% of women with POI have a family history of the condition [37].

About 20% of women with POI have a previous diagnosis of an autoimmune disease affecting a variety of different organs, including the heart, kidney, thyroid, pancreas, and the gastrointestinal tract. The autoimmune etiologies for POI are divided into two groups: endocrine and non-endocrine disorders [38–40]. Endocrine diseases include Addison's disease, Hashimoto's thyroiditis, hypophysitis, and diabetes mellitus type 1, while non-endocrine diseases include chronic candidiasis, rheumatoid arthritis, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, pernicious anemia, celiac sprue, alopecia vitiligo, systemic lupus erythematosus, Sjörgren's syndrome, chronic active hepatitis, primary biliary cirrhosis, and autoimmune polyendocrine syndromes I and II [41, 42]. Autoimmune disease-triggered POI is mediated through an antibody production against ovarian tissue that harms developing follicles in the ovaries and causes ovarian dysfunction [43].

Additional factors responsible for the development of POI include chemotherapy and radiation. Chemotherapy and radiotherapy cause POI by impairing follicle maturation or loss of primordial follicles directly or indirectly [44]. In chemotherapy, alkylating agents such as cyclophosphamide and anthracycline are most well known to cause ovarian dysfunction and POI [45]. The use of new targeted therapies, such as bevacizumab and tyrosine kinase inhibitors (imatinib, pazopanib), may also be associated with an increased risk of POI [46, 47]. Vascular endothelial growth factor A (VEGFA) is believed to play an important role in regulating ovarian angiogenesis [48], and the use of anti-angiogenesis drugs such as bevacizumab increases the risk of POI by inhibiting follicle formation and oocyte maturation [49]. Women receiving whole pelvic or spinal radiation are also at increased risk for developing acute ovarian failure [50, 51]. In particular, age, the distance between the irradiated site and the ovaries, the total dose, and the number of fractionation are important factors that determine the risk of POI [9, 52]. Cranial radiation may cause hypothalamic-pituitary disturbance resulting in amenorrhea [53].

Premature ovarian insufficiency management

POI is a challenging diagnosis that is associated with several emotional and physical consequences (e.g., osteoporosis and cardiovascular events). At the time of diagnosis, patients may experience moderate to severe emotional distress due to the unexpected nature and the health implications associated with POI [54]. It is the physician's role to deliver the news in a caring manner and provide patients with the support and

resources available. An early and timely diagnosis of POI is essential for both treatment and prevention of long-term complications of the hypoestrogenic state [6, 16]. Most patients with POI present with irregular menstrual cycles rather than amenorrhea, contributing to the delay in the diagnosis. Given the varied presentation in menstrual irregularities, it is prudent to consider POI in patients with abnormal uterine bleeding. In addition, the levels of estrogen, FSH, and ovarian ultrasound findings may be used to confirm the diagnosis [55]. Recent findings suggest that anti-Müllerian hormone (AMH) is the best biomarker of ovarian reserve currently available [56]. Its level in circulation is significantly correlated with the number of primordial follicles in healthy women [57].

After the diagnosis is confirmed, multidisciplinary approaches are pivotal in dealing with POI patients. Future fertility concerns and postmenopausal symptoms need to be addressed at the time of the diagnosis. Such concerns shape future treatment plans for patients. For example, assisted reproductive techniques like *in vitro* fertilization (IVF), cryopreservation, follicle retrieval, and oocyte or embryo donation should be discussed with patients who have future reproductive plans. However, while the fertility strategies are important, the focus on this paper is the management of the non-fertility issues associated with POI and the use of hormone replacement therapy (HRT). Such non-fertility issues include vasomotor instability, sexual dysfunction, and higher long-term risk of cardiovascular diseases and osteoporosis [58].

Three HRT agents are commonly used and include ethinyl estradiol, conjugated equine estrogen, and estradiol. Estradiol is recommended for menopausal women because of fewer side effects compared to ethinyl estradiol and conjugated equine estrogen. All women with primary ovarian insufficiency should be offered HRT unless there are contraindications to HRT or they refuse HRT due to informed/shared decisions [59]. However, in young women with an intact uterus, combined hormonal therapy, including progesterone, is recommended to prevent endometrial hyperplasia and carcinoma [6].

Animal models of premature ovarian insufficiency

The current knowledge of POI pathophysiology is based on studies in animal models. A common murine model of POI uses various anticancer drugs, including cyclophosphamide, busulfan, doxorubicin, gemcitabine, and cisplatin [60–64]. Strong evidence demonstrates that exposure to these anticancer agents leads to follicular atresia and apoptosis of granulosa cells [65, 66]. In addition, mice with exposure to high concentrations of galactose were used as a model for POI due to galactose-triggered toxicity causing pituitary dysfunction, resulting in a persistent high levels of follicle stimulation hormone (FSH) and low levels of estradiol (E2) [67]. Another murine model utilizes thymectomy to trigger POI by causing autoimmune oophoritis that progresses to acute oocyte loss with massive infiltration of mononuclear cells [68]. Additional POI models have been established by knockdown of genes involved in primordial germ cell migration and proliferation, including *G protein-coupled receptor 3* (*GPR3*), *basonuclin 1* (*BNC1*), *C2HC-type zinc finger 3* (*NANOS3*) [69–71], and knockdown of *FMR1* [72] involved in cell death. An additional group of genes comprised of oocyte-specific transcription factors such as *folliculogenesis-specific basic helix-loop-helix* (*FIGLA*) [73], oocyte-specific TGF-beta family such as *GDF9* [74], and the transcription factors associated with follicular development such as *Wilms tumor 1* (*WT1*) and *Forkhead box protein L2* (*FOXL2*) [75, 76]. Finally, knockdown of genes involved in follicular development and their receptors such as follicle stimulation hormone receptor (FSHR) [77] and *AMH* [78] have been used to establish the POI in an *in vivo* model. Different models of POI are summarized in Table 1.

Cell death

In mammalian females, the formation of primordial follicles, comprised of oocytes surrounded by granulosa cells, is completed prenatally, and the number decreases with aging [79]. Most of primordial follicles remain dormant after birth, but some initiate meiosis through reproductive age, as part of initial recruitment. The primordial follicles that have begun meiosis grow into primary and secondary follicles, undergo cyclic recruitment, and finally ovulate by the appropriate stimulation of gonadotropins [80]. In the absence of gonadotropin stimulation, the follicles undergo atresia and apoptotic cell death [81].

Apoptosis is closely associated with POI, and it is believed to be the major mechanism of cell death associated with oocyte loss in the process of maturation from primordial to antral follicles, or secondary due to chemotherapeutic treatments [82]. Trends of follicles in POI patients cannot be ethically studied. Thus, the effects of chemotherapy on ovarian follicles have only been studied in gene knockout mouse and human ovarian xenograft models [62, 83–85]. In human ovarian xenograft models, cyclophosphamide directly damages resting follicles, resulting in a reduced number of primordial follicles [84]. This phenomenon induces significant apoptosis of granulosa cells, which is the cellular basis of ovarian follicular atresia [86, 87], as it leads to reduced levels of sex hormones secreted by non-resting follicular granulosa cells [88].

Table 1 POI in vivo models

Animal	Background	Regimen Chemotherapy	Period	Route	Assessment	Reference
Mouse	C57BL/6	Busulfan 12 mg/kg, cyclophosphamide 200 mg/kg	Single dose	IV	Number of immature follicles in the ovary	[60]
Mouse	C57BL/6	Busulfan 12 mg/kg, cyclophosphamide 120 mg/kg	Daily, 2 weeks	IP	Number of zygotes retrieved and embryo development rate to blastocyst of zygotes	[61]
Mouse	C57BL/6	Cisplatin (2 mg/kg)	Daily, 10 days	IP		[61]
Mouse	ICR	Cisplatin (2.0 mg/kg)	Daily, 15 days	IP	Number of immature follicles in the ovary	[63]
Mouse	ICR	Doxorubicin (7.5 mg/kg)	Single dose	IP	Ovulation rate	[64]
Rat	Sprague-Dawley	Gemcitabine (200 mg/kg)	Single dose	IP	Number of blastocysts in the uterus	[65]
Rat	Sprague-Dawley	Cisplatin (50 mg/kg)	Single dose	IP		[65]
Rat	Sprague-Dawley	Cyclophosphamide (200 mg/kg)	Single dose	IP		[65]
		Pituitary dysfunction	Period	Route		
Rat	Sprague-Dawley	Food pellet with 35% galactose	Every day	Food pellet	Number of oocytes in the oviduct	[67]
		Surgery				
Mouse	C57BL/6	Thymectomy			Vaginal opening day and continuous diestrus cycle	[68]
		Gene knockdown				
Mouse	*Gpr3*$^{-/-}$	GPR3			Number of immature follicles in the ovary	[69]
Mouse	*Bnc1*$^{tr/tr}$	BNC1			Measuring the ovary weight relative to body weight and ovary size	[70]
Mouse	*Nanos3*$^{Neo/Neo}$	NANOS3			Number of pups	[71]
Mouse	*Fmr1*$^{-/-}$	FMR1			Number of primordial germ cells	[72]
Mouse	*Figα*$^{tm/tm}$	FIGLA			Number of growing follicles	[73]
Mouse	*Gdf9*$^{-/-}$	GDF9			Number of live births, number of growing follicles	[74]
Mouse	*Foxl2*$^{-/-}$	WT1			Total number of oocytes	[75]
Mouse	*Wt1*$^{+/R394W}$	FOXL2			Ratio of pregnancy, the ovulation rate	[76]
Mouse	*Fshr*$^{-/-}$	FSHR			Total number of follicles and the number of antral follicles	[77]
Mouse	*Amh*$^{-/-}$	AMH			Number of follicles	[78]

IV tail vein injection, *IP* intraperitoneal injection

In addition to apoptosis, inhibition of autophagy has been shown to be involved in follicular loss. Germ cell–specific knockout of the *autophagy-inducing gene* (*Atg7*) leads to reduced fertility due to severe ovarian follicular loss in female mice. Germ cell-specific *Atg7* knockout causes excessive germ cell loss at the neonatal transition period [89].

Cell-programmed necrosis (necroptosis) is a programmed cell death pathway that exhibits necrotic morphology and is executed by a defined cell signaling cascade that shares some key important members with apoptosis [90–93]. Necrosis and necroptosis have been shown to be the molecular mechanism of germ cell depletion in aging ovaries, but their role in POI has not been studied. In addition to apoptosis and autophagy, necrosis and necroptosis are involved in germ cell depletion from the mammalian ovarian cohort [94]. Oxidative stress and cytokines induce necrosis and necroptosis in the mammalian oocyte. Also, high levels of cytokines and oxidative stress induce necrosis and necroptosis in granulosa cells, resulting in follicular atresia. In granulosa cells, necrosis, as well as apoptosis, increases with the progression of follicular atresia [95]. Dehydroepiandrosterone (DHEA), reported to improve oocyte quality and pregnancy rates in patients with diminished ovarian reserve [96, 97], can attenuate starvation-induced up-regulation of receptor interacting protein kinase 1 (RIPK1) and RIPK3 that transmit necroptosis signaling in human granulosa cells without the induction of mitochondrial reactive oxygen species (ROS) production [98]. The necrostatin1

(NEC-1) inhibits RIPK1 in human granulosa cells affecting RIPK1 kinase activity [99]. Necrosulfonamide (NSA) inhibits mixed lineage kinase domain-like protein (MLKL) and prevents necroptosis in primary cultured human granulosa cells [100]. These necroptosis inhibitors have been suggested to play a role in protecting granulosa cells, resulting in prevention of germ cell depletion, and may be useful in the treatment of POI.

DNA damage and repair

No consistently modified gene variants exist across the POI cohort due to the small sample size of POI patients and their ethnic heterogeneity. Interestingly, genome-wide association studies (GWAS) and array-based comparative genomic hybridization (CGH) have revealed genes that are potentially associated with POI and have proposed relevant candidates [101]. These techniques revealed a large number of genetic mutations in genes involved in DNA damage and repair, homologous recombination (HR), and meiosis. These genes include *stromal antigen 3* (*STAG3*), *synaptonemal complex central element 1 (*SYCE1), *scaffolding protein involved in DNA repair* (*SPIDR*), *proteasome 26S subunit ATPase 3-interacting protein* (PSMC3IP), *ATP-dependent DNA helicase homolog* (*HFM1*), *mutS homolog* (*MSH*) *4*, *MSH5*, *MCM8*, *MCM9*, *cockayne syndrome B-piggyBac 3* (*CSB-PGBD3*), *nucleoporin-107 (NUP107*), and *breast cancer susceptibility genes* (*BRCA1* and *BRCA2*) [102]. In addition, a meta-analysis of 53 GWASs within 70,000 women identified 44 loci associated with POI [103]. Interestingly, two-thirds of harbored genes are involved in the DNA damage and repair pathway, including *exonuclease 1* (*EXO1*), *helicase*, *POLQ Like* (*HELQ*), *MCM8*, *MSH5*, *Abraxas 1*, *BRCA1 A Complex Subunit* (*FAM175A*), *fanconi anemia complementation group I* (*FANCI*), *tousled like kinase 1* (*TLK1*), *DNA polymerase gamma*, *catalytic subunit* (*POLG*), and *BRCA1*. A major association between reproductive longevity and the DNA damage pathway response genes has been suggested.

While many types of DNA damage exist, double-strand breaks (DSBs) are considered to be the most severe form [104]. Endogenous and exogenous factors trigger formation of DNA DSBs in primordial follicles. DNA damage accumulates in primitive follicles due to changes in cellular metabolism and elevated oxidative stress as part of ovarian aging. In the process of oxidative respiration in the primordial follicles, a small amount of oxygen is first converted to superoxide in the mitochondria and then to hydroxyl radicals. These hydroxyl radicals cause DNA single-strand breaks, which can cause DSBs and loss of primordial follicles if DSBs occur in multiple adjacent lesions [105]. Exogenous factors that cause DSBs include X-rays, chemotherapy, and environmental toxins [106]. Cisplatin, cyclophosphamide, and doxorubicin induce DNA DSBs in primordial follicles in human ovarian xenograft models and *in vitro*, causing apoptotic oocyte death associated with the activation of *ataxia telangiectasia mutated* (*ATM*) in most cases [66, 85, 107, 108]. Gamma rays and X-ray-generated photons form free radical clusters along their path through the body, which can directly damage DNA duplexes and cause DSBs [109].

Signaling pathways involved in the loss of the ovarian reserve

The phosphatase and tensin homolog (PTEN)/phosphoinositide 3-kinase (PI3-K)/protein kinase B (AKT)/forkhead transcription factor 3 (FOXO3) signaling pathway plays an important role in the recruitment from oocytes of primary and further developed follicles. *FOXO3a*-deficient mice develop initially normal primordial follicles, which later undergo spontaneous global activation, leading to premature loss of all oocytes [110, 111]. FOXO3a suppresses development of the oocyte, granulosa cells, and thecal cells in the follicle at early stages [112]. Downregulation of *FOXO3a* fails to rescue the apoptotic death of granulosa cells, resulting in oocyte loss [113]. Oocyte-specific deletion of *PTEN* causes global primordial follicle activation, similar to *FOXO3a*-knockout mice, resulting in POI [114]. Oocyte-specific deletion of *PTEN* activates *phosphatidylinositol-dependent kinase 1* (*PDK1*) through PI3K-induced conversion of secondary messengers, resulting in *AKT* activation [110]. *AKT* activation causes hyperphosphorylation of FOXO3a, leading to activation of primordial follicles. Therefore, *PTEN* downregulation may lead to follicular activation and excessive primordial follicle atresia. Furthermore, the PTEN/PI3K/AKT/FOXO3 pathway has been shown to be responsible for chemotherapy-induced POI [63].

The Hippo signaling pathway has been shown to specifically inhibit activation of primordial follicles. Fragmenting ovarian cortex increases actin polymerization and disrupts Hippo signaling, causing [115] increased nuclear localization of Hippo signaling effector and yes-associated protein (YAP), and its decreased phosphorylation leads to increased expression of connective tissue growth factor (CCN), resulting in accelerated follicular development [116].

Recently, an *in vitro* activation (IVA) model was developed based on the activation of primordial follicles using manipulation of the PTEN/PI3K/AKT/FOXO3 and Hippo pathways by fragmenting ovarian tissue to activate mechanical forces. In this methodology, the surgically

obtained ovarian cortex is first fragmented and incubated with AKT stimulators for 2 days. Next, fragments are ectopically transplanted under the serosa of the oviduct [115]. Utilizing this methodology, POI patients were able to deliver healthy babies [117]. IVA appears to be a promising treatment for patients with POI who desire improved fertility. However, IVA for POI patients is still highly experimental and pregnancy rates are low. In addition, special attention should be paid to potential carcinogenic effects, given this method stimulates the PTEN/PI3K/AKT/FOXO3 signaling pathway, which is involved in tumorigenesis [118].

Mesenchymal stem cells to restore ovarian function

Mesenchymal stem cells (MSCs) are multipotent adult stem cells that have capacity to self-renew preserving their stemness as well as capacity to differentiate into various cell types such as osteoblasts, chondrocytes, and adipocytes [119, 120]. One of MSCs properties is growing attached to plastic under standard culture conditions. MSCs express various cell surface markers including cluster of differentiation (CD)73, CD90, CD44, and CD105 and lacking expression of CD34, CD45, CD14 or CD11b, CD79a or CD19, and human leukocyte antigen (HLA) class II. MSCs are derived from various sources: bone marrow, adipose tissue, amniotic fluid, amniotic membrane, placenta, menstrual blood, endometrium, and umbilical cord [60, 121–129]. Cellular therapy using MSCs has been in the limelight in recent years as a promising treatment for various degenerative diseases, such as acute renal failure [130], acute lung injury [131, 132], myocardial infarction [133], and cerebral ischemia [134]. It has been reported that MSCs have a role in regulating different populations of immune cells such as T cells, B cells, NK cells, dendritic cells (DCs), and macrophages [135]. MSCs can migrate to damaged tissues by inducing peripheral immune tolerance. They can block the release of inflammatory cytokines, such as tumor necrosis factor-alpha (TNFα) and interleukin-6 (IL-6), and promote the survival of damaged cells [136]. Recently, MSC-based cellular therapy has been studied to restore ovarian function in POI patients. Transplantation of bone marrow-derived MSCs in a mouse POI model restored ovarian function, suggesting that MSCs were the regenerative factor responsible for the bone marrow transplantation phenomenon [137, 138]. Its effectiveness has been evaluated and confirmed in the mouse model of POI. In addition, the therapeutic effect of stem cells on POI has already begun to be demonstrated by clinical trials. Transplantation of human umbilical cord–derived MSC (hUCMSC) into the ovaries of POI patients increased estradiol levels, improved follicle development, and increased follicular follicle numbers. Some of the POI women after transplantation of hUCMSC achieved successful clinical pregnancies [139]. However, there are some ethical and methodological issues regarding treatment with stem cells such as protracted safety concerns that need to be resolved during the process of purification and transplantation of stem cells. These concerns include the potential for the emergence of dangerous clones, the risk of contamination with undifferentiated cells, genomic instability, and the possibility of epigenetic abnormalities [140]. MSCs from adipocytes, placenta, or umbilical cord can be extracted using minimally invasive procedures that do not harm donors, but samples are limited. Also, intra-ovarian injections into patients are invasive and can cause side effects such as an immune response [141]. There are limited clinical studies of MSC transplantation in patients with POI status. Only 10 clinical trials in this field have been conducted (ClinicalTrial.gov) (Table 2). In these clinical trials, autologous bone marrow–derived stem cells and hUCMSCs were used. These therapies restored ovarian function in POI patients, showing increase in AMH levels and follicle development and improved oocyte collection [142, 143]. Several of the POI patients whose ovarian function improved following transplantation of MSCs had successful clinical deliveries [139, 142–144].

Differentiation of MSCs into granulosa cells within ovary and reactivation of ovarian function through the paracrine pathway are two mechanisms that MSCs utilize to improve chemotherapy-induced ovarian dysfunction [145]. Adipose-derived MSCs injected into ovaries of cyclophosphamide-treated rats and mice were later located in the thecal layers but not in the follicles [123]. In addition, intraperitoneally transplanted human amniotic epithelial (hAECs)–derived green fluorescent protein (GFP)–positive cells migrate to mouse ovary and differentiate into granulosa cells, but not into follicles [125]. Therefore, restoration of ovarian function is achieved due to MSC differentiation into granulosa cells within the injured ovary, and not due to oocyte differentiation. MSCs secrete various cytokines, such as hepatocyte growth factor (HGF), vascular endothelial cell growth factor (VEGF), insulin-like growth factor-1 (IGF-1), epidermal growth factor (EGF), fibroblast growth factors 2 (FGF2), granulocyte-colony stimulating factor (G-CSF), and interleukin (IL)-6, IL-8, IL-10, IL-11, and IL-15 [123, 146, 147, 138, 148, 149]. MSCs have been shown to inhibit apoptosis of granulosa cell in mammalian model of POI [150] due to increased secretion of steroid hormone and inhibition of apoptosis in granulosa cells through IGF-1 pathway [151]. Transplantation of MSCs overexpressing microRNA-21, involved in apoptotic regulation, repaired the ovarian function and inhibited the apoptosis of granulosa cells by targeting PTEN and programmed cell death 4 (PDCD4) [152]. Transplantation of human placenta–derived mesenchymal stem cell (hPMSC) restored ovarian function in chemotherapy

Table 2 Clinical trials of MSC treatment for POI women

Identifier	Patients	Phase	Source of cells	Method of injections
NCT03816852	Meet diagnostic criteria of ESHRE No HRT and Chinese traditional medicine within 3 months	2	Human umbilical cord	Intravenous
NCT03069209	Women between age 20–40 years FSH > 20 IU/mL	1/2	Autologous bone marrow	Intraovarian
NCT03877471	Under 40 years of age Have established regular menstrual cycle, oligomenorrhea/amenorrhea ≥ 4 months FSH ≥ 25 IU/mL Bilateral ovaries are visible by ultrasound	1	Embryonic stem cell	Intraovarian
NCT02062931	Post-menarche female less than 40 years old FSH > 20 IU/mL Women with normal karyotyping	1/2	Autologous bone marrow	Intraovarian
NCT01742533	Between age 18–39 years Diagnosed with POI and currently receiving HRT	1/2	Human umbilical cord	N/A
NCT03033277	Diagnosed with POI Women between age 20–40 years Have fertility requirements, husband has sperm	1/2	Human umbilical cord	Intraovarian
NCT02603744	Women between age 20–40 years FSH > 20 IU/mL	1/2	Adipose	Intraovarian
NCT02644447	Diagnosed with POI Patients show no response to drug treatment Women between age 20 and 39 years	1/2	Human umbilical cord	Intraovarian
NCT02779374	Women with POI Less than 40 years Has amenorrhea ≥ 4 months FSH > 25 IU/mL	Not Applicable	Autologous bone marrow	Intravenous
NCT02372474	Post-menarche female less than 40 years Normal karyotyping female POI women FSH >20 IU/mL	1/2	Autologous bone marrow	Intraovarian

ESHRE European Society of Human Reproduction and Embryology, *HRT* hormone replacement therapy, *FSH* follicle-stimulating hormone, *POI* premature ovarian insufficiency

and autoimmune-induced POI mice model by regulating cytokines associated with regulatory T cells (Treg) via the PI3K/AKT signaling pathway [153, 126]. Also, hAEC transplantation promoted ovarian function by reducing inflammation and inhibiting the TNFα-mediated apoptosis [154]. MSCs secrete cytokines that promote angiogenesis, such as VEGF, FGF2, and angiogenin, causing recovery of damaged ovaries following transplantation of cryopreserved ovarian cortex [155]. Injection of hUCMSCs to mice with chemotherapy-induced POI increases total and phospho-AKT as well as VEGF expression, which promotes ovarian angiogenesis [127]. Moreover, EGF secreted by hPMSCs quenches ROS in POI by upregulating the nuclear factor erythroid 2 related factor 2 (NRF2)/heme oxygenase 1 (HO1) pathway that is involved in DNA repair and aging, apoptosis, and embryonic cell death [149]. Transplantation of human amniotic fluid-derived MSC (hAMSCs) attenuated the DNA damage as assessed by phosphorylation of variant histone H2A (p-γH2AX), BRCA1, PARP1, and X-Ray repair cross complementing 6 (XRCC6)) in granulosa cells of aged mice [156]. Based on the above findings, MSCs may play an important role in regenerating granulosa cells and restoring ovarian function through an anti-inflammatory and immunomodulatory effect, as well as through DNA repair. MSC regenerative therapies that have been evaluated *in vivo* in improving ovarian function are summarized in Table 3.

Conclusion

Overall, POI is a condition of estrogen deficiency that causes both short-term and lifelong implications for health and psychosocial well-being, compared to undergoing menopause at a later age. Healthcare professionals need to effectively manage these complex entities to ensure that physical, psychological, and emotional challenges resulting from POI diagnosis are addressed, and that the short and long-term wellbeing of these young women is preserved. Considering the lifelong health of POI patients, development of treatments to restore ovarian function earlier is essential to improve quality of life. Recent development of regenerative medicine allowed transplantation of various types of human MSCs

Table 3 MSC used to improve POI and ovarian function

MSC source	Animal	Background	POI-induced regimen	Regimen (how injected, number of cells, duration)	MSC location after injection	How ovarian function was improved	Ref.
Murine bone marrow	Mouse	C57BL/6	BUS (12 mg/kg), CTX (120 mg/kg), single, IP	Single IV, 2–5 × 10^7 cells	Oocytes	Number of follicles	[121]
Murine peripheral blood				Single IV, 2–4 × 10^7 cells	Oocytes	Number of follicles	[121]
Murine bone marrow	Mouse	C57BL/6	BUS (12 mg/kg), CTX (120 mg/kg), single, IP	Single IV, 2–3 × 10^7 cells	Oocytes	Number of immature follicles	[60]
Murine adipose	Mouse	C57/BL6	CTX (50 mg/kg) for 15 consecutive days, IP	Single IV, 1×10^6 cells	Ovarian stroma	Number of follicles	[122]
Murine adipose				Single IV, 1×10^5 cells	Ovarian stroma	Number of follicles	[122]
Rat or murine adipose	Rat	Wistar–Imamichi	CTX (50mg/kg) on the first day and then 8mg/kg for 13 consecutive days, IP	Single injection into the ovary, 2 × 10^6 cells	Unknown	Number of live birth	[123]
Rat bone marrow				Single injection into the ovary, 2 × 10^6 cells	Unknown	Number of live birth	[123]
Human amniotic fluid	Mouse	C57BL/6	BUS (30 mg/kg), CTX (120 mg/kg), single, IP	Single IP, 2–5×10^3 cells	Ovarian stroma or antral follicles	AMH expression in the ovary	[124]
Human amniotic epithelium	Mouse	C57BL/6	BUS (30 mg/kg), CTX (120 mg/kg), single, IP	Single IP, 2 × 10^6 cells	Ovarian tissue near the follicles	AMH expression in the ovary	[125]
Human menstrual blood	Mouse	C57BL/6	CTX (70mg/kg), single, IP	Unknown, approximately 1×10^3 cells	Ovary	Number of follicles	[128]
Human endometrial cell	Mouse	C57BL/6	BUS (30 mg/kg), CTX (120 mg/kg) single, IP	Single IV, 2×10^6 cells	Ovarian stroma	Number of follicles	[129]
Rat bone marrow	Rat	Wistar	CTX (200mg/kg) on the first day and then 8 mg/kg/day for the 15 consecutive days, IP	Single IV, 4 × 10^6 cells	The ovarian hilum and medulla	Serum estradiol levels, number of primordial, developing, and preovulatory follicles	[145]
Human placenta	Mouse	C57BL/6	pZP3 (100 μg), single, IV	Single SC, 1×10^6 cells	Unknown	Number of healthy follicles	[126]
Human umbilical cord–derived microvesicles	Mouse	ICR	BUS (20 mg/kg), CTX (200 mg/kg), single, IP	Single IV, unknown	The cytoplasm of granulosa cells	Number of primordial, developing, and preovulatory follicles	[127]

POI premature ovarian insufficiency, *BUS* busulfan, *CTX* cyclophosphamide, *pZP3* zona pellucida glycoprotein 3 peptide, *IV* tail veil injection, *IP* intraperitoneal injection, *SC* subcutaneous injection, *AMH* anti-Müllerian hormone

improving the ovarian function in POI mice. Transplantation of MSCs shows a significant positive effect in an animal model of POI and in some clinical studies, but it has not yet been applied to clinical practice due to methodological and ethical issues. The MSC transplantation regimen should be optimized to identify optimal injection site, frequency of each procedure, and cell number used to make MSC transplantation more effective.

Code availability Not applicable

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Declarations

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