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Advances in Stem Cell Therapy Based on Tissue Engineering in the Treatment of Female Infertility with a Focus on POF

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ABSTRACT

Background: In the last few decades, many studies have been done on the treatment of premature ovarian failure. This review was conducted to study different types of treatment with a focus on the 3D culture model of stem cells as a pluripotent source for repairment in regenerative medicine for this disease in recent decades.

Methods: To conduct this review, electronic databases of MEDLINE, Scopus, PubMed, and Web of Science were searched using MeSH terms. Only English articles were included, and case reports were excluded. The keywords used for the search were mentioned as the keywords of the paper.

Results: To transplant the stem cells into the patient's body, the 3D culture of these cells in vitro and the molecular and cellular aspects of these cells were considered, and their success rate and differentiation were compared to granulosa cells or oocytes.

Conclusion: The present study aimed to discuss the potential effects of stem cells for regeneration and recovery of ovarian function in premature ovarian failure as a useful therapy.

Keywords: Premature Ovarian Failure, Stem Cell Therapy, Three-dimensional Culture

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Introduction

Premature ovarian failure (POF) is a disease that occurs with normal ovarian dysfunction in women under the age of 40, with a prevalence rate of 1%. Several known factors cause POF, such as X chromosome abnormalities, genetics, autoimmune, metabolic, idiopathic, etc. (1-3).

The menopause of women occurs around the age of 50 (4). Many factors affect menopause in women, including economic status, body weight, smoking, race, cardiovascular diseases, amenorrhea, diabetes mellitus, as well as ethnicity (5-7).

In recent years, the incidence of cancer and subsequent chemotherapy and radiotherapy have increased the risk of developing POF in women. Since ovarian reserves are limited and cannot increase, it is essential to maintain primary follicles and ovarian reserves during cancer treatment. Symptoms of POF in women are similar to the physiology of menopause. So, patients with POF are at higher risk of cardiovascular diseases and osteoporosis (8, 9). Various methods have been proposed for POF treatment such as multipotent stem cells transplantation with new approaches for the development of oocytes from embryonic stem cells (ESC), induced pluripotent stem cells (iPS cells), ovarian stem cells (OSCs), pluripotent stem cells (PSCs), spermatogonial stem cells (SSCs), and very small embryonic-like stem cells (VSELs) (10). Also, optimal use of the 3D culture medium of these stem cells in vitro and its transplantation to POF patients and cellular approaches in oocytes, such as investigating the role of disorder mitochondria of the oocyte in the occurrence of POF, are discussed.

Symptoms

POF symptoms are similar to menopausal physiology such as infertility with stopping of follicular ovarian activity and hormonal defects. The major defect in POF patients is that they are prone to neurological, metabolic, and cardiovascular diseases and are at a high risk of osteoporosis (8, 11).

In healthy women, the amount of the follicle-stimulating hormone (FSH) level is normally lower than 10 mIU/ml. This hormone causes the growth of granulosa cells and depletion of follicles, which leads to further depletion of ovarian reserves (12). In POF patients, the FSH level will be higher than 10 mIU/ml (12).

The laparoscopy of people with POF shows the lack of follicles development, and the ovarian biopsy also shows a network of connective tissue with diffuse fibroblasts in the ovary. In addition, patients with decreased estrogen production often suffer from atrophy of the uterus and vagina (13).

Etiology

Many factors cause POF (8). These cases can be divided into two genetic and environmental mechanisms environmental and genetic groups (14).

The NR5A1, NOBOX, FIGLA, and FOXL2 genes, as specific transcription factors, are involved in the differentiation of primordial follicles into primary follicles (15).

Previous studies have shown that mutations in the β subunit of FSH and the LH receptor cause POF. The ovarian biopsy shows that primordial, early antral, and antral follicles are visible, but there is no pre-ovulation follicle, corpus luteum, and corpus albicans (16).

Estrogen is the steroid hormone derived from cholesterol; thus, the overall decrease in cholesterol in the arteries has been suggested as a cause of POF. Also, in patients with disorders of steroid hormone synthesis such as the 17α-hydroxylase deficiency, both adrenal and gonadal steroidogenesis are decreased, leading to ovarian failure (17). Moreover, estrogen levels can affect cognitive impairment, dementia, and Alzheimer's disease (18). So, the risk of developing chronic diseases such as type 2 diabetes, Parkinson's disease, and cardiovascular mortalities is higher in POF patients (19, 20).

Changes in the immune system may cause POF by destroying follicles or normal ovarian dysfunction. Autoimmune markers have been investigated in the serum of patients with POF. It has been suggested that antibodies can be produced against steroidogenic enzymes, gonadotropins and their receptors, corpus luteum, zona pellucida, and oocyte, which can lead to POF (21).

Chemotherapy and radiotherapy in young women with cancer are among the highest risk factors for POF (22) because chemotherapy agents damage granulosa and theca cells, which produce steroids, as well as oocytes (23, 24).

Any defect in the sex chromosome X, such as Turner syndrome and elimination in the long arm of the X chromosome (Xq), can lead to POF. There are three critical loci leading to ovarian

development on the X chromosome that include Xp22, Xq26-Xq28, Xql3-22 (14, 25).

Recent findings have shown that the SPO11(proline-to-threonine at position 306) is a topoisomerase-like protein that plays a pivotal role in the generation of DNA double-strand breaks (DSBs), synapsis, and initiating meiotic recombination of homologous chromosomes. Mutations in this gene reduce the detection of DSBs by DNA damage checkpoints and so increase segregation errors in the Meiosis I chromosome in oocytes. Therefore, mutation of SPO11P306T/P306T affects oogenesis in mice and can interfere in infertility in mice and POF (26, 27).

Mitochondria functions can directly affect different aspects of the cell such as oocyte quality, fertilization process, and embryo development (28, 29). So, the oocyte mitochondrial DNA (mtDNA) content is related to the probability of zygote development. It has been evidenced that mitochondrial genetic disorders and mitochondrial oxidative stress are associated with POF (30, 31).

Ovarian stem cell

Recent research has shown the presence of ovarian stem cells in postnatal mammalian ovaries, which requires further investigation. These stem cells are also called putative stem cells (PSCs) (32). Johnson *et al.* (2004) first reported the presence of these stem cells in mammals (33). Since then, many studies have been done in this field (34-38). Several articles have been published since 2017 on the existence of these stem cells, playing a major role in the development of ovarian cancer (39-46). Numerous articles have discussed the presence of these cells and how they are isolated and purified. But the presence of these cells and the differentiation of these cells into oocytes is still in an aura of ambiguity. Further research is needed to prove and make use of these cells.

Other types of stem cells in the treatment of POF

Many studies have focused on mesenchymal stem cell therapy as cell *sources* for repairment in regenerative medicine (Figure 1) (47-54).

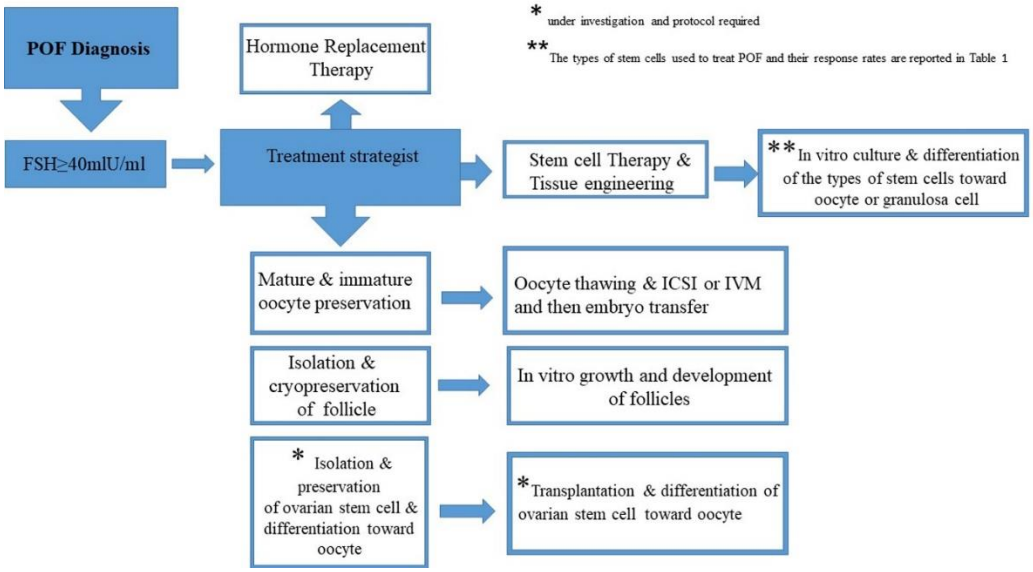

Figure 1. The recommended treatment of female infertility in POF patients

Although these stem cells have become very popular and have been used to treat many diseases such as muscular dystrophies, diabetes, heart failure, and spinal cord injury (55), there are still criticisms by some researchers. These cells are characterized by growing rapidly and are minimally invasive and safe for autologous transplantation. In addition, these cells are able to differentiate into many specialized cells and usually form a small percentage of the total cells of a member. These cells will remain indistinguishable until they have received a specific signal for differentiation (Table 1) (48, 56).

In 2013, Henningson *et al.* investigated the use of mouse engineered ESCs (endometrial stem cells), under the regular control of the Forkhead box L2 (Foxl2) gene promoter in ovarian granulosa cells, which is used to trace granulosa cellular function and fate in vitro and

in vivo. It was shown that these cells are capable of differentiating into somatic ovarian cells and expressing Foxl2 in vitro, synthesizing steroids, responding to FSH, and interfering in folliculogenesis in vivo; it is noteworthy that granulosa cells can produce steroid hormones (57).

Table 1. The types of stem cells used to treat POF and their results.

Stem cell types	Researchers	Method	Result
Very small embryonic-like (VSEL) identified in adult bone marrow	Kucia *et al.* (2006)	These cells can be differentiated into different types of cells	These cells can act as a good source for the ovaries regeneration in POF disease
Bone mesenchymal stem cell (MSC)	Fu *et al*. (2008)	Transplantation of MSC into POF ovaries rats	These stem cells differentiate into granulosa cells and decrease the expression level of BAX genes unlike Bcl2 in vivo.
Human amniotic fluid cells (HuAFCs)	Liu *et al*. (2012)	Transplantation of HuAFCs into POF mice	CD44+/CD105+ HuAFCs subpopulation represent potential seed cells for stem cell transplantation treatments for POF
Endometrial stem cells (ESCs)	Dori *et al*. (2013)	ESCs labeled with the forkhead box L2 (Foxl2) gene promoter	These cells are capable of differentiating into somatic ovarian cells
Adipose-derived stem cells (ADSCs)	Sun *et al.* (2013)	Transplantation of ADSCs into POF mice	These cells cause changes in the genes involved in follicle formation and ovulation
Human menstrual blood stem cells (HuMenSCs)	Wang *et al.* (2013)	Transplantation of HuMenSCs into POF mice	Ovarian function was improved by monitoring serum sex hormone levels and HuMenSCs tracking, Q-PCR.
Human menstrual blood stem cells (HuMenSCs)	Liu *et al*. (2014)	Transplantation of HuMenSCs into POF mice	These stem cells increase the mRNA expression pattern of ovarian markers [AMH, inhibin α/β, (FSHR)], and the proliferative marker Ki67.
Stem cells from amniotic fluid (AFSC)	Guan-Yu Xiao *et al.* (2014)	Transplantation of AFSC into POF mice	The exosomes produced by AFSC have anti-apoptotic effects on damaged granulosa cells after induction of POF in mice
Embryonic stem cells (ESCs)	Bahmanpour *et al*. (2015)	Differentiation of mouse embryonic stem cells into oocyte-like cells	The effects of BMP4, retinoic acid, and co-culturing ovarian somatic cells on differentiation of mouse embryonic stem cells into oocyte-like cells were detected
Endometrial mesenchymal stem cells (EnSC)	Dongmei *et al*. (2015)	Transplantation of EnSCs into POF mice	These cells restore ovarian function

Table 1. The types of stem cells used to treat POF and their results.

Skin-derived mesenchymal stem cells (SMSCs)	R Sun *et al*. (2015)	The effect of activin A on the differentiation of SMSCs into primordial germ cell-like cells after transplantation into POF mice	These cells improve ovarian function by increasing the expression of meiosis-relative genes, such as *Stra8*, Dmc1, Sycp3, and Sycp1.
Skin-derived mesenchymal stem cells (SMSCs)	Dongmei *et al*. (2015)	Transplantation of SMSCs into POF mice	These cells reduce the expression of pro-inflammatory cytokines TNF-α, TGF-β, IL-8, IL-6, IL-1β, and IFNγ and increase the expression of oogenesis marker genes Nobox, Nanos3, and Lhx8.
Human menstrual blood stem cells (HuMenSCs)	Lai *et al*. (2015)	Transplantation of HuMenSCs into POF mice	As GFP-labeled HuMenSCs was measured by live imaging and immunofluorescent methods indicated that GFP-labeled cells were undetectable in mouse ovaries.
Umbilical cord mesenchymal stem cell (UCMSC)	Elfayomy *et al*. (2016)	Transplantation of UCMSC into POF rats	These cells can reduce the FSH and E2 levels and CASP-3 expression, and increase the antral follicle count and PCNA expressions.
Human umbilical cord mesenchymal stem cells (UCMSCs)	Song *et al*. (2017)	Transplantation of UCMSC into POF rat	These cells restore ovarian function in POF rats.
Human embryonic stem cells(hESCs)	Jung *et al.* (2017)	hESCs differentiation of cells into ovarian follicle-like cells FLCs) in vitro.	The induction of two RNA-binding proteins (DAZL and BOULE) makes the stem cells, in the pluripotency state, enter the meiotic stage and produce FLCs.
Bone marrow mesenchymal stem cells (BMMSCs)	Badawy *et al.* (2017)	Transplantation of MSCs into POF mice	These cells after transplantation, differentiate into primordial follicles.
Umbilical cord mesenchymal stem cells (UCMSCs)	Ding *et al.* (2018)	Transplantation of UC-MSCs on collagen scaffold into POF patients with a long history of infertility	These cells contribute to an effective and practical treatment method
Bone marrow-derived mesenchymal stem cells (MSCs)	Chen *et al*. (2018)	Transplantation of MSCs into POF rats	These cells improve ovarian function in POF rats
Mesenchymal stem cells derived from the chorionic plate (CP-MSCs)	Li *et al.* (2018)	Transplantation of CP-MSCs into POF mice	Ovarian function was improved by monitoring E2 and FSH serum levels before and after transplantation.

Table 1. The types of stem cells used to treat POF and their results.

Human placenta-derived mesenchymal stem cell (hPMSC)	Yin *et al*. (2018)	Transplantation of hPMSCs into POF mice	Ovarian function was improved in POF mice by regulation of Treg cells and production of associated cytokines following hPMSCs transplantation.
Human placenta mesenchymal stem cell (hPMSC)	Zhang *et al*. (2018)	Transplantation of hPMSCs into POF mice	hPMSCs inhibit apoptosis of granulosa cells and increase AMH expression
Human menstrual blood stem cells (HuMenSCs)	Noory *et al.* (2019)	Transplantation of HuMenSCs into POF rat	These stem cells differentiated into granulosa cells and decreased the expression level of BAX genes unlike Bcl2 in vivo.
Human menstrual blood stem cells (HuMenSCs)	Manshadi *et al*. (2019)	Transplantation of HuMenSCs into POF rat	After transplantation, these cells are detected granulosa cells and increase the expression of Amh (Anti-Mullerian hormone) and FSHR (follicle-stimulating hormone receptor) and FST (Follistatin) genes
Human umbilical cord-derived mesenchymal stem cell (hUMSC)	Lu *et al.* (2019)	Transplantation of UCMSC into POF mice	These cells can reduce the ratio of Th1/Th2 cytokines and the expression of HOXA10 gene increase in the endometrium of the uterine.
Human umbilical cord mesenchymal stem cell (UCMSC)	Zheng *et al.* (2019)	Transplantation of UCMSC into POF rats	UCMSC improves ovarian function by the NGF/TrkA pathway in POF rats.
Human amniotic epithelial cells (hAECS)	Zhang *et al.* (2019)	hAECS-derived exosomes in the POF mouse model inhibit ovarian granulosa cell apoptosis	miR-1246 carried by hAECS-derived exosomes in POF mouse model inhibit ovarian granulosa cell apoptosis.
Bone mesenchymal stem cells (BMSCs)	Sun *et al.* (2019)	BMSC-derived exosomes in the POF mouse model inhibit ovarian granulosa cell apoptosis	miR-644-5p carried by BMSC-derived exosomes POF mouse model inhibit ovarian granulosa cell apoptosis.
Bone marrow mesenchymal stem cells (BMSCs)	Yang *et al.* (2019)	BMSCs-derived exosomes in the POF rat model inhibit ovarian granulosa cell apoptosis	BMSCs-derived exosome miR-144-5p in the POF rat model inhibit ovarian granulosa cell apoptosis by targeting PTEN.

Table 1. The types of stem cells used to treat POF and their results.

Human placenta-derived mesenchymal stem cells (hPMSCs)	Li *et al.* (2019)	Transplantation of hPMSCs into POF mice	hPMSCs inhibit apoptosis of granulosa cells induced by the IRE1α pathway in POF mice.
Human umbilical cord mesenchymal stem cells (UCMSCs)	Wang *et al.* (2020)	Transplantation of UCMSC into POF rats	UCMSCs upregulated the expression of Bcl-2, AMH, and FSHR in the ovary of POF rats and downregulated the expression of caspase-3.

Liu *et al.* (2012) showed that transplantation of CD44+/CD105+ human amniotic fluid cells (HuAFCs) into POF mice improves ovarian function (58).

In 2013, Sun *et al*. examined the therapeutic effect of adipose-derived stem cells (ADSCs) on POF mice and achieved positive results (59).

Many studies demonstrated that human menstrual blood stem cells (HuMenSCs) can play an important role in the treatment of rats and mice with POF, as HuMenSCs can improve ovarian function. Given that these cells are derived from endometrial cells, they can play a positive role in the restoration of ovaries than other stem cells, as well as inducing the expression of granulosa cell-specific genes in the ovaries of POF rats (Figure 2) (48, 49, 60-62).

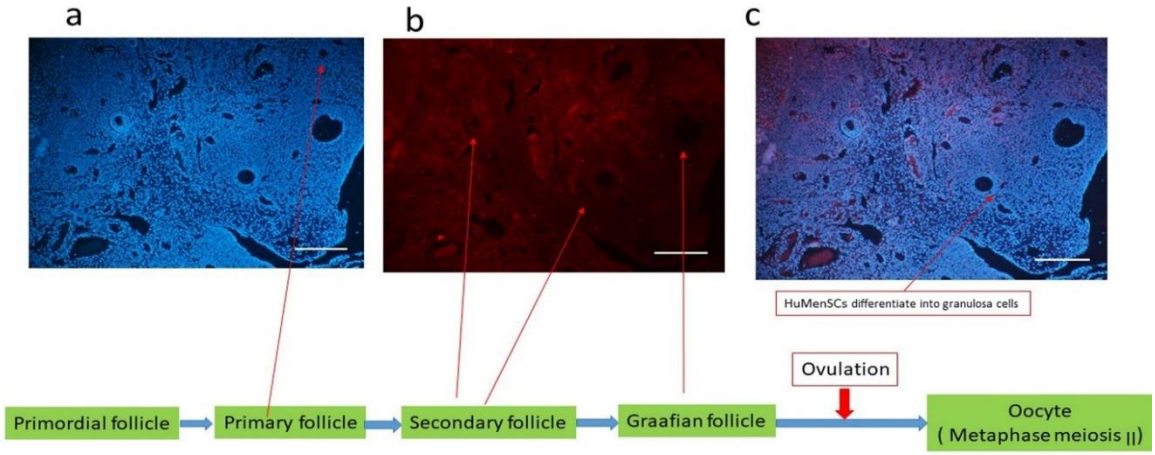

Figure 2. Transplantation of human endometrial mesenchymal stem cells (HuMenSCs) labeled with DiI (Noory et al., 2019). Nuclei were labeled with Hoechst (A)
HuMenSCs -Dil-labeled (B). Merged (C). (Fluorescent microscope, scale bar = 200 µm)

Lai *et al*. investigated the induction of intravenously endometrial mesenchymal stem cells (EnSC) on POF mice and showed that EnSC improved the estrus cycle and reduced the evacuation of germline stem cells (GSCs) (62).

In 2006, Kucia *et al*. reported that very small embryonic-like (VSEL) identified in adult bone marrow can differentiate into different types of cells. These cells can act as a good source for the regeneration of POF ovaries (63). The same experience was obtained in 2016 for mesenchymal stem cells (MSC) (64). Another study used umbilical cord mesenchymal stem cell (UCMSC) to treat POF; four weeks after transplantation, an improvement in regulation of folliculogenesis and inhibition of CASP3-induced apoptosis was seen (65). There are many articles in this manner (66-71). Lu *et al.* (2019) reported that transplantation of UCMSC on POF mice due to the increase in the expression of HOXA10 gene in the endometrium of uterine and reduce the ratio of Th1/Th2 cytokines [72].

In 2018, Badawy *et al.* reported that the bone marrow mesenchymal stem cells (BMMSCs) can differentiate into primordial follicles, after transplantation to POF mice; and proving this mechanism can revolutionize the treatment of POF using stem cell therapy (73).

Guan-Yu Xiao (2016) et al. declared that exosomes produced by the AFSC (stem cells

from amniotic fluid), like micro-RNA (where both miR-146a and miR-10a are very rich) and their potential target genes, have anti-apoptotic effects on damaged granulosa cells in POF mice (74).

Li *et al.* reported that mesenchymal stem cells derived from the chorionic plate (CP-MSCs) have therapeutic effects in the treatment of POF mice model (75). In 2019, Hongxing Li investigated the effect of human placenta-derived mesenchymal stem cells (hPMSCs) transplantation on POF mice model. It was concluded that through the IRE1α pathway, these cells induce a reduction in apoptosis in granulosa cells (76). In another study, researchers used the same cells and transplanted them to POF mice using the regulation of Treg cells and the production of associated cytokines to improve *ovarian* function (77). Among the studies that examined the effect of transplantation of these stem cells on animal POF models (70).

In recent decades, a larger number of studies have been done on the in vitro development of oocyte-like cells (OLCs), compared with stem cells (78-82). The empirical findings in these studies provide a new understanding of curing female reproductive disorders by neo-oogenesis and folliculogenesis. Sun *et al.* (2015) demonstrated that activin A plays a key role in the induction of skin-derived stem cells into primordial germ cell-like cells (83). Similarly, Souza (2017) found the effects of bone morphogenetic proteins (BMPs) 2 and 4, and follicular fluid on the differentiation of these stem cells into oocyte-like structures (84) and Lee showed that overexpression of Oct4 in porcine ovarian stem cells causes differentiation of oocyte-like cells in vitro and ovarian follicular formation in vivo (85).

Asgari *et al.* showed that human Wharton's jelly-derived mesenchymal stem cells express oocyte developmental genes during co-culture with placental cells (86).

Researchers have suggested that skin-derived stem cells (SDSCs) can be a good source of OLCs because they are very similar to the morphology of OLCs, and also, have hormonal secretion under gonadotropic stimulations and higher expression levels of oocyte-specific markers (52, 87-90). Despite this research, there have been articles in recent years in which human embryonic stem cells (ESCs) and mouse embryonic stem cells (ESCs) were differentiated into OLCs (78, 91). Other sources of OLCs are very small embryonic-like stem cells (VSELs) and micro-RNAs (miRNA); VSELs have also a special capability to treat POF (92-94).

Jung *et al.* (2016) examined the differentiation of human embryonic stem cells into late primordial germ cells, meiotic germ cells, and ovarian follicle-like cells (FLCs); and obtained positive results (78).

To better understand this disease, we included samples of a microscopic morphology of the ovary, with H&E staining, after induction of POF and a sample treated with stem cell therapy in Figure 3 (48).

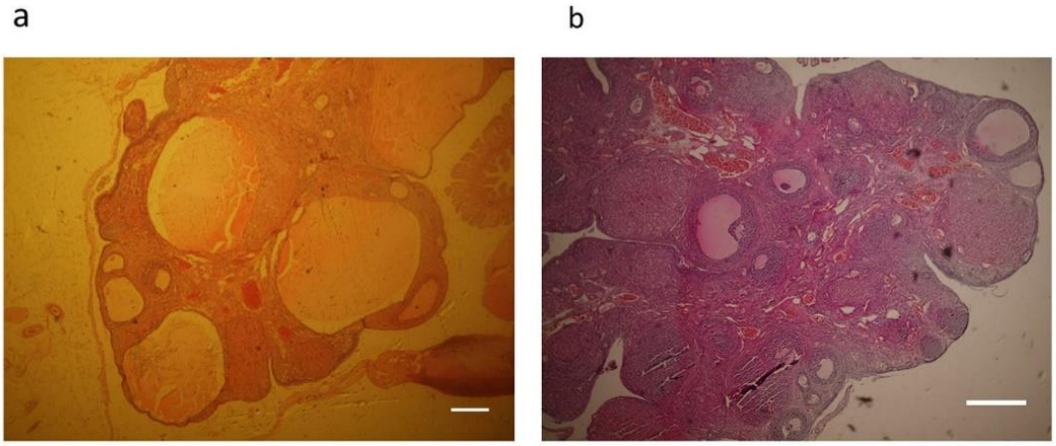

Figure 3. Microscopic ovarian morphology after induction of POF (a).
Demonstrating ovarian therapy with stem cell therapy (b) (Noory et al., 2019). **(**H & E staining, scale bar=300 µm).

Three-dimensional culture model and tissue engineering

Today, many researchers use tissue engineering to rehabilitate fertility in patients with POF as a new therapy. Tissue engineering is an interdisciplinary science in the field of medical sciences in which *new tissues* are *created for* the development of cells in vitro. The combination of scaffolds, cells (stem cells), and growth factors form a tissue engineering triad that creates polymeric biomaterials and provides structural support for cell attachment and subsequent tissue and organ development (95, 96). In the present study, the suitable scaffolds used in the treatment of POF in the last decade were reviewed.

In 2017, He *et al.* used a 3D model of hydrogels and ovarian follicles to demonstrate a beneficial strategy in the treatment of POF (97).

Chiti *et al.* used the fibrin-alginate scaffold to improve the development of secondary follicles. The results indicated positive effects of fibrin as a suitable scaffold for infertility treatment and ovarian function improvement (98).

Ding *et al.* reported that transplantation of umbilical cord mesenchymal stem cells (UCMSCs) on collagen scaffold in POF patients with a long history of infertility was effective and practical (99).

POF treatment

In recent decades, various methods such as hormone replacement therapy (HRT), ovarian tissue freezing, transplantation after treatment, and stem cell therapy have been used to treat POF (3, 10, 100). So far, different types of stem cells have been used to treat this disease (62, 63, 65, 67, 101).

Many studies have reported that human menstrual blood stem cells (HuMenSCs) are capable of repairing damaged tissues (102, 103). These studies aimed to investigate the effects of HuMenSCs transplantation as a treatment modality in patients with POF (48, 49, 60, 104). In addition, Rongxia Liu *et al.* confirmed the positive effect of human amniotic mesenchymal stem cells in the treatment of POF (105).

In 2020, Tkach *et al.* declared that small extracellular vesicles (sEVs) derived from embryonic stem cells (ESCs-sEVs) play a vital role in damaged ovaries and exploring the underlying molecular mechanisms (106). The findings of this study suggest that ESCs-sEVs can improve ovarian function in POF patients using the PI3K/AKT signaling pathway (107).

Y Zhao *et al*. used a variety of stem cells such as mesenchymal stem cells (MSCs), bone marrow stromal cells, adipose-derived stem cells, menstrual blood mesenchymal stem cells, and umbilical cord mesenchymal stem cells. They had a new approach to deal with a variety of female reproductive diseases such as POF, polycystic ovary syndrome, endometriosis, Asherman syndrome, etc. (108).

In order to provide better therapeutic cells for transplantation to POF patients, Ghahremani-Nasab *et al*. reviewed a series of articles on the cultivation of various stem cells on scaffolds (109).

There have been many articles on mitochondrial function as the organ playing a key role in the ROS production. According to the results of these articles, mitochondrial dysfunction can be a major factor in the development of POF. Thus, transplantation of healthy mitochondria into oocytes by assisted reproductive technology (ART) can prevent the transmission of POF to the female offspring (31, 110).

As it is known, none of the treatment methods mentioned so far has been able to completely cure POF and the disease stays an obstacle in female fertility. Since this review focuses more on the transplantation of different types of stem cells and was mentioned in the text, not all stem cells can be well-differentiated and the treatment can be effective; for example, human menstrual blood stem cells (HuMenSCs) differentiates into granulosa cells, while Embryonic stem cells (ESCs) differentiates into oocyte-like cells. Lack of differentiation of some stem cells into oocytes or granulosa cells, culture contamination, lack of rapid growth of some stem cells, and the high cost of this treatment are some of the disadvantages of this technique.

Conclusion

Stem cell therapy is a novel treatment for female infertility, including POF. Stem cell therapy along with tissue engineering is an effective treatment for POF treatment. This review was conducted to assess the association between multipotent stem cell therapy and tissue engineering. Also, new methods such as mitochondrial transmission to oocytes for POF treatment were demonstrated and the latest articles published in this field were reviewed.

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Authors' contributions

All authors wrote and reviewed this paper.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Conflict of interests

The authors declare that there are no conflicts of interests.

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