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REVIEW ARTICLE

Premature ovarian failure and tissue engineering

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Abstract

Premature ovarian failure (POF) usually happens former to the age of 40 and affects the female physiological state premenopausal period. In this condition, ovaries stop working long before the expected menopausal time. Of diagnostic symptoms of the disease, one can mention amenorrhea and hypoestrogenism. The cause of POF in most cases is idiopathic; however, cancer therapy may also cause POF. Commonly utilized therapies such as hormone therapy, in-vitro activation, and regenerative medicine are the most well-known treatments for POF. Hence, these therapies may be associated with some complications. The aim of the present study is to discuss the beneficial effects of tissue engineering for fertility rehabilitation in patients with POF as a newly emerging therapy.

KEYWORDS

cell therapy, premature ovarian failure, regenerative medicine, scaffold, stem cell, tissue engineering

1 | INTRODUCTION

Natural menopause of a woman is defined as the time point when menstrual cycles cease about 1 year. This phenomenon usually happens at the age of 49–52 in high-income countries. Different factors leave negative effects on this natural phenomenon, causing the loss of ovarian function at early age. This phenomenon is called premature ovarian failure (POF). POF is also known as the primary ovarian insufficiency, characterized by the loss of ovaries' normal function, menarche absence, or premature reduction of ovarian follicles and stopped folliculogenesis before the age of 40. In most POF cases the cause is idiopathic. This disorder affects 1/10000, 1/1000, and 1/100 of women at the age of 20, 30, and 40, respectively (Ayesha & Goswami, 2016; Coulam, Adamson, & Annegers, 1986; Gold et al., 2013; Goswami & Conway, 2005; Henderson, Bernstein, Henderson, Kolonel, & Pike, 2008; Isik et al., 2017; Kovanci & Schutt, 2015; Laven, 2016; Lin et al., 2017; Morabia & Costanza, 1998; Pal & Santoro, 2002; Zhu, Chung, Pandeya, Dobson, Cade et al., 2018). Some diagnostic criteria for POF are amenorrhea, hypoestrogenism, and high concentrations of serum gonadotropin (follicle-stimulating hormone [FSH] >40 mIU/ml; Ayesha & Goswami, 2016; Isik et al., 2017; Kovanci & Schutt, 2015; Laven, 2016; Lin et al., 2017). POF also affects women's quality of life (QOL) following hypoestrogenism, night sweats, hot flashes, osteoporosis, infertility, loss of fertility as well as cardiovascular diseases, amenorrhea, diabetes mellitus Type II, and the risk of mortality (Isik et al., 2017; Jin, Yu, & Huang, 2012; Zhu, Chung, Pandeya, Dobson, Cade et al., 2018).

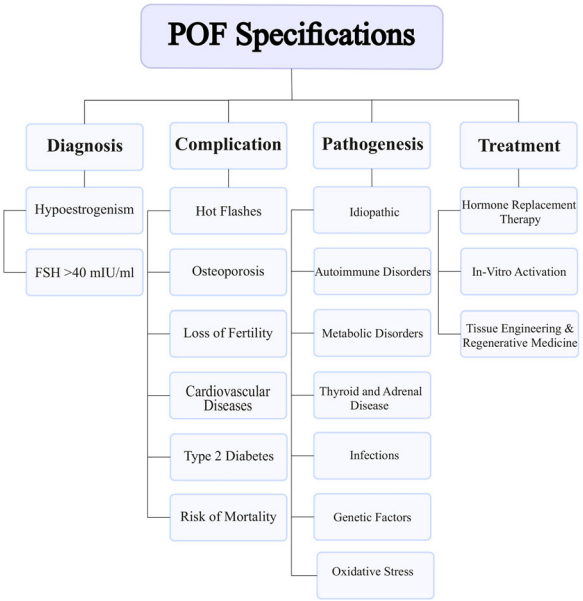

FIGURE 1 POF is a condition that happens in woman before age of 40. In this figure, its general characteristics, including its diagnosis, complication, pathogenesis, and treatment are mentioned. POF, premature ovarian failure

Pathogenesis of POF includes autoimmune and metabolic disorders (galactosemia), thyroid and adrenal diseases, infections (mumps), genetic factors (chromosomal abnormalities), iatrogenic factors (anticancer treatment), and oxidative stress (OS). Apoptosis of ovarian granulosa cells and diabetes mellitus are also observed in some cases (Ayesha & Goswami, 2016; Brand et al., 2015; Isik et al., 2017; Jin et al., 2012; Kovanci & Schutt, 2015; LeBlanc et al., 2017; Lin et al., 2017; Liu, Li, Wang, Chen, & Zheng, 2016; Lozano, Rosero, & Hagerman, 2014; Muka et al., 2016; Nelson, 2009; Shifren & Gass, 2014; Shuster, Rhodes, Gostout, Grossardt, & Rocca, 2010; Yrigollen et al., 2014; Zhu, Chung, Pandeya, Dobson, Cade et al., 2018). Factors affecting menopausal age are socioeconomic status, body weight, smoking, race/ethnicity, menarche age, and nulliparity. Smoking is the most important factor leading to menopause by almost 1 year earlier (Jungari & Chauhan, 2017; Mishra et al., 2017; Parente, Faerstein, Celeste, & Werneck, 2008; Schoenaker, Jackson, Rowlands, & Mishra, 2014; Zhu, Chung, Pandeya, Dobson, Kuh et al., 2018). POF is also considered as one of the side effects of chemotherapy (Liu et al., 2014; Figure 1). Different animal models have been used for POF-related investigations. Zhang et al. (2016) used female Institute of Cancer Research and Kunming mice, as well as Sprague Dawley rats to compare the POF induced by several different factors in animal models. For this purpose, they used inducers, such as cyclophosphamide (CTX), busulfan, cisplatin, 4-vinylcyclohexene diepoxide, galactose food pellet, and tripterygium glycosides (TGs; Zhang et al., 2016).

So far, several methods have been proposed for the treatment of patients with POF. Tissue engineering that benefits from stem cells and scaffolds, as two basic elements, may represent a promising candidate for POF treatment (Su et al., 2016). In the following, the application of tissue engineering and regenerative medicine in POF treatment will be discussed.

2 | POF TREATMENT

There are several available treatments to preserve fertility in women suffering from POF including (a) hormone replacement therapy (HRT), (b) in-vitro activation (IVA), (c) stem cell therapy, (d) tissue engineering and regenerative medicine.

Due to the insufficient levels of estrogen in these patients, HRT, after the diagnosis of POF, is recommended to manage the symptoms and protect against the opposing long-term health results (Kawamura, Kawamura, & Hsueh, 2016; Kovanci & Schutt, 2015; Liu, Zhang et al., 2014; Stefanick, 2005). However, HRT does not basically restore typical ovarian function. Recent studies have also reported HRT as a breast cancer inducing factor. As a result, new treatments are needed to restore ovarian function in patients with POF (Chen et al., 2018; van Kasteren & Schoemaker, 1999). IVA is another strategy in the treatment of POF enabling patients with POF to have children with their own genetics. Additionally, the number of mature oocytes can be increased following IVA treatment; however, this procedure is not beneficial for decreased quality of the age-related oocyte. Though these approaches may have deep clinical inferences, spontaneous retrieval of menstrual cycles following pregnancies have been reported in women with POF (Kawamura et al., 2016). Tissue engineering and regenerative medicine are interdisciplinary strategies that apply engineering and life science ideals to promote regeneration and restore diseased and injured tissues, using scaffolds, cells, and bioactive compounds. Adipose-derived stem cells (ADSCs) and collagen scaffolds have been also used in tissue engineering-based treatments of POF (Su et al., 2016).

3 | TISSUE ENGINEERING AND REGENERATIVE MEDICINE

Tissue engineering is an interdisciplinary science in the field of medical sciences mainly relying on the development of cells in the laboratory environment to produce new tissues. The combination of scaffolds, cells (stem cells), and bioactive compounds (like growth factors) are often considered as a tissue engineering triad that will be discussed in the following. Utilized scaffolds should have an efficient structure in terms of cell adhesion, migration, proliferation, and differentiation properties, to create and replace new tissues (Mahla, 2016).

3.1 | Scaffold

High cell proliferation is usually observed in the initial steps of two-dimensional (2D) cell culture. However, the proliferation will be arrested after the cells arriving at the maximum confluency. These limitations have made the researchers design scaffolds known as the

porous materials structures to cultivate cells. Scaffolds eliminate 2D cell culture limitations. Additionally, these structures provide a suitable surface for cell attachment and proliferation to mimic the in vivo structure and function of the studied tissues. Moreover, the release of oxygen, nutrients, and biologically active agents through scaffolds causes the survival of the majority of cells for longer period (Kim et al., 2013; Polverini, 1995; Xie, Yang, & Kniss, 2001).

Suitable scaffolds in tissue engineering lead to cell attachment and growth, promote cell proliferation and differentiation, make proper tissue perfusion by angiogenesis and neovascularization support, and mimic the mechanics of target tissue. The main features of these scaffolds are as follows: possessing nontoxic and noninflammatory properties to the host, biodegradability and biocompatibility, being highly porous for cells communication, nutrients delivery and oxygen exchange, and easy and inexpensive to be manufactured (Gunatillake & Adhikari, 2003; Hutmacher, 2000; Hutmacher et al., 2001; Mahla, 2016; Mano et al., 2007; Mikos, McIntire, Anderson, & Babensee, 1998; Soman et al., 2012; Taboas, Maddox, Krebsbach, & Hollister, 2003). In tissue engineering, scientists and engineers look for scaffolds for cell growth to replace injured tissues. Natural polymers are one of the purposes of the most preferred choice in this regard. As popular compounds in tissue engineering, these polymers can be derived from living organisms. One of the extensively used natural polymers in regenerative medicine is collagen with a high presence in the extracellular matrix (ECM) of connective tissues, such as tendon, bone, skin, and cartilage (Lyons et al., 2010; Mano et al., 2007).

3.2 | Stem cells

Stem cells are one of the key components in regenerative medicine. They are known as undifferentiated cells of a multicellular organism that have significant capability to be differentiated into other cell lineages with self-renewal properties (Chen et al., 2018; Mahla, 2016). Researchers in the field of regenerative medicine has benefited from these cells to treat different anomalies, such as inherited defects, age-related effects, and diseases. There are four types of stem cells including unipotent, multipotent, pluripotent, and totipotent stem cells. For tissue regeneration, autologous, allogeneic, and syngeneic stem cell transplantation can be performed. One of the main limitations in transplanting stem cells is the rejection of these cells by the host immune system. Therefore, the uses of immune suppressants and typing of human leukocyte antigens (HLA) tissue is recommended. For successful regeneration, transmitted stem cells must be survived, proliferated, and differentiated into a target somatic cell type and must be integrated into the circulatory system in the host body. There are some classes of stem cells in regenerative medicine including embryonic stem cells (ESCs), tissue-specific progenitor stem cells (TSPSCs), mesenchymal stem cells (MSCs), umbilical cord stem cells (UCSCs) and bone marrow MSCs (BM-MSCs; Mahla, 2016). octamer-binding transcription factor 4 (OCT4), cMYC, NANOG, and SOX2 are some of the pluripotency factors of stem cells (Thomson et al., 2011). ESCs are pluripotent stem cells with the capability of differentiating into more than 200 cell types that are considered for the treatment of different diseases. The ESCs pluripotency fate is mainly depended on the expression of transcription factors, such as OCT4, SOX2, and NANOG. Despite ESCs, TSPSCs can be differentiated into fewer cell types; however, they preserve tissue homeostasis via nonstop cell division. MSCs can be also differentiated only into tissues with the mesodermal origin. Their expression markers include $CD73^{+}$, $CD90^{+}$, $CD105^{+}$, $CD11b^{-}$, $CD14^{-}$, $CD19^{-}$, $CD34^{-}$, $CD45^{-}$, $CD79a^{-}$, and HLA-DR (Ghalamfarsa et al., 2018; Mahla, 2016). UCSCs also are another source of stem cells, with lesser ethical constraints than that of umbilical cord ESCs. They mainly include hematopoietic stem cells (HSCs) and MSCs, which have great regeneration potentiality (Shahrokhi, Menaa, Alimoghaddam, McGuckin, & Ebtekar, 2012). On the other hand, BM-MSCs, which originated from soft spongy bones, also contain HSCs. HSCs and stromal cells also can generate blood cells, fat, cartilage, and bones. There are also two types of bone marrow including red marrow which produces red blood cells (RBCs), platelets, and most of the white blood cells (WBCs), and yellow marrow which produces fat cells and also some WBCs (Ghaebi et al., 2017; Mahla, 2016).

By the progressions in regenerative medicine, variety of stem cells have been increasingly considered for the treatment of the disease that provides this therapeutic approach to the possibility of restoring and repairing injured tissues. In several studies, stem cell therapy is also suggested as an approach for POF treatment (He et al., 2018; Liu, Zhang et al., 2014). MSCs are very important cells in regenerative medicine. MSCs are differentiated into tissues with mesodermal origin including tendons, ligaments, bone, muscles, cartilage, and neurons (Liu, Zhang et al., 2014; Mahla, 2016). MSCs capabilities in migration and proliferation enable them to exhibit their protective and healing effects in injured tissues (Liu, Zhang et al., 2014). In MSCs transplantation, donor and receiver must have homogenous anatomical and physiological characteristics to reach an equal impact on therapeutic results (Sharma et al., 2011). There are several kinds of MSCs in regenerative medicine, such as umbilical cord mesenchymal stem cells (UCMSCs), ADSCs, ovarian granulosa-like cells derived from human induced pluripotent stem cells (ovarian granulose cells [OGLCs]-induced pluripotent stem cells [iPSCs]), human cord blood mononuclear cells, human endometrial MSCs, and BM-MSCs (Chen et al., 2018). Among them, BM-MSCs are brilliant candidates for regenerative medicine (Liu, Zhang et al., 2014).

MSCs secrete a large number of immune-modulating cytokines including transforming growth factor β (TGF-β) and interleukin-10 (IL-10), which create a suppressed immune region around the MSCs implantation area (Mohamed et al., 2018). On the contrary, in clinical trials, the administration of MSCs has been associated with improved graft-versus-host disease clinical signs (English, French, & Wood, 2010). Furthermore, Mohamed et al. (2018) reported that the reproductive performance impairment spectrum can be treated by allogeneic BM-MSCs transplantation. Thus, the mechanisms by which MSCs exhibit their therapeutic and immunogenic effects are in progress, which may be mediated by the multiple mechanisms created by both soluble agents and cellular contacts (Mohamed et al., 2018). Additionally, MSC interactions in the microenvironments may change their performance and may modify their therapeutic properties. MSCs can be also homed into injured tissues and recover local function after in vivo injection (Mohamed et al., 2018). The

homing mechanism causes the secretion of growth factors and chemokines, and the expression of extracellular matrix receptors on the surface of the MSCs, that in turn, contributes to interactions between CXCR-4/SDF-1 and CD44/hyaluronic acid (Mohamed et al., 2018). These cells can regenerate and repair damaged tissues through paracrine activities and by promoting several apoptosis inhibiting molecules (eg, vascular endothelial growth factor (VEGF) and TGF-β release, proangiogenesis, immunomodulation (eg, IL-10 and IL-6) and anti-fibrosis properties (English et al., 2010; Mohamed et al., 2018).

4 | TISSUE ENGINEERING AND POF

POF has long-term effects on reproductive capabilities and general health (Kovanci & Schutt, 2015). There are some curative methods for POF-related infertility including HRT, egg donation, stem cell therapy, and tissue engineering (Burgos et al., 2017; Kawamura et al., 2016). As previously explained, a stem cell has also curative potentials in patients with POF that represents them as a novel method for clinical treatments (Chen et al., 2018). Stem cells can be derived from different sources; however, different types of stem cells are still hard to gain. Preclinical studies have reported that transplantation of stem cells into POF animal models restored ovarian function and generated immature oocytes (Chiti, Dolmans, Donnez, & Amorim, 2017). Reproductive technology has been recently used in tissue engineering and regenerative medicine techniques to restore POF-related infertility by overcoming the donor supply limitations and immune system complications for tissue transplantation (Chiti et al., 2017; Volkova, Yukhta, & Goltsev, 2017).

In a study by He (2017), to mimic 3D culture condition in patients with POF, microfluidic technology, combined with hydrogels containing ovarian follicles, were used. He claimed that this system can facilitate in vitro follicle culture as a promising strategy to restore fertility in POF female patients (He, 2017). Some researchers have also used fibrin-based scaffolds in reproductive tissue engineering to preserve fertility in patients with cancer. Important features of fibrin include possessing biological nature, role in cell-ECM interaction, and cell attachment interference (Chiti et al., 2017). Songsasen, Guzy, and Wildt (2011) in their study used the fibrin-alginate scaffold to improve the growth and development of secondary follicles isolated from dog's ovary. The results indicated the beneficial effects of fibrin as a proper scaffold for fertility preservation purposes (Chiti et al., 2017).

On the other hand, human MSCs can be also considered as a potential treatment against follicles early atresia or primordial follicles quiescence following chemotherapy in the ovarian microenvironment (chemotherapy is one of the main underlying reasons of POF; Goswami & Conway, 2005; Chang et al., 2013). MSCs' capabilities for clinical application are undeniable and over the past years, many women with age-related or non-age-related infertility complications have benefited from this therapy (Mohamed et al., 2018). Dormant viable oocytes can be also reestablished following MSCs-based treatments (Isik et al., 2017). In a study, stem cell transplantation in a patient with POF resulted in an improved hormonal profile, menstruation renewal, pregnancy occurrence, and healthy term infant delivery (Chen et al., 2018). Chen et al. (2018) also reported that autologous MSCs transplantation in the POF animal model caused a significant increase in ovarian function. Various stem cells, such as BM-MSCs, ADSCs, amniotic fluid stem cells (AFSCs), human menstrual blood stem cells (HuMenSCs), and OGLCs have been also used in cell therapy and regenerative medicine for POF treatment (Liu et al., 2016; Liu, Huang et al., 2014; Sun et al., 2013; Xiao et al., 2014).

Due to the fact that POF is one of the main side effects of chemotherapy, animal models induced by chemotherapy have been also developed for in vivo POF cell therapy (Mohamed et al., 2018).

Chemotherapeutic drugs can exceedingly remove granulosa cells which are essential for oocyte survival and follicle development (Mohamed et al., 2018). Furthermore, TG and CTX-induced POF in rat models (Fu et al., 2012; Hershlag & Schuster, 2002; Sanders et al., 1996; Su et al., 2016; Takehara et al., 2013; Terraciano et al., 2014).

4.1 | Ovarian granulosa cells

Apoptosis of OGLCs is a main underlying mechanism for decreased ovarian function. Liu et al. (2016) reported that GFs can induce human-iPSCs differentiation into granulosa-like cells (OGLCs). They also demonstrated that iPSCs-derived OGLCs powerfully expressed granulosa cell markers including inhibin α and β, anti-Müllerian hormone, and follicle-stimulating hormone receptor (Liu et al., 2016). However, stem cell markers including OCT4, sex-determining region Y-box 2, Nanog, and stage-specific embryonic antigen were not expressed 4–12 days post induction. Additionally, following the transplantation of iPSCs-derived OGLCs in a CTX-induced POF mouse model, an improvement was observed in OGLCs growth when compared with the control group. Mature follicles can be also detected in the ovarian tissue of the OGLCs-iPSCs-POF group. Furthermore, transplanted OGLCs into the POF mice exhibited substantial growth in ovarian tissues with a powerful expression of ovarian granulosa cells (OGC) markers. Enzyme-linked immunosorbent assay data also showed a significant increase in estradiol levels in peripheral blood. The ovarian tissue weight and the number of atretic follicles were also significantly increased and decreased in OGLCs-iPSCs-POF group when compared to the controls, respectively. These findings suggest that iPSCs-derived OGLCs may efficiently enhance the OGC growth and repair damaged ovarian tissue, and also retain the ovarian tissue niche, which eventually promotes follicular development and maturation in a POF mouse model (Liu et al., 2016).

4.1.1 | Induced pluripotent stem cells

iPSCs are a type of PSCs which are reprogrammed from adult cells with specific factors. The iPSC technology was first used by the Shinya Yamanaka's Lab. They showed that certain genes have the ability to convert somatic cells to PSCs (Takahashi & Yamanaka, 2006). They are a vital source of renewable autologous cells in tissue engineering and regenerative medicine and hold promises for tissue engineering and cell therapy (Wang et al., 2011; Zhao, Zhang, Rong, & Xu, 2011). There are some applications of iPSCs in tissue engineering which improve disease symptoms, such as eye defects, diabetes, and lung degeneration

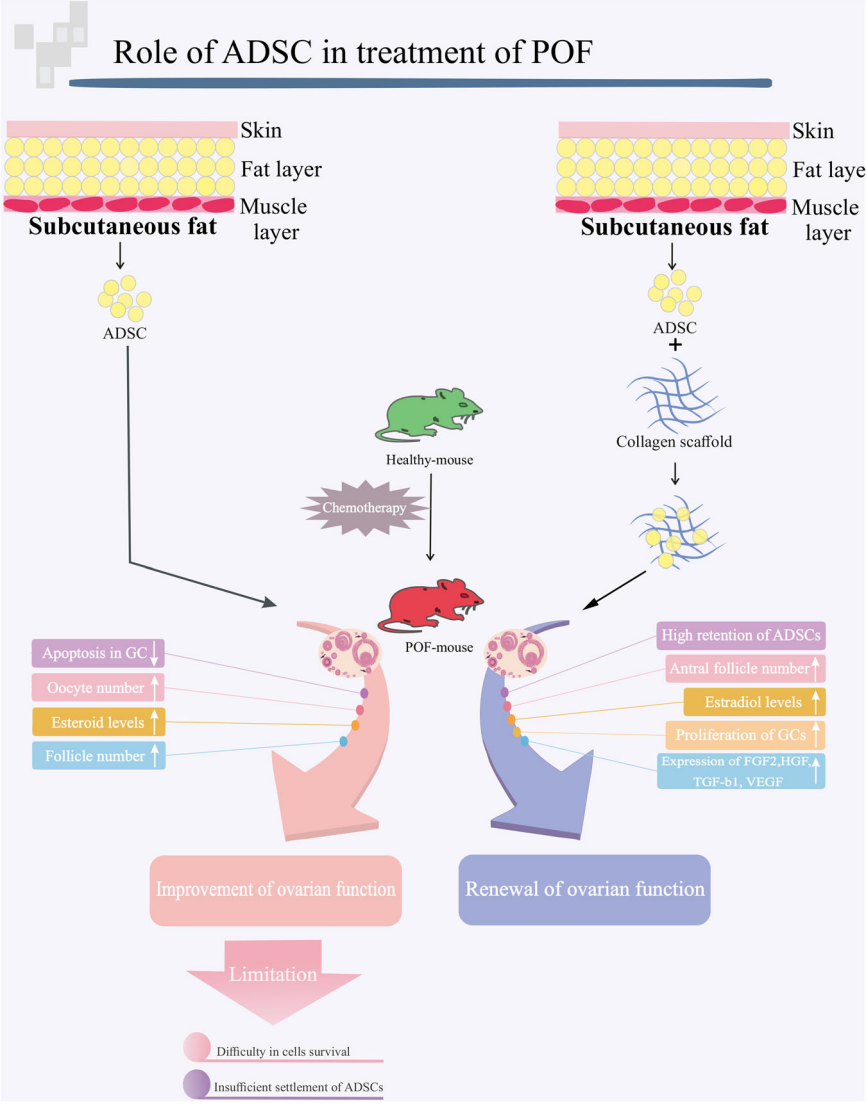

FIGURE 2 ADSCs are a type of MSCs. They are useful in the treatment of POF by cell therapy and tissue engineering. At first, researchers caused POF in the mouse by chemotherapy treatment. In cell therapy, ADSCs were directly transplanted into failed ovaries. After ADSCs therapy, ADSCs can decrease the apoptosis of granulosa cells (GC), increase the number of follicles and oocyte and also increase of estradiol level. Finally, ADSCs significantly improved ovarian function in patients with POF. There are some limitations in this treatment, one of them is an insufficient settlement of ADSCs in the ovary during transferring of cells. Another limitation is the difficultness of cell survival in the target tissue. In tissue engineering, ADSCs loaded on collagen as a scaffold and then transplanted into failed ovaries. The results show high retention of ADSCs also increase in the number of antral follicle and expression of FGF2, HGF, TGF-β1, and VEGF in vitro and proliferation of GC that they led to the renewal of ovarian function. ADSC, adipose-derived stem cell; FGF, fibroblast growth factors; HGF, hepatocyte growth factor; POF, premature ovarian failure; TGF-β1, transforming growth factor β1; VEGF, vascular endothelial growth factor

(Dye et al., 2015; Howden et al., 2015; Tsai et al., 2015; Yang et al., 2016; Zhu et al., 2016).

4.2 | Human menstrual blood stem cells

HuMenSCs can be isolated from menstrual blood (Meng et al., 2007). These stem cells are characterized by being self-renewal, abundant in vitro proliferation potentials, and differentiating ability towards diverse cell lineages in condition media (Liu, Huang et al., 2014). Initially, Gargett (Gargett, 2004) described these cells and harvested them directly from the endometrium. Then, numerous research groups explained the in vitro properties of HuMenSCs stem cells and progenitor cells as well as in vivo regenerative capabilities in damaged tissues (Gargett, 2004). Meng et al. (2007) and Patel et al. (2005) also reported high expression levels of MSC surface markers (CD29, CD44, CD49f, CD90, CD105, and CD117), and ESCs markers (Oct4 and SSEA3/4) in these cells. Other studies have also confirmed that HuMenSCs can be differentiated into various types of somatic cells including adipocytes, osteoblasts, chondrocytes, neurons, endotheliocytes, pulmonary epithelial cells, hepatocytes, islet cells, cardiac myocytes, and insulin-producing cells under certain conditions (Liu, Huang et al., 2014). Accordingly, a great bulk of evidence suggests the strong pluripotent features of HuMenSCs (Liu, Huang et al., 2014).

HuMenSCs retrieval is much easier than that of the other adult stem cells, and this possibility makes them a potential donor source in clinics (Liu, Huang et al., 2014). Recent findings have also indicated that the HuMenSCs are able to be differentiated into ovarian tissue-like cells in POF ovarian microenvironment (Liu, Huang et al., 2014). Therefore, these stimulated cells display the potency for major recovery of POF-related ovarian damage (Liu, Huang et al., 2014).

4.3 | Amniotic fluid stem cells

As an alternative choice, AFSCs can be also utilized in regenerative medicine, due to their easy harvest from amniotic fluid, quick self-renewal, ordinal karyotype retainment in long-term culture (Xiao et al., 2014). Compared with the other stem cells, these cells have shorter doubling time and express the ESCs marker OCT4 (Xiao et al., 2014). Furthermore, unlike ESCs and iPSCs, they exhibit no teratomatous activity in vivo (Xiao et al., 2014). Findings have also revealed that transplanted allogeneic AFSCs possess low immunogenicity and can escape from the immune rejection (Chang et al., 2013). The potential benefits of AFSCs in treating POF are further suggested following their use in the regeneration of the other organs including muscles, kidneys, lungs, and heart (Xiao et al., 2014). Increased healthy ovarian follicles and restored fertility are also reported by Xiao et al. (2014) study following direct transplantation of AFSCs into bilateral ovaries in a chemotherapy-induced POF mice model. In a study, AFSCs transplantation into POF mice maintained the number of healthy ovarian follicles by promoting de novo folliculogenesis (Xiao et al., 2014). Moreover, there was no remarkable difference in terms of atretic follicles between chemotherapy-AFSCs-mice and controls. This study strongly suggested that AFSCs, by preventing follicular atresia, increases the number of healthy ovarian follicles.

Follicular atresia is mainly mediated by the apoptosis of follicular cells, particularly granulosa cells which are essential for follicular development (Xiao et al., 2014). However, no evidence has been found on the straight differentiation of transplanted AFSCs into granulosa cells in POF mice ovary (Xiao et al., 2014). Recent studies have reported that AFSCs can secrete TGF-β, VEGF, and glia cell-derived neurotrophic factors, which is essential for follicular development. They can also inhibit follicular cell apoptosis and follicle atresia (Xiao et al., 2014).

4.4 | Bone marrow-mesenchymal stem cells

BM-MSCs are a member of low immunogenic adult stem cell family (Raeth et al., 2014). They are generally found in the bone marrow microenvironment. These cells possess renewal properties and under specific situations, can be differentiated into different cells, such as bone, cartilage, and adipocytes (Raeth et al., 2014). In addition, BM-MSCs can be easily isolated and amplified in vitro and migrate to the injured tissues (He et al., 2017). Furthermore, due to paracrine and immunomodulation functions, these cells can be differentiated into particular sorts of cells in the tissue to remake the local microenvironment (He et al., 2018). By enhancing the function of endogenous cells and regulation of immune response, they are committed to fix tissue damages. This function makes BM-MSCs as a suitable approach for transplantation (He et al., 2018). There are some promising results despite the low rate of survival and limited potential for differentiation following BM-MSCs transplantation (He et al., 2018). Additionally, the autologous transplantation of stem cells for medical treatment of POF is also developing (He et al., 2018). It has been reported that BM-MSCs recover POF ovarian supply (He et al., 2018). Cytokines induce the BM-MSCs movement toward damaged tissues. However, they do not distinguish the oocytes (He et al., 2018). Certain growth factors including VEGF, insulin-like growth factor, and hepatocyte growth factor (HGF) are also secreted by BM-MSCs to help the restoration of ovaries against apoptosis and fibrosis (He et al., 2018). They also maintain the function of ovaries by suppressing the inflammatory responses and reducing OS (He et al., 2018). Some cytokines, such as IL-6 also regulate the function of the immune system (He et al., 2018). As noted previously, chemotherapy is the most widely recognized method of treatment applied in patients with cancer underwent surgery and radiation therapy. Those treatments recommend just undefined fertility upgrades, and POF is a typical long-term consequence of chemotherapy and radiotherapy (Mohamed et al., 2018). These treatments may represent a significant risk for gonadal damage. The severity of the damage is directly related to dose and the patient's age at the time of treatment. It has been shown that these chemotherapy agents destroy ovarian follicles (Mohamed et al., 2018). Mohamed et al. (2018) indicated that chemotherapy causes an increase and decrease of FSH and estrogen levels, respectively, leading to impaired folliculogenesis and small nonfunctional ovaries in mice.

Furthermore, stem cell-based therapies have provided a promising strategy for fertility conservation in cancer survivors. However, some of these techniques are not able to preserve young women's prepubertal fertility (Wang et al., 2013). Furthermore, many of these advanced technologies are not promptly accessible, worldwide. It is clear that innovative approaches are needed to preserve fertility in cancer survivor females at the reproductive age and also infertility treatment associated with idiopathic POF (Mohamed et al., 2018). Stem cells also offer opportunities for the treatment of degenerative diseases (Wang et al., 2013). In addition, their ability to secrete several bioactive factors that modulate surrounding cells enables them to be differentiated into a diversity of cells (Wang et al., 2013). In more than 344 clinical examinations, transplantation of human BM-MSCs was used to treat different diseases. Multiple studies on stem cell transplantation have indicated their stimulation by the niche in a specific microenvironment (Mohamed et al., 2018). These microenvironmental stimuli, in turn, cause the release of cell developmental factors that support the regeneration of the surrounding tissue (Mohamed et al., 2018). Mohamed et al. (2018) showed that bone marrow transplantation improves fertility outcomes among adult female mice treated with chemotherapeutic agents. It has been also reported that bone marrow transplantation improves fertility outcomes by either reinstatement support of recipient oogenesis or restoration of existing oocytes following chemotherapy (Mohamed et al., 2018).

4.5 | Adipose-derived stem cells

ADSCs are multipotent adult stem cells that are separated from adipose tissue (Su et al., 2016). ADSCs can be differentiated into multiple cell lineages, such as adipocytes, osteoblasts, cartilage cells, vascular endothelial cells, myocytes, and neurons (Su et al., 2016). Adipose tissue is a weak immunogenic, stably proliferative, low-injury, and practical tissue source which plays key role in the reconstruction and regeneration of autologous cells (Su et al., 2016). Clinical applications of ADSCs, such as the treatment of ischemic myocardial dysfunction, kidney injury, carcinoma, and neuron system diseases have been demonstrated in several clinical trials that represent this tissue as an alternative stem cell source in the treatment of POF (Su et al., 2016). In patients who have undergone chemotherapy or radiotherapy, apoptosis is probably a relevant mechanism for POF generation (Su et al., 2016). It has been reported that following ADSCs therapy, the number of terminal deoxynucleotidyl transferase dUTP nick end labeling-positive cells is significantly decreased, and Zcchc11 expression is upregulated, pointing to the fact that ADSCs can decrease POF-mediated apoptosis (Su et al., 2016). ADSCs therapy may be also used in patients without distant metastasis. Sun et al. (2013) in a chemotherapy-induced POF mouse model, reinfused a patient's retrieved stem cells after chemotherapy. Findings revealed that in aggressive tumors, stem cells can be obtained after chemotherapy; however, the cell viability may be decreased, and the risk of cancer relapse may be increased (Sun et al., 2013). Su et al. (2016) also showed that the transplantation of ovarian ADSCs into TGs-induced POF mice resulted in the interstitial homing of these cells after 1 week. It indicates that ADSCs may not be directly differentiated into oocytes or granulosa cells, in vivo. ADSCs, as a stromal cell progenitor, maybe also recruited during the basal lamina and the theca layer formation to support the proliferation of granulosa cells and angiogenesis (Su et al., 2016). ADSCs can also simplify the proliferation of granulosa cells after ovarian failure. This effect has been also confirmed by the increase in estradiol level after ADSCs transplantation, which may play an important role in the ovarian function recovery. There are some limitations for ADSCs-based treatments, such as the inappropriate settlement of cells during the transfer process to the target tissue (Sun et al., 2013; Suuronen, Veinot et al., 2006; Suuronen, Muzakare et al., 2006). Difficult cell surveillance in the target tissue, due to biological factors interactions in injected areas, such as ischemia, inflammation, and apoptosis, is another limitation for this method (Su et al., 2016). Therefore, the maintenance of cell viability in grafted organs is crucial. Scaffolds provide a useful strategy for stem cell delivery and support (Su et al., 2016). In tissue engineering, collagen is extensively used as a scaffold. It is one of the most accessible and abundant proteins in animals which is highly biocompatible, biodegradable with low antigenic properties that supports numerous cell types and tissues (Ding et al., 2014; Suuronen et al., 2004; Suuronen, Muzakare et al., 2006; Suuronen, Veinot et al., 2006). Collagen fibers are also considered as a suitable niche for stem cells and play key role in cell anchoring, proliferation, migration, differentiation, and function (Boccafoschi, Habermehl, Vesentini, & Mantovani, 2005; Guan et al., 2013; Wang et al., 2007). Su et al. (2016) in their study used collagen scaffolds in a POF rat model to evaluate ovarian function maintenance by transplanted ADSCs. The results indicated the limited diffusion of ADSCs into ovary due to the attachment of ADSCs to the collagen fibers. Therefore, the retention rate of transplanted ADSCs within ovaries by the collagen scaffold was higher than that of ADSCs transplanted without collagen scaffold. Additionally, ADSCs in the collagen scaffold increased the number of antral follicles and litter size when compared with ADSCs transplantation alone. Compared with monolayer culture ADSCs in 3D scaffolds secrete more proteins and soluble factors into the extracellular matrix (Amos et al., 2010). Su et al. (2016) also reported that ADSCs culture in the collagen scaffold increased FGF2, HGF, TGF-β1, and VEGF expression, and the number of the antral follicles and litter size. Moreover, cultured ADSCs in collagen scaffolds showed paracrine activities and secreted more GFs. Within follicles, these growth factors contributed to the angiogenesis and proliferation of granulosa cells within follicles. The paracrine effect of ADSCs also increased estradiol levels yielding high-quality oocytes (Su et al., 2016; Figure 2).

5 | CONCLUSION

Losing the normal function of ovarian is a disorder known as POF. This condition happens in woman before the age of 40. Several methods for the treatment of POF have been investigated; however, cell therapy and tissue engineering techniques are known as novel approaches for its treatment. In cell therapy, stem cells are used to treat diseases; although, this method faces some limitations. As a result, tissue engineering seems to be a good alternative for POF patients' treatment. In tissue engineering, ADSCs are loaded on collagen-based scaffolds and then transplanted into failed ovaries. The results have shown ADSCs retention and increased number of the antral follicles and ovarian function renewal. Therefore, using MSCs, such as ADSCs and BM-MSCs in tissue engineering may provide viable therapeutic options for POF treatment.

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CONFLICT OF INTERESTS

The author declares that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

M. G. N. wrote the article. E. G. and Y. J. wrote the initial draft of the manuscript and prepared figures. A. M. reviewed and edited the final version of the manuscript. M. Y. supervised the study.

DATA AVAILABILITY STATEMENT

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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