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Review article

# Adipose-Derived Mesenchymal Stem Cells: A Promising Tool in the Treatment of pre mature ovarian failure

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ABSTRACT

Despite being rare, primary ovarian insufficiency (POI) is a significant cause of infertility and deficiency of ovarian hormone in women. Several health risks are also associated with POI, which include dry eye syndrome, reduced density of bones and enhanced fracture risks, troublesome menopausal symptoms, early development of cardiovascular disease, and psychological effects such as declined cognition, reduced perceived psychological support, anxiety, and depression. Replacing premenopausal levels of ovarian sex steroids through proper hormone replacement therapy could improve the quality of life for POI women and ameliorate related health risks. Herein, POI and its complications, in addition to hormone replacement therapies, which are safe and effective, are discussed. It is proposed that the use of HRT) Hormone replacement therapy (formulations which mimic normal production of ovarian hormones could reduce POI-associated morbidity rates if they are continued by the age 50, which is approximately the natural age of menopause. Particular populations of POI women are also addressed, which include those with enhanced risk of ovarian or breast cancer, those with Turner syndrome, those approaching natural menopause, and those who are breastfeeding. It is generally predicted that stem cell-based therapies would be both safe and effective. In fact, several types of cells have been described as safe, though their effectiveness and therapeutic application are yet to be defined. Several factors exist which could affect the results of treatment, such as cell handling, ex-vivo preparation strategies, variations in tissue of origin, potency, and immunocompatibility. Accordingly, cell types potentially effective in regenerative medicine could be recognized. Notably, products of MSCs from various sources of tissues show different levels of regenerative capabilities. The ultimate focus of the review is on adipose tissue-derive MCSs (ADMSCs), which possess exceptional features such as general availability, great ability to proliferate and differentiate, immunomodulatory capabilities, and low immunogenicity.

## 1. Introduction

Premature ovarian failure (POF) is among the most common diseases in women. This term refers to a condition in which the follicles in ovaries are destroyed or inactivated (Hoek et al., 1997; Kovanci & Schutt, 2015). Evidence with regards to the exact prevalence of POF do not exist yet. Almost 1% of women younger than 40 are estimated to be affected by spontaneous POF. Although particular information are lacking, the incidence of iatrogenic POF is increasing, which is concerning. As a result of increased survival rates following malignant diseases, more women now experience the long-term effects of treatments in this regard, including radiotherapy and chemotherapy (Maclaran & Panay, 2011).

Although the causes of ovarian failure have not been precisely identified, factors such as surgery, radiation or chemotherapy, genetic and chromosomal abnormalities, environmental factors (chemical agents, viruses, etc.), metabolic damage of ovarian autoimmunity (type 1 diabetes, galactosemia, deficiency of 17-OH and OH-21, etc.), endometriosis, and polycystic ovary syndrome are involved in the development of ovarian failure (Komorowska, 2016). Ovarian failure occurs with symptoms such as amenorrhea or infertility. However, comorbidities including hypotension, axillary and genital hair loss,

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hyperpigmentation or vitiligo (related to autoimmune adrenal insufficiency, thyroid enlargement, and exophthalmos can also be symptoms of ovarian failure (Ahonen et al., 1990; Betterle et al., 2002; Betterle & Volpato, 1998).

One of the recent treatment options for ovarian failure is the use of ADMSCs. Adipose tissue is totally available and is in fact a rich source for stem cells which possess multipotent characteristics that are proper for application in regenerative medicine and tissue engineering (Parhizkar et al., 2021). These are the reasons why ADMSCs have become popular among researchers (Bunnell et al., 2008).

Obtaining ADMSCs could be performed on adipose tissue using liposuction, washing, collagenase digestion, and centrifugation. The advantages of employing adipose stem cells over bone marrow cells include less invasion, facile application, and abundance of this tissue in the body (Aghlmandi et al., 2021). Reproduction, migration, and ADMSC differentiation can be regulated using estrogen. In this review, the causes of POF, effective treatment strategies, and the effect of Adipose-Derived Mesenchymal Stem Cell transplantation for the treatment of premature ovarian failure are reviewed.

## 2. Etiology of POF

Follicogenesis is a regular process in which primary follicles first develop into secondary follicles, and then into antral follicles, following which ovulation occurs. If this natural process changes, it will lead to POF. There exist three cell types in ovarian follicles, including oocytes, granulosa cells, and theca cells. Receptors for luteinizing hormone and follicle-stimulating hormone (FSH) exist on theca and granulosa cells, respectively, which are vital to follicle growth and development (Costa-Carvalho et al.).As a regulated and organized process, folliculogenesis involves the conversion of primordial follicles into primary, preantral, and antral follicles, respectively. Following these processes, ovulation takes place (Fig. 1) (Sheikhansaria et al., 2018). Factors involved in the emergence of POF include chemotherapy, chromosomal and genetic aberrations, autoimmunity, enzymes, and external factors. (Table1).

**Table 1**
Causes of premature ovarian failure.

| Causes | Example | References |
|---|---|---|
| Chemotherapy and radiation therapy | Docetaxel Pirarubicin ifosfamide | (Anderson & Cameron, 2011; Anderson et al., 2006; Anderson & Wallace, 2013; Bath et al., 2003; Himelstein-Braw et al., 1978; Long et al., 2016) 1087–1092; Mahajan, 2015; Meirow et al., 2010; Meirow et al., 2007; Meirow & Nugent, 2001; Meirow & Wallace, 2009; Sklar et al., 2006; Su et al., 2014; Waxman, 1983) |
| x-chromosome | Turner syndrome Fragile X pre-mutations | (Sheikhansaria et al., 2018; Morgan, 2007; Trovó de Marqui, 2015) |
| Autoimmunity and POF | Addison's diseases Viltiligo Myasthenia gravis Celiac disease APECED Ovarian autoantibody Immune cells inbalance: Increase of Increase of CD4 + T cell | (Carp et al., 2012; Dragojević-Dikić et al., 2010; Euthymiopoulou et al., 2007; La Marca et al., 2010; Silva et al., 2014; Welt, 2008; Wémeau et al., 2013) |
| Enzymatic | 17α-hydroxylase aromatase | (Sheikhansaria et al., 2018) |
| Environment | Viral infections Smoking | (Ebrahimi & Akbari Asbagh, 2011; Jankowska, 2017; Kaufman et al., 1980) |

### 2.1. Chemotherapy

Medications used during chemotherapy play a significant role in inducing infertility, which could include breast cancer medications such as DTC (docetaxel + pirarubicin + ifosfamide) (Long et al., 2016) 1087–1092). To evaluate how drugs and cancer treatments affect the ovaries, the rate of ovarian function loss during the treatment, as well as changes in ovarian function after treatment should be considered. Chemotherapy destroys the primordial follicle pool (ovarian storage),

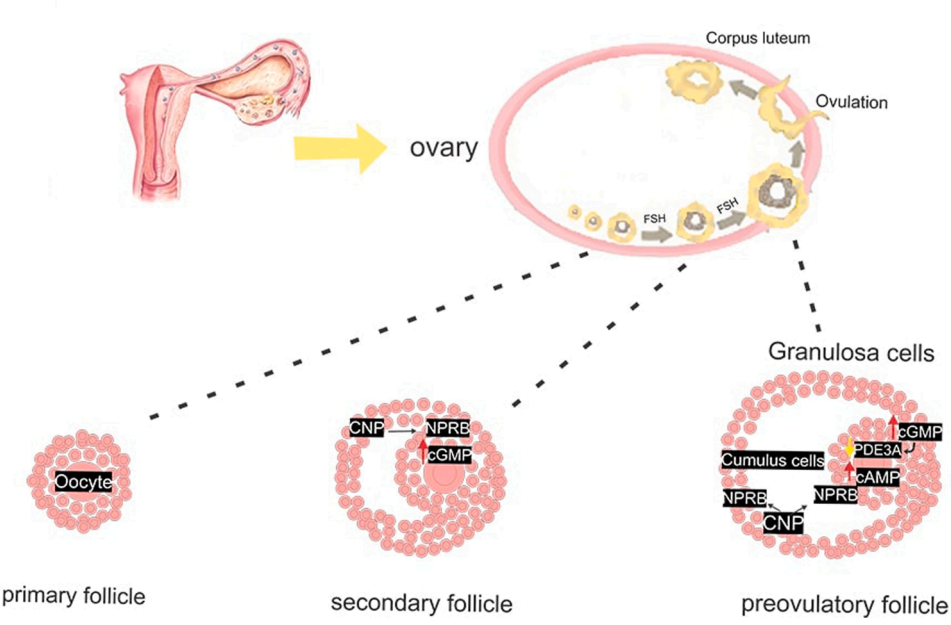


**Fig. 1. Ovarian follicles and their constituent cells.** In this process, primary follicles first develop into secondary follicles, and then into antral follicles, following which ovulation occurs. Abbreviation: CNP (C-type natriuretic peptide), ANP (atrial natriuretic peptide), BNP (brain natriuretic peptide), PDE3A (natriuretic peptidereceptor-B, phosphodiesterase 3A).

which is significant as it regulates the potential for improved fertility and activity of ovaries (Meirow et al., 2007). Chemotherapy can also have negative effects on non-follicular sections of the ovary, such as vasculature and stroma (Anderson & Cameron, 2011; Su et al., 2014).

Damages to several organs, based on sex and age of the patient, and dose of drug, could be done by chemotherapy, which has remained the standard of care for cancer (Mahajan, 2015; Meirow & Wallace, 2009; Sklar et al., 2006). Vital cell processes are inhibited by chemotherapeutics. For example, they arrest the proliferation of cells, and in ovaries, induce aberrant activation of dormant follicles. Induction of different levels of ovarian injury through cancer therapeutics, which result in the repression of fertility, has been reported by several studies (Anderson et al., 2006; Bath et al., 2003). Also, solutions for ameliorating ovarian atrophy and preventing follicle reserve loss and infertility have been presented (Himelstein-Braw et al., 1978; Meirow & Nugent, 2001; Waxman, 1983). The burn-out of dormant follicle pool in older women is still of paramount importance, even though they possess a reduced follicle pool and suffer increased susceptibility to POF, in comparison to young women. Attributed causes in this regard include the chemotherapy-triggered apoptosis of somatic cells in developing follicle as well as fibrosis of stromal blood vessel in the ovary (Anderson et al., 2006; Anderson & Wallace, 2013; Meirow et al., 2010; Meirow & Nugent, 2001; Meirow & Wallace, 2009).

### 2.1.1. Chemotherapeutic drugs

In the following, a classification of many anti-cancer drugs, depending on their action and type is presented. Firstly, considerable damaging effect to ovarian tissue could be induced by alkylating molecules, including cyclophosphamide. Therefore, the greatest rates of age-related ovarian failure is attributed to these molecules. Secondly, amenorrhea and DNA damage in ovaries could be induced by platinum-based molecules, including cisplatin, through the activation of p63 and inhibition of c-Abl tyrosine kinase. Early embryonic death and oocyte aneuploidy could also be induced by cisplatin. Thirdly, oxidative stress in mature/premature oocytes could be induced by anthracycline compounds, including doxorubicin, which is capable of triggering aneuploidy and dominant fatal mutations. However, as shown by clinical evidence, doxorubicin has been suggested to have lower risks of application compared to other chemotherapeutics. Nonetheless, in a study by Hortobagyi et al, the frequency of amenorrhea was shown to be much greater in doxorubicin-receiving women older than 30 years (96% in those above 40, and 33% in those between 30 to 39), as compared to women younger than 30 years of age. Fourth, an elevated level of aneuploidy could be induced by vinca alkaloids, including vinblastine, in animal models. Nevertheless, a decreased risk of ovarian failure was shown by a clinical study in this regard. Fifth, fertility is not affected by anti-metabolites, including 5-fluorouracil and methotrexate. However, limited evidence exist in this respect. General application of methotrexate includes the treatment of ectopic pregnancy without the existence of any agent-related side effects. Sixth, controversial effects on fertility have been reported for taxane family-related drugs, including paclitaxel. Accordingly, low or no risk of amenorrhea have been proposed by many studies, while gonadal toxicity through high levels of follicle stimulating hormone (FSH), as well as enhanced risk of amenorrhea have been shown by other studies. Consequently, these agents mostly act as therapeutic adjuvants following primary chemotherapy, since they show fewer side effects and reduced threats to fertility. Together, more clinical data are required in this regard. Treatment of patients often involves the aforesaid agents or their combinations. However, predicting ovarian damage is challenging as there exist inter-individual variations. Although a major combination of vincristine, prednisone, procarbazin, and cyclophosphamide potentially triggers POF (Jang et al., 2017), a combination of vincristine, dacarbazine, bleomycin, and Adriamycin used for lymphoma is less ovotoxic (Table 2) (Behringer et al., 2013; Bonadonna et al., 2004; Decanter et al., 2010).

**Table 2**
Chemotherapeutic drugs.

| | Classification | examples | Side effect | Mechanism |
|---|---|---|---|---|
| 1 | alkylating molecules | cyclophosphamide | The greatest rates of age-related ovarian failure is attributed to these molecules. (Meirow et al., 1999) (Ataya et al., 1995) ( Familiari et al., 1993) | Inducing DNA crosslinking that leads to the formation of adducts that prevent DNA replication. Also affects mitochondria, leading to a reduction in transmembrane potential and cytosolic cytochrome c accumulation. (Spears et al., 2019) |
| 4 | platinum-based molecules | cisplatin | amenorrhea and DNA damage in ovaries could be induced by platinum-based molecules, Early embryonic death and oocyte aneuploidy. ( Blommaert et al., 1996) (Gonfloni et al., 2009; Maneschi et al., 1994) (Nozaki et al., 2009) | through the activation of p63 and inhibition of c-Abl tyrosine kinase |
| 6 | anthracycline compounds | doxorubicin | Oxidative stress in mature/ premature oocytes could be induced by anthracycline compounds. ( Mailhes, 1995) | which is capable of triggering aneuploidy and dominant fatal mutations |
| 7 | vinca alkaloids | vinblastine | risk of ovarian failure (Mailhes, 1995) | An elevated level of aneuploidy is induced by vinca alkaloids. |
| 8 | anti-metabolites | 5-fluorouracil and methotrexate. | Fertility is not affected by anti-metabolites. ( Bines et al., 1996) | - |
| 9 | taxane family-related drugs | paclitaxel | low or no amenorrhea risk have been proposed by many studies while gonadal toxicity through high levels of follicle stimulating hormone (FSH), as well as enhanced risk of amenorrhea have been shown by other studies. (Davis et al., 2005) (Abusief et al., 2010) ( Ganz et al., 2011) (Han et al., 2009) (Reh et al., 2008) | - |

#### 2.1.2. Mechanisms of chemotherapy-induced ovarian disorder

Either cell division is inhibited, or DNA damage is induced by anticancer drugs, both of which lead to cell apoptosis. Apoptosis of oocytes and somatic granulosa cells in the ovary could be activated by chemotherapy-induced DNA damages, including DNA double-strand breaks (Di Giacomo et al., 2005; Jurisicova, Lee, D'Estaing, Tilly, & Perez, 2006; Perez et al., 2007). Additionally, aberrant activation of dormant primordial follicles is stimulated by chemotherapy, which leads to POF (Bines et al., 1996; Waxman, 1983) (Cruz et al., 2014; S. Morgan et al., 2012). Importantly, both reaction and the response of chemotherapeutics depend on cells. Accordingly, understanding the mechanisms of chemotherapeutics and signal transduction is significant to preserve germ cells in the ovary. Although anticancer drugs are capable of inducing apoptosis in somatic cells, including cumulous and granulosa, and oocytes in large follicles, toxic effects of chemotherapeutics on dormant primordial follicles have not been investigated thoroughly (Carroll & Marangos, 2013; Di Giacomo et al., 2005; Gonfloni et al., 2009; Higdon et al., 1992). It was shown by Oktem and Oktay that cyclophosphamide is capable of rapidly decreasing the levels of primordial follicles, and inducing apoptosis in human-mice ovarian xenograft models (Oktem & Oktay, 2007). It was shown by Xiang et al. that cyclophosphamide, as an alkylating molecule, is capable of inducing the depletion of dormant follicle pool through indiscriminate activation of primordial follicles without the induction of death, which indeed leads to POF induction (Jutras et al., 2013). Also, cisplatin, as a platinum-based agent, is a potent inducer of the activation of primordial follicles without the induction of follicle death (Chang et al., 2015; Jang et al., 2016). The activation or death of primordial follicles in the ovary could be explained by two central pathways. First one is TP53-dependent pathway, which is a tumor suppressor protein known as p53. Importantly, its involvement in the apoptosis of ovarian granulosa cells in rats has been reported (Harris & Levine, 2005; Zwain & Amato, 2001). On the other hand, less expression of TP53 in human ovarian follicles was shown by Depalo et al (Depalo et al., 2003). In *TP53*-deficient mice, doxorubicin was not capable of stimulating apoptosis in mature oocytes (Jang et al., 2017). These propose independent mechanisms of chemical-induced DNA damage and TP53-mediated follicle apoptosis. The presence of TAp63, as a homologue of TP53, was demonstrated in the nucleus of oocytes (Kurita et al., 2005). Also, in the oocyte of primordial follicles, it regulates DNA damage or repair systems (Livera et al., 2008; Suh et al., 2006). In the lack of TAp63, oocytes become resistant to DNA damage induced by radiation (Suh et al., 2006). As a significant transcriptional factor in the PI3K signaling pathway, FOXO3a is capable of regulating primordial follicle activation (Castrillon et al., 2003). Through the activation of a primordial follicle, phosphorylation of FOXO3a, and its exportation to the cytoplasm, take place (Jang et al., 2016). FOXO3a acts as an activator of transcription in the nucleus and induces $p27^{Kip1}$ expression, which is capable of encoding a cyclin dependent kinase (CDK) inhibitor protein to maintain the dormancy of primordial follicles (Jang et al., 2017). $P27^{Kip1}$ deficiency, indeed, leads to the extreme activation of primordial follicles, which results in POF in mice (Rajareddy et al., 2007).

### 2.2. Chromosomal and genetic aberrations

Approximately 4-31% of POF disorders are familial. Some types of genetic defects and chromosomal aberrations on the X and autosome chromosomes are linked to POF (Cramer et al., 1995; Torgerson et al., 1997; Vegetti et al., 1998), among which X chromosome aberrations, including Turner syndrome and Fragile X pre-mutations, are the most important causes of the disease (Baronchelli et al., 2011; Castillo et al., 1992; Ceylaner et al., 2010; Janse et al., 2010; Lakhal et al., 2010; Portnoï et al., 2006).

#### 2.2.1. X chromosome disorder

X-chromosome disorder has an incidence of 1/2500 in girls (Trovó de Marqui, 2015). A decreased complement of X-chromosome-expressed genes in females causes the Turner syndrome. Under normal conditions, random inactivation of one X chromosome in the first week of life (existence of >200 embryonic cells) occurs. Together, the fact that possessing a single X chromosome could cause clinical costs might seem paradoxical. In Turner syndrome, nonetheless, not the whole genes from second chromosome are inactivated. Some genes could possibly escape X-inactivation through a process that is initiated by the X-inactivation-specific transcript *(XIST)* gene, the exclusive transcription of which is performed on inactive genes. Losing such non-inactivated X genes could result in the phenotypic emergence of Turner syndrome signs, including short stature (T. Morgan, 2007). POF might also be caused by Trisomy X syndrome (Sheikhansaria et al., 2018).

#### 2.2.2. Autosomal disorder

Other genetic factors capable of causing POF involve single-gene disorders, which include mutations in FSH and LH receptors, mutation in inhibin, and galactosemia. 80% of galactosemia patients have shown POF. POF has also been shown to be induced through the mutations of Splicing factor 1 (SF1), Growth/differentiation factor 9 (GDF9), Newborn ovary homeobox gene (NOBOX), Forkhead Box protein L2 (FOXL2), and Inhibin alpha (Schallmoser, Henschler, Gabriel, Koh, & Burnouf), all of which play important parts in folliculogenesis. As an encoder of the forkhead transcription factor, FOXL2 is a single-exon gene, the expression of which occurs in ovarian undifferentiated granulosa cells. Also, it possesses vital roles in maintaining and developing ovaries. NOBOX functions in early folliculogenesis. Studies have demonstrated that the transition from primordial to growing follicles is blocked in the lack of NOBOX in mice.

SF1 gene is located on 11q13 chromosome, is expressed in several types of cells in fetus and adults, and functions in the development of reproductive system. It has been confirmed that INHA has roles in reducing the secretion of FSH in folliculogenesis. It has been shown that INHA gene polymorphisms are associated with POF due to the significant roles of INHA in folliculogenesis. The expression of GDF9, which is capable of encoding soluble factors involved in reproductive functions, takes place in oocytes. Regulation of the proliferation of granulosa cells depends on the synergistic function of BMP15 and GDF9 (Sheikhansaria et al., 2018).

### 2.3. Autoimmunity and POF

The presence of organ and non-organ-specific autoantibodies and autoreactive T cells is associated with the development of autoimmune diseases (La Marca et al., 2010; Silva et al., 2014). There exist different types of ovarian autoimmune disorders, including adrenal autoimmunity-involved, non-adrenal autoimmunity, and isolated idiopathic POI (Carp et al., 2012). Also, most Addison's disease patients suffer additional endocrine disorders. POI is strongly associated with autoinmune Addison's disease with respect to two autoimmune polyendocrine syndromes (APS) types (Ahonen et al., 1990; Betterle et al., 2002). Ectodermal dystrophy Candidiasis autoimmune polyendocrinopathy (APECED) is the first type, which manifests as chronic cutaneous mucosal candidiasis, adrenal insufficiency, and hyperparathyroidism in young children. Association of POI with local or non-adrenal systemic disorders is also possible (Welt, 2008; Wémeau et al., 2013). The most important hypoadrenalism occurs clinically and simultaneously with hyperparathyroidism (Dragojević-Dikić et al., 2010), hypophysitis, and type 1 diabetes.

Approximately 10-30% of POI women suffer a comorbid autoimmune disease, the most common of which is hypothyroidism (Welt, 2008; Wémeau et al., 2013), and the most significant of which is clinical adrenal hypoadrenalism. Also, hyperparathyroidism (Dragojević-Dikić et al., 2010), hypophysitis, type 1 diabetes, endocrine autoimmune

hemolytic anemia, malignant anemia, vitiligo, alopecia areata, celiac disease, inflammatory bowel disease, primary biliary cirrhosis, glomerulonephritis, multiple sclerosis (Euthymiopoulou et al., 2007), and Myasthenia gravis (Carp et al., 2012) have been reported to be associated with the disease.

### 2.4. External factors

Some viral infections, such as mumps, cytomegalovirus, and varicella zoster virus can cause POF. Other factors capable of causing POF could be tuberculosis, malaria, and Shigella infection (Ebrahimi & Akbari Asbagh, 2011). Another environmental factor affecting early menopause is smoking, which can eventually lead to POF (Jankowska, 2017; Kaufman et al., 1980).

### 2.5. Enzymes

The steroidogenic pathway is one of the effective enzyme pathways in the emergence of POF. Also, deficiency of enzymes such as 17-hydroxylase and aromatase could cause POF. Deficiencies of 17-hydroxylase and 17,20-desmulase in the ovaries and adrenals lead to decreased levels of serum follicular fluid, androstenedione, testosterone, and estradiol in the steroidal pathways (Sheikhansaria et al., 2018).

## 3. Diagnosis

Doctors may face the condition (POF) by examining young women who struggle to get pregnant or experience secondary amenorrhea. In this case, to make the diagnosis, determining whether there exist any menopausal symptoms might be beneficial. Assessments of the medical history of POF patients typically show a normal age of menarche and usual menstrual cycles, which are followed either by oligomenorrhea or sudden amenorrhea. Some cases might also show secondary loss of menses when they stop taking contraceptive pills. Some other frequent side effects involve dryness of mucous membrane and skin, loss of hair, excessive sweating, and hot flushes. A hypergonadotropic-hypogonadic hormone profile is generally revealed by the tests, which is also termed primary hypogonadism, and is determined by low oestradiol (E2) levels ($< 20$ pg/ml), elevated gonadotropin levels (follicle-stimulating hormone [FSH] $> 20$ IU/l), low anti-Müllerian hormone AMH) levels – $<$ 0.5 ng/ml ($< 1$ ng/ml), and low inhibin B levels. Levels of FSH above 40 IU/l, which are recorded two times at least with intervals of 4-6 weeks, could suggest the diagnosis of POF. The levels of AMH do not hinge on cycle day. However, its concentrations decline with age, suggesting it as a decent marker for determining fertility potential. POF patients show very low or negligible levels of AMH. Women suffering polycystic ovary syndrome (PCOS) show significantly increased levels of AMH as excessive amount of ovarian follicles characterize the condition, though there is no folliculogenesis). With the aim of assessing the ovarian reserve, inhibin B could be advantageous. However, it should be noted that to measure inhibin B, the cycle phase should be considered as granulosa cells of the early antral follicles produce it majorly in the follicular phase of the menstrual cycle. Both number and quality of ovarian follicles could be determined by inhibin B levels in the early follicular phase. Overall, POF patients show reduced inhibin B levels (Jankowska, 2017).

## 4. Current treatments

There are several treatments for POF, but none are definite because of the complexity of POF. Overall, some of the best recent treatments for POF include exercise and diet, hormone replacement therapy, donor oocytes, use of androgens, biochemical hormones, dehydroepiandrosterone, Melatonin and cell therapy (Table3) (Sheikhansaria et al., 2018).

Stem cell therapy is particularly significant among the aforesaid treatments, since MSCs as multipotent somatic stem cells are capable of differentiating into both mesodermal and non-mesodermal lineages which enjoy the ability to produce trophic factors for regenerative purposes. MSCs are potentially applicable in regenerative medicine because of their unique features, including immunomodulatory properties, multipotential differentiation, and ease of culture expansion and isolation (Heo et al., 2016).

### 4.1. Hormone replacement therapy

Standard sex steroid replacement (sSSR) can be used to ameliorate symptoms in postmenopausal women. PSSR (physiological sex steroid replacement) is also used to regulate the levels of hormones in aberrant ovarian function. Recently, the application of analogous glandular hormone luteinizing hormone (LHRHA) was suggested to reduce the incidence of POF associated with therapies, such as chemotherapy, in clinical trials (Sheikhansaria et al., 2018). In case of estradiol-deficient young women, hormone therapy is in fact “replacement” therapy. On the other hand, in those with regular menopause, hormone therapy is indeed hormone “extension”. POI-developing young women are in need

**Table 3**
Treatment methods for premature ovarian failure.

| Treatment | Method | References |
|---|---|---|
| 1. Hormone replacement therapy | 1. Ovarian sex steroid replacement<br>2. Oral estradiol administration<br>3. Transdermal estrogen use<br>4. The use of analogous glandular hormone luteinizing hormone (LHRHA) | (Canonico et al., 2007; Canonico et al., 2008; Sheikhansaria et al., 2018; Mishell et al., 1971; Mohammed et al., 2015; Scarabin et al., 2003; Sidney et al., 2013) |
| 2. Melatonin supplementation | 1. Activates T-lymphocyte<br>2. Activates macrophage<br>3. Activates cells of spleen, lymph node, and bone marrow<br>4. Stimulates the production of cytokines, including interleukin (IL)-2, interferon (IFN)-γ, and IL-6 | (Acuña-Castroviejo et al., 2014; Ateşşahin et al., 2006; Bubenik & Konturek, 2011; Caballero et al., 2008; Coto-Montes et al., 2016; Cruz et al., 2014; Dair et al., 2008; Drazen et al., 2001; Galano et al., 2015; Galano et al., 2011; Garcia-Mauriño et al., 1997; Sheikhansaria et al., 2018; Hardeland et al., 2009; He et al., 2015; Hill et al., 2013; Kilic et al., 2013; Konakchieva et al., 1995; Liu et al., 2001; Parlakpinar et al., 2002; Pioli et al., 1993; Raghavendra et al., 2001; Reiter, 1998; Reiter et al., 1981; Reiter et al., 1980; Reiter et al., 2013a; Reiter et al., 2002a; Reiter et al., 2014a; Reiter et al., 2004; Reiter et al., 2013a; Reiter et al., 2014a; Sánchez-Barceló et al., 2010; Tan et al., 2013; Tan et al., 2007; Venegas et al., 2012; Wajs et al., 1995; Zhang & Zhang, 2014; Zhao et al., 2014) |
| 3. Dehydroepiandrosterone (DHEA) | 1. Use of dehydroepiandrosterone | (Elias et al., 1997; Gleicher & Barad, 2011; Narkwichean et al., 2013; Wierman et al., 2014; Yilmaz et al., 2013) |
| 4. Immunomodulation therapy | 1. Use of Corticosteroids<br>2. Use of monoclonal antibodies | (Austin et al., 1979; Sluss & Schneyer, 1992) |
| 5. Stem cell therapy | 1. ASCs<br>2. EnMSC<br>3. hUCMSCs<br>4. hBMMSCs | (Sheikhansaria et al., 2018; Lee et al., 2007; Mohamed et al., 2018) |

of long-term ovarian sex steroid replacement, even for decades in some cases. Currently existing therapies are capable of controlling symptoms and preventing diseases associated with estradiol deficiency. Normal ovarian function would ideally be mimicked by replacement. Developing artificial ovaries capable of continuously delivering parenteral infusion of appropriate hormone mixes to mimic endogenous ovarian production during a menstrual cycle would be of huge advantages. Also, an effective replacement is the equivalent dose of oral estradiol. Nonetheless, transvaginal and transdermal administration routes are capable of delivering the hormone directly into circulation, and avoiding first pass effect difficulties that are observed in the liver in case of oral administration of estrogen (Mishell et al., 1971; Scarabin et al., 2003). An enhanced risk of venous thromboembolism is observed when administrating estrogen orally, as compared to transdermal administration (Canonico et al., 2007; Canonico et al., 2008; Mohammed et al., 2015; Scarabin et al., 2003). Supra-physiologic amounts of synthetic progestin and estrogen are provided by steroidal hormone agents exploited as contraceptives, with the aim of suppressing ovulation in women with normal cycles. Therefore, steroid hormones more than needed are provided by such agents for replacing the rates of ovarian production. The association of contraceptive steroid hormones with enhanced risk of subarachnoid hemorrhage, stroke, thromboembolism, and worsening cardio metabolic risks, such as unfavorable lipid profiles and elevated blood pressure, has been demonstrated. More specifically, ~2-fold elevated risk of arterial thrombotic events and venous thromboembolism, such as stroke and acute myocardial infarction, has been shown to be associated with drosperinone-containing formulations (Sidney et al., 2013).

### 4.2. Melatonin supplementation

One of the most effective ways to treat POF is the application of melatonin. Melatonin restores menstruation and fertility, increases gonadotropin levels, and improves thyroid function. Melatonin is involved in folliculogenesis, since FSH, LH, estrogen, and androgen receptors are present in the pineal gland (Sheikhansaria et al., 2018). The production of melatonin in several tissues, such as reproductive tissues (e.g. placenta and ovary), was demonstrated lately (Reiter et al., 2013a; Reiter et al., 2014a,b; Tan et al., 2013; Venegas et al., 2012). As a lipophilic molecule, melatonin exerts antioxidant effects and acts as a free radical scavenger (Galano et al., 2015; Hardeland et al., 2009; Reiter, 1998; Reiter et al., 2002a,b; Tan et al., 2007; Zhang & Zhang, 2014). Also, its presence in biological fluids, including breast milk, bile, saliva, cerebrospinal fluid, amniotic fluid, and synovial fluid, has been demonstrated (Acuña-Castroviejo et al., 2014; Reiter et al., 2013b). Moreover, protective effects of exogenous melatonin in testes (Ateşşahin et al., 2006), uterus (Dair et al., 2008; He et al., 2015), ovaries (Cruz et al., 2014), lungs (Zhao et al., 2014), nervous system (Reiter, 1998; Reiter et al., 2004), kidneys (Kilic et al., 2013; Parlakpinar et al., 2002), and against oxidative stress (Galano et al., 2011) have been shown. As the production and levels of melatonin progressively decrease with age (Reiter et al., 1981; Reiter et al., 1980), it could significantly impact the quality of life of the elderly (Coto-Montes et al., 2016). In addition, decreased melatonin levels have been demonstrated in the progression of several diseases (Bubenik & Konturek, 2011; Hill et al., 2013). Melatonin supplementation has also been shown to be capable of improving the quality of life for patients and the elderly (Caballero et al., 2008; Sánchez-Barceló et al., 2010). Together, it could be concluded that melatonin, as a pleiotropic molecule, modulates cellular responses temporally and spatially. On top of that, melatonin has been suggested to have anti-cancer and anti-oxidant roles through the regulation of several cellular mechanisms, such as angiogenesis and cell proliferation. Melatonin is capable of activating cells of bone marrow and lymph node (Wajs et al., 1995), spleen cells (Drazen et al., 2001), macrophages (Pioli et al., 1993), and T-lymphocyte (Konakchieva et al., 1995; Pioli et al., 1993; Raghavendra et al., 2001). It is also capable of stimulating cytokine production (e.g. interleukin (IL)-2, interferon (IFN)-γ and IL-6) (Garcia-Mauriño et al., 1997; Liu et al., 2001).

#### 4.2.1. Melatonin as an antioxidant in ovarian follicles

As a potent antioxidant, melatonin is capable of preventing free radical damages induced by oxidative stress in the body, which could cause several diseases, such as reproductive diseases, rheumatoid disease, neurological diseases, and cancer (Agarwal et al., 2005; Pham-Huy et al., 2008; Ruder et al., 2008). In premenopausal women, early ovarian follicle loss could result in POF. Primordial follicles could undergo three stages throughout the reproductive life; including atresia, activation, and dormancy (Choi & Rajkovic, 2006; Lim & Choi, 2012). In order for the oocytes to undergo maturation, a state of quiescence in most primordial follicles is essential before activation. Rapid maturation of oocytes takes place once primordial follicles are recruited and activated. Significant oxidative stress is caused by such dynamic process. Oocyte quality was shown by Tamura et al to be decreased by oxidative stress (Tamura et al., 2008). A considerable amount of melatonin could be found in follicular fluids (Tamura et al., 2009). In ovarian fluid, melatonin is capable of protecting granulosa cells and oocytes through the amelioration of oxidative stress throughout ovulation, which is essential to natural maturation (Tamura et al., 2009; Tamura et al., 2008; Tamura et al., 2012). Supplementing melatonin could increase oocyte quality (Kim et al., 2013; Ma et al., 2017; Tamura et al., 2008). The expression of MT1 and MT2, as receptors of melatonin, takes place in the ovary (Chattoraj et al., 2009; Jablonska et al., 2014; Soares et al., 2003), which suggests scavenging roles for melatonin through its receptors. It was recently shown that melatonin treatment enables ameliorating POF through SIRT1 signaling-mediated reduction of oxidative stress damage (Ma et al., 2017). Two types of melatonin receptors exist in mammals, including MT1 and MT2, which are G protein-coupled receptors with significant roles in several cellular processes and responses to drugs. It was shown by Santoro and colleagues that melatonin is capable of activating p38 MAPK-dependent phosphorylation of p53, and that the signaling pathway is in fact mediated by the receptor of melatonin (Jang et al., 2017).

#### 4.2.2. Melatonin as a Fertoprotective agent in preserving fertility

Not only could the apoptosis of granulosa cells be activated in the ovary by anti-cancer drugs such as cisplatin and cyclophosphamide, but the over-activation of dormant primordial follicles could also be stimulated, leading to POF (Bines et al., 1996; Cruz et al., 2014; Di Giacomo et al., 2005; Jurisicova et al., 2006; S. Morgan et al., 2012; Perez et al., 2007; Waxman, 1983). POF could cause female infertility. Preserving the potential of fertility is of paramount importance for cancer female patients. Accordingly, discovering ferto-protective agents capable of protecting germ cells and increasing the efficiency of anti-cancer drugs throughout chemotherapy could be of great advantages. Melatonin could act as a potential adjuvant to chemotherapy, as its treatment enables reducing chemotherapy-associated side-effects through the removal of peroxyl radicals, hydrogen peroxide, and superoxide anion (Casado-Zapico et al., 2010; Mills et al., 2005; Pariente et al., 2016; Reiter et al., 2002a,b; Tan et al., 1998). During chemotherapy, melatonin treatment is capable of protecting germ cell depletion in gonads. Also, the administration of melatonin enables preventing cisplatin-induced testicular toxicity, and reduces sperm motility in male reproductive organ (Ateşşahin et al., 2006). In the ovary, it was shown by Chang and colleagues that cisplatin is capable of inducing follicle depletion through the over-activation of dormant primordial follicles (Chang et al., 2015). Protective effects of melatonin were also examined by this team on cisplatin-treated ovaries, where it was shown that combining cisplatin and melatonin treatment enables significant prevention of primordial follicle loss. Signals of melatonin are provided via two receptors in mammals, including MT1 and MT2 (Reppert et al., 1996). The presence of melatonin receptors in granulosa cells and oocytes of the ovary of several species, such as humans, has been

demonstrated (C. J. Lee et al., 2001; Niles et al., 1999; Soares et al., 2003; Wang et al., 2012; Woo et al., 2001). As G protein-coupled receptors, melatonin receptors possess significant parts in several processes of cells and responses to drugs (Overington et al., 2006). Accordingly, melatonin's protective effects in follicles are believed to be assisted by pathways dependent on G protein-coupled receptors (Jang et al., 2016). Importantly, melatonin could be produced by the ovaries (Tamura et al., 2009). High melatonin levels could be found in follicular fluid of growing follicles (Nakamura et al., 2003; Shi et al., 2009). Oocyte quality could be improved in vitro through melatonin treatment-induced oocyte maturation (Kim et al., 2013; Shi et al., 2009). Therefore, it could be deduced that endogenous melatonin is not adequate to prevent chemo-induced loss of primordial follicles, though it is essential for the development of oocytes. Detailed description of the molecular mechanisms controlling protective responses of melatonin against chemotherapy-induced ovarian damage require further research.

#### 4.2.3. Adverse effects of melatonin

Administrating high doses of melatonin could exert several adverse effects, including sleepiness, nausea, headache, and dizziness. Particularly, a 66 year-old man was administered with 24 mg/kg of melatonin, orally, aimed at relaxing and sleeping prior to operation, when lethargy and disorientation were observed due to overdose. However, the man fully recovered post operation (Meng et al., 2017).

### 4.3. Dehydroepiandrosterone (DHEA)

Ovarian follicular steroidogenesis possesses a significant part in POF development. DHEA concentrations decrease with age, so the use of dehydroepiandrosterone for patients with POF is a decent treatment option because of the increased chance of pregnancy and reduced risk of miscarriage (Qin et al., 2017).

As an endogenous androgen, DHEA is produced by adrenal glands and ovaries, and possesses several parts in ovarian folliculogenesis. POI women have reduced androstenedione levels, in comparison to normally-cycling women (Elias et al., 1997). Since DHEA is considered as a food supplement in the U.S., it is available over-the-counter. Available evidence do not support routine application of DHEA for women with POI (Wierman et al., 2014).

Nonetheless, few fertility centers have employed DHEA treatment for improving ovarian response in women with ovarian insufficiency (Gleicher & Barad, 2011; Narkwichean et al., 2013; Yilmaz et al., 2013). Markers of ovarian response, such as serum Inhibin B, AMH, and FSH levels, could be improved, and antral follicle counts could be increased in women with diminished ovarian reserve (occult ovarian insufficiency) through supplementing DHEA for 6 weeks (Yilmaz et al., 2013). A meta-analysis on the administration of DHEA to women with overt POI or occult ovarian insufficiency reported enhanced reproductive outcomes for the treatment (Gleicher & Barad, 2011). Overall, controversial data exist with regards to fertility-improving effects of DHEA in women with ovarian insufficiency, and minimal clinical benefits have been reported accordingly.

### 4.4. Immunomodulation therapy

One of the causes of POF is ovarian autoimmune damage. Under such circumstances, treatment is performed through immune modulation. Corticosteroids and monoclonal antibodies are used to treat immunosuppression in this method. Some autoantibodies detected in POF are autoantibodies against theca cells, hila cells, granulosa cells, and corpus luteum cells (Sluss & Schneyer, 1992). In the sera of some POF patients, the existence of antibodies against gonadotropin receptors, which are capable of blocking the LH receptor, has also been confirmed (Austin et al., 1979).

### 4.5. Stem cell therapy

Stem cell therapy has no side effects, as compared to hormone therapy and other treatments, which is why it has received so much attention today (H. J. Lee et al., 2007; Mohamed et al., 2018). Cells of germ line in the ovaries and testis differentiate into gametes, and after fertilization, these gametes eventually form embryo cells which are capable of transferring the genome from parents to offspring. Stem cells are undifferentiated cells that exist in the fetus and adults, and have received much attention in recent infertility treatments because of their regenerative nature and division capabilities (Pourakbari et al., 2020). Different types of stem cells are used to treat POF, and there are different protocols for separation, isolation, and culturing of stem cells (Sheikhansaria et al., 2018).

## 5. Mesenchymal stem cells

Due to their availability and poor immunogenicity, mesenchymal stem cells (MSCs) are potent candidates for regeneration-related purposes (Aghebati-Maleki et al., 2019; Jahanbani et al., 2020). Adipose tissue, cord blood, and bone are rich in these cells (Izadpanah et al., 2020). POF was treated through the application of rat umbilical cord-derived MSCs by Wang et al. in 2013. Moreover, enhanced levels of sex hormones, restored function of ovaries, and reduced apoptosis of cumulus cells were observed by their team. Also, they performed a comparison between RNA expression of the treated group and POF model and wild-type control group, the results of which indicated analogies between the wild-type group and the group treated with umbilical cord-derived MSCs. Lee et al. showed in 2017 that transplanting human umbilical cord MSCs in mice results in the reduction of FSH, enhancement of E2 and AMH, and improvement of follicle count and ovarian storage function. Moreover, they showed that hUCMSCs (human Umbilical Cord Mesenchymal Stem Cells) are capable of secreting hepatic growth factor (HGF), vascular endothelial growth factor (VEGF), and insulin-like growth factor-1 (IGF) cytokines. Transplanting bone marrow-derived MSCs of male rabbits elevates the levels of VEGF, reduces FSH, and enhances the amount of normally structured follicles in rabbits. Restored fertility and improved estrous cycle in mice were reported in a study by Lai et al. in 2015 on human endometrial MSCs (EnSCs) isolated from menstrual blood. Moreover, decreased rate of stem cell pool emptying (GSCS) was observed by transplanting EnSCs to mice with injured ovaries. Mohammad et al. transplanted human bone marrow-derived MSCs (BMSCs) into mice. Sun et al. reported the application of adipose-derived stem cells (ADMSCs) in mice who had chemotherapy-induced ovarian damage. With the aim of evaluating the function and amount of follicles, intravenous and bilateral injections were carried out. Increased follicle population, improved ovulation, and enhanced ovarian function were shown in this study. Enhanced count of normal follicles, levels of E2 in plasma, ovarian weight, and levels of ovarian markers were reported by Liu et al. following the transplantation of human menstrual blood stem cells (hMensSCssd) into mice. Moreover, decreased interstitial ovarian fibrosis and apoptosis of granulosa cells were shown by Wang et al. following the application of human menstrual-derived stem cells (MenSCs). Improved ovary microenvironment and increased follicle number were also reported (Sheikhansaria et al., 2018).

### 5.1. ADMSC

#### 5.1.1. The advantages of ADMSCs over other types of stem cells

ADMSCs possess exceptional features such as general availability, great ability to proliferate and differentiate, immunomodulatory capabilities, and low immunogenicity. Application, suitability, and approaches aimed at improving the regenerative capacity of ADMSCs are emphasized (Ntege et al., 2020).

*5.1.2. Source*

Adipose tissue could have several sources, including subcutaneous tissue (Salomone et al., 2013), visceral tissue (Potdar & Sutar, 2010), omentum (Huang et al., 2016), inguinal fat pads (Deng et al., 2016), and peritoneal fat (Tautenhahn et al., 2016). Extraction of ADMSCs from subcutaneous adipose tissue is more commonly performed than visceral adipose tissue. Both ADMSCs have similar markers, including CD105, CD13, SOX2, OCT4, LIF, and NANOG. The types of ADMSCS used include allogeneic ADMSCS and autologous ADMSCS. Isolation of the allogenic ones is performed from a cell donor except for the cell recipient. On the other hand, the isolation of autologous ADMSCS is performed from the cell recipient. Autologous ADMSCs are used as a perfect source because they show low immune rejection (J. Gimble & Guilak, 2003).

*5.1.3. ADMSC phenotype*

Studies on the superficial phenotype of ADMSCs isolated from humans and other species have identified cultures related to the surface antigens of these cells. ADMSCs adhesion molecules include CD9, CD29, CD49, CD54, CD105, and CD166. ADMSCs also uses CD44 and CD71 receptor molecules. Markers such as CD34, ABCG2 CD29, CD44, CD73, CD90, and CD166 can also be used to identify them (J. M. Gimble et al., 2007). Also, markers which are not expressed include CD11b (αb integrin), CD18 (β2 integrin), CD50 (ICAM-3), CD56 (NCAM), CD62 (E-selectin), CD104 (α4 integrin),CD31,CD45(Bonab et al., 2012), and CD16 (Fc receptor) (Table 4) (J. M. Gimble et al., 2007).

*5.1.4. Impacts of ADMSCs on the immune system*

*5.1.4.1. Regulation of the immune system.* HMSCs, due to the low number of MHC1, and the absence of markers including CD80, CD86, and CD40, are not able to induce the proliferation of allogeneic and genogenic lymphocytes, and are therefore very suitable for therapeutic applications. They essentially express low levels of MHC-1 molecules and do not express MHC class II molecules, and yet act as antigen-presenting cell and activate immune responses under proper circumstances. Some studies have identified MSC cells as antigen-supplying cells, and have reported the presence of both MHC I and MHC II. Therefore, MSCs can elicit T cell responses (Herrero & Pérez-Simón, 2010).

*5.1.4.2. Roles in innate immunity.* Mesenchymal stem cells (MSCS) modulate immune functions through interactions with the immune system and anti-inflammatory effects. Therefore, they possess significant parts in the treatment of inflammatory diseases. MSCS exert a variety of therapeutic effects in several diseases through the secretion of biologically active molecules, including cytokines. MSCs stimulate macrophages that have the ability to regenerate tissues, mediate the immune system, and regulate the proliferation of cells depending on the media. Macrophages with important roles in immunity are typically divided into two subgroups, namely M1 and M2. MSCSs lead to polarization towards the M2 subtype, which expresses CD206 by producing immunosuppressive and anti-inflammatory cytokines, including interleukin IL-10. M2 macrophages have anti-inflammatory activity and regulate the immune system and tissue regeneration. For one, they possess an essential part in healing of wounds. An illustrative example of MSCs includes human umbilical cord-derived MSCS. In a study by Lee et al., these UCMSCs led to the differentiation of macrophages towards M2 phenotype. Nonetheless, in the case of the effect of adipose-derived MSCs (ADMSCS) on macrophages, little information is available. Together, to use ADMSCS in treatment strategies, acquiring a deeper comprehension of the interaction between macrophages and ADMSCs is vital. Nonetheless, we herein assumed that the interaction between ADMSCs and macrophages polarizes M2. One of the effective mediators in the transfer of proteins and other cellular factors, such as RNA, DNA, and lipids, from MSCs to other cells are exosomes. A growing amount of evidence has shown that MSCs are cell-dependent, though they could affect the activation, flexibility and function of macrophages independent of contact. Today, attempts are being made to produce anti-inflammatory M2 macrophages via exosomes for cell-free stem cell-based treatment of inflammatory diseases associated with the production of ADMSC-derived exosomes in vitro (Heo et al., 2019).

*5.1.4.3. Adaptive immunity*

*5.1.4.3.1. Roles of ADMSCs in adaptive immunity.* Through co-culturing PBMCs (Peripheral blood mononuclear cells) with hADMSCs (human adipose-derived mesenchymal stem cells), 17β-estradiol, and their combination, enhanced levels of CD4+ CD25+ Foxp3+ Tregs were observed. The immunomodulation of Tregs could be promoted by the synergistic effects of 17β-estradiol and hADMSCs. In PBMC populations, 17β-estradiol could considerably enhance the proportion of CD4+ CD25+ Foxp3+ Tregs. On the other hand, through upregulating Foxp3 expression levels, hADMSCs are capable of increasing the proportion of CD4+ CD25+ Foxp3+ Tregs. Thus, the use of ADMSC in POI patients can lead to an increase in Tregs, as well as an increase in regularization in the body (Song et al., 2018). ADMSC can also be mediated through cytokines, such as IL -1a, -6, -10, TLR2, TLR4, TNF-a, TGF-B, FGF-b (Mazini et al., 2019). VEGF leads to angiogenesis, reduces apoptosis and fibrosis, and increases anti-inflammatory processes.

Humoral immunity is another significant arm of the immune system, for which B cells are responsible. These cells produce natural antibodies, present antigens, express MHC class II molecules, are responsible for the selection and survival of T cells, and regulate the complement and cell-mediated immunity.

Effector antibodies act systemically, involving T cell-B cell interactions and presentation of antigen to naïve T cell, which leads to the generation of high affinity antibodies. Regulation of the responses of T cells and the production of high affinity antibodies via Treg and Breg are local (Platt & Cascalho, 2019).

*5.1.4.3.2. Roles of innate and adaptive immunity in ADMSC transplantation.* Among transplantation issues when using stem cells is the response of the immune system to this connective tissue, which could potentially result in graft versus host disease (GVHD). The disease develops when T cells of the donor are activated and respond to HLA (Human Leukocyte Antigen) differences on the tissue of host (Ferrara et al., 2009). Responses of these cells are dependent on the differences between the recipient and donor in regards to HLA (Ferrara et al., 2009). Although CD8 + T cells respond to variations in MHC class I molecules (HLAA, -B, and -C), MHC class II molecules (HLA-DR, -DQ, and –DP) are responded to by CD4 + T cells. Exacerbation of T cell-induced inflammation is performed through the synergistic work of both adaptive and innate immune cells. To lyse their target cells, cellular mediators, including natural killer (NK) cells and cytotoxic T lymphocytes (CTLs), use perforin/granzyme and Fas/Fas ligand (FasL) pathways (Ghimire et al., 2017). Moreover, through the synergistic work of CTLs with

**Table 4**
Markers of ADSC.

| References | Surface-Negative Antigens | Surface-Positive Antigens | Antigen Category |
|---|---|---|---|
| (Gimble et al., 2007) | CD11b (αb integrin), CD18 (β2 integrin), CD50 (ICAM-3), CD56 (NCAM), CD62 (E-selectin), CD104 (α4 integrin),), CD 31, CD45 | CD9 (tetraspan), CD29 (β1 integrin), CD49 days (α4 integrin), CD54 (ICAM-1), CD105 (endoglin), CD166 (ALCAM) | Adhesion molecules |
| (Bonab et al., 2012) | CD16 (Fc receptor) | CD44 (hyaluronate), CD71 (transferrin) | Receptor molecules |
| | | CD34, ABCG2 | Stem cell |
| | | CD29, CD44, CD73, CD90, CD166See | Stromal |

inflammatory cytokines, additional tissue injury and potential dysfunction of target organ would result (Ferrara et al., 2009). Additionally, LPS and similar microbial secretions that are released throughout conditioning, could leak through injured skin or intestinal mucosa, stimulating mononuclear cells (monocytes/macrophages) for secreting inflammatory cytokines which results in an increase in the cytokine storm (Ferrara et al., 2009). ADMSCs modulate cytokine storm and are thus regarded as an effective treatment against several diseases, including infertility.

### 5.1.5. Methods

*5.1.5.1. Mouse model.* 50 mg/kg of cyclophosphamide (CTX) was intraperitoneally injected into female mice for 15 successive days, following which the transplantation of ADMSCs was performed either via intravenous injection or directly into bilateral ovaries. Next, excision of the ovaries was performed either 1 week or 1 month post treatment. Then, counting and categorization of follicles was performed, and ovarian histologic sections were stained for TUNEL. Evaluation of the ovarian function took place through monitoring ovulation. Inner mechanisms of injury and repair were assessed by real-time polymerase chain reaction, microarray analyses, ADMSC tracking (Fig. 2) (Sun et al., 2013).

*5.1.5.2. Human model.* It was demonstrated in a pre-clinical mouse model of chemotherapy-induced POF that the transplantation of stem cells rescues ovarian function. Nonetheless, it is challenging to maintain the survival of these transplanted cells in human ovarian tissues when the purpose involves enabling patients with POF regain the function of ovaries and achieve effective pregnancy. Cell transplantation in human models was examined in a study aimed at exploring the potential of ADMSC transplantation for POF women who had undergone autologous fat transplantation. Patient serums were kept for laboratory analysis prior to surgery. Through abdominal fat abortion, 100 ml of fat was harvested from the abdomen of POF patients. Also, using autologous serum, ADMSCs were isolated and cultured *in vitro*. Flow cytometry revealed ADMSC, CD29, and CD44 biomarkers in ADMSC cultures. When cells reached a density of 5-10 × 106, ADMSCs were transplanted into bilateral ovaries directly. Examinations of patients' clinical conditions were performed 1, 2, 4, and 8 weeks post transplantation. Evaluation of ovarian function was performed through sexual hormone levels and follicle diameter. Number of follicles was counted, and data of radiology were kept for further analyses. To help patients conceive and ensure high pregnancy rates, hormone replacement treatment and intercourse guided by physician might be advantageous. Separation of fat was performed from POF patients who underwent autologous fat grafting operation. Next, purification of ADMSCs was performed, which were then injected into both ovaries of patients.

### 5.1.6. Adverse effects could be anticipated with stem cell therapy

Following bone marrow transplant, acute and chronic complications might emerge. Factors affecting the incidence of such complications could include the type and intensity of the preparative regimen, the source of stem cell transplant, baseline performance status, and patient's age. In the first 90 days, acute complications could occur, including Aspergillus, Candida, CMV, HSV, gram-positive/gram-negative infections, acute graft versus host disease, mucositis, sinusoidal obstruction syndrome (SOS), thrombocytopenia, anemia, and myelosuppression with neutropenia. On the other hand, chronic complications could involve chronic GVHD, infection with encapsulated bacteria and VZV. As immunosuppression is observed post hematopoietic stem cell transplant, prophylaxis is warranted. Also, for each of the above, prophylaxis should be performed. Table 5 lists the drugs required for each prophylaxis (Khaddour et al., 2021).

### 5.1.7. Patients who can use this method (Effects of ADMSC Therapy in Women with POF)

Patients who have decided to have children but have been diagnosed with ovarian failure by a physician and do not respond well to medication, are the best candidates for stem cell therapy. The age range of patients should be between 20 and 39 years. It should be noted that patients with chromosomal abnormalities, congenital ovarian

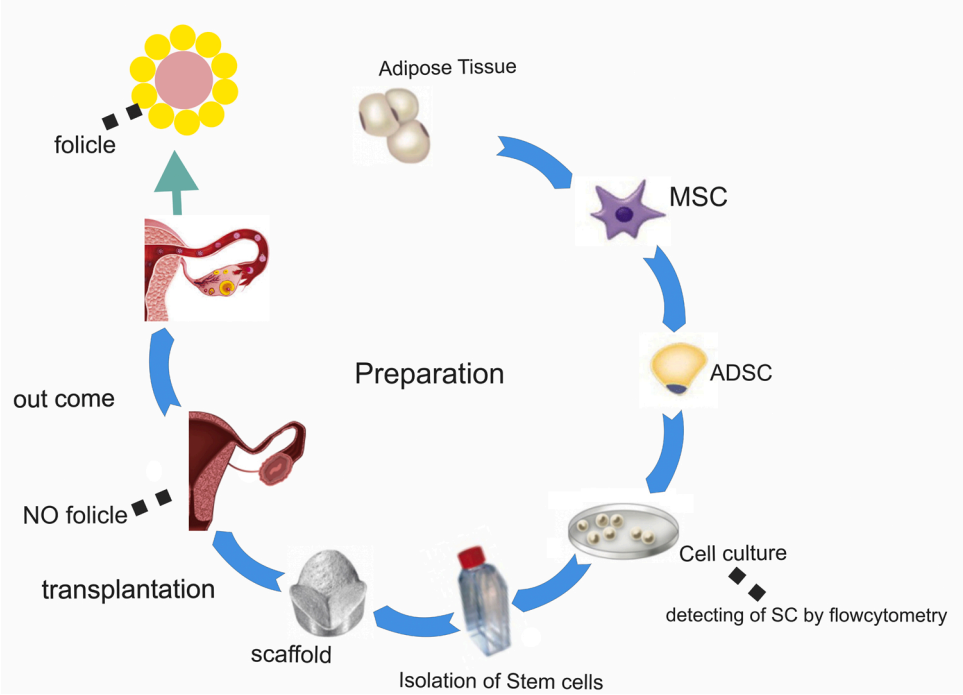


**Fig. 2. Using ADMSCs for the treatment of premature ovarian failure.** Through the injection of ADMSCs to ovaries of POF mice, they will be able to produce proper eggs that lead to fertility.
POF, Premature ovarian failure. MSC, Mesenchymal Stem Cells. ADMSCs, Adipose stem cells

**Table 5**
Complications after bone marrow transplantation and Prophylaxis.

| Complications | Prophylaxis | References |
|---|---|---|
| Neutropenia<br>Fungal infections<br>HSV and VZV<br>CMV | Levofloxacin<br>Fluconazole<br>Acyclovir<br>Ganciclovir | (Khaddour et al., 2021) |
| Complications | Prophylaxis | References |
| Neutropenia<br>Fungal infections<br>HSV and VZV<br>CMV | Levofloxacin<br>Fluconazole<br>Acyclovir<br>Ganciclovir | (Khaddour et al., 2021) |

HSV(Herpes simplex virus), VZV(Varicella zoster virus), CMV (Cytomegalovirus).

abnormalities, severe endometriosis, thyroid dysfunction, and contra-indications cannot use this method.

## 6. Conclusion

Ovarian failure causes complications that can lead to infertility, though they have not been determined precisely yet and require further study. One of the most effective treatments in this regard is the application of stem cells, which have received a lot of attention due to possessing unique self-renewal and proliferative features. Also, treatment with stem cells does not have the side effects of other treatments, such as hormone therapy. Therefore, it is a valuable treatment option. Among stem cells, adipose-derived stem cells (ADMSCs) are easier to obtain and are more abundant than other stem cells. They also increase Tregs in the body. Overall, stem cells are great candidates for the treatment of POF, though more studies are required to be implemented in this regard in the future.

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## Declaration of Competing Interest

The authors report no declarations of interest.

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