

Special Article - Premature Ovarian Failure

Premature Ovarian Failure Treatments: A Review Study with Focus on Stem Cell Therapy as Pluripotent Source for Repairment in Regenerative Medicine

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***Corresponding author:** Shadan Navid, Department of Anatomy, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran**Received:** June 12, 2018; **Accepted:** July 18, 2018;**Published:** July 25, 2018**Abstract**

Infertility is a disorder that occurs in 10-15% of young couples. Premature Ovarian Failure (POF) is a disease that causes amenorrhea, hypergonadotropic and hypostenogenism and ultimately infertility in women less than 40 years of age, with a prevalence of 1%. POF can be due to a variety of causes such as X chromosome abnormalities, genetics, autoimmune, metabolic, infectious and anti-cancer treatments (chemotherapy and radiotherapy) but most of them remain idiopathic. Today, with an increase in the incidence of cancer and its subsequent control methods, such as chemotherapy and radiotherapy, the risk of developing POF is increasing. The toxicity of the chemotherapy substance results in ovarian follicular depletion and, consequently, menopause and infertility. Since ovarian reserves are limited and cannot increase, preserving the storage of primordial follicles and restoring ovarian function during cancer is essential. Because the symptoms are similar to the physiology of menopause, people with POF are at the risk of cardiovascular disease and osteoporosis. Various methods have been proposed for maintaining fertility in women with POF such as Hormone Replacement Therapy (HRT) and suggested to prevent complications from the disease. One of the methods currently under study is the multi potent stem cells transplantation that has therapeutic potential and derived from various sources such as bone marrow, adipose tissue, amniotic fluid and menstrual blood that all of them have been shown the potential for regeneration and recovery of ovarian function in POF model mice.

Keywords: Premature ovarian failure; Infertility treatment; Stem cell therapy; Ovarian**Background**

Premature Ovarian Failure (POF) is a disease with symptoms such as primary and secondary amenorrhea, hypergonadotropics, and hyperproteinemia before the age of 40 [1-3].

Approximately 1% of women under the age of 40, 0.1% of women under the age of 30, 8-10% of women with primary amenorrhea and 4% -18% of women with secondary amenorrhea have been diagnosed with POF disease [4-6].

At embryonic time, the germ cells appear in the urogenital ridge and then migrate to the primary ovary. The number of these cells in both ovaries is 7 million potential oocytes. Before birth, as part of the quality control mechanism, two-thirds of these are eliminated during the apoptosis process. After birth until the age of 40, the eggs gradually decrease from one million to 10,000 in per ovary. About the age of 40 years, the degradation process is increased, and at the age of 50, a few oocytes are remained [7]. Menopause of women occurs at an average age of 50.7 years [8]. Therefore, since the process of atresia of the follicles is persistent, women with fewer follicular reserves at their onset of life or faster apoptosis in their follicles are at a higher risk for POF disease [9].

Symptoms

Symptoms of POF patients such as menopausal physiology

include infertility with thirst, heat dissipation, flushing, anxiety, depression, fatigue. Hormonal defects may also cause neurological, metabolic or cardiovascular events, and may increase the risk of osteoporosis [10].

One of the symptoms of this disease is the stopping of follicular ovarian activity, the concentration of Follicle Stimulating Hormone (FSH) is more than 20 to 40 mIU / Ml [11].

Follicle-Stimulating Hormone (FSH) produced by the pituitary, stimulates the growth of granulosa cells in follicles, as a feedback response, the ovaries secrete estradiol, which inhibits the secretion of FSH from the pituitary to maintain FSH level less than 10 mIU/ml. In POF patients, the ovaries are evacuated from the follicles, there will be no feedback inhibition and the FSH level will exceed 10 mIU/ml [12] which leads to further depletion of ovarian reserves.

In 2006, Anderson et al. demonstrated a decrease in Anti-Müllerian hormone (AMH) concentration during chemotherapy in patients with breast cancer. AMH is secreted by granulosa cells of primary follicles on initiation of growth until the early antral stages, in this case, either the follicles overcomes AMH that are selected become atretic [13]. The low levels of inhibit β can cause follicular evacuation too [10].

In some people with POF, laparoscopy, show the lack of developing

follicles and the ovarian biopsy show a network of connective tissue with diffuse fibroblasts in the ovary. Previous studies have reported the atrophy of the uterus and vagina in patients with POF due to the lack of estrogen stimulants from inactive ovaries [14].

Etiology

POF has several causes. Including Iatrogenic (surgery, chemotherapy, radiations), autoimmune, Infections (herpes zoster, cytomegalovirus), Chromosome X defects, monogenic defects (syndromic and isolated defects), Idiopathic. Syndromic defects can be noted Congenital disorders of glycosylation, Galactosemia, Blepharophimosis-ptosis-epicanthus in versus syndrome (BPES) and Pseudo hypo parathyroid's (PHP) and isolated defects including; FSHR, LHR, FOXL2 and BMP15 mutations [10].

The cause of the POF is unknown in many cases. But the cause of POF can be divided into two genetic and environmental mechanisms [7].

The onset of the formation of primordial follicles and their differentiation into primary follicles are dependent on the expression of specific oocyte genes, which are adjusted by specific transcription factors. The screening of transcription factors folliculogenesis in various POF populations has led to the identification of several scientific mutations in the NR5A1, NOBOX, FIGLA and FOXL2 genes [15].

Any defect in the sex chromosome X can lead to POF. One of the most common forms of X chromosome defect is Turner syndrome. The patients have only one X chromosome in the form of monosomy 45XO in their genome, and the other chromosome is missing during chromosomal non-detachment. These patients have no germ cells at the beginning of their life and there is gonadal dysgenesis. A study of partial deletions of X chromosome suggests that at least there are 3 critical locus to ovarian development: Xp22, Xq26-Xq28, and Xq13-22. POF is seen in rare hereditary diseases such as galactosemia, fragile X syndrome and blepharophimosis. In each case, the mechanism of ovarian damage is unknown [7].

Previous studies have shown that mutation in the β subunit is seen in FSH in primary amenorrhea. The patient will have secondary sexual characteristics and poor infertility. Since FSH does not have the ability to bind to its receptor, follicular growth does not occur, and estrogen does not secrete, resulting in hypergonadotropic. The mutation in the LH receptor gene also causes the POF. Normally, LH stimulates theca cells and produces androstenedione, and then is converted to the estradiol by the aromatase enzyme in granulosa cells. These patients have amenorrhea and normal secondary sexual characteristics and a mild increase in FSH. Ovarian biopsy shows primordial, early antral and antral follicles, but there is no pre-ovulation follicle, corpus luteum and corpus albicans [16].

One of the causes of POF is lack of cholesterol in the arteries, and patients with steroid hormone synthesis disorders and rarely reaches puberty. The 17 α -hydroxylase deficiency reduces both adrenal and gonadal steroidogenesis, and these patients have high blood pressure and ovarian failure [17].

The autoimmune mechanism comprises 30% of POF pathogenesis. Many antibodies have been investigated as serum

ovarian autoimmune markers, which contain antibodies against steroidogenic enzymes, gonadotropins and their receptors, corpus luteum, zonapellucida and oocytes [8].

Changes in the immune system may produce POF by destroying follicles or normal ovarian dysfunction. There is some evidence suggesting the potential role of the immune system in causing POF destruction, including association with other autoimmune diseases, detection of anti-ovarian antibodies, histopathological evidence of oophoritis and reversibility after immunotherapy. There are different autoimmune diseases associated with POF, include diabetes type1, Addison's disease, polyendocrine autoimmunity, hypothyroidism, pernicious anemia, vitiligo, myasthenia gravis, Crohn disease, non-organ-specific systemic lupus erythematosus (SLE) and rheumatoid arthritis [18].

POF is also associated with a variety of endocrine (thyroid, adrenal, hypo parathyroid, diabetes mellitus, and hypophysitis) and non-endocrine (chronic candidiasis, idiopathic thrombocytopenic purpura, vitiligo, alopecia, autoimmune hemolytic anemia, pernicious anemia, systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease, Sjögren's syndrome, myasthenia gravis, primary biliary cirrhosis, and chronic active hepatitis autoimmune disorders [19,20].

One of the risk factors for young women with malignant tumor is chemotherapy and radiotherapy. The radio sensitivity of the oocyte is 2 Gray and the higher dose of 6 Gray cause premature ovarian failure in people over 40 years of age. The effect of radiotherapy is dependent on dose and age, and radiation field. Radiation outside the scope of the ovary, in young women requiring pelvic irradiation, helps in preserving their ovarian function [21].

Chemotherapy agents damage granulosa and theca cells (which produce steroids) and oocytes, resulting in premature ovarian failure and infertility. The risk of POF after chemotherapy in older women with lower primordial follicles pools is higher than in younger women [22] increased plasma concentrations of FSH in women treated with alkylating agents for acute lymphoblastic leukemia, brain tumors and Hodgkin's disease has been accessed [23].

Since these women are suffering from premature ovarian failure after chemotherapy and radiation, it is clear that chemotherapy is one of the most common causes of POF in the future [24].

Pelvic surgery can damage the ovaries via the affecting on the blood supply and inflammation. Uterine artery embolization also has a potential to result in POF [25].

Treatment

Since young women with POF are at risk for osteoporosis, cardiovascular disease, and depression, Hormone replacement therapy (HRT) should be used for these women until the age of menopause. Different compounds of HRT can be used by the oral, vaginal or subcutaneous ways. Exogenous estrogens have beneficial effects on cardiovascular conditions and bone density and increase levels of cardio protective high-density lipoproteins (HDL) and decrease total cholesterol and low-density lipoprotein levels (LDL). alongside HRT, general actions like physical activity, a calcium-rich diet, vitamin D supplementation and avoidance of smoking and

alcohol can be effective [3].

Over the past years, researchers have been able to create appropriate models of POF in rats and mice for further studies on premature ovarian failure using various chemotherapy agents.

There are several ways to preserve fertility in people before chemotherapy and radiation therapy. One of these methods is the ovarian hormone stimulation followed by the inoculation of the resulting oocytes and eventually freezing of the embryos. In the follicular phase of the menstrual cycle, only one follicle can grow to a pre-ovulation stage and then release its oocyte for fertilization, while other follicles develop atresia. However, gonadotropin stimulating protocols are released several oocytes. These hormones are usually associated with suppressing the function of the pituitary gland, which may have long-lasting effects on the body. Excessive excitation also occurs in two percent of the ovarian stimulation protocols that may even lead to death [26].

Another method is ovarian tissue freezing and its transplantation after treatment, due to the high probability of remobilization tumor cells, has side high risks [27].

In recent years, there has been much research on the treatment of premature ovarian failure with mesenchymal stem cell transplantation. The stem cells are cells that have excellent reproductive capacity in the medium and have the unique ability to produce the same cells, in addition to being able to differentiate into many specialized cells. These cells usually form a small percentage of the total cells of a member. These cells will remain indistinguishable until they have received the specific signal for differentiation [28].

Based on the power of differentiation and reversibility, stem cells can be divided into totipotent, pluripotent, multipotent, and unipotent types [29].

Multiple-stem cells can only produce derivatives of a specific germline. These cells are also called adult stem cells, which appear in the embryo and after birth [30]. Adult stem cells are undifferentiated cells that are found among differentiated cells of the tissues and organs of the body and can reproduce and transform into differentiated cells of the same tissue. Many recent studies have shown that these cells also have the ability to convert to other cells in other tissues. Consequently, many studies have been done on the use of adult stem cells for cell therapy [31].

Mesenchymal stem cells are a category of multipotent stem cells that were first described in bone marrow about 40 years ago [32]. In addition to bone marrow, fibroblastic-like stem cells have been found in other adult tissues, including blood circulation, cord blood, placenta, amniotic fluid, heart, skeletal muscle, adipose tissue, synovial tissue and pancreas [33].

In 2007, Lee et al. reported the effects of bone marrow stem cell transplantation on the production of immature oocytes which are able to rescue long-term fertility in POF model mice caused by chemotherapy [34].

In 2008, Xfu et al. stated that bone marrow stem cell transplantation in the ovary of the POF model induced by cyclophosphamide chemotherapy improves ovarian function by secreting cytokines such as VEGF, HGF, IGF-1 and inhibition of granulosa cell apoptosis by

adjusting upstream BCL2 and increasing its expression [35].

In 2010, Tan, Shun-Jen et al. examined the histopathologic evidence of busulfan effect on gonadal dysfunction and investigated the protective effect of triptorelin (an analog of GnRH) on busulfan-induced POF, which based on their findings, showed an increase in the number of primitive and primary follicles, which itself showed a positive protective effect on the analog of GnRH [36].

In 2010, Ghadami et al. treated POF with intra-ovarian injection of adenoviral, which expresses FSHR for the restore of folliculogenesis in female FORKO mice [37].

In 2010, Teliu et al. showed that after CD44 + / CD105 + human amniotic fluid cells (HuAFCs) were transferred to the ovary tissue of the POF mouse, these stem cells exhibited natural cell cycle and self-renewal over a long time in ovarian tissue. According to the characteristics of mesenchymal stem cells and long-term survival conferred by CD44 + / CD105 + HuAFCs. They found a novel way to treat POF using CD44 + / CD105 + HuAFCs *in vivo*. The results suggest the potential use of stem cells for treatment of POF [38].

In 2013, Dori et al. examined the use of mouse engineered ESCs (endometrial stem cells) that express the discosoma SP red fluorescence receptor (DsRed), under the regular control of the Fork head box L2 (Foxl2) gene promoter for ovarian granulosa cells, it is used to track granulosa cellular characteristics, function, and fate *in vitro* and *in vivo*, and showed that Foxl2 expression of somatic ovarian cells, which differentiate in ESCs *in vitro*, actively interact with germ cells *in vitro*, synthesize steroids, respond to FSH, and participate in folliculogenesis *in vivo* [39].

In 2013, Sun et al. investigated the effect of ADSCs-derived stem cells via intra-ovarian or intravenous injection of POF-induced cyclophosphamide CTX and found that ovarian function of the mouse after ADSC transplant was improved. In this study, the follicle population in the differentiation and ovulation stage after treatment significantly was increased and apoptosis was decreased [40]. Adipose-derived stem cells (ADSCs) are a type of mature stem cell that is isolated from fat tissue. The cultivated ADSCs can be differentiated into various cell types, including osteoblasts, cartilage, fat, myositis, vascular endothelial cells and neural cells [41].

In 2014, Liu et al. transplanted menstrual stem cells in the mouse ovaries model of POF and found that these stem cells survived for at least two weeks in the mouse ovary and the ovaries carrying these transplanted cells have higher expression of the specific ovarian markers, including AMH, inhibin α , FSHR and Ki67 proliferative marker. Also, ovarian weight, production of estrogen hormone and normal follicles were significantly increased compared to control group [42].

In 2015, Dongme et al. injected intravenously endometrial mesenchymal stem cells of MSCs into infertile mice induced by chemotherapy and measured their restorative effects on ovarian function and showed that EnSC increased the weight of the mouse and improved the estrus cycle and reduced the evacuation of germline (GSCs) stem cells [43].

In 2016, Yuan Pan et al. reviewed the biological and biomechanical properties of the rat model of Chemotherapy-

Induced Ovarian Dysfunction (CIOD) after transplantation with Umbilical Mesenchymal Stem Cells (UCMSC) and human amniotic mesenchymal stem cells (h-AMSCs) and reported improvement in ovarian function after transplantation of both cells [44].

In 2016, Dan Song et al. reported that after human Umbilical Cord Mesenchymal Stem Cell transplantation (UCMSC), hormone secretion and folliculogenesis in POF rats were improved and ovarian cells apoptosis were decreased. UCMSCs in the ovaries were also detected by fluorescence in situ hybridization (FISH). The results showed that transplanted human UCMSCs can be located in ovarian tissue and survive for a relatively long time without obvious proliferation [45].

In 2016, Guan-Yu Xiao et al. demonstrated that exosomes produced by the AFSC (stem cells from amniotic fluid) through micro-RNA's (where both miR-146a and miR-10a very rich) and their potential target genes (involved in apoptosis), show anti-apoptotic effects on damaged granulosa cells 72 hours after induction of POF on mice [46].

In 2016, Elfayomy et al. examined the transplantation of human umbilical cord blood mesenchymal stem cells on paclitaxel-induced ovarian failure. According to their findings; they reported a decrease in FSH and E2 and an increase in the number of antral follicles for 4 weeks after transplantations well as an increase in the expression of CK8/18, TGFB, and PCNA. These molecules are effective in regulating folliculogenesis and inhibition of CASP3-induced apoptosis. According to their findings, these cells are able to repair of the damaged ovarian niche by activating of CK8/18, TGFB and PCNA and restricting of CASP3 [47].

In 2017, Che Ding et al. compared the therapeutic potential of hAMSCs (human amniotic mesenchymal stem cells) and hAECs (human amniotic epithelial cells) in mice model of premature ovarian failure, and then reported that hAMSCs showed better therapeutic activities on ovarian function in the high dosage group and increased proliferation of ovarian granulosa cells in POF patients. The results also showed that the biological properties of hAMSCs are superior to hAECs, but not to express immune molecules [48].

In 2017, J Li et al. stated that after the transplantation of hUCMSCs (human umbilical cord stem cells) in the ovary of the rats model of POF, estradiol (E2) and AMH increased while FSH is reduced; the ovarian structure was improved and The number of follicles increased and the expression of growth factors such as HGF, VEGF, and IGF-1 significantly increases in the ovary. RT-PCR and Western blot analysis showed that hUCMSC has the ability to secrete HGF, VEGF, and IGF-1 cytokines and thereby improve ovarian function [49].

In 2017, Zhen Wang et al. investigated the effect of intravenous injection of menstrual blood stem cells in cisplatin-induced POF mice and they showed that the Men SCs and CM (conditioned media) extracted from them, through the secretion of FGF2, had a protective effect and an anti-apoptotic role on damaged ovaries. It also reduces fibrosis in the ovarian interstitium and increases the number of follicles, thereby returning the level of hormones to normal [50].

Conclusion

POF is a complex disease with multiple causes. The similar

pathogenic mechanism is the decrease in follicular reserve of ovaries and the loss of ovarian function and subsequently amenorrhea. Today, researchers have been able to carry out extensive research using multipotent stem cell transplantation in chemotherapy and radiation therapy-induced POF animal models. Recent studies indicate the ability of these cells in regeneration of damaged and evacuated tissues in the POF ovaries suggesting hope for fertility and restore of ovarian function in women undergoing chemotherapy.

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