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Review

Current approaches for the treatment of premature ovarian failure with stem cell therapy

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ABSTRACT

One of the common disorders found in women is premature ovarian failure (POF). Recently some studies have explained premature ovarian insufficiency (POI). The causes of it are unknown although various types of study have been done. The most common causes such as genetic and autoimmune conditions can have a role in POF and can lead to infertility. Some characterization of POF are hypo-oestrogenism (estrogen deficiency), increased gonadotropin level and most importantly amenorrhea. The main purpose of this review is to describe the cause and treatment of POF, especially stem cell therapy proposed in previous studies. Stem cells have self-renewal and regeneration potential, hence they can be very effective in the treatment of ovarian failure and consequently infertility. There are several kinds of stem cells such as, mesenchymal stem cells (MSCs), stem cells from extra-embryonic tissues, induced pluripotent stem cells (iPSCs), and ovarian stem cells that are used in POF stem cell therapy as observed in previous studies. This article reviews the latest studies on POF to summarize current understanding and future directions.

1. Introduction

Premature ovarian failure or Primary ovarian insufficiency and in other words, premature menopause, is a mysterious and complicated disease. The prevalence of POF is 1 in 250 women under the age of 35 years and 1 in 100 women under the age of 40 years [1–3]. The features of POF are hypooestrogenism, hypergonadotropinism, amenorrhea that contribute to female infertility and premenopausal syndrome [4]. In addition, POF have negative consequences such as increased risk of cardiovascular diseases, sexual dysfunction and osteoporosis [5]. Ovarian follicles contain 3 types of cell, oocyte, granulosa cell and theca cell. Granulosa and theca cells have receptor for follicle-stimulating hormone (FSH) and luteinizing hormone (LH), respectively that are essential for the growth and development of the follicles. In this cell, principal explained gene have a role in POF. Folliculogenesis is an organized and regulated process. In this process, primordial follicles turn into primary follicles then preantral and finally antral follicles and after this stage ovulation occurs (Fig. 1) [6]. This normal process is altered during POF. For premature ovarian failure, two histopathological types have been reported. In type 1, the ovarian follicles deplete completely while in type 2, there are follicular structures that are preserved in the ovary [7]. Probably, the most important mechanism in POF are follicle dysfunction and follicle depletion [8]. Although the cause of POF is not fully known, genetic, endocrine, paracrine, mitochondrial dysfunction and metabolic factors can affect the quality of the follicular pool and oocytes [9]. The routine diagnosis for this disease is module of serum FSH [10,11]. The age for natural menopause is about 50 years and this indicates the regular setting and conserved trait but due to environmental factors, the age of menarche is down over the past century [12]. POF has two pattern of inheritance, sporadic and familial. About 4–31% of POF are familial [13,14]; therefore, X-chromosome abnormality has the most important role in this disease [15].

2. Etiology of premature ovarian failure

2.1. Role of genetics in premature ovarian failure (POF)

Studies have shown that gene defects such as X and autosomes

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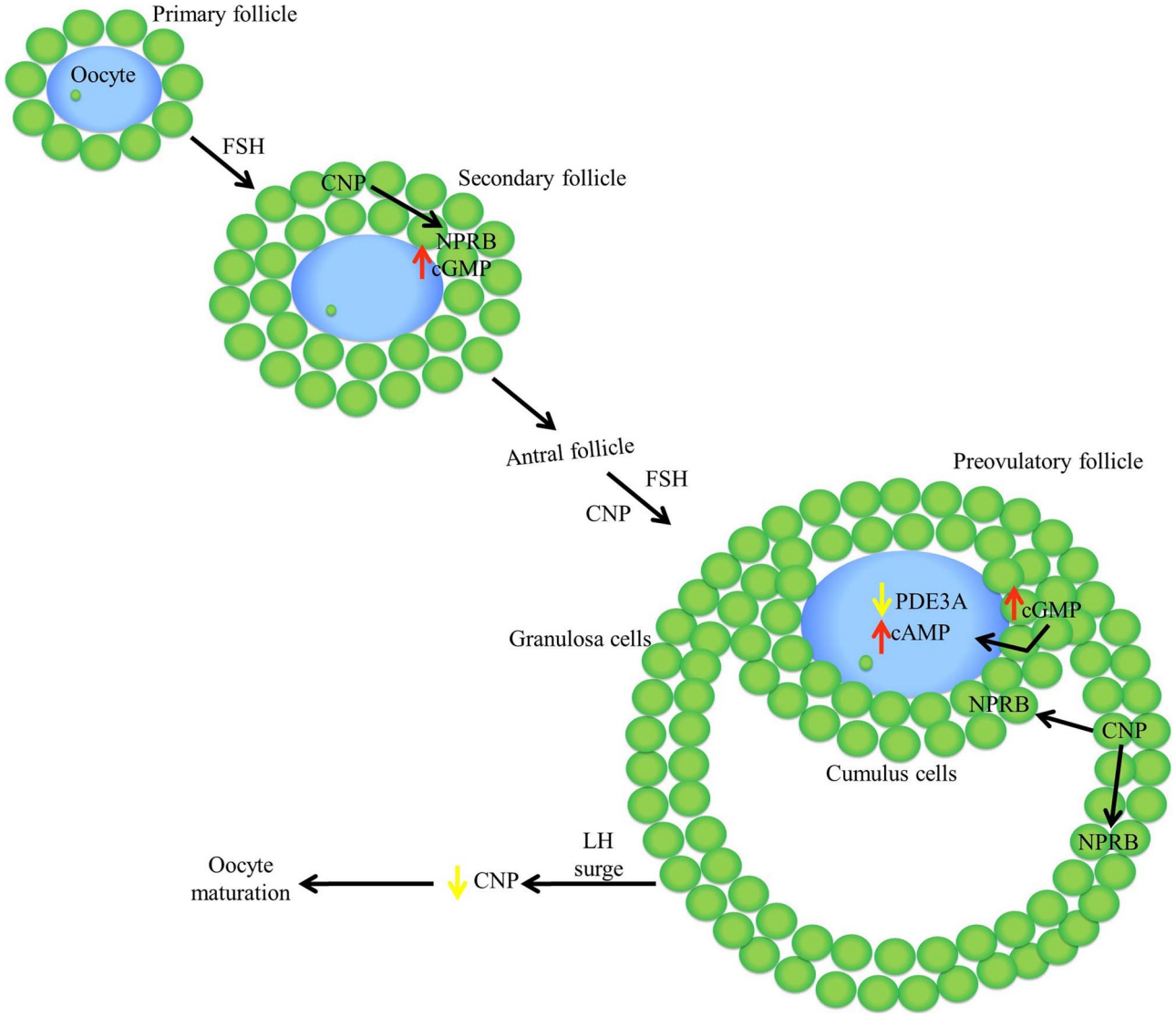

Fig. 1. Folliculogenesis: ovarian follicle include of somatic cells and an immature oocyte. Maturation of ovarian follicle describes the passage of a number of small primordial follicles into pre-ovulatory follicle and finally oocyte maturation. Abbreviation: C-type natriuretic peptide (CNP), atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), natriuretic peptide receptor-B, phosphodiesterase 3A (PDE3A).

chromosome abnormalities have important role in POF [15–20]. Most especially, structural anomalies and translocation of X with autosomes in X chromosome [21–25]. Turner syndrome, trisomy X, mutations and pre-mutations of X linked gene and abnormalities of autosomal related genes have been observed in POF cases [26].

2.1.1. X chromosome disorder

Turner syndrome have been seen in 1 of 2500 females that are born. One of the characteristic features of turner syndrome is POF. After the third month of fetal life, apoptosis of oocytes is accelerated [27–29]. Therefore, just 10% of turner syndrome women achieve menarche. Likely undetected X chromosome mosaicism could result in some unexplained POF cases [30]. The deletion of small part of X chromosome gene in turner syndrome women causes oocyte depletion. Some X chromosome genes involved in ovarian function are Zinc finger X-chromosomal protein (ZFX), ubiquitin specific peptidase 9 X-linked (USP9X), and Bone Morphogenetic Protein 15 (BMP15). These genes are located on short arm of X-chromosome (XP) [11]. Other X-linked ovarian failure such as X chromosome deletions, duplications and inversions are the most common reasons for POF [11]. Trisomy X syndrome may also result in POF [31]. Also, studies reported missense mutation of heterozygote *BMP15* resulted in POI [32–34]. The location of this gene is on Xp11·2 and encode the BMP 15 protein. Exclusively the expression of *BMP15 gene is in ovaries and* involved in follicular development [35].

2.1.2. Fragile X pre-mutations

About 20% of women with fragile X pre-mutation will show symptom of fragile X-associated primary ovarian insufficiency(FXPOI) [36]. Fragile X syndrome is a triple repeated disease [37,38]. Fragile X mental retardation 1 (FMR1) gene mutations cause fragile X syndrome and carriers of Fragile X pre-mutation include 55–200 CGG repeats in the 5' untranslated FMR1 gene region [39]. Women with fragile X chromosome have increased FSH and decreased inhibin B levels proposing ovarian ageing [40].

2.1.3. Autosomal disorder

Other genetic causes of POF are single gene disorders that include mutation in the receptor of LH and FSH, galactosemia and inhibin mutation [41]. POF have been seen in 80% of galactosemia patient [42]. Several studies have demonstrated that the mutation of Forkhead Box protein L2 (FOXL2), Newborn ovary homeobox gene (NOBOX),

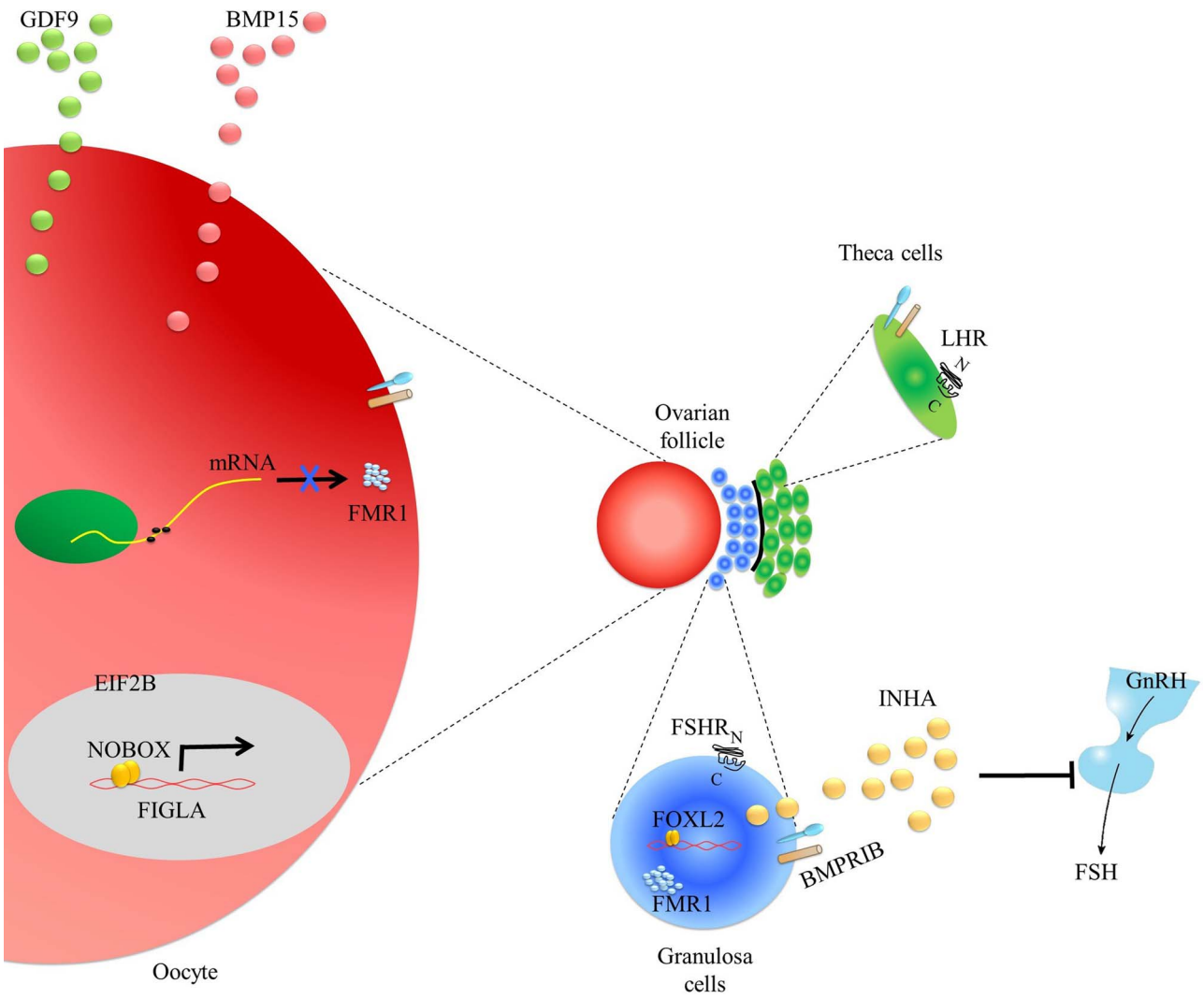

Fig. 2. Illustration of Genes and hormones known to be involved in POF pathogenesis and site of these genes.

Growth/differentiation factor 9 (GDF9), Splicing factor 1(SF1), Inhibin alpha (INHA), that have role in Folliculogenesis (Fig. 2) resulted in POF [33,43,44]. FOXL2 is a single-exon gene expressed in ovarian undifferentiated granulosa cells and encode the forkhead transcription factor. It has essential role in maintenance and development of ovary [45,46]. NOBOX function is in early folliculogenesis [47]. Study has been demonstrate the transition from primordial to growing follicles was blocked in the lack of NOBOX in mice [48]. The location of SF1 is on 11q13 chromosome and is expressed in different cell types in adult and fetus. The function of this gene is reproductive development system [49]. The role of INHA in reducing the secretion of follicle stimulating hormone in folliculogenesis have been confirmed [50]. Studies have been shown gen polymorphisms of INHA have association with POF because of important roles of it in folliculogenesis [51]. GDF9 are expressed in oocyte and encode soluble factors which involved in reproductive functions. Regulation of granulosa cell proliferation is depend on act of GDF9 and BMP15 synergistically [52,53].

2.2. Enzymatic

Protein and enzyme defects involved in steroidogenic pathway, such as 17α-hydroxylase and aromatase deficiencies can be attributed to POF [54]. In the adrenal and ovary 17-α-hydroxylase and 17,20desmolase defects result in low level of serum and androstenedione follicular fluid, testosterone, *Estradiol* (E2), respectively in the steroidogenic pathways [55].

2.3. Autoimmunity and POF

Autoimmune disease have been seen in 15–20% of POF patients [56]. The autoimmune diseases associated with POF are Addison's disease, vitiligo, myasthenia gravis, Sjögren's syndrome, systemic lupus erythematosus, celiac disease and autoimmune polyglandular syndrome. This syndrome has three type. Autoimmune polyendocrine syndrome type1 (APS-1) or Whitaker syndrome or candidiasis-hypoparathyroidism-Addison's disease syndrome, in this type defect or mutation in the AIRE (autoimmune regulator) gene have been seen. The role of AIRE gene is immune tolerance. Autoimmune polyendocrine syndrome type2 or Schmidt's syndrome. This type is more common, and associated with HLADR3 and HLADR4, consist of insulin–dependent diabetes, Addison's disease and POF. X-linked polyendocrinopathy or immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) is rare and could associated with dysfunction of forkhead box P3 (FOXP3) which involved in function and development of regulatory T cell. POF can be occur simultaneously or after autoimmune polyglandular syndrome (APS) manifestation [57–59]. About 35 years ago, the first antibody against oocyte was detected [60]. Thereafter, many other antibodies were also detected against adrenal cortex, testis and other organs [61]. In 50–60% unexplained fertility patients, ovarian antibody have been reported. Ovarian autoantibody is recognized

against p450-17α-hydroxylase and FSH receptor. Several studies have demonstrated zona pellucida autoantibody [62]. Abnormality of cellular immunity have also been seen in POF. $CD4^+$ Tcell increases and the ratio of $CD4^+/CD8^+$may rise [63], also an increase in B cell can be seen [64].

2.4. Vaccination

In recent years, POF after HPV-vaccination was recorded. Autoimmune responses to vaccination are the main facet of the autoimmune/inflammatory syndrome. They serve as adjuvant and result in POF [7].

2.5. Chemotherapy and radiation therapy

The most important and common causes of POF are chemotherapy and radiation therapy that are utilized to treat cancer. This treatment have several side effects such as decreasing oocytes by damaging the DNA and disturbing the functional and structural features of oocyte [65]. The study have been done in 2016 showed that toxic effect of the anticancer drug (doxorubicin,paclitaxel) was assessed and scientist saw reduction in primordial and developing follicles number in caprine preantral follicles [66]. Other study has been demonstrated the higher incidence of premature ovarian failure in women with breast cancer because of using DTC (docetaxel + pirarubicin + ifosfamide) chemotherapy regimens [67]. The effects of chemotherapy are depends on dose and drug [9].

2.6. Environmental

Viral infections such as Varicella zoster virus, Cytomegalovirus, and mumps virus [68] can result in POF. The exact incidence of this effect is unknown [10,68]. Also, smoking can result in POF [69]. Epidemiological studies shown decreased in menopausal age with smoking [70]. The composition of cigarette is polycyclic aromatic hydrocarbon. Oocytes and granulosa cell have aromatic hydrocarbon receptor so pro-apoptotic gene BAX (Bcl-2-associated X protein) is activated by binding this ligand and receptor [71]. Most POF causes are unexplained [8]. The causes of POF are summarized in Table 1.

Table 1
Summary of POF causes.

Causes	Example	References
Genetic		
x-chromosome	Turner syndrome Fragile X pre-mutations BMP15	[11,40]
autosomal	Mutation in receptor of LH and FSH Galactosemia and inhibin mutation Mutation of FOXL2, PMM2, GDF9, FRAX	[41,44]
Enzymatic	17α-hydroxylase, aromatase	[54]
Autoimmunity	Related diseases: Addison's diseases Viltiligo Myasthenia gravis Sjögren's syndrome Systemic lupus erythematosus Celiac disease Autoimmune polyglandular syndrome Ovarian autoantibody Zona pellucida autoantibody Immune cells inbalance: Increase of Increase of $CD4^+$ T cell and B cell	[57]
Vaccination	HPV-vaccination	[7]
Chemotherapy And radiation therapy	Cyclophosphamide, Busulfan, Nitrogen Mustard	[65]
Environmental	Viral infections, Smoking	[68,69]
idiopathic	75%–90% of all POF patient	[8]

POF, Premature ovarian failure; BMP15, Bone morphogenetic protein 15; LH, Luteinizing hormone; FSH, Follicle-stimulating hormone; FOXL2, Forkhead box L2; PMM2, Phosphomannomutase 2; GDF9, Growth/differentiation factor 9; FRAX, Fragile X Syndrome or the associated gene.

3. Diagnosis to evaluate ovarian reserve

By testing of anti-Müllerian hormone (AMH), inhibin B, FSH, estradiol (E2), and antral follicle count (AFC), we can evaluate the ovarian reserve. Anti Mullerian hormone is belong to transforming growth factor beta superfamily. AMH is expressed by pre-antral and small follicles granolosa cell. With increasing age and size of follicle, the concentration of AMH has diminished. Most important role of this is prevention of further recruitment of other follicles during follicular development [72,73]. For effective evaluation of the ovarian reserve, assessment of AMH is a good and helpful test [74,75].

4. Treatment strategies

As a result of the complexity of POF, different remedies have been suggested. However, none of them have been completely effective to be approved as the best treatment. Diverse approach to the treatment of POF includes; hormonal replacement therapy, psychological support, use of androgen, compounded bioidentical hormones, dehydroepiandrosterone, diet and exercise, donor oocytes, and stem cell therapy [76].

4.1. Hormone replacement therapy

Previous studies have shown that there are two types of sex-steroid replacement, standard sex steroid replacement (sSSR) and physiological sex steroid replacement (pSSR). sSSR have been used for amending symptoms in postmenopausal women while pSSR is utilized for the regulation of hormonal levels in abnormal ovarian function [76]. In recent years, the provisional suppression of the ovary during chemotherapy also conserve fertility and the use of gonadal luteinizing hormone-releasing hormone analogues (LHRHa) have been proposed to decrease the risk of treatment-related POF in clinical trials [5].

4.2. Melatonin supplement

Recently, it has been shown that the use of melatonin have a positive effect on increasing the level of gonadotropin, enhancing the function of the thyroid and restoring fertility and menstruation. Due to the existence of LH, FSH, estrogen and androgen receptor on the pineal gland, it has been demonstrated to be involved in folliculogenesis. Moreover, the mechanism involves in the regulation of ovarian function is not yet discovered [77].

4.3. Dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone originates from ovarian theca cells and the adrenal cortex zona reticularis. DHEA is important and necessary in follicular steroidogenesis of ovarian. It is important for formation of E2.With age the concentration of DHEA decreases [78]. Prescription of Dehydroepiandrosterone to patients who have POF, augment pregnancy chances and decreases the risk of miscarriage [79].

4.4. Immunomodulation therapy

Treatment of POF using immunomodulation therapy is effective when the POF is caused by autoimmune ovarian damage. In this treatment, use of corticosteroid for immunosuppressive therapy and monoclonal antibodies are common [80,81]. Some autoantibody have

been identified in POF are steroid-producing cell antibodies, this antibody bind to corpus luteum, granulosa cells, hilar cells and theca cells [82]. This auto-antibody have been identified in patients that have POF and Addison's disease simultaneously [83]. If the zona pellucida antibodies interfere with development of follicle, the follicular depletion may be occurs in animal model [84]. Antibodies to gonadotropin receptors have been seen in serum of patients with POF. These antibodies blocked the luteinizing hormone (LH) receptor [85].

4.5. Application of stem cell therapy in treatment of POF

Risk of cancer increases after the use of hormone replacement therapy and because of the side effects associated with other POF and infertility treatments [86,87], scientists have addressed other therapeutic measures such as stem cell therapy. Germ line establishment and differentiation is essential for human fertility because only this type of cell can transfer genome between parents and their offspring. Germ line cells in the testis and ovary differentiates into gametes [88].

Undifferentiated cells, called stem cells have been seen in embryonic, fetal, and adult life stages [89]. Stem cells have general properties such as ability to divide, they are unspecialized and are able to renew themselves [90]. In stem cell-based therapy for infertility, embryonic stem cell (ESCs), mesechymal stem cells (MSCs), stem cells from extra-embryonic tissues, induced pluripotent stem cells (iPSCs), spermatogonial stem cells and ovarian stem cell are used [91]. In POF patients, stem cell therapy can be used for the production of ovule in women. Many studies have explained different protocol for the separation, isolation and culture of stem cells in order to use these cells for treatment [90]. In recent studies, the use of different types of stem cells for the treatment of POF have been reported (Table 2).

4.5.1. Mesenchymal stem cell

Mesenchymal stem cells are multi-potent stem cells and the advantages of this cells are readily available and imperfectly (poorly) immunogenic [92,93]. It can be derived from bone, umbilical cord blood and adipose tissue [94]. In 2013, Wang et al. used the umbilical cord derived mesenchymal stem cells (UCMSCs) of mice to treat premature ovarian failure. They discovered reduced cumulus cells apoptosis, recovering ovarian function and an increase in the level of sex hormone. Finally, they compared the expression of RNA in treated group with wild-type control group and POF model. They observed similarity between treated group with umbilical cord derived mesenchymal stem cells and the wild-type group [93]. Furthermore, in 2017, Li et al. discovered that after transplantation of human umbilical cord derived mesenchymal stem cells (UCMSCs) to rats on Days 14, 21, and 28, there was reduced FSH, increased AMH and E2, also the function of ovarian reserve and the number of follicle was improved. In addition, this article showed that hUCMSCs can secrete insulin-like growth factor-1 (IGF-1), Vascular endothelial growth factor (VEGF) and Hepatocyte growth factor (HGF) cytokines [95]. Scientists have demonstrated that transplantation of male rabbit mesenchymal stem cells derived from the bone marrow of male rabbits to POF-induced rabbit increased vascular endothelial growth factor, declined follicle-stimulating hormone and increased follicle numbers with normal structure [96]. A study done in 2015 by Lai et al. reported that Human endometrial mesenchymal stem cells (EnSCs) isolated from menstrual blood improved estrous cycle and restored fertility in mice. Also, germline stem cells (GSCs) pool depletion declined after transplantation of EnSCs to mouse with damaged ovary [97]. Transplantation of human mesenchymal stem cells derived from bone marrow (BMSCs) to mice have been carried out by Mohamed et al. in 2017. They found an increase in ovarian weight, body weight and ovarian weight thereby rehabilitating ovarian hormone production and restoring folliculogenesis after transplantation of BMSCs [87]. The use of adipose-derived stem cells (ADSCs) in mice with chemotherapy-induced ovarian damage have been reported in 2013 by Sun et al. ADSCs transplanted in two ways directly into bilateral ovaries or intravenous injection after 1 week or one month, excised ovaries and assessed the number and function of follicles. The result of this study showed improvement in ovarian function and increased ovulation and population of follicles [98]. Liu et al. in 2014 have also reported that the transplantation of human menstrual blood stem cells (hMensSCs) to mice caused higher levels of ovarian markers and increased ovarian weight, plasma E2 level and normal follicles number [99]. Also in 2017, Wang et al. studied the use of human menstrual-derived stem cells (MenSCs) and showed reducing apoptosis of granulosa cells and ovarian interstitium fibrosis. In this way, the ovarian microenvironment improved and the numbers of follicular were augmented. Also, the secretion of fibroblast growth

Table 2
Summary of recent literature about stem cell therapy in POF disease.

Authors name	Year	Type of stem cell	Outcome	Reference
Wang et al.	2013	UCMSCs	Reduction in cumulus cells apoptosis, recovering of ovarian function and increase in the level of sex hormone in POF-induced mice.	[93]
Wang et al.	2013	hAECs	Differentiation of hAECs into granulosa cells and Anti-Müllerian hormone increased in treated mouse ovaries	[103]
Abd-Allah et al.	2013	Male rabbit MSCs	Increased follicle numbers of POF-induced rabbit with normal structure	[96]
Sun et al.	2013	ASCs	Improved ovarian function and increase in ovulation and population of follicles in mice	[98]
Liu et al.	2013	hiPSC	Decreased expression of vimentin and fibronectin level in ovarian tissues and also increased of E2 and ovarian weight in mice.	[108]
Liu et al.	2014	hMensSCs	Expression of higher levels of ovarian markers and increased ovarian weight, plasma E2 level, normal follicles number in mice	[99]
Xiao et al.	2014	AFSCs of transgenic mice	Prevented follicle atresia and maintained the healthy follicle in mice.	[102]
Lai et al.	2015	EnSCs	Cells improved estrous cyclicity and restored fertility in mice	[97]
Liu et al.	2016	hiPSC-derived OGLCS	Growth in ovarian tissues, expression of ovarian granulosa cell markers, increased in the estradiol hormone and reduction of atretic follicles number	[109]
Xiao et al.	2016	AFSC	Down regulation of miR-10 and miR-146, decreased anti-apoptotic effects, CTX-damaged GCs in-vitro and inhibition of atresia of ovarian follicular in mice	[105]
Li et al.	2017	hUCMSCs	Decreased FSH, increased AMH and E_2 and improvement in the function of ovarian reserve	[95]
Mohamed et al.	2017	hBMMSCs	Restored ovarian hormone production and reactivated folliculogenesis in mice	[87]
Wang et al.	2017	Mice MenSCs	Improved the ovarian microenvironment and exerted protective effects on damaged ovaries of mice	[100]
Fu et al.	2017	MSCs	Overexpression of miR-21 in MSCs decreased apoptosis	[104]
Zhang et al.	2017	hAECs or hAEC-CM	healthy and mature follicle have been seen in ovary of treated mouse	[106]

Abbreviation of stem cell population: MSC, Mesenchymal Stem Cells; hESCs, Human embryonic stem cells; hUCMSCs, human Umbilical Cord Mesenchymal Stem Cells; AFSCs, amniotic fluid stem cells; hAECs, Human amniotic epithelial cells; hiPSCs, human Induced pluripotent stem cells; OGLCs, Ovarian granulosa like cells; HuMenSCs, Human Menstrual Blood Stem Cells; hBMMSCs, Human bone marrow Mesenchymal Stem Cells; OSE, hormone-sensitive ovarian epithelial; ASCs, Adipose stem cells; MenSCs, Menstrual Blood Stem Cells; EnSCs, Human endometrial mesenchymal stem cells.

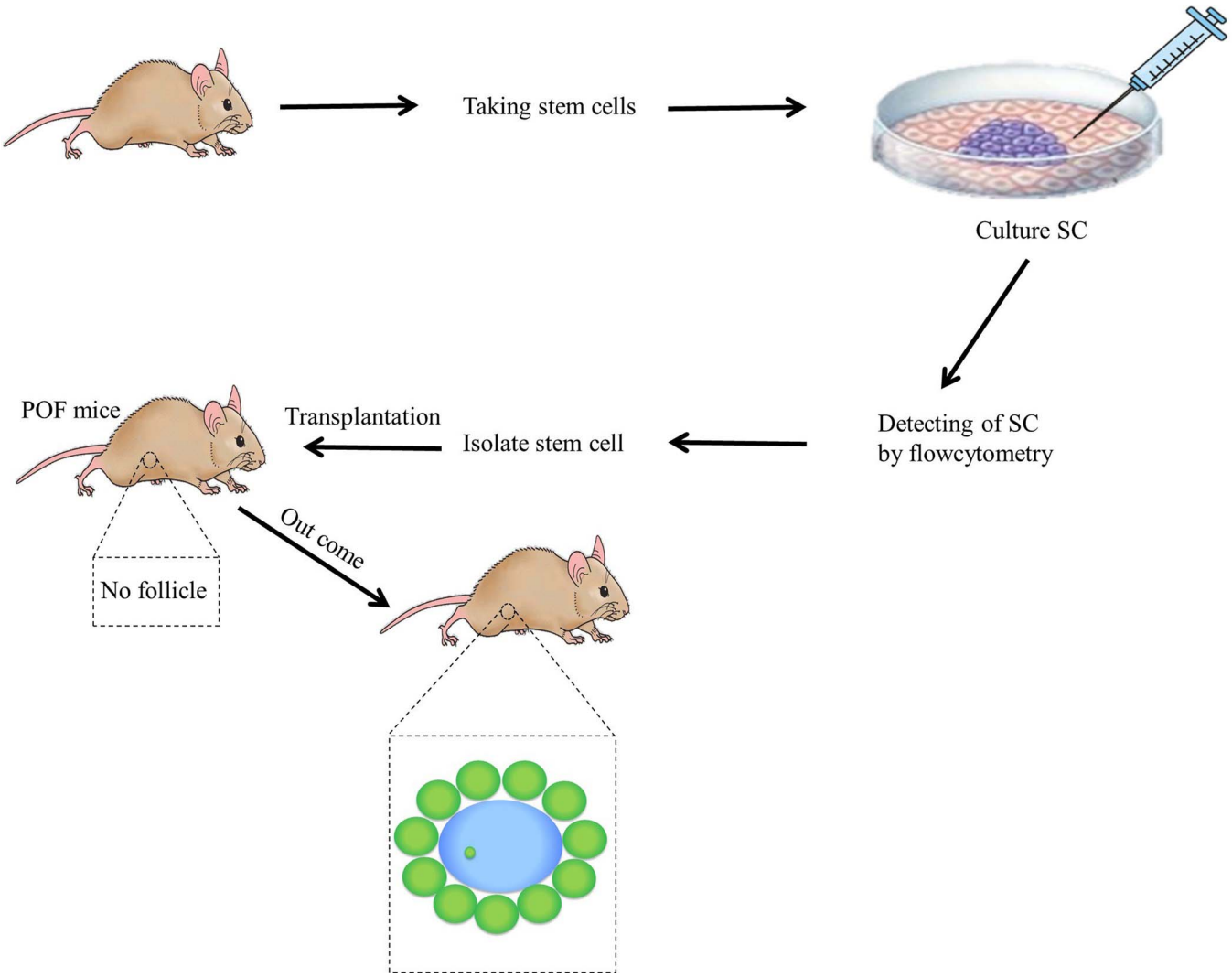

Fig. 3. Treatment of premature ovarian failure (POF) with stem cell therapy. Using stem cell to understand and treat POF mice and renewal follicle after transplantation of stem cell. Stem cell therapy leads to treatment of mice with POF.

factor 2 (FGF2) by MenSCs had protective effects on damaged ovaries [100].

4.5.2. Extra-embryonic stem cells

Amniotic fluid stem cell derived from extra-embryonic layer, is a multi-potent population that expresses markers of embryonic and adult stem cells [101] and in comparison to mesenchymal stem cells, it proliferates faster [102]. The study carried out by Xiao et al. in 2014 demonstrated that the transplantation of Amniotic Fluid Stem Cells (AFSCs) of transgenic mice inhibited follicle atresia and maintained the healthy follicles [102]. Also in 2013, using human amniotic epithelial cells (hAECs) showed differentiation of hAECs into granulosa cells. Therefore, the marker of ovarian function such as anti-müllerian hormone was noticeable in the ovaries of treated mouse [103]. Fu et al. also explained that Programmed cell death 4 (PDCD4) and Phosphatase and tensin homolog (PTEN) were targeted by miR-21 which in turn inhibited the apoptosis of granulosa cells. Therefore, the overexpression of miR-21 in mesenchymal stem cell (MSCs) decreased the apoptosis of germ cell (GC) and follicle number while estradiol (E2) increased and follicle-stimulating hormone (FSH) reduced [104]. Xiao et al. explained that miR-10a derived from amniotic fluid stem cell have anti apoptotic effect. The target genes of theses MicroRNAs are essential for apoptosis. In this study, scientist via down regulation of miR-10 and miR-146 illustrated the decrease of anti-apoptotic effects on GCs which are damaged with chemotherapy (CTx) in-vitro and demonstrated exosomes which are derived from AFSC inhibited atresia of ovarian follicle in POF induced mice [105]. Zhang et al. in 2017 showed after injection of Human amniotic epithelial cells (hAECs) or hAEC-conditioned medium (hAEC-CM) in to the unilateral ovary of POF mouse, healthy and mature follicle have been seen in ovary of treated mouse and they saw 109 cytokines in hAEC-CM have role in biological processes such as angiogenesis, immune response, cell cycle and apoptosis [106].

4.5.3. Induced pluripotent stem cells

To induce pluripotent stem cells, scientist showed that octamer-binding transcription factor 4 (OCT4), lin-28 homolog A (LIN28), sex determining region Y-box 2(SOX2h or SRY) and Nanog Homeobox (NANOG) have important roles in reprogramming human somatic cell into pluripotent stem cell [107]. A study done in 2013 by Liu et al. showed the differentiation of human-induced pluripotent stem (hiPS) cells into hormone-sensitive ovarian epithelial (OSE)-like cells by use of microRNA-17-3p (miR-17-3p). The function of miR-17-3p is to suppress the expression of vimentin. OSE-like cells were transplanted into POF induced mice and a decrease in the expression of vimentin was seen and fibronectin level in ovarian tissues, E2 and ovarian weight increased [108]. Use of ovarian granulosalike cells derived from human induced pluripotent stem cells have been demonstrated in 2016. Liu et al. showed that human induced pluripotent stem cellsderived ovarian

granulosalike cells (OGLCs) transplanted into POF mice caused growth in ovarian tissues, expression of ovarian granulosa cell markers, increase in the estradiol hormone and reduction of atretic follicles number [109].

4.5.4. Ovarian stem cell

Recent studies have rejected the belief that adult mammalian ovary is endowed with a fixed number of oocytes. If ovarian Germ-line stem cells (GSCs) have the ability to grow and develop, this would provide new treatment for POF therapy. Although this ovarian GSCs are well known in non-mammalian model organisms [110], new studies in mice, rats, and humans have revealed the presence of GSCs in ovary that will improve infertility treatment and perhaps can solve POF disorder in the near future [111]. Putative ovarian Mesenchymal stem cells (PO-MSCs) existing in ovarian cortex biopsies have also been described recently. Gene expression analysis have been shown that PO-MSCs are different from fibroblasts also express CD44, CD90 and stromal cell precursor surface antigen (STRO-1) [112]. Scientists could use PO-MSCs as a new type MSCs in treatment of POF.

Treatment of premature ovarian failure (POF) mice with stem cell therapy have been shown in Fig. 3.

5. Conclusion

Premature ovarian failure contributing to infertility causes a feeling of sadness and depression in many couples. Because of the complexity of this disorder, no specific treatment has been recommended yet and the use of combined treatment with decreased complication have been adopted. If the main cause of POF will be detected, the remedy for it will be easier. The detection and identification of the cause of POF require further study and novel method in future. Different types of stem cells with their therapeutic potential have been used in the last decade. Recent studies have also illustrated that stem cells can differentiate into ovarian follicles and restore ovarian function. Almost all of the researches pointed to the efficiency of stem cells in POF treatment. Recent studies show adult ovarian GSCs could replenish oocytes but there is many unknown data about these cells so further characterization needs to be established for isolation and development of these cells. Considering of previous studies and science progress we will expect to see observable improvement in treatment of infertile or POF women with doing human clinical trial studies in near future. This success is not possible except with providing condition for doing clinical trial studies. One of the essential item is to prove safety of transplantation of stem cells to women ovary. Fortunately nowadays stem cells have noticed so much and many studies will be done in future because of identification of new features of stem cell.

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