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REVIEW

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The need to identify novel biomarkers for prediction of premature ovarian insufficiency (POI)

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Abstract

Background: Premature ovarian failure (POF)/premature ovarian insufficiency (POI) is characterized by disrupting ovarian function under 40 years old. A major health problem of this disorder is female infertility. There are no proven treatments to increase the rate of pregnancy with autologous oocytes in these patients. This review aims to summarize our present knowledge about POI-induced infertility treatments and to highlight the importance of future researches in the discovery of diagnostic biomarkers and treatment of patients with this disorder.

Methods: A literature review was carried out using PubMed and Google Scholar databases by relevant keywords, such as POI, POF, premature ovarian failure, premature ovarian insufficiency, and biomarkers.

Results: Two hundred three studies were included in the study following the search for the keywords. Titles and abstracts of the identified articles were evaluated for detecting relevant full-length articles.

Conclusion: Anti-Mullerian hormone (AMH) level appears to have considerable value as a diagnostic test for POI, but it is not reliable enough to be able to predict accurately the timing of onset of impending POI. Using an accurate biomarker, POI can be diagnosed early and infertility treatment that is concerned about can be done on time. Biomarkers in combination with other diagnostic tests could result in prediction of POI before the development of complete ovarian failure.

Keywords: Premature ovarian insufficiency, POI, Biomarker, Female infertility

Background

POI is a major health problem and causes some severe consequences such as infertility that is characterized by disrupting ovarian function under 40 years old [1]. The prevalence of POI is 1% in women younger than 40 years old and 0.1% before 30 years old [2]. According to the European Society of Human Reproduction and Embryology, it is defined by oligo/amenorrhea for at least 4 months and increased follicle-stimulating hormone (FSH) level > 25 IU/l on two samples > 4 weeks apart [3]. The prominent demonstration of this disorder is infertility and hyper-gonadotropic hypogonadism amenorrhea. Jankowska [4] described two types of POI based on histopathology. In type I, there is no follicle in ovaries and the most likely causes of this type are gonadal dysgenesis, chromosomal aberrations, and disorders of sex development. The absence of ovarian follicles is a consequence of failure in germinal cell development [5]. In type II, follicles are present in the ovary and many cases may be associated with autoimmune disease. Also, ovarian dysfunction in type II can be a result of the hyposensitivity of the FSH receptor or its abnormal structure [4].

POI has serious consequences include psychological distress, osteoporosis, sexual disorder, ischemic heart disease, and increased mortality rate. The most likely causes of POI are genetic, iatrogenic, infection, immunologic,

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metabolic, and environmental [2, 6–8]. However, the etiology of POI in many patients is unknown [9]. In some patients, there are no indications that the patients will go into POI soon. Patients with a family history of POI who the suspected of POI could benefit from such testing to diagnose the possibility of future POI. This paper will review the research conducted on novel treatment of infertility in these women and aimed to address the following research questions: Can patients with POI get pregnant with their oocytes? And is it possible to predict POI development at early ages by suitable biomarkers?

Methods

A literature review was carried out using PubMed and Google Scholar databases by relevant keywords, such as POI, POF, premature ovarian failure, premature ovarian insufficiency, and biomarkers. All original articles published in the English language that was available online until the end of January 2021 were included in the search. In total, 203 studies were identified following the search for the keywords. Titles and abstracts of the identified articles were evaluated for detecting relevant full-length articles, and concerning animal studies, priority was given to studies relevant to the human.

Clinical presentation and diagnosis

Symptoms of POI are highly variable and the first indicator of ovarian insufficiency is menstrual abnormalities that can range from oligomenorrhea to even polymenorrhea and subsequent amenorrhea. Loss of regular menses for four consecutive months in a healthy and non-pregnant woman needs further investigation, and POI should be considered among the possible causes. Menopausal symptoms (an estrogen-deficient state such as hot flashes, vaginal dryness, and sleep disturbances), autoimmune disorders like vitiligo and hyperpigmentation-adrenal insufficiency, are some of the clinical presentations of POI. Primary amenorrhea may be seen in up to 10% of cases of POI [10] and women with primary amenorrhea may never experience menopausal symptoms. However, for some women, diagnosis of POI may be discovered only during evaluation for subfertility/infertility. Infertility is the most disturbing aspect of POI and there are no proven treatments to increase the rate of pregnancy with autologous oocytes. Despite marked advances in the field of reproductive medicine, there are no treatments that can reliably improve residual ovarian reserve parameters and conception rates in women with POI.

Amenorrhea (primary or secondary) in any woman younger than 40 years is consistent with a diagnosis of POI. Unlike women with menopause, which marks an irreversible state of ovarian senescence, women with POI retain some degree of ovarian function [11]. A thorough evaluation of medical and family history, clinical characteristics, environmental factors, physical examination, serum FSH, and AMH levels can help to the diagnosis of POI. A timely and correct diagnosis before the opportunity for fertility preservation is missed can help patients with POI for biological parenting. Therefore, biomarkers for early and accurate prediction of POI may aid infertility management in these patients.

Etiology of POI

POI or hypergonadotropic hypogonadism refers to the loss of ovarian activity under the age of 40 years. There are different etiologies for POI include idiopathic, genetic, autoimmune causes, infections, metabolic, toxin-related, and iatrogenic including following chemotherapy, radiation, or surgery [12]. Idiopathic POI occurs in up to 30% of women with a family history of early menopause suggesting a genetic etiology [13]. Known genetic causes are Turner syndrome, Fragile X syndrome, and X-linked and autosomal mutations. Further studies to identify possible genetic causes like associated single-nucleotide polymorphisms (SNPs) in the case of idiopathic POI are needed. Recent evidence suggests that previous PCOS (polycystic ovarian syndrome) is an important risk factor for the increase of POI [14]. The environmental factors may be linked with POI and there is some evidence that pollutants may affect ovarian follicular reserve during prenatal and adult life [15]. EDCs (endocrine disrupting chemicals) can affect folliculogenesis [16], and induction of oxidative stress is seen generally as a factor that is strongly related to apoptosis of antral follicles [17]. Also, environmentally induced epigenetic modification may have been an important factor in the alteration of ovarian action [18].

Infertility treatment strategies in POI

Infertility is the most disturbing aspect of POI and there are no proven treatments to increase the rate of pregnancy with autologous oocytes. Oocyte donation currently offers the best chance of achieving a pregnancy for infertile patients with POI. The impact of hormonal interventions for POI treatment is not completely effective [19, 20]. Li et al. [21] reported that treatment with melatonin probably by inhibition of reactive oxygen species (ROS) production and protection of the process of normal follicle development, is an effective approach to suppress POI. According to several studies, the application of Platelet-Rich Plasma (PRP) intra-ovarian infusion may be linked to the increased obtained oocyte, clinical pregnancy, and live birth rate [22–24]. The result of this procedure in the disease was heterogeneous because many factors affect the result including procedure time and the volume required for injection [25]. However, this

procedure is still at the experimental level and there is a need for large clinical trials to evaluate the real effect of PRP intra-ovarian infusion on POI. Artificial gametes are also a new method as a solution for patients with ovarian insufficiency, but current evidence is based on animal and in vivo models [26].

In recent years, there has been an increasing amount of literature on the role of stem cells in the treatment of POI. In the field of infertility treatment, embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), stem cells from extra-embryonic tissues, induced pluripotent stem cells (iPSCs), and ovarian stem cell are used [27]. Stem cell therapy in POI patients is still at the experimental level and there is a need for future studies. A recent study reported by Zhang et al. [28] also supported the hypothesis that human placenta mesenchymal stem cell (hPMSC) could decrease follicular atresia and granulosa cell apoptosis and increase AMH level and FSH receptor expression. Noory et al. [29] showed human menstrual blood stem cells (HuMenSCs) could differentiate into granulosa cells and have been introduced as a cost-effective and practical method for POI treatment. CHEN et al. [30] published a meta-analysis in which they described stem cell therapy improved ovarian size and endometrial thickness and affect serum levels of FSH and E2. Most studies have been performed in animal models through chemotherapy-induced POI, and up to now, there has been little evidence from human studies.

In recent years, researchers have investigated MSCs therapy in humans with infertility [23]. The result showed that it is possible to achieve pregnancy spontaneously or via IVF through MSCs transplantation in humans but the study population was small [23, 31]. It has been shown an increase in serum AMH level, number of the follicles, and obtained oocyte. However, it is necessary to keep in mind that this procedure has some disadvantages including invasiveness, the ability of stem cell tumor formation, and metastasis at higher passage [32]. Lee et al. [33] introduced primordial follicle activation as a new treatment for primary ovarian insufficiency. Overall, all of the procedures mentioned earlier like stem cell therapies, PRP intra-ovarian infusion, and primordial follicle activation require further research and confirmation of efficacy and safety.

Biomarkers for early prediction of POI

The measurement of a specific product of the ovary would be a valuable biomarker in women with POI in the diagnosis and perhaps the prediction of this disorder. AMH is produced by the granulosa cells of growing follicles and is therefore likely to be of value in this context. AMH levels in POI patients could identify women with persistent follicles in the ovaries. It has been demonstrated that AMH could be useful in discriminating POI patients with a follicular population from patients with no or few ovarian follicles [34]. Serum AMH < 8 pmol/L before the age of 36 years appears to be a risk factor for POI. It has been suggested that these women require regular follow-up, especially if their menstrual cycles are irregular [35]. AMH appears to have considerable value as a diagnostic test for POI, but it is not reliable enough to be able to predict accurately the timing of onset of impending POI [36]. Biomarkers detection in combination with other diagnostic tests could result in prediction of POI before the development of complete ovarian failure.

There are very few biomarkers available to diagnose cases with POI. Some complete blood count (CBC) parameters have been introduced to be diagnostic biomarkers for several disorders associated with the inflammatory process and chronic inflammatory process that may be underlying pathophysiology of POI. Sanverdi et al. [37] assessed the predictive value of CBC parameters for POI diagnosis. They suggested the mean platelet volume/lymphocyte ratio as a new biomarker in early POI because it is cheap and easily accessible compared to AMH [37]. Insulin-like peptide 3 (INSL3) is secreted into the circulation and acts as a valuable biomarker to monitor the growth of antral follicles. It is increased in PCOS and decreased in women with POI. There is know very little about its involvement in the pathogenesis of PCOS or POI, and its role as a new biomarker of female function needs to be explored more widely to improve diagnosis and treatment of ovarian dysfunction [38]. Other markers that have been identified in association with POI diagnosis or pathology follow below. Some of these markers may be beneficial for the early prediction of POI after further research and confirmation.

Protein biomarkers

Data from some research may have clinical potential to generate therapeutic targets to manage women's infertility and develop biomarkers that predict dysfunction of the reproductive organs. For example, Granulin is a growth factor and its high levels are associated with many cancers, likely because of its roles in mitosis, migration, and cell survival [39]. It has been reported that Granulin and its precursor were specifically expressed in oocytes rather than granulosa or theca cells in rats [40]. Ersoy et al. [41] reported that serum Granulin levels in patients with POI were significantly lower than in the control group. Since it is easily and non-invasively detected in the serum by ELISA test, it could be used as a biomarker for early detection of POI if confirmed by studies in a larger population. Dysregulation in A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) family have been associated

with reproductive disorders such as PCOS and POI [42]. These enzymes take part in extracellular matrix (ECM) remodeling which has been shown to contribute to ovulation and follicular functions. Ersoy et al. [43] compared serum levels of ADAMTS-19 enzyme in patients with different fertility situations. ADAMTS-19 was found to be higher in PCOS patients than in POI patients and may have a potential for being an important marker of ovarian function and oocyte pool [43].

Few proteomics studies have been performed on the POI disease. Lin et al. [44] reported that the protein network consisting of the cytochrome P450 family Fdx1, Cyp17a1, Cyp11a1, and Cyp2u1 is a potential new biomarker of mouse ovarian granulosa cells damage in POI in mice model. Human proteomics studies on POI may reveal new potential protein biomarkers in relation to the disease. Lee et al. [45] using the proteomics tool, introduced 5 reproductive system-related proteins (Ceruloplasmin, Complement C3, Fibrinogen α, Fibrinogen β, and SHBG) that their different expression levels demonstrated the possibility of using them as biomarkers to screen POI. These pre-clinical data suggesting the possibility of using these proteins as biomarkers to identify putative POI [45]. Liu et al. [46] detected multiple proteins in serum of POI and healthy fertile subjects as control groups by a solid-phase antibody array. As a result, eleven proteins, including Neurturin, Frizzled-5, Serpin D1, MMP-7, ICAM-3, IL-17F, IFN-gamma R1, IL-29, IL-17R, IL-17C, and Soggy-1, were uniquely downregulated, and Afamin was particularly upregulated in POI serum. All of these factors were firstly found to be associated with POI in this study, and for the first time suggesting these targets may be able to serve as novel serum biomarkers for POI [46]. Therefore, future studies to investigate the biological functions of these proteins to demonstrate their possibility as diagnostic biomarkers of POI is recommended.

Di-2-ethylhexyl phthalate (DEHP) is one of the environmental factors that may cause POI. Differential expression levels of several deubiquitinating enzyme (DUB) genes including *USP12*, *COPS5*, *ATXN3L*, *USP49*, and *USP34* in ovarian cell models (Treated with Di-2-Ethylhexyl Phthalate) at the mRNA and protein levels have been observed [47]. These results suggest that these genes at the protein level should be investigated as potential biomarkers of human POI prediction; however, further research and confirmation of efficacy and safety is needed. The list of potential protein biomarkers in POI is presented in Table 1.

Table 1 List of potential protein biomarkers in POI

Proteins	Expression status	Sample	Reference(s)
Granulin	↓	Human	[41]
ADAMTS-19	↓	Human	[43]
Fdx1	↓	Mouse	[44]
Cyp17a1	↓	Mouse	[44]
Cyp11a1	↓	Mouse	[44]
Cyp2u1	↓	Mouse	[44]
Ceruloplasmin	↑	Human	[45]
Complement C3	↑	Human	[45]
Fibrinogen α	↑	Human	[45]
Fibrinogen β	↑	Human	[45]
SHBG	↑	Human	[45]
Neurturin	↓	Human	[46]
Frizzled-5	↓	Human	[46]
Serpin D1	↓	Human	[46]
MMP-7	↓	Human	[46]
ICAM-3	↓	Human	[46]
IL-17F	↓	Human	[46]
IFN-gamma R1	↓	Human	[46]
IL-29	↓	Human	[46]
IL-17R	↓	Human	[46]
IL-17C	↓	Human	[46]
Soggy-1	↓	Human	[46]
Afamin	↑	Human	[46]
USP12	↑	Human ovarian cancer cell line	[47]
COPS5	↑	Human ovarian cancer cell line	[47]
ATXN3L	↑	Human ovarian cancer cell line	[47]
USP49	↑	Human ovarian cancer cell line	[47]
USP34	↓	Human ovarian cancer cell line	[47]

Immunological biomarkers

It has been demonstrated that POI patients may have underlying autoimmunity [48]. Although anti-ovarian antibodies have been reported to be one of the probable causes of unexplained infertility, POI, and IVF/embryo transfer failures, none of the autoantigens have been established as ideal serological biomarkers for diagnosis of these infertile cases [49]. Mande et al. [49] carried out a study to identify cognate immunodominant antigens that could be used to screen sera for diagnosis and/or prognosis of POI. This study provided strong evidence to suggest that three proteins include non-muscle αACTN4, HSPA5, and cytoplasmic ACTB should be targeted in idiopathic POI cases and women undergoing IVF/embryo transfer programs [49]. Future research to study the possible roles of these proteins in ovarian autoimmunity may lead to a possibility for these biomarkers to be used in the diagnosis

of autoimmune-induced infertility. A specific non-invasive diagnostic test is particularly essential for a reliable diagnosis of an autoimmune etiology and is essential to detect future associated disorders. This may aid to select the patients in whom immune-modulating therapy may restore, at least temporarily, ovarian function and fertility in patients with POI.

It has been reported that antiphospholipid antibodies (APAs) are associated with decreased levels of AMH, supporting the hypothesis that non-specific autoimmunity may adversely affect ovarian reserve [50]. This may not be necessarily diagnostic but may suggest a hyperactive immune system that represents a risk for autoimmune-associated POI. Therefore, autoimmune-associated ovarian failure does not have to be characterized by anti-ovarian autoimmune mechanisms and could be the consequence of anti-adrenal autoimmunity [50]. Sundblad et al. [51] have identified α-enolase as an autoantigen for POI. They suggested that in those patients with suspected autoimmune-associated POI, the presence of anti-enolase antibodies might be an indicator of a defect in immune-regulation and a possible autoimmune etiology for POI [51]. The presence and the inhibitory mechanisms of circulating Ig-FSHR have been evaluated in patients with POI, and it has been suggested that determination of the presence of circulating immunoglobulins that inhibit FSH binding to its receptor could be used in diagnosing these patients [52].

Antibodies to selenium binding protein 1 (SBP1), an autoantibody, have been identified in patients with POI that may predict the risk of POI and could be useful in identifying women for more intense development of serious ovarian cancer [53]. Bertone-Johnson et al. [54] assessed the relation of the inflammatory markers include the soluble fraction of tumor necrosis factor alpha receptor 2 (sTNFR2), C-reactive protein, and interleukin-6 levels with an incident of early menopause. They observed a significant association of sTNFR2 levels and risk of early menopause and suggested that sTNFR2 is associated with early menopause and menopause timing, independent of AMH and established risk factors [54]. Further prospective studies may reveal whether sTNFR2 is a novel risk factor for early menopause. Suggested factors that may impair ovarian immunoregulation and have a possible role in POI- associated autoimmunity are presented in Fig. 1. The evidence available is not much to use these biomarkers for POI prediction, so further research is needed.

Genetic biomarkers

Single-nucleotide polymorphisms (SNPs)

Identification of SNPs in correlation with POI patients may help in early molecular diagnosis, prognosis, and genetic counseling. Chemokine (C-X-C motif) ligand 12 (CXCL12/stromal cell-derived factor 1) has been suggested to play an essential role in primordial germ cell (PGCs) migration, colonization and survival, and in the primordial to primary follicle transition. Wang et al. [55] reported a strong association between a *CXCL12* polymorphism and POI in Chinese patients, suggesting that *CXCL12* might be a candidate gene involved in POI and is a possible risk factor for developing POI. Various variants were found in *SOHLH2* [56] and *SALL4* [57] genes in association with human POI etiology in Chinese

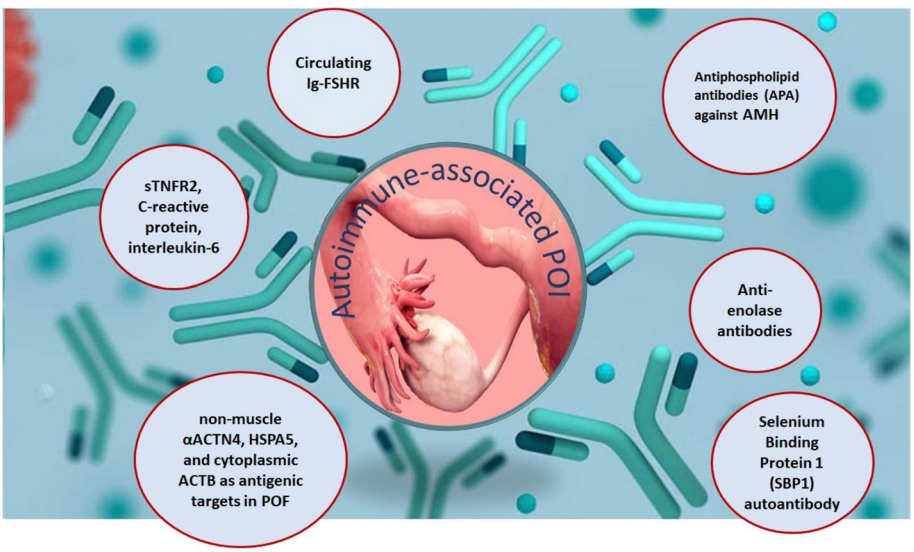

Fig. 1 Suggested factors that may impair ovarian immunoregulation and have a possible role in POI- associated autoimmunity

subjects. However, further studies are necessary to confirm the association of these SNPs with the risk of POI.

MicroRNAs

Along with identifying the optimal biomarkers for molecular profiling of POI, micro-RNAs (miRNAs) appear as one of the ideal markers. miRNAs are involved in the complex post-transcriptional mechanisms that cells used to regulate gene expression. They are short non-coding RNA molecules composed of 18–24 nucleotides [58]. The expression levels of miRNAs in the reproductive tissues seem to be related to female fertility and embryo developmental potential [59]. Since miRNAs have a fundamental role in cellular and gene expression regulation, so from a molecular point of view, they may help POI patient's diagnosis and prognosis in the IVF treatment programs and facilitate the practice of individualized medicine.

There have been limited human studies evaluating miRNA in patients with POI. The first study was performed on three patients with POI and revealed mir-23a which is shown to promote granulosa cell apoptosis is upregulated [60]. A larger study, in Chinese women with POI, revealed 22 upregulated and 29 downregulated miRNAs in plasma samples of these patients. Upon further evaluation, it has been demonstrated mir-22-3p which regulates pituitary FSH secretion may be related to POI pathophysiology [61]. Chen et al. [62] investigated the role of miRNA-146a in ovarian granulosa cell apoptosis and found that miRNA-146a is upregulated in patients with POI which has been associated with cell apoptosis. miR-146a regulates the expression of IRAK1 and TRAF6 which have several roles in ovarian physiology, as well as in inflammatory responses [62]. It has been reported that gene-gene interaction between miR-146 and miR-196a2 could involve in POI progress [63]. Liu and et al. [64] reported that overexpression of miR-15b could induce premature ovarian failure in mice. It has been reported that miR-518 gene polymorphisms [65] and miR-449b rs10061133 AA genotype [66] are involved in the pathogenesis of POI. miRNAs as biomarkers aiming to facilitate diagnosis of disorders in the field of medicine. To determine the role that miRNA plays in POI pathophysiology and discovering possible new non-invasive biomarkers for the prediction of POI further studies are recommended.

Conclusions

Despite much progress in the treatment of infertility, POI is a more challenging issue and there is a lot of psychological stress in these patients. Oocyte donation is one of the therapeutic options in POI but these patients tend to get pregnant with their oocytes, and in some country and population oocyte donation are not accepted. There are several novel treatments for this condition including PRP intra-ovarian infusion, stem cell therapy, artificial gamete, and ovarian transplantation. These methods are still at the experimental level and further research should be done to investigate the short-term and long-term adverse effects of these procedures. A timely and correct diagnosis before the opportunity for fertility preservation is missed, can help patients with POI for biological parenting. Therefore, biomarkers for early accurate prediction of POI may aid infertility management in these patients. If POI could be diagnosed at an earlier age, these patients can be advised not to delay pregnancy or to do ovarian tissue cryopreservation for possible future transplantation to their ovaries to restore fertility. A specific non-invasive diagnostic test is particularly essential for a reliable early prediction of POI and is essential to detect concomitant or future associated disorders. For instance, identification of patients in whom immunomodulating therapy may restore, at least temporarily, ovarian function and fertility is very helpful in the management of these patients. Choice of treatment strategy based on etiology of POI may enrich the data required to practice individualized medicine.

More importantly, in some patients, there are no indications that the patients will go into POI soon. Patients with a family history of POI who the suspected of POI could benefit from such testing to diagnose the possibility of future POI. Discovering biomarkers for early prediction of POI may aid infertility management in these patients. The evidence is not enough to conclude which of these potential biomarkers are the best ones for early prediction of POI and further research and confirmation of their efficacy and safety is needed. It is worth mentioning that one of the most important limitations in the biomarker research area is cost. Proper biomarkers should be as much as possible most cost-effective and non-invasive. These issues should be in mind in future studies.

Abbreviations

POF: Premature ovarian failure; PCOS: Polycystic ovarian syndrome; POI: Premature ovarian insufficiency; AMH: Anti-Mullerian hormone; FSH: Follicle-stimulating hormone; SNPs: Single-nucleotide polymorphisms; EDCs: Endocrine disrupting chemicals; DHEA: Dehydroepiandrosterone; ROS: Reactive oxygen species; PRP: Platelet-rich plasma; ESCs: Embryonic stem cells; MSCs: Mesenchymal stem cells; iPSCs: Pluripotent stem cells; UCMSCs: Umbilical cord mesenchymal stem cells; hAD-MSCs: Human amnion derived mesenchymal stem cell; hPMSC: Human placenta mesenchymal stem cell; CP-MSCs: Chorionic plate-derived mesenchymal stem cells; HuMenSCs: Human menstrual blood stem cells; CBC: Complete blood count; INSL3: Insulin-like peptide 3; ADAMTS: Adisintegrin and metalloproteinase with thrombospondin motifs; ECM: Extracellular matrix; DEHP: Di-2-ethylhexyl phthalate; DUB: Deubiquitinating enzyme; APAs: Antiphospholipid antibodies; SBP1: Selenium binding protein 1; sTNFR2: Soluble fraction of tumor necrosis factor alpha receptor 2; PGCs: Primordial germ cell.

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Authors' contributions
Roya Kabodmehri and Nasrin Ghanami Gashti designed the project, collected the data, and wrote the manuscript. Seyedeh Hajar Sharami and Zahra Rafiei Sorouri collected the data and revised the manuscript. All authors read and approved the final manuscript.

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