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Literature Review

# A Literature Review of Stem Cells Therapy on Premature Ovarian Insufficiency

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## Abstract

**Introduction:** Premature ovarian insufficiency (POI) is defined as a primary ovarian defect, characterized by an absent menarche (primary menarche) or premature loss of ovarian follicles before 40 years of age (secondary amenorrhea). Hormone replacement therapy (HRT) has been used to treat POI. However, HRT both increases the risk for recurrence of cancer and fundamentally fails to restore normal ovarian function. Stem cell therapy has recently been identified as a potential and alternative therapeutic means of potentially repairing and restoring the normal function of damaged tissues, presenting a novel approach for clinical treatment of POI. Research on stem cell transplantation for the treatment of POI is mostly limited to preliminary animal experiments.

**Objective:** To elaborate stem cells therapy as one of the promising therapy on premature ovarian insufficiency.

**Method:** Based on literature review.

**Discussion:** Mesenchymal stem cells are multi-potent stem cells and the advantages of this cells are readily available and imperfectly (poorly) immunogenic. MSC can be derived from several tissues in the adult or infant human body, including adipose tissue, peripheral blood, umbilical cord blood, banked umbilical cord blood, umbilical cord membrane, umbilical cord vein, Wharton's jelly of the umbilical cord, placenta, decidua basalis, amniotic fluid, etc. MSC have been found to secrete growth factors, including VEGF, IGF-1, and HGF into culture medium, to reduce germ cell and stromal cell apoptosis, and to enhance folliculogenesis through improvements in the microenvironment. Moreover, human amniotic fluid stem cells (hAFSC) are stem cells obtained during amniocentesis procedures or at delivery and characterized by both embryonic-specific cell markers and mesenchymal-specific cell markers. The $CD44^+$/$CD105^+$ subpopulation can be directly sorted from human amniotic fluid and cultured for *ex vivo* expansion. Previous studies have demonstrated the ability of these cells to differentiate into ectodermal, endodermal, mesodermal, hepatic cells and cardiac muscle cells. Additionally, hAFSC express a variety of growth factors, including EGF, bFGF, TGF-β, and BMP-4. Lastly, induced pluripotent stem cells and ovarian stem cells are still under investigation.

**Conclusion:** The mechanism of stem cells to improve ovarian function is questionable because the ability of stem cells to develop *in vivo* into fully functional follicles is still rare; the transplanted stem cells have been proven to differentiate into GC-like cells much more easily than into oocytes.

***Keywords:*** *Stem Cells Therapy; Premature Ovarian Insufficiency; Follicles*

## Introduction

Premature ovarian insufficiency (POI) is defined as a primary ovarian defect, characterized by an absent menarche (primary menarche) or premature loss of ovarian follicles before 40 years of age (secondary amenorrhea). POI is relatively common, affecting around

1-3% of women in the reproductive age below 40 years and around 0.1% in women below 30 years of age. Incidence of spontaneous onset POI has increased due to increasing success rate of cancer treatment in girls and young women [1].

Hormone replacement therapy (HRT) has been used to treat POI and should be provided to eliminate symptoms of estrogen deficiency, although there are no data indicating that these young women are at increased risk of side effects from HRT. However, HRT both increases the risk for recurrence of cancer and fundamentally fails to restore normal ovarian function [2-4].

Stem cell therapy has recently been identified as a potential and alternative therapeutic means of potentially repairing and restoring the normal function of damaged tissues, presenting a novel approach for clinical treatment of POI. It has been argued that mechanisms involved in these stem cells can restore ovarian function for the following reasons: (1) The *in vivo* evidence of their ability to develop into fully functional follicles is still rare. (2) The transplanted stem cells have been proven to differentiate into GC-like cells much more easily than into oocytes. (3) The improved ovary after stem cell transplantation is a complex mix of many unclear factor requiring further investigation. (4) Stem cell therapy for POI may increase ovarian granulosa cell tumour (GCT) occurrence. Previous pre-clinical studies have revealed that the transplantation of stem cells into animal models of POI restores ovarian function and generates immature oocytes. However, research on stem cell transplantation for the treatment of POI is mostly limited to preliminary animal experiments [5,6].

## Premature ovarian insufficiency

Premature ovarian insufficiency (POI) also known as premature ovarian failure or hypergonadotropic ovarian failure or menopause precocity is defined as a primary ovarian defect, characterized by an absent menarche (primary amenorrhea) or premature loss of ovarian follicles before 40 years of age (secondary amenorrhea). Characteristic features include cessation of ovulation or amenorrhea for 4 months or more, hypoestrogenism (estradiol levels < 50 pg/mL) and high serum gonadotropin levels, especially two serum follicle-stimulating hormone (FSH) level (> 4 weeks apart) in menopausal range (> 40 IU/L) [1,2].

The exact mechanism for development of POI is not known. It can be due to: (1) preliminary decrease in primordial follicle pool, (2) accelerated atresia of follicles, and (3) defective maturation/recruitment of primordial follicles. Furthermore, accelerated follicular atresia can be due to apoptosis rate change, defective follicle maturation blocking, and abnormalities in primordial follicle activation that causes decreased number of available functional follicles/accelerated atresia [1,5,6,8].

## Stem cells therapy on premature ovarian insufficiency

Risk of cancer increases after the use of HRT, 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. Stem cells have general properties such as ability to divide, they are unspecialized and are able to renew themselves. In stem cell-based therapy for infertility, embryonic stem cell (ESC), mesenchymal stem cell (MSC), stem cells form extra-embryonic tissues, induced pluripotent stem cells (iPSC), and ovarian stem cell are used [3,4,7].

## Mesenchymal stem cell (MSC)

Mesenchymal stem cells are multi-potent stem cells and the advantages of this cells are readily available and imperfectly (poorly) immunogenic. MSC can be derived from several tissues in the adult or infant human body, including adipose tissue, peripheral blood, umbilical cord blood, banked umbilical cord blood, umbilical cord membrane, umbilical cord vein, Wharton's jelly of the umbilical cord, placenta, decidua basalis, amniotic fluid, etc. MSC have been found to secrete growth factors, including VEGF, IGF-1 and HGF into culture medium, to reduce germ cell and stromal cell apoptosis, and to enhance folliculogenesis through improvements in the microenvironment [7,13,14].

A study done in 2015 by Lai., *et al.* reported that human endometrial mesenchymal cells (EnSC) isolated from menstrual blood improved estrous cycle and restored fertility in mice. In autologous cell repair and regeneration, EnSC present major advantages over other

sources of MSC, including ease of access and the ability to achieve repeated sampling in a non-invasive manner. Significantly, EnSC exhibit low immunogenicity and possess immunoregulatory functions [3,7].

### Extra-embryonic stem cell

Human amniotic fluid stem cells (hAFSC) are stem cells obtained during amniocentesis procedures or at delivery and characterized by both embryonic-specific cell markers and mesenchymal-specific cell markers. The $CD44^+/CD105^+$ subpopulation can be directly sorted from human amniotic fluid and cultured for *ex vivo* expansion. Previous studies have demonstrated the ability of these cells to differentiate into ectodermal, endodermal, mesodermal, hepatic cells, and cardiac muscle cells. Additionally, hAFSC express a variety of growth factors, including EGF, bFGF, TGF-β, and BMP-4. More importantly, hAFSC lacks MHC class II antigens and express only low levels of MHC class I antigens [12,17].

### Induced pluripotent stem cell (iPSC)

Induced pluripotent stem cell could be another source of MSC. iPSC can be obtained with minimally invasive procedures, and avoid the ethical concerns about embryo use and hESC. A study done by Liu et al. showed the differentiation of human iPSC cells into hormone-sensitive ovarian epithelial (OSE)-like cells by use of microRNA-17-3p in order to suppress the expression of vimentin and fibronectin so estradiol and ovarian weight increased. Thus, iPSC derived ovarian granulosa-like cells (OGLC) transplanted into POI mice caused growth in ovarian tissues, increase in the estradiol, and reduction of atretic follicles number [7,13].

### Ovarian stem cell

Recent studies have rejected the belief that adult mammalian ovary is endowed with a fixed number of oocytes. New studies in mice, rats, and humans have revealed the presence of germ-line stem cells (GSC) in ovary that will improve infertility treatment. Putative ovarian mesenchymal stem cells (PO-MSC) existing in ovarian cortex biopsies are different from fibroblasts also express CD44, CD90 and stromal cell precursor surface antigen (STRO-1) [7,12].

## Conclusion

1. Premature ovarian insuffiency is a diagnosis that is often considered a threat to a woman's identity: infertility, which affects the woman's emotional, physical-spiritual health. There is a 5 - 10% chance of spontaneous conception. However, there is no proven strategy to increase the chances of conception through ovarian function.
2. Recent studies illustrated that stem cells can differentiate into ovarian follicles while restoring ovarian function. Scientists tried to calculate the efficiency of stem cells in POI therapy. Adult ovarian stem-line stem cells can replenish oocytes, but many things are still unknown from these cell lines so further research is needed. Another important point is to prove the safety of stem cell transplantation in ovaries.
3. Mesenchymal stem cells are the most efficient and good candidates (low immunogenicity) to be implicated in POI therapy. Other degenerative and immune-related diseases have been reported as responding to MSC transplantation. These cells can be obtained from various tissue such as bone marrow, adipose, umbilical, placenta, amniotic fluid, endometrium, wharton's jelly, and menstrual blood that successfully to be concern of previous studies. Various studies reported that MSC can improve ovarian function through antiapoptotic, antifibrosis, anti-inflammatory, and immunoregulatory effects.
4. The mechanism of stem cells to improve ovarian function is questionable because the ability of stem cells to develop *in vivo* into fully functional follicles is still rare; the transplanted stem cells have been proven to differentiate into GC-like cells much more easily than into oocytes.

## Bibliography

1. Kumar N and Manesh I. "Premature ovarian insufficiency: Aetiology and long term consequences". *International Journal of Women's Health* 3.2 (2017): 45-58.
2. Rebar RW. "Premature Ovarian Failure". *The American College of Obstetrician and Gynecologist* (2009).
3. Wang Z., *et al*. "Study of the reparative effects of menstrual-derived stem cells on premature ovarian failure in mice". *Stem Cell Research and Therapy* (2017).
4. Chen L., *et al*. "Effect of stem cell transplantation of premature ovarian failure in animal models and patients: A meta-analysis and case report". *Experimental and Therapeutic Medicine* (2017).
5. Nelson LM. "Primary Ovarian Insufficicency". *New England Journal Medicine* 360.6 (2009).
6. Dan S., *et al*. "Pathogenesis and stem cell therapy for premature ovarian failure". *OA Stem Cells* 2.1 (2014): 4.
7. Sheikhansari G., *et al*. "Current approaches for the treatment of premature ovarian failure with stem cell therapy". *Biomedicine and Pharmacotherapy* (2018).
8. Rafique S., *et al*. "A New Approach to Primary Ovarian Insufficiency". *Journal of Obstetric and Gynecology Clinical North American* (2012).
9. Torrealday S., *et al*. "Premature Ovarian Insufficiency - an update on recent advances in understanding and management". *F1000 Research* 6 (2017): 2069.
10. Hayashi K., *et al*. "Reconstitution of mouse oogenesis in a dish from pluripotent stem cells". *Protocol Extension* (2017).
11. Dan S., *et al*. "Pathogenesis and stem cell therapy for premature ovarian failure". *OA Stem Cells* 2.1 (2014): 4.
12. Vanni VS., *et al*. "Advances in improving fertility in women through stem cell-based clinical platforms". *Expert Opinion on Biological Therapy* (2017).
13. Yoon SY. "Mesenchymal stem cells for restoration of ovarian function. Clinical Expertise Reproductive Medicine". *The Korean Society for Reproductive Medicine* (2019).
14. He Y., *et al*. "The therapeutic potential of bone marrow mesenchymal stem cells in premature ovarian failure". *Stem Cell Research and Therapy* (2018).
15. Mohamed SA., *et al*. "Umbilical Cord Blood Mesenchymal Stem Cells as an Infertility Treatment for Chemotherapy Induced Premature Ovarian Insufficiency". *Biomedicines* (2019).
16. Lai D., *et al*. "Human endometrial mesenchymal stem cells restore ovarian function through improving the renewal of germline stem cells in a mouse model of premature ovarian failure". *Journal of Translational Medicine* (2015).
17. Liu T., *et al*. "$CD44^+/CD105^+$ Human amniotic Fluid Mesenchymal Stem Cells Survive and Proliferate in the Ovary Long-Term in a Mouse Model of Chemotherapy-Induced Premature Ovarian Failure". *International Journal of Medical Sciences* (2012).

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