Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Review Article

J Exp Clin Med
2023; 40(1): 122-126
doi: 10.52142/omujecm.40.1.26

Stem cell applications in female infertility – A rewiev

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Received: 25.07.2022 • **Accepted/Published Online:** 01.10.2022 • **Final Version:** 18.03.2023

Abstract

Infertility is a problem that affects approximately 15% of couples today. Although assisted reproduction techniques are widely used today, only 40-50% of couples who apply can have children with their own genetic structure. Especially in people with premature ovarian failure, the rate of conception does not exceed 5-10% with the treatments applied today. For this reason, many studies are carried out to obtain oocyte from stem cells with their proliferation and differentiation feature. In addition, regenerative cellular therapies that can replace assisted reproductive techniques and correct impaired fertility are also being investigated in both animal and human studies. In recent years, research has been carried out on stem cell-derived extracellular vesicles, which will eliminate immunological problems. In terms of safety and efficacy, clinical studies involving large populations are needed.

Keywords: infertility, premature ovarian failure, embryonic stem cells, adult stem cells

1. Introduction

Infertility is not being able to conceive despite one year of regular, unprotected intercourse (1). Infertility is encountered approximately in 12–15% of couples and 72 million people worldwide are diagnosed with infertility (2).

Despite all the developments in assisted reproduction today, most infertile patients cannot get pregnant with these methods. For this reason, stem cells are intensively investigated as an alternative method in the treatment of infertile patients (3,4,5,6,7,8,9,10,11).

It can be used as an alternative method in the treatment of infertility, as well as in the treatment of pathologies that indirectly cause infertility. These four diseases are as follows:

Premature Ovarian Failure (POF): According to the definition made by the European Society of Human Reproduction and Embryology (ESHRE), it is defined as a condition under 40 years of age, defined as oligo/amenorrhea lasting at least 4 months and Follicle Stimulating Hormone (FSH) value >25 IU/l measured at least 4 weeks apart. Its incidence has been reported to be 1% on average (13). The etiology of the disease has not been fully elucidated and genetic, environmental, enzymatic, infectious and iatrogenic factors are blamed (14). Current treatments are insufficient and different treatment modalities are needed.

Polycystic ovary syndrome (PCOS): It is a cause of infertility that causes increased ovarian function and anovulation. It is characterized by high androgen levels, irregular menstruation and the presence of numerous small cysts in the ovary. Its incidence is among 5-10% women of reproductive age and it is the most common endocrine disorder among women of reproductive age (15,16). Current treatments are inadequate in many patients. Regenerative medicine applications are being investigated in the treatment of inflammatory and immunological processes.

Endometriosis: It is a chronic inflammatory disease in which the basal layer of the endometrium is located outside the uterine cavity. Its frequency is between 6% and 10% and it is a multifactorial disease (17). Genetic, environmental and immunological mechanisms are involved in its pathogenesis. Today, treatments for infertility and pain cannot provide sufficient success for these patients.

Asherman's Syndrome: It is characterized by intrauterine adhesions, hypomenorrhea, or amenorrhea. Scar tissue formed in the uterus may disrupt embryo implantation and cause infertility or recurrent pregnancy loss (18). There is a history of pregnancy-related curettage in 90% of the patients. Although hysteroscopy and hormonal treatments are applied today, developments in regenerative methods may increase the success in the management of the disease.

Stem cells are undifferentiated cells found in embryo or adult tissues. These cells are cells that can renew themselves or differentiate when necessary.

Stem cells are divided into embryonic stem cells, induced pluripotent stem cells, adult mesenchymal stem cells, spermatogonial stem cells and ovarian stem cells according to

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their origin.

Embryonic stem cells are cells that can transform into all three germ sheets obtained from the inner cell mass of the embryo. It has been observed that both human and mouse embryonic stem cells are transformed into primordial germ cells in vitro, from which male and female gamete cells are formed by meiosis (19). It has also been shown that embryonic stem cells are effective in the restoration of endometrial tissue (20). However, due to ethical concepts, studies on the subject are limited.

Induced pluripotent stem cells were obtained from mouse fibroblast culture in 2006 and it has been shown that they can form all three germ sheets and maintain the same karyotype as embryonic stem cells (21). Since these cells are produced from adult cells, ethical problems caused by embryos are eliminated. In addition, since it is produced from people's own cells, immunological reactions are also less (22). Eguizabal et al. produced haploid gamete-like cells from keratinocytes and cord blood. They used a culture medium containing retinoic acid. Then forskolin, human recombinant leukemia inhibiting factor (LIF) and CYP26 inhibitor R115866 were used (23). Ramathal et al., on the other hand, transplanted skin cells from azoospermic and fertile men, together with Bone morphogenetic protein 4 (BMP4), Bone morphogenetic protein 8 (BMP8), retinoic acid (RA) and LIF, into mouse testis and studied germ cells. Ramathal et al. transplanted skin cells from azoospermic and fertile men together with BMP4, BMP8, RA and LIF into mouse testis and obtained germ cell-like cells (GCLCs) (24). Sasaki et al. human induced pluripotent stem cells in the presence of Activin A, CHIRON, BMP4, stem cell factor (SCF), epidermal growth factor (EGF) and LIF in human primordial stem cells. demonstrated that they can transform into germ cells. These cells are epithelial cell adhesion molecule (EpCAM) and Integrin α6 are distinguished from other cells by markers (25). Another study showed that human fibroblast-derived induced stem cells were transformed into spermatogenic cells both in a normal culture medium and by xenotransplantation (26). In their study, Yamashiaro et al. (27) and Gell and Clark (28) first transformed somatic cells into induced stem cells, then incipient mesoderm-like cells (iMeLCs) with Activin A and Chiron and then into human primordial germ cells and these cells were transformed into female mouse embryonic cells. Oogonia cells were obtained by culturing with ovarian-derived gonadal cells. Although induced pluripotent stem cells are promising, they carry teratogenic potential and the use of nucleic acid integration procedures, epigenic changes and genomic instability limits their use in treatment (29,30,31).

Mesenchymal stem cells are cells that can transform into osteoblasts, adipocytes and chondroblasts containing CD105, CD73 and CD90 surface antigens (32). These can be stem cells from bone marrow, stem cells from adipose tissue, stem cells from menstrual blood, stem cells from the umbilical cord and stem cells from amniotic fluid, depending on the tissue from which they are obtained. Mesenchymal stem cells contribute to the restoration of the ovary by going to the damaged ovarian tissue and secreting various cytokines. It increases new vessel formation with insulin-like growth factor (IGF-1), vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) and reduces apoptosis and fibrosis. The proliferation and differentiation abilities of mesenchymal stem cells decrease with age (33). Increased telomerase activity causes fetal stem cells to live longer than adult stem cells (34). Fetal mesenchymal stem cells can also be obtained from extraembryonic tissues such as amnion, umbilical cord, and placenta. Fetal stem cells contain CD105, CD29 and CD90, which are the surface markers of mesenchymal cells, as well as Octamer-binding transcription factor 4 (Oct-4), Nanog and Rex-1 markers of pluripotent cells (34). Fetal and adult mesenchymal stem cells use different pathways (35). For example, it was observed that fetal mesenchymal cells act through melatonin membrane receptor and antioxidant activity in mouse ovary damaged by cyclophosphamide (36).

Bone marrow-derived stem cells were obtained by Owen and Friedenstein in 1988 (37). Jing et al. showed that bone marrow-derived stem cells increased endometrial thickness after intravenous injection in mice while increasing anti-inflammatory cytokines and decreasing inflammatory cytokines (38). Wang et al. found that bone marrow-derived stem cells injected intravenously or directly into the uterus of mice with which they formed intrauterine adhesion increased the estrogen-progesterone receptor of the endometrium and decreased the fibrotic area. has shown to increase glands (39). Abd-Allah et al. provided the restoration of ovarian follicles by downregulating the FSH receptor of bone marrow-derived stem cells, downregulating the estrogen and upregulating the VEGF receptor in mice, in which they caused ovarian failure by giving cyclophosphamide in rabbits (3). Santamaria et al., in a prospective study of patients with Asherman syndrome, gave CD133+ bone marrow-derived stem cells to spiral arterioles and 10 of 16 patients became pregnant spontaneously or after the transfer (5).

Menstrual blood-derived stem cells are cells that can differentiate and proliferate like other mesenchymal stem cells and are obtained noninvasively. Liu et al. found that in the treatment with menstrual blood-derived stem cells in mice with premature ovarian failure with cyclophosphamide, Anti-Müllerian Hormone (AMH), Inhibin and estrogen levels improved and ovarian functions improved compared to the control group (40). Zheng et al., in their study, transformed MB-Mesenchymal stem cells (MB-MSC) cells into endometrial cells in vitro and then transplanted them into mice with adhesions in vivo to regenerate the endometrium (41). The ability to differentiate cells of menstrual origin comes from the presence of the OCT-4 transcription factor. Tan et al. used menstrual stem cells together with hormonal therapy in seven Asherman patients, while five patients became pregnant on

their own, while two patients became pregnant after the transfer (42).

Endometrial stem cells stromal consists of epithelial and endothelial cells. Stromal ones contain CD44, CD73 and CD90 but CD34 and CD45 are negative, epithelial ones are stage-specific embryonic antigen (SSEA-1), N- cadherin and NTDPase2 are positive, endothelial ones are in CD 31 and CD 34 phenotype (43). endometrial in the absence of injury, these cells remain silent. In the presence of endometrial damage, these cells are directed to the damaged area by means of chemokines and C-X-C chemokine receptor type 4 (CXCR4) (44).

Umbilical cord-derived stem cells are CD29, CD44, CD73, CD90 and CD105 positive, CD31, CD45 and HLADR-85 negative. It is very advantageous to obtain easily, low tumor risk and low immunological response. In animal POI models, the ovarian function has been shown to provide ovarian restoration by antiapoptotic activity in granulosa cells, decreasing FSH levels and increasing estrogen and progesterone (45,46). In addition, the dehydroepiandrosterone-induced mouse PCOS model has been shown to reduce inflammatory cytokines and improve infertility (47). Umbilical-derived stem cells prevent granulosa cell apoptosis by using various signaling pathways. Mitogen-activated protein kinase signaling pathway, G protein-associated receptors and insulin signaling pathways (48). In animal models, umbilical cord-derived stem cells have been shown to be beneficial by interfering with damaged endometrial cells by changing vascularity and inflammation (49). In addition, it was seen that it showed the same effect by activating matrix metalloproteinase 9 (50). In premature ovarian failure patients, it phosphorylates transcription factor forkhead box protein O3a (FOXO3a) and Forkhead Box protein O1 (FOXO1), providing primordial follicle activation and thus increasing the number of follicles (51)

Amniotic fluid-derived stem cells are frequently used in regenerative medicine due to their immunoregulatory properties and their ability to differentiate. VEGF, *Transforming growth factor* alpha and beta (TGFα and β) of these cells' growth It has been shown to improve ovarian function by activating factor (EGF) and bone morphogenic protein (BMP) signaling pathways (48). In mouse POF models, these cells are follicular especially if they have CD4C/CD105+ antigen. It has been shown to prevent atresia and restore ovarian function (52,53).

Amnion-derived mesenchymal stem cells ovarian in POF animal model's dysfunction prevents (54.55). Besides, inflammatory it decreases cytokines, increases neovascularization, and reduce apoptosis.

Placenta-derived mesenchymal stem cells increase folliculogenesis by activating the Phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase B (PI3K/Akt) signaling pathway in animal POF models and restore ovarian function by changing the expression of hormones and receptors (56,57). Li et al. inositol-requiring ovarian cells using enzyme 1 (IRE 1) α pathway. showed that it corrects the dysfunction (58).

Adipose tissue-derived mesenchymal stem cells are frequently preferred because of their easy availability. In animal experiments, snowed that when the ovarian graft is applied together with the stem cell, it gains function faster by increasing VEGF expression (59). It has been shown to increase neovascularization and follicle proliferation in mouse ovarian defects induced by chemotherapy (60). It has been observed that mesenchymal stem cell and hormone therapy accelerate endometrial regeneration in Asherman syndrome (61).

Ovarian stem cells: In 2012, White et al. obtained stem-cell-specific marker VASA-positive cells from the human ovarian cortex and showed that follicle synthesis occurred after xenotransplantation of these cells into diabetic immunodeficient mice (62). However, the fact that these cells are very few in number and decrease with age has unfortunately hindered the progress of research. In addition, differentiation of these cells in vitro culture medium takes quite a long time.

Today, mesenchymal stem cell-derived extracellular vesicles are used to reduce the immunological reactions of stem cell therapy (63). However, although all these methods are promising, many studies are needed before they can be put into routine practice.

Conflict of interest

The authors have no conflicts of interest to declare.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

None to declare.

Authors' contributions

Concept:A.Z.Ö.,A.Ş.T.,Design:A.Z.Ö.,A.Ş.T.,Data Collection or Processing:A.Z.Ö.,A.Ş.T.,Analysisor Interpretation:A.Z.Ö., A.Ş.T.,Literature Search:A.Z.Ö., A.Ş.T.,Writing:A.Z.Ö., A.Ş.T.

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