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Research Progress on New Methods to Prevent and Treat Ovarian Senescence: A Review

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ABSTRACT

Ovarian senescence is a special type of organ senescence and the ovaries are the earliest aging organs. The ovaries have approximately 1 million to 2 million follicles at birth, but only approximately 1000 primordial follicles are left in menopause. Ovarian function also decreases with age. Women's fertility also declines. The ovaries are the core female reproductive organs and are of great significance for maintaining reproductive system function and endocrine stability. Ovarian aging is also considered an indicator of female body aging, which drives the aging of many organs of the body. Therefore, how to prevent and treat ovarian aging has become a research question that has been widely studied by biomedical scientists and geriatric researchers in recent years. Recently, studies have shown that bone marrow mesenchymal stem cells (BMSCs) can prevent and treat ovarian aging. This article reviews the characteristics of ovarian aging, the advantages and disadvantages of various clinical treatment measures and the advantages of bone marrow mesenchymal stem cell therapy, aiming to provide references for the prevention and treatment of ovarian aging. My article was written at the Basic Medical Laboratory of the 920th Hospital of the Joint Logistics Support Force of PLA and written from 2021 to 2022.

Key words: Bone marrow mesenchymal stem cells, Clinical treatment, Ovarian senescence, Stem cell, Transplantation.

Since the implementation of the two-child policy in China, an increasing number of elderly women have chosen to have children again and the number of age-dependent infertility patients is increasing. The problem of how to prevent and treat ovarian aging has become more prominent in this social situation. Improving the ovarian function of elderly women and improving the quality of oocytes are essential to solve the infertility caused by reproductive aging (Pacu *et al*., 2014). Ovarian aging, including physiological ovarian aging and pathological ovarian aging, is affected by various factors, such as age, heredity, environment and lifestyle (Li *et al*., 2015). Physiological ovarian aging is the natural aging process of ovarian function affected by age, while premature ovarian failure (POF) and premature ovarian insufficiency (POI) are pathological ovarian aging processes. At present, the main treatment measures for ovarian aging include hormone replacement therapy, immunotherapy, ovarian tissue cryopreservation and transplantation. Although these treatment measures can improve the symptoms of ovarian aging and promote the fertility of patients, they cannot fundamentally restore ovarian function and there are ethical concerns and adverse reactions. Therefore, finding an efficient and safe treatment method to restore ovarian function is a top priority in geriatric research (Keyvani *et al*., 2019).

Characteristics of ovarian aging

Ovarian aging in women is characterized by a gradual decline in the number and quality of follicle-containing oocytes in the ovarian cortex, which eventually manifests as sterilization and menopause (Awad, 2020). In mammals, a fixed population of primordial follicles is established in the early ovary and serves as the source of follicle and oocyte development throughout the reproductive life of the organism. Ovarian aging inevitably occurs throughout an organism's lifespan, regardless of whether new follicles are formed during adulthood. It has been reported that the decrease in oocyte quality with ovarian aging is mainly due to aneuploidy in the early embryo caused by meiotic nondisjunction (Demko *et al*., 2016). As a woman ages, when the number of primordial follicles drops below 1000, her primordial follicle pool will gradually and steadily shrink and menopause will occur (Pu *et al*., 2017). Despite the gradual loss of primordial follicles over time, their relative abundance makes them an attractive source of material to combat ovarian aging.

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Several current treatment methods for treating ovarian aging and their advantages and disadvantages

Hormone replacement therapy

This therapy is a treatment method that involves supplementing estrogen and progesterone in postmenopausal women with estrogen deficiency to relieve their menopausal symptoms. Through periodic supplementation with estrogen and progesterone, the negative feedback regulation of the hypothalamic-pituitary-ovarian (HPO) gonadal axis reduces FSH levels and restores the sensitivity of follicles to gonadotropins (Comhaire, 2016).

Methods using HRT offer a potential physiological solution for the timely control of hormone release and restoration of HPO gonadal axis function. HRT can be effective because its use after a transplant restores the natural hormonal environment and endocrine function of the ovaries and 4-5 months after transplantation, estradiol levels rise, FSH and LH levels fall, returning to premenopausal levels and leading to the cessation of menopausal symptoms and recovery of the menstrual cycle in the vast majority of transplant patients (Jensen *et al*., 2015; Gellert *et al*., 2018). However, it cannot restore reproductive function. Long-term use will increase the probability of breast cancer and endometrial cancer and relapse can easily occur after drug withdrawal. Patients with premature ovarian failure who do not have fertility requirements often use this therapy (Kalantaridou *et al*., 2006).

Immunosuppressive therapy

This is one of the main treatment methods for patients with ovarian aging. It is mainly aimed at those with positive immune tests. Glucocorticoids are often used in clinical practice because the immune-mediated process will be temporarily reversed in the short-term use of high-dose glucocorticoids and adrenocorticoid therapy for autoimmune antibody-positive patients (Comhaire, 2016).

However, there are some doubts about immunotherapy. To date, there is no clear method to determine the role of immune factors in the treatment of ovarian aging and there is no clear indication or standardized drug regimen for immunotherapy. The blind application of immunosuppressive therapy to patients with ovarian aging may cause serious adverse reactions, so the clinical selection of immunotherapy should be done with caution.

Assisted reproductive technology

With the increase in the development of assisted reproductive technology, IVF has become the first choice for many patients with premature ovarian failure. The main assisted reproductive technology used in China is *in vitro* fertilization. This technology is *in vitro* embryo transfer (IVF-ET), which fertilizes the egg of the donor with the male's sperm *in vitro*. Before fertilization, estrogen and progesterone replacement therapy should be given to promote the complete exfoliation of the endometrium and prepare for further embryo transfer (Toner *et al*., 2016).

Although assisted reproductive technology continues to develop, it still faces ethical controversy, a low success rate, an insufficient egg reserve and a high cost in clinical practice. This method is often used in patients with premature ovarian failure who have a desire for fertility and the clinical operation is often carried out at the same time as hormone replacement therapy.

Cryosurgery preserves reproductive capacity

The use of cryopreservation to preserve the reproductive capacity of patients is a common treatment plan that includes the three methods of freezing eggs, freezing embryos and freezing ovaries (Bach *et al*., 2020). Cryopreserved cells and tissues can be transplanted after menopause when ovarian function is no longer present, but several procedures may be required to achieve the long-term recovery of ovarian function (Kolibianaki *et al*., 2020). Embryo freezing is suitable for married women. The use of ovulation-stimulating drugs promotes the maturation of follicles. The mature follicles and sperm are combined into embryos *in vitro* and the embryos are frozen. The success rate of embryo freezing is much higher than that of egg freezing. Ovarian tissue cryopreservation refers to the cryopreservation of mature oocytes or immature oocytes and primordial cells, which are then thawed and transplanted into the recipients. At present, ovarian cryopreservation has achieved success in animal experiments, but human ovarian cryopreservation still requires further research (Rodriguez-Wallberg *et al*., 2016; Syafruddin *et al*., 2018).

In most cases, transplantation restores ovarian function (Yding Andersen *et al*., 2019). However, it is unclear whether it maintains the normal pulsatile secretion of steroids or how long it lasts, but given the small pool of follicles contained in the graft, it may be similar to perimenopause. Therefore, perimenopausal symptoms such as hot flashes, sleep disturbances and abnormal uterine bleeding may still occur. There are still many technical difficulties in frozen ovarian transplantation, including minimizing the damage to egg cells caused by freezing and thawing, making immature egg cells and primordial cells mature *in vitro* and finally being able to fertilize the eggs and induce pregnancy. In addition, the ovaries of cancer patients may have egg cells that contain oncogenes that will be implanted. Even if allogeneic transplantation is possible, there are still safety concerns. At the same time, the technical problems of egg freezing and lysis and ischemia-reperfusion injury of the transplanted tissue have not been completely solved. Ovarian tissue freezing to delay menopause is an invasive method that requires at least one laparoscopic surgery and one or more transplants to restore and maintain ovarian function. Although the risks associated with laparoscopy are small, they cannot be ignored.

Mitochondrial transplantation therapy

In oocytes, mitochondria play an important role and are the main source of ATP during preimplantation embryonic development. Impaired energy metabolism of oocytes is an

important cause of decreased quality of oocytes and embryos in aging ovaries (Tilly and Sinclair, 2013). It is widely believed that mitochondrial dysfunction in oocytes is a key factor in the poor developmental potential of oocytes in older women and a number of approaches, including drug therapy, cytoplasmic transfer, nuclear transfer and mitochondrial transfer, have been used to enhance mitochondrial growth in aging oocytes and their integrity, activity and quantity (Darbandi *et al*., 2017). Studies have also shown that cytoplasmic transfer can significantly promote embryonic development, pregnancy and a healthy fetus.

This transplantation technique has a complex composition and heterogeneity of mitochondrial genes, which would lead to several ethical issues, which led to its suspension by the US Food and Drug Administration (FDA) in 2002 (Darbandi *et al*., 2017). In addition, allogeneic mitochondrial transplantation, the extraction of unfertilized oocytes of patients with mitochondrial abnormalities and transplantation into enucleated donor oocytes containing healthy mitochondria, is not fully clinically effective and there are ethical disputes involving the two mtDNA genomes (Sharpley *et al*., 2012). It has been reported that autologous mitochondrial transplantation can significantly improve oocyte quality in elderly women and increase the success rate of pregnancy (Woods and Tilly, 2015), but some studies have pointed out that autologous mitochondrial transplantation does not improve oocyte quality (Sheng *et al*., 2019). Therefore, the safety and efficacy of mitochondrial transplantation remain to be confirmed.

Prevention and treatment of ovarianaging using bone marrow mesenchymal stem cells

Stem cell transplant therapy

With the development of regenerative medicine, various types of stem cells provide new directions for the treatment and repair of aging or damaged tissues and stem cell therapy is also considered a new way to treat ovarian aging. Stem cells are defined as pluripotent cells with the ability to self-renew and differentiate into a variety of cell types and can be divided into two broad categories: embryonic stem cells, which are derived from the inner cell mass of the blastocyst and have the ability to proliferate indefinitely and embryonic stem cells that exist throughout the tissues of the body, such as adult stem cells of the brain, bone marrow, pancreas, liver, skin and skeletal muscle and are critical for tissue maintenance and regeneration (Rumman *et al*., 2015; Mingli and Guan, 2016). The development of stem cell transplantation- based therapies to combat age-related functional decline has recently attracted considerable attention because of stem cells' potency to differentiate into and generate all cell types offers new opportunities for regenerative medicine and in fact, has been observed in various aged tissues. Stem cell genotypes exhibit an attenuated response to tissue damage, dysregulated proliferation and reduced regenerative potential (Yeo *et al*., 2021). Stem cell therapy is a recently emerged method for treating ovarian aging. After orthotopic transplantation of mononuclear cells from human umbilical cord blood into a rat model of premature ovarian failure, the levels of estrogen in the rats increased and the levels of LH and FSH decreased (Kim *et al*., 2020). At the same time, the discovery of germinal stem cells in human ovarian tissue after birth also brings hope of treatment for women with ovarian insufficiency and premature ovarian failure (Jiao *et al*., 2020). After mice with premature ovarian failure were injected with bone marrow-derived mesenchymal stem cells through the tail vein, new primordial follicles were formed in the ovaries of the mice, which stimulated the recovery of ovarian structure and tissue (Badawy *et al*., 2017; Kim and Lee, 2022). To date, clinical trials of stem cell transplantation have shown that, although the live birth rate remains low, stem cell therapy for POI is not only histopathologically promising but also does not have any major risks or adverse effects in terms of clinical outcomes (Bao *et al*., 2018).

Bone marrow mesenchymal stem cells

Relevant studies in recent years have shown that several aspects of mammalian aging are associated with an age-related decline in adult somatic stem cell function; that is, aging may reflect the depletion of adult stem cells (Kattekola, 2021). It is not surprising that age-related pathology and rejuvenation of aged tissues are of great interest. The fact that adult stem cells remain in tissues throughout life makes them particularly sensitive to the accumulation of cellular damage, which can ultimately lead to cell death, senescence and loss of regenerative potential. As a kind of adult stem cell, bone marrow mesenchymal stem cells (BMSCs) have become the main focus of regenerative medicine researchers due to their advantages of multidifferentiation potential, low immunogenicity and easy access. BMSCs have been confirmed to differentiate into bone, cartilage, muscle, fat, nerve cells, *etc*. A large number of studies have shown that BMSCs contribute to tissue damage repair (Fu *et al*., 2008; Farjah *et al*., 2018; Bahrehbar *et al*., 2020). In the field of reproduction, BMSCs have shown certain advantages. Fu *et al*. (2008) demonstrated that BMSCs can repair ovarian structural damage after intraperitoneal transplantation. Some studies have shown that the size, shape and estrous cycle of the ovaries after transplantation of MSCs in animal models are restored to a certain extent and a significant increase in the number of ovarian follicles at all levels, granulosa cell growth and anti-granulosa cell apoptosis can also be observed in pathological tissue sections. Endocrine function can also be improved and fertility may even be restored (He *et al*., 2018).

Famous foreign scholars (Mohamed *et al*., 2018) proposed in 2018 that impaired reproductive performance can be treated by allogeneic bone marrow mesenchymal stem cell transplantation, which may be due to the immunogenicity of soluble drugs and cell contact and the secretion of growth factors and chemokines, to express

extracellular matrix receptors on the surface of mesenchymal stem cells, thereby promoting the interaction between CXCR-4/SDF-1 and CD44 hyaluronic acid; this is achieved through the production of apoptosis-inhibiting molecules [such as vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β)] that help repair damaged tissue and promote angiogenesis, immunomodulation [such as interleukin-10 (IL-10) and interleukin-6 (IL-6)] and anti-inflammatory fibrosis, thereby exerting a therapeutic effect (Isik *et al*., 2017). Studies have shown that after systemic transplantation, BMSCs migrate to the injury site and play an immunomodulatory role, promoting tissue repair through growth factors and signaling molecules that guide the regeneration of resident tissue cells (Yeo *et al*., 2021; Jaiswal *et al*., 2020).

The clinical utility of MSCs is undeniable and many women with age-related or nonage-related complications of infertility have benefited from this therapy over the past few years; dormant live oocytes can also be reconstituted after MSC-based therapy (Isik *et al*., 2017). Bone marrow-derived mesenchymal stem cell transplantation for POF patients can improve hormone levels, restore menstruation, increase pregnancy rates and promote healthy full-term infant delivery (Chen *et al*., 2018).

CONCLUSION AND OUTLOOK

Low fertility caused by ovarian aging is an important factor affecting delayed fertility. In recent years, increasing attention has been given to the prevention and treatment of ovarian aging. However, the mechanism of ovarian aging is complex and the reasons are diverse, resulting in difficult clinical interventions and different outcomes. The clinical intervention of the disease requires a hierarchical and individualized diagnosis and treatment based on the etiology and there is currently no unified standard. Some interventions currently used in clinical practice have certain limitations and it is difficult to fundamentally improve ovarian function and fertility. Therefore, it is urgent to find a safe and economical method for treating premature ovarian failure and infertility. In recent years, basic research has made great progress in the field of stem cell transplantation therapy and some research results have been applied in various clinical trials involving tumor diseases, autoimmune system diseases, nervous system diseases, cardiovascular diseases, *etc*. In terms of research, many clinical data have also been obtained and many reports related to the clinical application and research of stem cells have been published. At present, clinical BMSC treatment is mainly used in local implantation, system transplantation, gene therapy, tissue engineering, etc. and it has been proven to improve ovarian function and pregnancy rates in patients with low ovarian function and has good clinical application prospects. More in-depth research will open up new avenues for the treatment of ovarian aging, but it is worth noting that clinical research still needs to be widely applied in the treatment of ovarian aging with stem cells to confirm the effectiveness and safety of stem cells for patients with low ovarian function. Technology to prevent and treat ovarian aging still has a long way to go.

Conflict of interest

All authors declare that they have no conflict of interest.

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