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Editorial

Ovarian Rejuvenation: Turning Dreams into Reality

Throughout the history, the desire to appear youthful and delay the signs of aging has always been a common aspiration of mankind. A literature review on historical texts shows that different methods and materials have been used by individuals in past centuries to achieve youthfulness. However, most of these approaches were unscientific, immoral, and even illegal. One organ that undergoes a drastic change by aging is the ovary, subsequentially affecting fertility potential and the ability to conceive. In women, the impact of age on fertility is much more evident compared to men, as testicular activity and sperm production in males persist throughout the adulthood following puberty. Women are born with a limited and constant population of oocytes in their ovaries, which gradually diminishes over time until around the age of 50, marking the onset of a new phase called menopause. Premature ovarian insufficiency (POI) affects approximately 1% of women under 40 and 0.4% of women under 35. The ovary undergoes accelerated aging compared to other tissues and organs, likely due to evolutionary factors. The termination of ovarian function serves as a mechanism to prevent fertility and pregnancy at older age, avoiding further risks for both the mother and the fetus. The onset of menopause is characterized by irregular menstruation cycles, attributed to a decrease in the production of steroid hormones by the ovaries. This decline gives rise to the classic symptoms of menopause, including hot flashes, night sweats, heart palpitations, insomnia, headaches, dysphoria, and various mood changes. Menopause also significantly reduces vaginal secretions and tissue elasticity and increases vaginal acidity, contributing to dyspareunia. Additionally, hormonal and physiological changes of menopause also lead to a gradual decrease in bone mass and quality, resulting in development of osteoporosis. Therefore, the proper function of ovaries guarantees the long-term health and fertility of women (1).

Aside from declined fertility, the complications of menopause are very similar to other age-related health issues, resulting from accumulation of cellular and molecular damage in tissues and organs over time. In recent times, there have been contemporary efforts to preserve women's fertility and delay or eliminate menopause-related symptoms through new biomedical technologies. These approaches involve repairing damaged cells or replacing them with new ones, particularly utilizing stem cells as well as employing ovarian tissue grafts. These advancements have the potential to significantly prevent or reverse menopause-related complications. A new term that has gained popularity in public and professional discussions, as well as scientific literature, is "ovarian rejuvenation".

Ovarian rejuvenation is an example of regenerative medicine, and recent studies have explored using bone marrow derived stem cells, menstrual blood stem cells, as well as platelet-rich plasma (PRP) to restore function and rejuvenate the pre-menopausal or menopausal ovary. These treatments are based on successful identification and isolation of germline stem cells (GSCs) from the ovaries of women in their reproductive age. Additionally, about 5 to 10 percent of POI cases may experience spontaneous follicular growth, menstruation, and pregnancy within a year of diagnosis. This occurrence is attributed to the presence of a number of quiescent primordial follicles or even GSCs in the ovary that are unable to resume their development to mature oocytes due to endocrine and paracrine changes during the menstrual cycle. Instead, they require a stronger stimulus to trigger a change in the ovarian niche. Although the occurrence of de novo oogenesis in adult women has not been proven based on current research, the administration of stem cells or growth factors and the resumption of ovarian activity after cessation of ovarian function can put an end to the theory of the ovary as a non-renewable pool of female germ cells (1, 2).

With the progress in ovarian rejuvenation, different types of stem cells have been used for quiescent follicles recovery and ovarian niche restoration. Among them, mesenchymal stem cells (MSCs) have emerged as the most widely used, demonstrating promising outcomes. The successful and encouraging results from animal studies involving MSC injection into the ovary have provided a strong foundation for their application in human clinical trials. A diverse range of MSCs from different tissue sources, including MSCs of amniotic fluid, umbilical cord MSC (UCMSCs), menstrual blood-derived stromal cells (MenSCs), adipose tissue derived MSC (ADMSCs), bone marrow-derived stem cells (BMDSCs), and even human embryonic stem cells (ESCs) has been employed for ovarian rejuvenation (2).

In addition to the aforementioned approaches, other types of stem cell sources are being investigated in several randomized controlled trials (RCTs) for ovarian rejuvenation in different countries. However, most of them are still ongoing and their results have not yet been reported. In the latest findings reported by our team,

intraovarian injection of autologous MenSC led to increased rates of spontaneous pregnancy, elevated levels of anti-Müllerian hormone (AMH), and a higher antral follicle count in the experimental group compared to the controls. Furthermore, in cases treated through ICSI/IVF cycles, MenSC injection resulted in higher number of mature oocytes and embryos (3).

MSC therapy is a labor-intensive, time-consuming, and expensive process. There are potential risks associated with *in vitro* MSC expansion, such as the risk of infection, as well as the risk of graft-versus-host disease (GVHD) and tissue specialization of MSCs. Hence, researchers have been exploring more effective methods with fewer side effects and complications. One such method is intraovarian injection of platelet rich plasma (PRP). PRP has a history of at least 70 years and was initially recognized as the standard platelet concentrate for transfusion in the 1960s. Over the past decades, the use of PRP has gradually expanded and it is now employed in various medical fields including dermatology, orthopedics, sports medicine, hair and beauty, dentistry, urology, and ophthalmology. The use of PRP in reproductive medicine is relatively new and dates back to recent years. In addition to ovarian rejuvenation, PRP has been investigated in several studies for the treatment of recurrent implantation failure (RIF), thin endometrium, and endometriosis. Intraovarian administration of PRP, similar to stem cells, has shown the potential to improve AMH levels, decrease serum FSH levels, improve oocyte retrieval, increase antral follicle count (AFC), and promote spontaneous pregnancy (2,4).

Therefore, intraovarian PRP injection serves as a convenient, cost-effective, and applicable alternative to MSC treatments. PRP promises a bright future for improvement of menopause-related symptoms and ovarian rejuvenation. However, our understanding of its long-term side effects, optimal treatment duration, mechanism of action, and other outcomes remains limited. Therefore, it is crucial to conduct several double-blind randomized clinical trials with long-term follow-up to thoroughly assess the outcomes of ovarian rejuvenation before recommending it as a routine treatment for women with POI and diminished ovarian reserve (DOR).

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