UTILIZATION OF STEM CELL THERAPY AS A NEW APPROACH TO OVERCOME REPRODUCTIVE DISEASES IN WOMEN

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ABSTRACT

The human body contains approximately 37.2 trillion cells, each specialized to perform specific functions within tissues and organs. Stem cells, particularly mesenchymal stem cells (MSCs), have emerged as a promising therapeutic option for various medical conditions due to their regenerative and differentiation capabilities. Female infertility, which significantly impacts quality of life, often results from reproductive disorders such as premature ovarian failure (POF), polycystic ovary syndrome (PCOS), endometriosis, Asherman syndrome, and preeclampsia. Conventional treatments like hormone therapy are limited by long-term risks, including heart disease and cancer, while assisted reproductive technologies are hindered by ethical, safety, and financial concerns. This review explores MSC-based therapies as innovative alternatives for addressing female reproductive disorders. MSCs demonstrate potential in regenerating ovarian cells, restoring hormonal balance, and repairing uterine tissue. For POF, MSC therapy replenishes ovarian cells, improves hormone levels, and restores function. In PCOS, MSCs reduce inflammation and fibrosis while enhancing ovarian function. Endometriosis management benefits from MSCs' ability to repair endometrial damage and improve uterine receptivity. MSCs also show efficacy in reducing fibrosis and increasing vascularization in Asherman syndrome and repairing placental damage in preeclampsia by mitigating oxidative stress and inflammation. This review synthesizes findings from recent studies to highlight MSCs' role in advancing gynecological medicine, presenting them as a safe, effective, and sustainable therapeutic approach for treating infertility and enhancing reproductive health.

Keywords : PCOS; POF; mesenchymal stem cells

INTRODUCTION

The adult human body, there are roughly $3{,}72 \times 10^{13}$ trillion cells, each designed with its own specific shape and purpose. Every cell has its own specialization to perform specific tasks according to the type of tissue and organ in which it resides (Bianconi et al., 2013).Understanding the multi-omic molecular aspects of stem cells can provide important information for treating various diseases, including gynecological disorders, as well as supporting the development of healthy cells for regenerative therapy (Ivkosic et al., 2023).

Infertility is a widely experienced issue globally and is not limited to one gender. This indicates that the inability to have children can affect both men and women. Reproductive disorders in women, such as premature ovarian failure, polycystic ovary syndrome, endometriosis, fallopian tube blockage, and Asherman's syndrome, can result in infertility (Zhao et al., 2019). Female infertility (the inability of a woman to conceive or have children) can have a significant negative impact on the quality of life, as well as on emotional and mental well-being, both for the

woman herself and for her partner. Hormone therapy can address hormone deficiencies in women, but its long-term use carries the risk of causing serious diseases, such as heart disease and cancer. Therefore, safe and effective alternative treatments are needed to sustainably improve women's overall and sexual health (Hoang et al., 2022). Recently, translational medicine has made rapid progress, and clinical researchers are now focusing on addressing female infertility by applying new approaches. MSC (Mesenchymal Stem Cells) have the ability to self-renew and develop into various cell types; recent research considers them a promising option for cell therapy in regenerative medicine (Ding et al., 2011; Ullah et al., 2015; Liao et al., 2021).

Assisted reproductive technology is often effective, but its use can be limited due to safety concerns, ethical considerations, or high costs (Liu et al., 2023). In the past ten years, interest in the potential use of stem cells to treat various diseases and medical disorders has increased significantly. Stem cells are now considered for addressing various types of diseases, whether acute, chronic, congenital, or acquired throughout life (Ivkosic et al., 2023). Recently, stem cell therapy has emerged as a promising approach for addressing infertility linked to ovarian dysfunction and conditions affecting the uterine lining (endometrium) (Naji et al., 2013; Squillaro et al., 2016; Galipeau and Sensebe, 2018; Liu et al., 2023). This review aims to deepen knowledge about the latest therapeutic methods using stem cells and to raise awareness of this issue in the context of gynecology and medicine as a whole.

MATERIALS AND METHODS

This review was conducted by gathering sources from PubMed and Google Scholar. The literature criteria used as the basis for the review include English-language literature available from 2019 to 2024. Keywords used in the literature selection, both independently and in combination, are stem cells, female reproductive system, polycystic ovary syndrome, female reproductive diseases, infertility, mesenchymal stem cells, ovarian reserve failure, and premature ovarian insufficiency. Articles will be filtered according to the topic of the study under review. Articles will be selected based on their titles and full text. The researchers also conducted a manual search to find other materials relevant to the research topic.

RESULT AND DISCUSSION

Disorders in the female reproductive system are conditions related to abnormalities in one or more organs within the reproductive system. The organs that may experience abnormalities include the ovaries, uterus, fallopian tubes, and cervix (Esfandyari et al., 2020). Abnormalities in the ovaries, for example, can interfere with the production of eggs or hormones essential for reproductive function. In the uterus, disorders may occur in the wall lining or other structures, which can affect the ability to sustain a pregnancy. Abnormalities in the fallopian tubes can obstruct the meeting of egg and sperm, while abnormalities in the cervix can affect the sperm's pathway to the uterus or cause other complications in the reproductive process. These disorders can cause quite serious symptoms, such as pelvic pain, frequent urges to urinate, and changes in the menstrual cycle (Dahiphale et al., 2024). Additionally, this condition is also associated with negative impacts on reproductive outcomes, including an increased risk of miscarriage and infertility issues (Esfandyari et al., 2020).

There are five main types of disorders that most commonly cause infertility in women: premature ovarian failure (POF), polycystic ovary syndrome (PCOS), endometriosis, Asherman's syndrome, and preeclampsia.

Premature Ovarian Failure (POF)

Premature ovarian failure (POF) is a health issue and condition that can occur in women before the age of 40. This condition is characterized by several key symptoms, such as amenorrhea (absence of menstruation), low estrogen levels, infertility, high levels of gonadotropin hormones, and a minimal number of mature follicles in the ovaries. The causes of POF include various factors, such as certain genetic abnormalities, autoimmune disorders, and environmental influences (Shareghi-Oskoue et al., 2021).

The incidence of premature ovarian failure (POF) varies based on a woman's age. At 20 years old, the prevalence of POF is recorded at 0.01%. This figure increases to 0.1% for women at 30 years old and reaches 1% for women at the age of 40 (Zhang, 2020; Dai et al., 2023). Clinically, long-term hormone replacement therapy (HRT) is the most common treatment given to women with premature ovarian failure (POF). This therapy generally involves estrogen and progesterone hormones to replace the deficient hormones due to reduced ovarian function. However, HRT has side effects for patients. Therefore, there is a need for more advanced treatment strategies. Recently, the role of stem cells in treating animal models of premature ovarian failure (POF) has been gradually researched (Dai et al., 2023).Stem cells have the ability to differentiate into ovarian cells when placed in a microenvironment resembling the conditions of premature ovarian failure (POF). This differentiation serves to replenish the reduced number of normal ovarian cells (Shareghi-Oskoue et al., 2021). Ovarian cells regenerated from stem cells can produce female hormones, help maintain hormonal balance, and alleviate symptoms caused by decreased ovarian function (Fu et al., 2021).

Stem cell therapy can improve ovarian marker levels as well as follicle-stimulating hormone receptors. This therapy also has the potential to increase ovarian weight, raise plasma estradiol (E2) levels, and increase the number of follicles formed to meet standard levels (Shareghi-Oskoue et al., 2021).

Polycystic Ovary Sindrom (PCOS)

Polycystic ovary syndrome (PCOS) is a chronic disorder commonly experienced by women of reproductive age, which can lead to weight gain, infertility, and depression. This condition is one of the most common endocrine disorders worldwide. PCOS occurs when follicles fail to release an egg, causing a collection of immature follicles to accumulate in the ovaries and form a polycystic pattern (Prayitno et al., 2022). The increased signaling of gonadotropin-releasing hormone (GnRH) from the hypothalamus, caused by insufficient progesterone levels during the luteal phase, is the primary cause of PCOS (Taylor et al., 2019).

Mesenchymal stem cell (MSC) therapy has shown promising results as a treatment option for PCOS, due to its ability for self-regeneration, potential for differentiation, and its immunomodulatory effects, particularly in diseases related to inflammation. The application of UC-MSC transplantation has the potential to address the pathological changes occurring in PCOS, improve ovarian function, and may play a role in controlling ovarian issues triggered by dehydroepiandrosterone (DHEA). This effect is influenced by a decrease in the expression of inflammatory cytokines, including interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and interferon gamma (IFN-γ), as well as a reduction in genes related to fibrosis, such as connective tissue growth factor (CTGF) (Esfandyari et al., 2020). In addition,

the use of secretome can enhance the effectiveness and impact of this therapy. The paracrine mechanisms of stem cells, allowing the duration of MSC effects to be prolonged (Prayitno et al., 2022). Exosomes, which are vesicles derived from MSCs, play a key role in transmitting proteins, lipids, and miRNA to target cells. They regulate inflammation in damaged tissues and, in addition to the secretome, can enhance anti-inflammatory activity. These exosomes also facilitate communication between MSCs and the ovarian microenvironment (Zhao et al., 2022).

Endometriosis

Damage to the endometrium is one of the main factors contributing to infertility, while the effectiveness of conventional treatments tends to be limited. Endometriosis (EM) is a chronic estrogen-dependent disorder characterized by the abnormal growth of endometrial-like tissue, including typical endometrial stroma and glands, outside the endometrial lining (Artemova et al., 2023). One promising area in the management of endometriosis is the use of cell therapy. This approach holds potential by leveraging principles of disease pathogenesis control, such as inhibiting estrogen receptor activity, angiogenesis, fibrosis formation, and reducing the number of stem cells at endometriosis sites (Yang & Huang, 2014; Gurung et al., 2018; Artemova et al., 2023). Furthermore, the use of stem cells, which has been widely applied, has shown significant success in reducing endometrial fibrosis, repairing endometrial damage, and enhancing the uterus's ability to receive an embryo (Jiang et al., 2019).

The endometrium is divided into two layers: the basal layer and the functional layer. Endometrial stem cells are located in the basal layer and serve as a source of progenitor cells that differentiate to form endometrial tissue (Cen et al., 2022). Exogenous endometrial stem cells have the ability to differentiate into endometrial cells within the uterus, making secretome plays a role in mediating the

them a potential therapeutic option for repairing uterine injury. Additionally, endometrial stem cells have been proven to be an ideal source for addressing infertility caused by endometrial damage (Mutlu et al., 2015; Cen et al., 2022).

Asherman's Syndrome

Asherman syndrome (AS) is a condition of severe intrauterine adhesions (IUA), where the entire layer of the endometrium is replaced by fibrous tissue (Asherman, 1948). The main causes of Asherman syndrome are gynecological surgery or pregnancy complications. Acquired syndrome occurs due to damage to the endometrium and often results in infertility or recurrent miscarriages, chronic pelvic pain, menstrual disorders (such as hypo- or amenorrhea), and dysmenorrhea. The main risk factors typically include curettage after abortion or childbirth, infections, myomectomy, and hysteroscopic procedures, which are actions that can damage the basal layer of the endometrium (Benor et al., 2020).

The regenerative ability of stem cells has been shown to provide better outcomes in improving fertility and reducing fibrosis in rats and humans with Asherman syndrome. In mice with uterine damage, mesenchymal stem cell (MSC) therapy has shown promising results. The use of MSCs has been proven to reduce the amount of scar tissue (fibrosis) in the uterus while enhancing the formation of new blood vessels (vascularization). Additionally, staining results using specific methods such as VEGF, PCNA, and Ki-67 indicate increased regenerative activity. These findings suggest that MSC therapy plays a role in repairing damaged uterine tissue. The combination of stem cell therapy with estrogen has been shown to be highly effective in supporting the recovery of the endometrial lining, which is crucial for addressing

Asherman syndrome. This condition is characterized by the presence of uterine scarring that can hinder fertility (Zhang et al., 2021).

Preeclampsia

PE is a syndrome involving multiple factors and affecting various organs, thereby increasing the risk of morbidity in mothers and newborns. This condition is typically characterized by the presence of proteinuria and high blood pressure, which generally manifest after 20 weeks of gestation (Chaiworapongsa et al., 2014). Preclinical and clinical research findings indicate that MSC-based therapy holds great potential for the treatment of ischemic and inflammatory diseases. PE, characterized by ischemic and inflammatory damage to the placenta, has now become a target for MSC-based therapy. The application of MSCs and their derivatives has been shown to improve maternal-fetal conditions in PE rat models by enhancing cellular metabolism, reducing oxidative stress, balancing angiogenesis, and alleviating inflammation (Jin et al., 2022).

Mesenchymal stem cells found in perinatal tissues are classified based on the location of the placental tissue, namely decidua-derived MSC (dMSC), MSC from the amniotic membrane (AM-MSC), MSC from the umbilical cord (UC-MSC), MSC from amniotic fluid (AF-MSC), and MSC from chorionic villi (CV-MSC) (Jin et al., 2022).

MSCs originate from the mother's body, either from surrounding tissues (in situ) or from the bone marrow, and play a role in forming the uterine lining (endometrium/decidua) and placenta. These MSCs can differentiate into various cell types, such as blood vessel cells, vascular muscle cells, and other supporting cells, to create new tissue and repair existing tissue. Additionally, progesterone and cAMP molecules can transform MSCs into specialized cells known as decidual stromal cells, which are crucial for helping the embryo attach to the uterine wall, initiating implantation, and ensuring the mother's immune system does not attack the fetus. MSCs also produce numerous chemical signals (cytokines) that stimulate the growth and movement of trophoblast cells, which form the placenta. This process is vital for expanding the placental villi (structures that absorb nutrients from the mother) and modifying the maternal blood vessels to increase blood flow to the fetus (Jin et al., 2022).

SUMMARY

Disorders of the female reproductive system involve abnormal conditions in organs such as the ovaries, uterus, fallopian tubes, or cervix, which can lead to infertility, pelvic pain, changes in the menstrual cycle, and an increased risk of miscarriage. Major conditions include Premature Ovarian Failure (POF), Polycystic Ovary Syndrome (PCOS), endometriosis, Asherman syndrome, and preeclampsia.

Mesenchymal stem cell (MSC) therapy has shown great potential in addressing these disorders. In POF, MSCs aid in regenerating ovarian cells, boosting hormone levels, and restoring ovarian function. For PCOS, MSCs and their exosomes reduce inflammation and fibrosis, improve ovarian function, and stabilize the hormonal environment. In endometriosis, MSC therapy repairs endometrial damage, reduces fibrosis, and enhances uterine receptivity for embryos. MSCs are also effective in repairing the damaged uterine lining in Asherman syndrome by reducing scar tissue and increasing vascularization. Meanwhile, in preeclampsia, MSCs help repair placental damage by reducing oxidative stress, balancing angiogenesis, and decreasing

inflammation. Overall, MSC-based therapy offers an innovative approach to treating enhancing tissue regeneration, hormonal function, and the reproductive environment. various female reproductive disorders by

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