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Recent Research Progress in Premature Ovarian Failure

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Abstract: Premature ovarian failure refers to ovarian function failure in women before the age of 40 years due to follicular depletion or follicular dysfunction resulting in abnormal hormone levels. The etiology and pathogenesis of premature ovarian failure may be related to genetic, immunological, medical, environmental, infectious, psychological and enzyme deficiencies. The treatment involves Western medicine, Chinese medicine, and a combination of Chinese and Western medicine, and the treatment level includes hormone level, cellular level, surgery and psychological aspect. This paper would like to review the progress of the etiology, pathogenesis and treatment of premature ovarian failure in recent years.

Keywords: Premature ovarian failure; Etiology; Pathogenesis; Treatment

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1. Introduction

The ovary is the core reproductive organ of women, which is important for maintaining the normal operation of the reproductive system and endocrine stability. Premature ovarian failure (POF) usually refers to amenorrhoea caused by ovarian follicular depletion or follicular dysfunction before the age of 40 years, accompanied by serum follicle-stimulating hormone (FSH) > 40 U/L at least twice (the interval between the two examinations is > 1 month) and the level of estradiol (E2) is < 73.2 pmol/L, with clinical manifestations such as menstrual disorders, infertility or with perimortem symptoms such as hot flushes, hyperhidrosis, restlessness, decreased libido, vaginal dryness and so on [1]. Currently, the incidence of POF is on the rise compared with the past, with a global prevalence of about 1.0% and a range of 1–3.8% in China, with primary amenorrhoea accounting for 20–28% of POF cases and secondary amenorrhoea accounting for 4–20%, and the cause of about 74–90% of POF cases is unknown [2]. The disease has many causative factors and complex pathogenesis, but no highly satisfactory treatment options exist. In order to clarify the etiology, pathogenesis and treatment options of POF, this article will provide a review of the research progress on the etiology, pathogenesis and related treatments of premature ovarian failure, which will provide a certain reference value for clinical research.

2. Causes and pathogenesis of POF

There are many causes of POF, including genetic, immunological, medical, environmental, infectious, psychological, vaccination and enzyme deficiencies.

2.1. Genetic factors

Some studies have shown that among the causes of POF, genetic factors account for 20% to 25%, including chromosomal abnormalities and gene mutations, and 10% to 13% of POF patients also have chromosome number and structural abnormalities, of which the X-chromosome abnormality rate can be as high as 94% [3]. Heterochromatin rearrangements in the region of xq13 to q21 have been shown to affect oocyte expression during follicular maturation. This region is a breakpoint of the X chromosome in patients with POF, which has an important role in ovarian function and female reproductive life span [4]. The most typical disease with abnormal X chromosome number is Turner syndrome, which is characterized by a total deletion (45, XO) or partial deletion of one X chromosome and is characterized by short stature and congenital ovarian hypoplasia. Half of the patients with diseases caused by X-chromosome abnormalities develop gonadal hypoplasia or primary amenorrhoea [5]. Case reports have shown that female patients with trisomy X have a significantly increased risk of developing POF [6,7]. In addition, genetic mutations cause abnormalities in the development of the female ovaries, which in turn leads to the development of POF. The fragile X mental retardation 1 gene (FMR1), an X-linked gene located on the X chromosome, contains a polymorphic CGG trinucleotide sequence in its 5 untranslated regions with repeat lengths ranging from 55 to 200 (known as a premutation), which leads to fragile X-associated tremor/ataxia syndrome and fragile X-associated premature ovarian involution (FXPOI) [8]. Moreover, increased susceptibility to POF at all stages of idiopathic POF is positively correlated with premutation in the FMR1 gene and the severity of POF does not correlate with the length of the intervening repeat sequence of the FMR1 gene [9].

2.2. Autoimmune factors

In addition to the immune system's role in maintaining the organism's homeostasis, the hypothalamic-pituitary axis secretes hypothalamic hormones that affect the pituitary gland, which secretes FSH and LH. This will then affect the female physiological cycle and participate in the regulation of ovarian development, follicular growth and development, maturation, ovulation, and corpus luteum formation, and the regulation of the endocrine function of the ovary [10]. The ovary can also serve as a common target of autoimmune attacks in organ-specific and systemic autoimmune diseases. Up to 20% of POF cases have been diagnosed with other autoimmune diseases, often thyroid disease, adrenal and pancreatic disease, and systemic lupus erythematosus [11].

2.3. Medical factors

POF caused by medical factors mainly occurs during gynaecological surgery and radiotherapy and chemotherapy in addition to surgery in patients with malignant tumours.

2.3.1. Gynaecological surgery

In clinical practice, common gynaecological surgeries include ovariectomy, ovarian mass removal, ovarian perforation, hysterectomy, salpingo-oophorectomy and so on. In different gynaecological surgeries, the path of surgical procedure, the scope of resection, the area of resection, and even the different ways of haemostasis of the surgery will have different impacts on the patients' ovarian function and the quality of life after the surgery [12].

Some studies have shown that women with preserved ovaries after hysterectomy have an increased chance of early menopause [13]. After a hysterectomy, the uterine arteries are destroyed, reducing the patient's

ovarian blood supply, resulting in a reduction of blood oxygen levels in the ovaries and, impaired follicular development, destruction of the endometrium. This will affect the growth and development of granulosa cells, which in turn affects the development and maturation of normal follicles, weakening the ovaries' reserve function and increasing the risk of POF. In recent years, some studies have shown that when one side of the ovary is removed, it induces a decrease in the overall level of hormones secreted by the ovary. In contrast, the level of FSH in the body increases, affecting the function of the contralateral ovary and increasing the incidence of POF [12].

2.3.2. Radiotherapy and chemotherapy

Currently, the incidence of suffering from malignant tumours is increasing year by year, narrowing the scope of surgery and improving the survival rate through radiotherapy. Still, radiotherapy increases the chance of inducing POF in female patients during treatment.

Radiotherapy is one of the common methods used to treat malignant tumours and ionising radiation causes premature ovarian failure [14]. Radiation and ionizing radiation disrupt the synthesis of DNA, the genetic material in the body and the mitosis of cells, killing cells in the body in the process. Different magnitudes of irradiation and different sites of irradiation cause different degrees of ovarian damage in women of different ages. A radiation dose of 4.0 Gy can be used to establish a rat model of POF, and although it does not lead to severe ovarian failure, radiotherapy-induced ovarian damage may lead to oxidative and inflammatory damage, down-regulation of the expression levels of P13k and Akt, and up-regulation of FOXO3a [15]. Moreover, ovaries are highly sensitive to radiation where a low dose (0.1 Gy) γ-ray radiation induces a significant decrease in mature oocytes in the ovaries [16].

Similarly, chemotherapy is a commonly used treatment for malignant tumours, which kills the cells through chemicals that reach all parts of the body through blood circulation system. Still, it also causes some damage to normal tissues and organs, in which chemotherapeutic drugs can damage ovarian granulosa cells, follicles, oocytes, and mesenchymal stromal cells. It can also cause accelerated follicular atresia and a reduction in the number of primordial follicles, resulting in POF of medical origin [17]. The main chemotherapeutic agents commonly used in the clinic are cyclophosphamide, cisplatin, tretinoin and adriamycin (doxorubicin) [18]. Among them, cyclophosphamide is an alkylating agent with high ovarian toxicity, which causes POF mainly by blocking DNA replication and inducing apoptosis in oocytes and granulosa cells [19]. Cisplatin kills cancer cells by inducing the formation of inter- and intra-strand DNA complexes, while high doses of cisplatin lead to hyperactivation of dormant primordial follicles, which results in loss of ovarian reserve function [20]. Adriamycin (doxorubicin) triggers DNA damage mainly by inducing DNA double-strand breaks in tumour cells; low doses of adriamycin do not disrupt follicular growth but adversely affect meiosis to the maturation of the oocyte [21], triggering impaired ovarian function and even the development of POF.

2.4. Environmental and infection factors

Environmental problems are becoming more prominent today, such as air pollution, water pollution, soil pollution, noise pollution, pesticide pollution, plastic products, rubber products, hard-to-burn substances, etc. These pollutants can produce toxic substances acquired by the human body and affect the growth and development of follicles, leading to changes in the number of follicles and affecting the function of the ovaries, thus causing POF. Spontaneous active smoking in females and passive second-hand smoke contains harmful substances such as nicotine and polycyclic aromatic compounds in tobacco smoke, which can lead to a decrease in ovarian follicle reserve capacity, an increase in follicular atresia, a decrease in follicle number, a decrease in a woman's

fertility, and even an early onset of menopause. There is evidence that smoke can directly disrupt folliculogenesis. It is becoming increasingly clear that maternal smoking affects ovarian function in multiple generations of offspring [22]. Also, exposure to cigarette smoke leads to inhibition of autophagy and activation of cellular pyroptosis in ovarian tissue [23].

The ovaries are normally resistant to infection. However, mumps virus infection in early childhood complicates ovarian inflammation, which destroys the function of the ovaries, making them insensitive to pituitary gonadotropin stimulation and viraemia, and gonadal destruction, if it occurs, can likewise lead to rapid follicular depletion upon entering puberty, triggering POF.

It has also been found that novel coronaviruses are present in stromal and granulosa cells as well as oocytes of the immature rat ovary via angiotensin-converting enzyme 2 (ACE2), which is widely expressed in the ovary, uterus, vagina and placenta, affecting female reproductive function and leading to ovarian hypoplasia, infertility, menstrual disorders and foetal distress [24].

2.5. Psychological factors

With society's progress, people's pace of life is accelerated, work pressure increases, and competition is stimulated, which makes people mentally nervous and causes more and more women to develop POF. Psychological stresses such as chronic anxiety, sadness, fear, and other negative emotions can lead to POF by altering the function of the hypothalamus-pituitary-target gland axis, which leads to the emergence of the disorder of the hypothalamus-pituitary-ovarian axis.

2.6. Enzyme deficiencies

Clinical studies have shown that certain enzyme deficiencies in the body can disrupt oestrogen synthesis, causing delayed puberty, elevated gonadotropin levels and primary amenorrhoea. Examples include 17-alpha-hydroxylase/17,20-cleaving enzyme deficiency (17OHD), galactosemia, Tet 1 enzyme deficiency, and phosphomannuronidase-2 gene (PMM2).

It has been shown that 17-alpha hydroxylase deficiency leads to elevated gonadotropin levels in patients, causing POF [25]. In addition, 17-alpha hydroxylase and 17,20-cleaving enzyme deficiencies lead to decreased serum levels of cortisol, androstenedione, testosterone, and estradiol, which are then positively associated with the development of POF [26]. Galactose has an ovotoxicity effect that leads to accelerated follicular reserve failure, a dramatic decrease in the number of follicles and an increased risk of POF. When serum anti-Müllerian hormone (AMH) levels are undetectable, together with the previous reports suggesting a critical role for glycosylation in oocyte development and function, it has been found that PMM2 congenital dysglycosylation (PMM2-CDG) almost always leads to POF, mainly due to defects in oogenesis and/or oocyte-dependent early folliculogenesis, rather than defects in glycosylation leading to impaired FSH/ LH bioactivity. LH bioactivity is impaired. Therefore, it is recommended to check PMM2 in patients with syndromic POF, especially in patients with cerebellar ataxia/hypoplasia [27].

In addition to this, data suggest that Tet 1 enzyme is involved in DNA demethylation and plays a key role in stem cell pluripotency and differentiation that changes with age In studies, it was found that Tet 1 enzyme deficiency reduces fertility and that follicular reserve is significantly reduced in Tet 1 enzyme-deficient mice and is further reduced with age. These molecular changes are also consistent with oocyte senescence, follicular atresia and depletion found in premature ovarian failure or insufficiency. Tet 1 enzyme plays a role in the maintenance of oocyte mass, oocyte number and follicular reserve and its deficiency can lead to POF [28].

3. Treatment of POF

To address the causes of POF, different treatment modalities need to be adopted, taking into account the patients' age, clinical symptoms and fertility requirements.

3.1. Western medical treatment

3.1.1. Hormone replacement therapy (HRT)

Hormone Replacement Therapy (HRT) is a commonly used treatment for POF at home and abroad, which is mainly used to balance the hormone levels in women's bodies, simulating the natural physiological cycle of the human body, regulating the hypothalamus-pituitary-ovary axis, improving the growth and development of some follicles in the body, and alleviating the low estrogen state in the body. However, this treatment method is not suitable for long-term use as long-term implementation may increase the risk of coronary heart disease, stroke, breast cancer and ovarian cancer.

3.1.2. Stem cell therapy

In recent years, research on the treatment of POF by stem cells has gradually increased, and many studies and clinical trials have shown that stem cell therapy is a potential alternative treatment in the treatment of POF. Stem cell therapy mainly includes embryonic stem cell and mesenchymal stem cell therapy. In a chemotherapeutic drug-induced mouse model of POF, human embryonic-derived MSCs restored cisplatin-damaged ovarian structure and function, providing new insights into the great clinical potential of human embryonic-derived MSCs in the treatment of POF [20].

3.1.3. Ovarian transplantation therapy

Ovarian tissue freezing and transplantation are performed for young patients with POF induced by benign ovarian disease, who preserve their reproductive function by undergoing oophorectomy and freezing them, in addition to female patients with genetic or immunological disorders. It has been shown that cryopreservation of ovarian tissue is one of the effective options for preserving fertility in young patients facing toxic adenoma [29]. In addition, autologous transplantation after ovarian tissue cryopreservation is an effective method for restoring fertility (57% live birth rate).

3.1.4. Psychological interventions

When women are suffering from POF, the estrogen in their bodies is lacking, and there are many patients who feel that they have lost their ability to bear children after being diagnosed with POF. The burden in their hearts slowly increases, and some patients resist treatment or even lighten their lives. In order to have a better treatment effect, many hospitals adopt psychological intervention treatment for patients. Some studies have shown that improving physical and mental outlook and strengthening psychological care in clinical nursing interventions for patients with POF can alleviate patients' adverse emotions, enhance their psychological state, eliminate patients' concerns, improve treatment adherence, improve patients' quality of life, and increase nursing effectiveness and satisfaction [30].

3.2. Chinese medicine treatment

From the perspective of TCM, POF is a disease of deficiency of the liver, kidney and spleen for women, and TCM treatment mainly focuses on tonifying the kidney, filling the essence and adjusting the deficiency. The use of electroacupuncture (EA) is a useful non-pharmacological therapy in the clinic and EA can improve ovarian

function and menstrual cycle in POF. EA regulates energy metabolism and neurotransmitter metabolism in the liver and kidney, and it is noteworthy that EA has a good effect in regulating the energy metabolism in the kidneys and the metabolism related to neurotransmitters in the liver [31]. Other studies have shown that the implementation of Chinese medicine treatment for POF patients can significantly improve the clinical effect, improve the hormone level in the patient's body, and accelerate the patient's recovery [32].

4. Summary

In summary, the etiology of POF is mainly related to genetic, immune and medical factors, and to a lesser extent to the environment and personal behaviour. In the treatment of POF, hormone replacement therapy is mainly used in clinical practice, which cannot restore the ovarian function of patients but can change their quality of life. Stem cell therapy and ovarian transplantation have yet to be tested in clinical trials so that they can be used in the clinic as soon as possible. Psychological interventions and Chinese medicine are effective means of better treatment and reducing the pain and burden of patients. The current research on POF is mixed, but only a small part of it has been recognized and it is still to be further improved so that the etiology and pathogenesis of POF can be clarified and verified as early as possible to provide a strong basis for early diagnosis, so as to achieve early detection, early diagnosis, and early treatment, and to reduce the incidence of POF.

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