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Research progress in the pathogenesis and treatment of premature ovarian failure

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Abstract: *Premature ovarian failure (POF) in females Amenorrhea before the age of 40, accompanied by elevated FSH levels (FSH>40 U/L), decreased estrogen levels, and other endocrine abnormalities and menopause Form; Refers to premature and complete failure of ovarian function. POF is a highly heterogeneous clinical disease with a mixed etiology. The occurrence of premature ovarian failure is related to abnormalities in granulosa cells, genetic factors, immune factors, mitochondrial dysfunction, environmental factors, and personal habits. The main signs and symptoms of POF include hot flashes, night sweats, facial skin flushing, decreased libido, vaginal dryness, genital atrophy, menstrual irregularities or amenorrhea. May be accompanied by diseases such as osteoporosis and infertility. The clinical treatment of premature ovarian failure often uses artificial cycle therapy with estrogen and progesterone. Although the effect is fast, it is easy to relapse after stopping the medication and requires long-term drug treatment, with significant adverse reactions. In recent years, research has found that traditional Chinese medicine has significant effects in delaying and protecting ovarian function in immune premature ovarian failure. This article explores the etiology, clinical manifestations, pathogenesis, ovarian histological changes, and related treatments of premature ovarian failure.*

Keywords: *Premature ovarian failure; Pathogenesis; Treatment*

1. Introduction

Premature ovarian failure (POF) refers to the phenomenon of elevated serum follicle stimulating hormone (FSH) levels measured twice within the menopausal range at least 6 months after amenorrhea in women under the age of 40, often accompanied by symptoms of perimenopausal syndrome[1-3]. Its characteristic is the loss of normal ovarian function, loss of menarche, or premature reduction of ovarian follicles, and the cessation of follicle formation before the age of 40. Some cases may be caused by abnormal recognition of the body by the autoimmune system, which can be referred to as autoimmune premature ovarian failure. When the autoimmune system malfunctions, antibodies that recognize the ovaries are recognized by ovarian antigens, causing an immune response to attack the ovaries, further leading to autoimmune premature ovarian failure. The diagnostic criteria for POF are amenorrhea before the age of 40, insufficient estrogen, and high concentrations of serum gonadotropins (follicle stimulating hormone [FSH]>40 mIU/ml), accompanied by symptoms of perimenopausal syndrome.

2. Clinical manifestations and complications

The main signs and symptoms of POF include hot flashes, night sweats, facial skin flushing, decreased libido, vaginal dryness, genital atrophy, menstrual irregularities or amenorrhea [4]. It can be complicated with osteoporosis, infertility, type II diabetes and cardiovascular disease. Amenorrhea is the main clinical manifestation of POF. Menstrual changes and amenorrhea are the main clinical manifestations of POF. According to past menstrual cycles, it can be divided into primary amenorrhea and secondary amenorrhea. Estrogen deficiency symptoms can also occur, such as hot flashes, night sweats, depression, anxiety, memory loss, vaginal dryness, vulvar itching, sexual pain, difficulty urinating, and osteoporosis during the perimenopausal period. Pelvic examination shows symptoms of estrogen deficiency such as vaginal mucosal congestion and submucosal bleeding points. When POF is combined with autoimmune diseases, corresponding symptoms may appear, such as hypothyroidism

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manifested as fatigue, fear of cold, poor reaction, hyperthyroidism manifested as excitement, irritability, irritability, fear of heat, sweating, overeating, and emaciation, and diabetes manifested as polydipsia, polydipsia, polyuria, and emaciation.

Autoimmune premature ovarian failure has no obvious symptoms in the early stages of onset. During the occurrence and development of the disease, there may be different stages of ovarian function due to autoimmune disorders, which can lead to clinical manifestations such as secondary amenorrhea, infertility, and decreased E2 levels. The presence of autoimmune premature ovarian failure includes:①autoimmune dysfunction; ②different levels of reproductive hormones compared to healthy women of the same age; ③significant decline in ovarian reserve function.

3. Pathogenic factors and ovarian tissue morphology

In most cases of POF, the cause is idiopathic. Currently, research has found that the pathogenesis of POF includes autoimmune diseases, immune cells, related factors, and antibodies, metabolic disorders (galactosamia), infections (mumps, tuberculosis, pelvic inflammatory disease, etc.), genetic factors (Turner syndrome, chromosomal abnormalities), pelvic radiation, pelvic surgery, HPV vaccine, environmental factors Personal lifestyle habits and oxidative stress (OS). In some cases, apoptosis of ovarian granulosa cells was also observed [5]. Many studies have found that a high fat and high blood sugar diet can seriously affect ovarian function and oocyte quality [6, 7]. Traditional Chinese medicine believes that it is related to the liver, spleen, and kidney. There are two main types of POF. In the first case, there are almost no residual follicles, which may include genetic diseases, chemotherapy, pelvic radiation therapy, and surgery. The second type is follicular overgrowth, which can be caused by autoimmune ovarian disease, which destroys mature follicles while the original follicles remain intact [8].

Chen Yue et al. found in their research that the model group mice induced by pZP3 had a decrease in ovarian volume, an increase in atresia follicles, and a significant decrease in the number of follicles[9] .A study by Wang Ke showed that cyclophosphamide (CTX) induced a decrease in the number of primordial follicles, primary follicles, secondary follicles, and mature follicles in the model group rats, and an increase in the apoptosis rate of ovarian granulosa cells in rats[10].A study by He Yi showed that in the autoimmune POF model, the ovarian morphology of the model group rats showed a smooth surface, unclear follicle structure, significant reduction in ovarian volume, interstitial fibrosis of the ovaries, distortion of the zona pellucida within the follicles, and infiltration of inflammatory cells into the cortex and granulosa cells. The number of primitive and atretic follicles significantly increased, while the number of primary and secondary follicles significantly decreased[11-17].

4. Animal model of premature ovarian failure

Clarifying the pathogenesis of POF is crucial in its clinical treatment. Animal models can elucidate the pathophysiological mechanisms of diseases.

5. The pathogenesis of premature ovarian failure

The occurrence of premature ovarian failure is related to abnormalities in granulosa cells, genetic factors, immune factors, mitochondrial dysfunction, environmental factors, and personal habits[18-23].Traditional Chinese medicine believes that kidney deficiency is the main pathogenesis of this disease, and is closely related to liver depression, spleen deficiency, blood stasis, etc[24].In addition to chromosomal edges, genetic abnormalities caused by radiation and viral infections can also lead to premature ovarian failure.The above factors may directly damage the ovaries, primarily reduce the total number of oocytes, or shorten the duration of occlusion[25].

Currently, numerous studies have shown that autoimmune diseases related to premature ovarian failure include Addison's disease, vitiligo, myasthenia gravis, autoimmune polygonal syndrome, systemic lupus erythematosus, and rheumatoid arthritis.Umbilical cord mesenchymal stem cells can restore ovarian function in POF mice by activating autophagy regulated by the JNK/Bcl-2 signaling pathway [26]. TP-5 can reduce the BMP4/Smad9 signaling pathway in the ovaries of premature ovarian failure mice, reduce immune cell activation, and reduce damage caused by inflammation and oxidative stress reactions [27].The traditional Chinese medicine Mu Ni Zi Qi can promote the proliferation and secretion function of damaged ovarian granulosa cells, and the mechanism of action may be related to

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TGF in granulosa cells- β Expression and Smad-2, Smad-3 phosphorylation related[28].Research suggests that patients with premature ovarian failure experience a decrease in CD3+and CD4+cell content, an increase in CD8+cell content, a decrease in CD4+/CD8+ratio, and immune function. After treatment with Bushen Shugan Formula combined with artificial cycle therapy, the CD4+and CD4+/CD8+ratio increase, and the number of CD8+cells decreases, which has a good therapeutic effect on immune premature ovarian failure[29].

Studies have shown that high macrophage mobility factor (MIF) is an important factor in the occurrence of autoimmune premature ovarian failure. By releasing inflammatory factors such as IL-2 and IL-6, it exacerbates the immune disorders of autoimmune premature ovarian failure[30].Research shows that acupuncture treatment can improve IFN in patients' bodies-γ,TNF- αInhibiting ovarian granulosa cell apoptosis and delaying and protecting the occurrence of premature ovarian failure through the expression of[31].Research has shown that there are also target antigens for anti-thyroid antibodies in the ovaries, which are harmful to the quality of oocytes. The pathogenesis of POF is related to TG-Ab[32-33].

6. Treatment of premature ovarian failure

Due to the complex pathogenesis of premature ovarian failure, there is currently no fully successful treatment strategy, including hormone replacement therapy, melatonin therapy (DHEA), immune regulation, stem cell therapy, assisted reproductive technology, fertility preserving surgery, gene therapy, and traditional Chinese medicine therapy.

Hormone replacement therapy can alleviate symptoms related to estrogen reduction in POF patients, but it cannot restore and treat symptoms such as ovarian function and infertility. Moreover, long-term hormone replacement therapy may lead to systemic diseases related to autoimmune, breast, and metabolism. Stem cells have the ability to self-renew, differentiate into specific cell types under appropriate conditions, and exhibit strong paracrine potential, bringing new hope to the field of reproductive health [34]. Numerous studies have shown that stem cells from different sources have the potential to restore ovarian function in chemotherapy induced POF models. Traditional Chinese medicine compound therapy has minimal systemic side effects due to multi target therapy [35]. In recent years, research has found that traditional Chinese medicine has significant effects in delaying and protecting ovarian function in immune premature ovarian failure. Understanding the pathogenesis of premature ovarian failure may provide assistance in developing new safe and effective treatment strategies for POF.

Some studies have shown that stem cell therapy may lead to a recovery of hormone levels, follicle activation, and ovarian function[36].Siwu Tang (a herbal medicine) can improve ovarian function in cyclophosphamide induced POF mice by reducing granulosa cell apoptosis and inhibiting the expression of PI3K/Akt signaling pathway.Siwu Tang (a herbal medicine) can improve ovarian function in cyclophosphamide induced POF mice by reducing granulosa cell apoptosis and inhibiting the expression of PI3K/Akt signaling pathway.Li Junling and others have shown that the combination of Yikun Tongjing Tang and Western medicine artificial cycle treatment is more satisfactory for patients with premature ovarian failure. During the process, the Treg and Treg/Th17 ratio in peripheral blood increase, while Th17 decreases.

7. Conclusion

Women with POF are severely affected both physically and mentally, and must face infertility, amenorrhea, osteoporosis, some cardiovascular diseases, and so on. The etiology of premature ovarian failure is complex, and the most common clinical treatment is still hormone replacement therapy (HRT). However, the role of HRT in promoting fertility remains controversial and there are many long-term complications. According to reports, 20% of POF patients also suffer from autoimmune diseases. When POF is caused by ovarian autoimmune damage, immunomodulatory treatment of POF is an effective method. However, the specific mechanisms by which the immune response attacks the ovaries and leads to premature ovarian failure, such as the manner, timing, and targets, are still unclear. In order to predict the occurrence of premature ovarian failure and find accurate and effective methods to cure it, further understanding the pathogenesis of premature ovarian failure is the key to future research. Immune factors are one of the main causes of POF, and it is of great significance and value to study its pathogenesis and develop reasonable and effective immunological treatment plans to improve patients'

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quality of life and meet their reproductive needs.

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