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Research Progress of Chinese and Western Medicine on the Etiology of Premature Ovarian Failure

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Abstract: The incidence rate of premature ovarian failure is complex. In recent years, the incidence rate is increasing. The incidence of the disease is gradually aging, which is harmful to the female reproductive health and affects the quality of life. Through consulting relevant literature, this paper finds that traditional Chinese medicine puts forward opinions from the aspects of spleen and kidney, heart and liver, blood stasis, and so on, while western medicine studies from the aspects of genetics, immunity, and metabolism and so on. They reveal the related pathogenic factors and possible pathogenesis of premature ovarian failure from different angles. This paper discusses the etiology of premature ovarian failure in many aspects.

Premature ovarian failure (POF) refers to amenorrhea, FSH>40IU/L, decreased estrogen levels before the age of 40 due to ovarian failure, accompanied by different degrees of perimenopausal symptoms such as hot flashes, sweating, facial flushing, low libido, etc.(See Figure 1), which is the final stage of premature ovarian insufficiency (POI) [1]. The overall incidence rate of premature ovarian failure is 1% - 2% [2]. There are many pathogenic factors of the disease, and the pathogenesis is still unclear. Traditional Chinese medicine and western medicine have explored this in many ways, Based on a large number of literature reviews, this paper summarizes and lists the different understanding of the etiology of premature ovarian failure (POF) obtained after the exploration of traditional Chinese and western medicine.

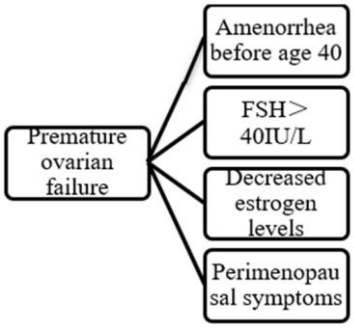

Figure 1: Diagnostic criteria for premature ovarian failure.

1. Western Medicine Knowledge

1.1. Genetic Factors

Genetic factors are one of the important factors leading to POF, and the normal structure of the two X chromosomes is crucial to the normal maintenance of ovarian function. The deletion, inversion, and translocation of X chromosome will lead to egg dysfunction, leading to the occurrence of POF. Chen Zijiang et al. [3] found that the abnormal rate of X chromosome was 93.7% through karyotype analysis of POF patients. X chromosome long arm or short arm deletion and X autosomal translocation are common abnormal karyotypes. At present, it is believed that mutations in the Xq21.3-q27/Xq26.1-q27/Xq13.3-q21 region are related to deletion or POF [4]. Fragile X mental retardation 1 gene (FMR1), located in Xq27.3, is an important candidate gene for POF. Permutation of FMR1 gene will increase the risk of POF, which may be related to the intermediate trinucleotide repeat (CGG) of FMR1 gene [5]. In addition, BMP-15, FOXO3, FOXL2, and other genes are also related to POF, and their genetic factors need to be further studied.

1.2. Immunological Factors

Some POF patients have other autoimmune diseases. Under an abnormal immune state, the body produces anti-ovary autoantibodies, such as anti-ovary antibody (AOA), anticardiolipin antibody (ACA), and anti-zona pellucida (ZP) antibodies. After these antibodies combine with related antigens in the ovary, they produce excessive antigen-antibody reactions, leading to premature egg failure. At present, it is believed that the abnormal immunity of the body is related to cellular immunity. The change of the number and function of T lymphocyte subsets will cause the abnormality of cellular immunity, make them produce antibodies against their own components, damage their own tissues, and lead to the occurrence of autoimmune diseases. Treg is a subset of T cells with immune regulation function. The abnormality of Treg cells and their related factors may be related to the occurrence and development of POF [6].

1.3. Enzyme Defect and Metabolism

Seventeen α – hydroxylase/17, 20-Lyase deficiency leads to steroid hormone synthesis disorder and the decrease of estrogen level leads to the increase of gonadotropin, leading to POF. The deficiency of galactose-1 uridine phosphate transferase (GALT) leads to the disorder of galactose metabolism, which increases the level of galactose in the body, increased galactose and its metabolites affect oocytes, damage ovarian parenchyma, change gonadal hormone activity, and accelerate follicle depletion. However, some studies have shown that the effect of galactose on the ovary is mainly related to the abnormal follicle stimulating hormone (FSH) in the circulating blood, rather than directly damaging the ovary [7].

1.4. Mitochondria

Granular cells are rich in mitochondria, which are the main source of energy for oocytes. Follicular atresia is closely related to granulosa cell apoptosis. Mitochondrial dysfunction (such as mitochondrial DNA defects) is related to granulosa cell function, which may be one of the causes of POF [8].

1.5. Iatrogenic Factors

Surgery, radiotherapy, and chemotherapy will affect ovarian function. Pelvic surgery mainly damages ovarian tissue and affects ovarian blood supply, resulting in decreased ovarian function and POF. Oocytes are quite sensitive to radiation dose. Under the irradiation of 20Gy radiation dose, ovarian function will be completely lost. Chemotherapy drugs may damage granulosa cells and oocytes, resulting in decreased ovarian function. The dose, type and patient age of chemotherapy drugs are closely related to the degree of ovarian function decline after chemotherapy [9].

1.6. Psychological Factors

The population with premature ovarian failure tends to be younger, which is related to the excessive pressure brought by the fierce competition in study and work. Long term mental stress will interfere with the regulation of the hypothalamus-pituitary ovary axis, causing abnormal gonadotropin secretion and disrupting ovarian function. Zhang Yuanyuan et al. [10] found that premature ovarian failure is clearly related to anxiety and depression. Patients with premature ovarian failure have a high probability of anxiety and depression, and their mental health is worrying.

1.7. Other Factors

Gonadotropin dysfunction, insufficient primordial follicle reserve, environmental pollution, inflammatory infection, and personal bad habits (smoking, etc.) will have adverse effects on ovarian function, increasing the risk of POF [11].

2. Understanding of Traditional Chinese Medicine

There is no specific record of premature ovarian failure in Chinese medicine, and it is not regarded as an independent disease. According to its related description, it can be scattered in "amenorrhea", "blood dry", "rare menstruation", "late menstruation", "early water break" and other diseases. TCM believes that premature ovarian failure is mainly due to kidney deficiency, which is closely related to heart, liver, and spleen.

2.1. Kidney Asthenia is Fundamental

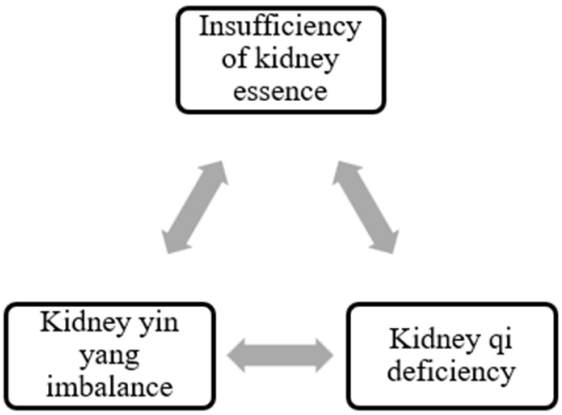

Figure 2: Links leading to kidney deficiency.

The kidney stores essence and is responsible for reproduction. It is the nature of Tiangui and the foundation of life. Follicles in the ovary are nourished by kidney essence, which is the essence of reproduction. Premature ovarian failure (POF) is caused by the decline in the number, quality, and function of follicles and the inhibition of follicular maturation. Therefore, deficiency of kidney essence is the root cause of this disease. Kidney yin and kidney yang participate in the process of kidney essence transformed into kidney qi, and directly affect the results of kidney essence transformed into kidney qi(See Figure 2). The yin and yang of the kidney should be both full and relatively balanced to maintain the normal operation of the kidney Tiangui Chongren Uterus. The perimenopausal symptoms of patients with premature ovarian failure are caused by insufficient kidney yin and YIN failing to keep YANG well. Zhu Ling [12] believes that women use blood, and yin blood is often consumed. Deficiency of liver yin affects kidney yin, causing deficiency of kidney essence. The kidney yin is insufficient, the essence and blood are insufficient, the kidney yang is insufficient, and the spleen and stomach cannot be warmed, the blood and Qi are insufficient, and the amount of menstruation decreases or even amenorrhea occurs. Therefore,tonifying the kidney and tonifying the essence is the basic principle of tcm in treating premature ovarian failure. Drugs that nourish the liver and kidney and warm the kidney and promote yang, such as cooked rehmannia, dodder seed, epimedium, and cornus, are high-frequency drugs for treating POF in traditional Chinese medicine [13]. Pharmacological studies found that [14] kidney tonifying herbs have sex hormone-like effects, which are very effective in regulating hormone levels and promoting follicular development, helping to restore the function of the hypothalamus pituitary ovary axis, regulating immune function and improving bone structure, and can effectively prevent osteoporosis. So, kidney deficiency is the cause of this disease.

2.2. Spleen Deficiency is Essential

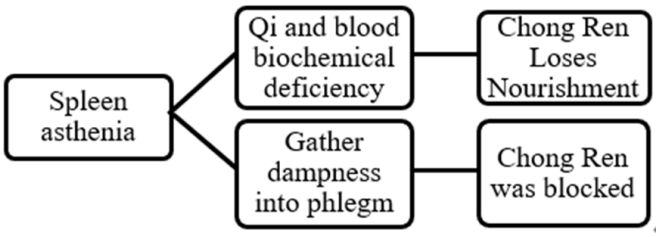

Figure 3: The Influence of Spleen Deficiency on Responsibility.

Spleen is the foundation of acquired nature, which dominates transportation and transformation. Loss of splenic key transport, it is difficult to generate Qi and blood, and the meridian blood lacks its source. Body fluid is difficult to be distributed, and phlegm dampness is endogenous. Chong Ren, uterus, or amenorrhoea due to asthenia or block due to excess. You Zhaoling [15] believed that patients with premature ovarian failure were born wasted, which could be acquired. Revitalizing the spleen could awaken the primordial follicles in the ovary and improve ovarian function. Cui Xiaoping [16] found that excessive weight loss caused by weight loss seriously harms reproductive function and increases the probability of POF. Qi and blood deficiency are caused by spleen deficiency .The endometrium cannot grow on time, and the blood sea cannot be filled on time and amenorrhea occurs. Lei Lei [17] found that the majority of amenorrhea patients in recent years are obese or are related to modern people's addiction to eat too much greasy food, and excessive exertion or comfort. The dampness accumulates into phlegm, and the spleen yang loses its function, which stagnates in Chong Ren and causes amenorrhoea. It can be seen that spleen deficiency is the key factor of POF (See Figure 3).

2.3. Stagnation of Liver Qi and Heart Qi Depletion

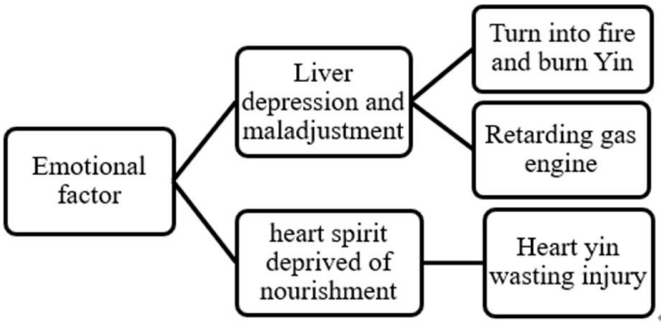

Figure 4: Influence of emotional factors on heart and liver

In the pathogenesis of premature ovarian failure, emotional factors cannot be ignored. The liver stores blood and is mainly used for relieving. It not only promotes the circulation of fluid and blood, but also promotes ovulation and menstruation in women. The heart hides the spirit and commands the human body's conscious thinking activities. The heart pulse is connected with the uterus; heart and liver regulate menstruation together. The abnormal reproductive function caused by emotional factors is the external manifestation of their internal changes (See Figure 4). Modern women are under great pressure, persistent and excessive pressure tends to breed negative emotions such as anxiety, depression, and irritability, resulting in depression of liver qi and mental dystrophy. Liver depression, heart qi depletion, menstrual disorders, decreased ovarian function, premature ovarian failure, etc. [18] Li Zhiyuan stressed that [19] the responsibility for this disease lies heavily on the liver. Liver depression forming fire can consume heart yin and cause heart and liver diseases, affecting the circulation of qi and blood. Cause less menstruation, amenorrhea, etc. Teng Xiuxiang [20] found that stagnation of liver qi will affect the endocrine function of women, resulting in the decline of ovarian function. Emotional factors are common inducements for patients to get sick.

2.4. Stasis Venation

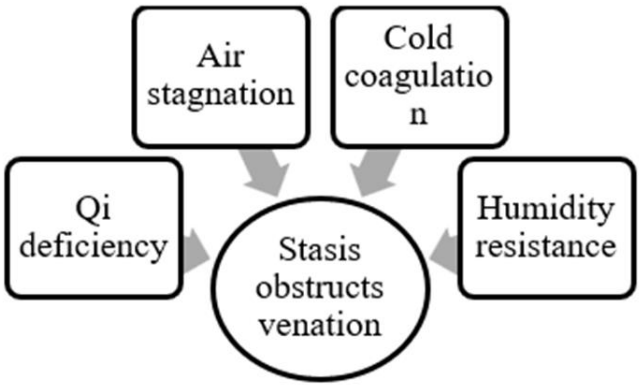

Figure 5: Conditions leading to blood stasis

The disease has a long course, and Chinese medicine believes that "long illness with more blood stasis." During the long course of the disease, the healthy qi is gradually consumed, slow blood flow,and blood stasis is endogenous, the pulse channel will be unobstructed. If Chong Ren are blocked, the uterus will lose its nourishment and become ill. In addition, the stagnation of qi caused by liver depression, the weakness of qi and blood circulation caused by spleen deficiency, and persistent phlegm and dampness will promote the formation of blood stasis and aggravate the

degree of blood stasis (See Figure 5). Kidney deficiency, liver depression, and blood cold can all lead to blood stasis. Stasis of venation is the pathological state throughout the disease. Qiao Yangyang et al. [21] used transvaginal ultrasound to detect the ovaries of patients with premature ovarian failure and found that the ovarian matrix blood flow bundle was thin and difficult to measure, with low flow rate and high resistance. The existence of blood stasis in patients with premature ovarian failure was confirmed from the perspective of modern medicine. Xu Xiaofeng et al. [22] found that the traditional Chinese medicine for tonifying the kidney and activating blood circulation is superior to the simple traditional Chinese medicine for tonifying the kidney in promoting the recovery of ovarian function. Wang Huimin et al. [23] used the method of tonifying the kidney and activating blood circulation to treat immune premature ovarian failure, which can improve the patient's immune function, improve the local ovarian microcirculation, improve the estrogen level, and have an overall regulatory effect. So blood stasis is another important factor in the occurrence of this disease.

3. Summary

To sum up, Chinese medicine believes that the occurrence of premature ovarian failure is mainly related to the imbalance of yin and yang of zang fu organs and qi and blood. Western medicine believes that heredity, immunity, metabolism, and other factors affect the number, quality, and function of follicles causing this disease. The causes of premature ovarian failure are complex, but with the deepening of research, more pathogenic factors have been found, Chinese medicine's analysis of the etiology and pathogenesis of premature ovarian failure is constantly improving. In terms of emotional disease and blood stasis disease, many views and views of Chinese and Western medicine are quite similar, which is worth further discussion. The joint efforts of the two have provided a broader idea for the clinical diagnosis and treatment of premature ovarian failure and have a profound guiding significance for clinical practice.

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