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Research Progress of Traditional Chinese Medicine in the Treatment of Premature Ovarian Failure

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Abstract. In recent years, premature ovarian failure (POF) has become a hot topic in the medical field. Clinically, it has evolved into a common disease among women, affecting those aged 18 to 40, with the highest incidence in women under 35. The onset age is trending younger, and POF even occurs in adolescent females.Traditional Chinese Medicine (TCM) is a conventional therapeutic approach in China. Some domestic doctors have actively explored TCM-based treatments for POF, achieving certain clinical efficacy. TCM treatments for POF mainly include traditional decoctions, acupuncture, and the combination of acupuncture and medication. However, currently there is no unified standard for syndrome differentiation and treatment methods, requiring further research and development. By discussing the existing research foundation, this research comprehensively and in depth examines the application of TCM in POF treatment. It aims to provide more feasible and targeted treatment plans and references for TCM-based POF therapy, contribute to improving the theory and practice of TCM in treating POF, and promote the application and development of TCM in the field of POF. Meanwhile, it intends to offer more effective treatment options for patients and drive the application and innovation of TCM in gynecology.

Keywords: Premature Ovarian Failure (POF), etiology and pathogenesis, syndrome differentiation and treatment

1. Introduction

Premature Ovarian Failure (POF) refers to a clinical syndrome in which women experience pathological decline of ovarian function before the age of 40, which in turn leads to amenorrhea [1].

Unhealthy lifestyles, including alcohol abuse, smoking, frequent hair dyeing, prolonged staying up late, irregular work and rest schedules, poor sleep quality, high work pressure, fast pace of life, high-oil and high-salt diet, dietary restriction for weight loss, and inattention to personal eating habits during menstruation, are also potential risk factors for POF [2]. The clinical manifestations of POF include reduced menstrual flow or even amenorrhea, premature menstruation or oligomenorrhea, hot flashes and sweating, and vaginal dryness. These symptoms can lead to sexual dysfunction and early menopause, which in turn increase the risk of diseases such as depression, cardiovascular diseases, and osteoporosis [3].

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With reference of the Position Statement on Ovarian Reserve Testing and Interpretation issued by the American Society for Reproductive Medicine (ASRM) in 2020 and Selection and Application of Examination Items for Reproductive Endocrine Diseases in 2016, the diagnostic criteria for POF are as follows: age between 18 and 40 years old with menstrual cycle disorders for ≥ 4 months; baseline follicle-stimulating hormone (FSH) > 25 IU/L detected at least twice with an interval of more than 4 weeks; baseline FSH/luteinizing hormone (LH) ≥ 2; anti-Müllerian hormone (AMH) < 1.1 ng/ml; and antral follicle count (AFC) < 5 in the baseline ovary [4, 5].

The etiology of POF is complex, and it is closely associated with living environment, iatrogenic factors, and unhealthy lifestyles (such as alcohol abuse, smoking, staying up late, and a diet high in oil and salt). The ovary is not only a vital reproductive organ but also a crucial endocrine organ for women. There is a close link between ovarian function and female aging—once POF occurs, it affects physical health and reduces quality of life. Therefore, ovarian aging is metaphorically referred to as the "pacemaker of female bodily aging" [6-8]. For the treatment of POF, Western medicine mainly adopts hormone replacement therapy (HRT). However, due to its limitations in use and adverse reactions such as obesity, diabetes, arthritis, and femoral head necrosis, long-term use may increase the risk of thrombosis, breast cancer, and other diseases, resulting in suboptimal clinical efficacy [9].

In contrast, TCM characterized by its holistic regulation, has demonstrated unique advantages in POF treatment through therapies like traditional decoctions, acupuncture, and the combination of acupuncture and medication. Currently, however, there is no unified standard for syndrome differentiation and treatment methods, and further in-depth research and development are needed to standardize and normalize TCM treatment for POF.

2. Etiology and pathogenesis

POF is a condition in modern medicine and has no direct equivalent in ancient TCM classics. However, based on its clinical manifestations and symptoms, it can be categorized into TCM domains such as "xueku" (blood exhaustion), "amenorrhea", "infertility", and "syndromes around menopause".The earliest record related to POF can be found in the chapter "Yin-Yang Yingxiang Dalun" (Great Discourse on the Correlation Between Yin-Yang and Phenomena) of Huangdi Neijing Suwen (Inner Canon of the Yellow Emperor Plain Questions). The Emperor asked, "How to regulate these two (Yin and Yang) ?" Qibo replied, "If one can understand the 'seven impairments and eight benefits' (a TCM concept referring to methods for regulating Yin-Yang through daily life), then the two can be regulated; if one fails to apply this, it will lead to the onset of premature aging. Yin-Qi is naturally reduced by half at the age of forty, and daily activities begin to decline." Additionally, Fu Qingzhu Nvke·Tiaojing Pian (Fu Qingzhu's Gynecology·Chapter on Menstrual Regulation) states, "Menstruation ceases prematurely before the age of forty-nine", which is similar to the symptoms of POF and consistent with its pathogenic characteristics [10-12].

In TCM theory, the "Kidney-Tiangui-Chongren-Uterus" axis is the core of female reproductive function. This bears striking similarities to the hypothalamic- pituitary- ovarian-axis (HPOA) in modern medicine, as both align closely in their approach to regulating human reproductive function [13]. In 1982, Professor Luo Yuankai proposed that the Kidney plays a dominant role; Tiangui (a vital substance in TCM governing reproductive function) is the key material determining the initiation and cessation of the reproductive axis; the Chong and Ren Meridians serve as the hub; and the Nüzibao (uterus) is the reproductive organ responsible for storing and excreting (essence), governing menstruation and conception [14].

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The regular changes in five stages—Tiangui's arrival, replenishment, flourishing, decline, and exhaustion—reflect the life cycle of female reproductive function. For women, "regular menstrual flow" indicates the arrival of Tiangui, while "physical deterioration and infertility" are closely associated with Tiangui's exhaustion. Xuezheng Lun (Treatise on Blood Disorders) states: "The Guishui (Tiangui, literally 'Yin water') transformed by the Yang Qi of Tianyi (primordial Qi) reaches the uterus through the Kidney Meridian." Tiangui originates from Kidney Qi, and the kidney also acts as a channel for transporting Tiangui to the uterus, thereby promoting human growth, development, and reproductive function [15, 16].

The kidney is in charge of storage and serves as the foundation of Yin and Yang. Deficiency of Kidney Essence is the fundamental pathogenesis of POF. Prolonged Kidney deficiency inevitably affects the five Zang organs: Liver Yin deficiency leads to insufficient blood storage and blocked meridians; Spleen Qi deficiency results in inadequate production of Qi and blood, leaving the Chong and Ren Meridians empty; Heart Blood deficiency causes weak propulsion, leading to unsmooth menstruation; Lung Yin deficiency obstructs the water passage, resulting in menstrual exhaustion and amenorrhea. Ultimately, this causes the uterus to lose control over storing, overflowing, accumulating, and excreting (essence), leading to uterine dysfunction and menstrual disorders [17].

3. Syndrome differentiation and treatment

In clinical practice, most physicians take the combination of Eight-Principle Syndrome Differentiation and Zang-Fu Organ Syndrome Differentiation as the core method. The key syndromes include Kidney deficiency, Liver stagnation, and Spleen deficiency, and the treatment adheres to the principle of "simultaneous treatment of the three organs"—nourishing the Kidney, soothing the Liver, and invigorating the Spleen. Among these, Kidney deficiency is the most common syndrome in clinical settings [18, 19].

Some physicians apply Six-Meridian Syndrome Differentiation and propose the concept of "regulating the pivot of Qi movement, pivot of cold and heat, and pivot of blood circulation". If the pivot function of the Shaoyin Meridian is impaired, leading to dysfunction in the opening and closing of the Taiyin and Jueyin Meridians, the treatment focuses on smoothing the opening and closing to regulate the Shaoyin pivot. They also conduct syndrome differentiation with modifications based on the Zang-Fu organs associated with the Shaoyin Meridian and its meridian circulation, and use prescriptions from the "Shaoyin Disease Chapter" (of Treatise on Febrile Diseases) to treat POF [20].

4. Treatment methods

4.1. Internal therapy

Common TCM syndromes of POF include Kidney Yin deficiency, Spleen-Kidney Yang deficiency, Spleen-Kidney deficiency, Kidney deficiency with blood stasis, and Kidney deficiency with Liver stagnation.Treatment can nourish Kidney Essence and regulate the Chong and Ren Meridians to improve ovarian function, increase the number of follicles, and adjust the levels of gonadotropins such as FSH and LH in the body. This thereby promotes estrogen secretion and the combination of sperm and egg, enhancing the conception rate. Commonly used Chinese herbs include Shudihuang (Rehmannia Glutinosa Root, processed), Gouqizi (Goji Berry), and Shanyao (Chinese Yam Rhizome).

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Eighty POF patients with the syndrome of "Kidney deficiency and Liver stagnation" were selected and randomly divided equally into an observation group and a control group. The control group was treated with oral Kuntai Capsules combined with estrogen-progestin therapy, while the observation group received modified Bushen Tiaojing Decoction (Kidney-Nourishing and Menstruation-Regulating Decoction) treatment.After 3 months, the level of estradiol (E2) in the observation group increased significantly, while the levels of FSH and LH decreased markedly, and the therapeutic effect was superior to that of the control group [21]. After treatment with modified Wenjing Decoction (Meridian-Warming Decoction), the ovarian volume, endometrial thickness, number of follicles, and peak systolic velocity of ovarian blood flow in the treatment group were all higher than those in the control group. Meanwhile, the incidence of adverse reactions decreased to 19.57% (42.55% in the control group). This therapy shows significant efficacy in treating POF with the syndrome of "Spleen-Kidney Yang deficiency" and is suitable for clinical promotion and application [22]. Zishen Huoxue Decoction (Kidney-Nourishing and Blood-Activating Decoction) can regulate the body's sex hormone levels, improve progesterone's ability to inhibit the pituitary gland from secreting LH and FSH, reduce the levels of LH and FSH, and restore normal sex hormone balance [23].Taking Guishen Pills are able to increase local oxygen supply to the uterus and ovaries, enhance their oxygen metabolism capacity, and maintain the balance of local microcirculation. This provides the possibility of reversing premature ovarian failure and achieves the goal of improving ovarian function [24].

4.2. External therapy

In the external therapy of TCM for POF, acupuncture therapy is the core method, which regulates the body's functions through multiple pathways and has shown significant clinical potential.

4.2.1. Acupuncture therapy

By stimulating specific acupoints, acupuncture regulates the HPOA, improves the patient's endocrine status, enhances ovarian reserve function, and promotes blood circulation in the uterus and ovaries. Meanwhile, it can also inhibit gene expression, prevent the apoptosis of ovarian granulosa cells, and thereby improve ovarian function [9].

4.2.2. Warm Acupuncture combined with Umbilical Moxibustion

Warm Acupuncture combined with Umbilical Moxibustion stimulates acupoints through warm heat, improves the state of high resistance in ovarian blood flow, and promotes smooth blood circulation. Clinical studies have shown that after treatment with Warm Acupuncture combined with Umbilical Moxibustion, patients' serum E2 levels increased significantly, FSH and LH levels decreased significantly, the ovarian blood flow peak systolic velocity (PSV) in patients accelerated obviously, and the pulsatility index (PI) and resistance index (RI) decreased significantly. This suggests that the therapy can effectively improve the ovarian microenvironment [25].

4.2.3. Acupuncture combined with Fire Dragon Moxibustion Therapy

Acupuncture combined with Fire Dragon Moxibustion Therapy stimulates the PI3K/Akt/mTOR signaling pathway, increases mRNA and protein expression, and promotes the secretion of E2 and AMH. Meanwhile, it reduces the expression of inflammatory factors, inhibits the apoptosis of

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ovarian granulosa cells, promotes the recovery of ovarian function, enhances ovarian reserve function, and thereby improves serum hormone levels [26].

4.2.4. Acupoint application combined with Acupuncture

According to the theory of Midnight-Noon Ebb-Flow, acupoint application combined with Peiyuan Tiaoshen Acupuncture was performed at traditional Chinese time Youshi (17:00-19:00) and Choushi (01:00-03:00) for 3 consecutive months. After the treatment, the ovarian peak PSV and end-diastolic velocity (EDV) increased, while the RI decreased. Additionally, the TCM syndrome score and Self-Rating Anxiety Scale (SAS) score in the treatment group decreased significantly, suggesting that this therapy not only improves ovarian hemodynamics but also alleviates patients' emotional symptoms [27].

4.2.5. Acupoint catgut embedding therapy

Catgut embedding is an innovation in diagnostic and therapeutic techniques based on acupuncture theory. It involves implanting absorbable protein threads into acupoints, and through the process of liquefaction and absorption of the threads, the acupoints are stimulated persistently and stably, thereby prolonging the therapeutic effect. Studies have shown that after treatment with acupuncture combined with Back-Shu and Front-Mu acupoint catgut embedding and Shenque acupoint external application, the ovarian volume increased from 6.27±0.92 cm^3 to 7.85±1.03 cm^3, the number of antral follicles increased from 3.31±0.60 to 5.86±1.13, and the diameter of antral follicles increased from 2.75±0.69 mm to 9.22±1.68 mm, indicating that the therapy significantly improves ovarian reserve function and structural parameters [28, 29].

4.3. Combination of internal therapy and external therapy

In clinical practice, some physicians treat POF by combining oral Chinese herbal decoctions with TCM external therapies such as acupuncture, moxibustion, and tuina. This combination regulates the Kidney-Tiankui-Chong Ren-Uterus axis, alleviates patients' symptoms, enhances ovarian reserve function, also promotes the growth, development, and ovulation of follicles.

For POF patients with kidney deficiency and liver depression syndrome, the "three-viscera simultaneous treatment" acupuncture combined with Bushen Shugan Tiaozhou Yangjing Decoction (a decoction for tonifying the kidney, soothing the liver, regulating the menstrual cycle, and nourishing the menstruation) can significantly improve clinical symptoms and sex hormone levels, as well as increase endometrial thickness, enlarge ovarian volume, and enhance ovarian reserve function, with remarkable curative effects [18]. When Xianxian Decoction is combined with warm acupuncture to treat POF patients with kidney deficiency and liver depression syndrome, after 6 months of treatment, the levels of LDL-C, HDL-C, TG, and TC in the acupuncture-medicine combination group are significantly lower than those in the Chinese herbal medicine alone group and the Western medicine group. Xianxian Decoction combined with warm acupuncture can regulate qi and blood, warm and tonify the spleen and kidney, which can significantly improve patients' sex hormone levels and increase AFC levels [30].

5. Discussion and prospect

Current treatment methods generally use hormones, which are prone to causing complications and have suboptimal clinical effects. The application of TCM in treating POF can reduce drug resistance

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and the incidence of complications. Clinically, the two can be combined to treat POF.

Existing clinical studies have shown that POF cannot be cured after diagnosis, but only alleviate symptoms; the damage to the ovaries is irreversible, which greatly increases the difficulty of treatment. Avoiding ovarian damage and maintaining a healthy lifestyle are the keys to preventing POF. In the prevention of POF, how to apply the TCM theory of "preventive treatment of disease" (Zhi Wei Bing) will be the focus of future research.

6. Conclusion

Premature Ovarian Failure (POF), as a clinical syndrome possibly leads to amenorrhea, is usually developed in women experience pathological decline of ovarian function. This article comprehensively and in-depth summarizes various TCM approaches for treating POF, clarifies that TCM acts on the pathological mechanism of POF through multi-targets and multi-pathways, and significantly improves endocrine status, ovarian blood flow, and reserve function. It applies the "four diagnostic methods combined" (Si Zhen He Can) and simultaneously emphasizes emotional regulation, embodying the advantages of TCM's holistic concept and syndrome differentiation and treatment. This study contributes to improving the theory and practice of TCM in treating POF, provides more effective treatment options for patients, and promotes the application and innovation of TCM in the field of gynecology.

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