DOI: 10.53469/jcmp.2024.06(06).38

Advancements in the Research of Therapeutic Mechanisms of Kidney-Nourishing Approach for Premature Ovarian Failure

Xiaomeng Han, Jinghong Shi*

Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
**Correspondence Author*

Abstract: ***Premature ovarian failure (POF) is a prevalent condition that significantly impairs the quality of life for women during their reproductive years. Its implications for patients and their daily routines are profound, and the disease's chronic progression can even trigger a range of other systemic ailments. In recent years, numerous studies have highlighted the reduced toxicity and side effects of Traditional Chinese Medicine (TCM) in treating POF, along with its notable therapeutic effects. TCM holds that the kidney governs reproduction, and a robust kidney essence leads to strong reproductive function. The kidney-produced "Tiangui" directly oversees menstruation. As such, the approach of nourishing the kidney and regulating menstruation in treating POF is grounded in solid theory and rich practical experience. This paper, from the perspective of kidney nourishment in TCM, reviews relevant research both domestically and internationally on how TCM's kidney-nourishing prescriptions improve POF. It also summarizes the mechanisms involved, aiming to provide valuable insights for clinical efficacy and treatment strategies for POF.***

Keywords: Premature ovarian failure, Traditional Chinese Medicine, Kidney-tonifying methods, Mechanism of action.

1. Introduction

Premature ovarian failure (POF) is a common clinical gynecological endocrine disease. According to the epidemiological investigation, the incidence of premature ovarian failure in Chinese women is generally 2.8%[1]. Premature ovarian failure before the age of 40 years in women by various factors leading to the destruction or depletion of the inner ovarian follicles, The decrease in the oocyte quality, To make sex hormone deficiency, Thus by ovarian failure and fertility, With Follicle-stimulating hormone (FSH)> 40 IU / L, low estrogen levels, Major clinical features such as irregular menstruation, amenorrhea, hot flashes, night sweats and vaginal dryness, The long-term progress of the disease may also appear to be osteoporosis, Diseases of the neurological and cardiovascular and cerebrovascular systems, Women's physical and mental health is seriously affected [2-4]. Now the main means of modern medical treatment of POF for hormone replacement therapy (HRT), HRT can quickly improve low estrogen status and perimenopausal symptoms, restore to maintain uterine periodic bleeding, reduce long-term complications, it has certain curative effect, but cannot make the ovarian function recovery, spontaneous ovulation still uncertain, stop after relapse, unsustainable problems, long application hormone or easy to improve the risk of endometrial cancer, breast cancer and other diseases [5, 6].

2. The Etiology of Premature Ovarian Failure

The term "premature aging" originating from the "Yin and Yang should be like a big theory" pertains to an early decline in physiological function. However, ancient TCM texts lack a record of the term "premature ovarian failure." Clinically, its manifestations are categorized as "blood deficiency", "infertility", "amenorrhea" and related symptoms. The kidney is the source of the days, and the filling and failure of menstruation are dominated by kidney qi. The text "Plain Questions · On the Natural Integrity of the Ancients"[7] states: "A girl at seven years old, with kidney qi in full bloom, experiences tooth replacement and hair growth. At fourteen, Tiangui arrives, the Ren Meridian becomes unobstructed, and the Chong Meridian is abundant, leading to the regular occurrence of menstruation and thus fertility... At forty-nine, the Ren Meridian weakens, the Chong Meridian declines, Tiangui depletes, and the menstrual passage is blocked, resulting in physical deterioration and infertility." The prosperity or decline of kidney qi guides the abundance or depletion of menstruation. The text "Lingshu · Patterns of Diseases of Viscera and Pathogens" [8] says: "A faint and sluggish kidney pulse indicates absence of menstruation." The "Medical Orthodoxy" [9] mentions: "Menstruation relies entirely on the nourishment of kidney essence. When kidney essence is deficient, menstrual blood dries up day by day." Only when kidney essence is sufficient can menstruation occur regularly. If kidney essence is deficient, menstrual blood has no source [10]. The "Fu Qingzhu's Gynecology" [11] states: "Menstrual blood originates from the kidneys"; "Premature cessation of menstruation seems to indicate the depletion of kidney essence"; "If kidney qi is inherently weak, how can it be full enough to transform into menstrual blood and discharge it externally?" "Menstrual blood" refers to menstruation, and the kidney's dominance in the production of menstruation emphasizes Fu Qingzhu's fundamental viewpoint of emphasizing kidney nourishment [12]. The text "Jingyue Complete Works · Women's Regulations" [13] says: "However, menstruation is essentially yin blood, which is present in every organ. Only the blood of all organs converges in the Chong Meridian, and the Chong Meridian is the sea of blood for the five-Zang and six-Fu organs. Therefore, it is said that when the Chong Meridian is abundant, menstruation occurs regularly. This shows that the Chong Meridian is the foundation of menstruation."

On the basis of the classic theory of traditional Chinese medicine, modern and even modern doctors summarize and put forward new thinking. Long jiang Han's gynecology

department believes that the imbalance of "kidney qi-Tiangui-Chong and Ren Meridians-uterus" is the pathogenesis of POF, kidney deficiency and liver dysfunction, so it created the "liver and kidney theory" [14,15]. Professor Chen Huinong, proposed that the disease for the first time should be "Tiangui early exhaustion disease" [16]. Professor Cui Xiaoping, under the guidance of the theory of "Yin and Yang" and "kidney reproduction", It is proposed that "kidney deficiency" is a POF pathogen to adjust ovarian function and restore ovulation function, which can be realized by tonifying the kidney and balancing the water and fire in the kidney [17]. National TCM Master, Xiao Chengcong, believes that the core pathogenesis of premature ovarian failure is kidney deficiency and pulse disorders. She takes the basic treatment of premature ovarian failure infertility and uses the kidney as the basic prescription [18].

The kidney, the master of reproduction, holds a pivotal role in female physiology and pathology. When kidney yang falters, its warming and nourishing prowess diminishes, hindering the transformation of kidney essence into Tiangui. Consequently, Tiangui's motivating force weakens, impeding the flow of menstrual blood. If kidney yin is impoverished, it depletes the fountain of menstrual blood, resulting in blood insufficiency in the Chong and Ren meridians. Tiangui, unfed, dwindles, stalling follicular growth and maturation. The uterus, deprived of nourishment, lacks menstrual blood to release, ultimately leading to menstrual cessation. When kidney essence wanes and the vital gate fire dims, blood and qi stagnate in the Chong and Ren meridians, starving the uterus of its life-giving essence. Thus, menstruation fails to arrive as per schedule [19]. These manifestations align with the clinical symptoms of POF, including menstrual disorders and infertility. According to TCM principles, the kidney governs reproduction, and the root of POF lies in kidney deficiency. This deficiency, if prolonged, impairs the qi of the Zang-Fu organs and weakens the Ming-Men fire, essentially reflecting an imbalance in the yin and yang of the kidney.

3. Treatment Mechanism of Premature Ovarian Failure by Kidney-tonifying Method

The Zang-Xiang theory of TCM diverges from anatomical forms, focusing on reasoning human physiological and pathological traits. Consequently, ovarian functions parallel the kidney's governance of reproductive essence. Nourishing the kidney modulates the kidney-Tiangui-Chong and Ren Meridians-uterus axis, replenishing kidney essence, inhibiting ovarian cell senescence and apoptosis, and regulating ovarian functions. As TCM posits, the kidney stores essence, which is homologous to blood, mutually dependent and inter - generating. Therefore, kidney-nourishing formulas enhance essence and blood, balance yin and yang, enrich ovarian blood flow, improve microcirculation, and ultimately optimize ovarian function to prevent and treat POF.

3.1 Role of Neuroendocrine Regulation of the Hypothalamic-pituitary-ovarian Axis on Ovarian Function

The hypothalamus-pituitary-ovarian (HPO) axis governs folliculogenesis and ovulation. Dysfunction therein leads to hormonal imbalances, resulting in ovarian ovulation disorders. Intriguingly, this regulation mechanism parallels the kidney-Tiangui-Chong and Ren Meridians-uterus axis in TCM. By nourishing kidney essence, one can modulate the kidney-related axis, harmonize the HPO axis, restore hormonal balance, and ultimately enhance ovarian function.

The Bu-Shen-Cu-Yun formula improves ovarian function, normalizes menstrual cycles, and upregulates Estradiol (E2), Anti-Müllerian Hormone (AMH), and Gonadotropin - Releasing Hormone (GnRH) secretion while suppressing FSH levels. This intervention modulates the hypothalamus – pituitary - ovarian (HPO) axis, leading to an increase in follicle counts across stages and fostering follicular maturation [20]. The Bu-Shen-Huo-Xue formula enhances sex hormone and AMH levels, increases normal follicular development, restores disrupted estrous cycles, and improves ovarian reserve function in a rat model of Decreasing Ovarian Reserve (DOR) [21]. The Bu-Shen-Jian-Pi formula modulates the HPO axis via upregulation of AKT and mTOR in the PI3K/AKT/mTOR pathway. This alters sex hormone secretion, reducing FSH and GnRH, while increasing E2 and AMH. The result is enhanced follicular development, ovulation, ovarian reserve, and improved ovarian aging [22]. The Bu-Shen-Shu-Gan formula may improve ovarian ovulation function and restore ovarian morphology in POF rats by modulating the HPO axis, downregulating serum FSH and GnRH levels, and upregulating serum E2 and Gonadotropin-Releasing Hormone Receptor (GnRH-R) levels [23]. The Bu-Shen-Cu-Pai-Luan decoction regulates sex hormone levels through the HPO axis, elevating serum E2 and progesterone (P) while decreasing pituitary luteinizing hormone (LH) and testosterone (T) levels. This modulates ovarian function and upregulates hypothalamic GnRH expression, promoting ovulation [24]. The primary cause of ovarian function decline is the low expression of follicle-stimulating hormone receptor (FSHR) and estrogen receptor (ER) in the hypothalamus, pituitary, and ovarian tissues. Zuo-Gui-Wan elevates FSHR and ER expression in these regions by promoting ovarian synthesis and secretion of E2 and reducing serum FSH and LH levels, thereby enhancing estrogen activity, regulating HPO axis balance, delaying ovarian decline, and alleviating POF [25, 26]. There are more studies on ovarian function, whose function is tonifying kidney, nourishing Yin and nourishing blood [27]. Zuo-Gui-Wan promotes follicular growth and development in rats, thereby improving ovarian function. Experiments confirm that this is achieved by upregulating Notch1 expression, activating the Notch/Hes1 signaling pathway, increasing ovarian coefficients, and augmenting the number of follicles and corpora lutea [28].

3.2 Inhibition of Ovarian Granulosa Cell Apoptosis

Granulosa-oocyte interdependence is essential for ovarian function, and inhibiting granulosa cell apoptosis preserves ovarian function. Granulosa cell growth, differentiation, and apoptosis correlate with follicle development, maturation, and atresia, with apoptosis initiating atresia. Atresia eliminates abnormal follicles during ovarian physiology. Imbalanced apoptosis prematurely depletes ovarian reserve, causing POF [29]. Kidney-tonifying prescriptions can prevent POF by inhibiting granule cell apoptosis.

The Yulin formula, based on kidney-tonifying therapy, enhances ovarian granulosa cell function in DOR rats, altering their ultrastructure, increasing serum Inhibin B (INHB) secretion, effectively inhibiting follicle apoptosis, and significantly improving the quantity and quality of oocytes in the ovary [30]. The traditional Chinese medicine for nourishing kidney and promoting blood circulation can suppress oxidative stress in DOR mouse models, inhibiting the activation of Bcl-2 associated X protein (Bax), cytochrome C (Cyt C), and Cysteinyl aspartate specific proteinase 3 (Caspase-3), thereby reducing granulosa cell apoptosis and follicular atresia, thus maintaining normal follicular development [31]. The Yi-Shen-Tiao-Jing formula effectively inhibits ovarian granulosa cell apoptosis in rats by downregulating caspase-3 and Bax expressions and upregulating Bcl-2 expression, thereby improving ovarian function [32]. The Bu-Shen-Cu-Luan formula can downregulate Caspase-3 expression by promoting BMP-7 expression, alleviate ovarian pathological processes, and inhibit ovarian granulosa cell apoptosis in mice [33]. The Yi-Shen-Shu-Gan decoction can improve the pathological state of DOR model rats, enhance ovarian reserve function, likely through inhibiting ovarian granulosa cell apoptosis and upregulating Bcl-2 expression while downregulating Bax and Caspase-3 protein expressions [34].

The Yi-Shen-Tiao-Jing formula also improves ovarian function in DOR rats by inhibiting phosphatase and tensin homolog deleted on chromosome 10 (PTEN), upregulating mRNA and protein expressions of PI3K, AKT, and phosphorylated protein kinase (p-AKT), leading to increased gonadal index and number of ovarian growth follicles [35]. In vitro studies on the effect of Yi-Shen-Shu-Gan decoction-containing serum on tripterygium glycosides - treated rat granulosa cells suggest that it may inhibit granulosa cell apoptosis by activating the PI3K/AKT/mTOR pathway [36].

The Smads protein was the only substrate protein in the transforming growth factor- β 1 (TGF- β 1) signaling pathway [37]. Research [38] confirmed that the Bu-Shen-Zhu-Yun decoction promotes proliferation and differentiation of cultured ovarian granulosa cells in vitro, enhancing follicular development by upregulating Smad3 and Smad4 expressions via increased TGF-β levels. The Bu-Shen-Yang-Jing granules upregulate the expressions of VEGF, TGF-β, and IGF-1 in ovarian granulosa cells, while downregulating NF-κ B and TNF-α expressions, thus inhibiting apoptosis in ovarian granulosa cells and promoting follicular development [39]. The Bu-Shen-Yang-Jing granules significantly inhibit apoptosis in ovarian granulosa cells of rats with premature ovarian insufficiency (POI), potentially related to the activation of the Hedgehog signaling pathway. The underlying mechanism may involve downregulating apoptotic genes and upregulating anti-apoptotic gene expressions [40].

Reduced ovarian reserve function in rats is associated with increased expressions of Phospho-Extracellular regulated protein kinases 1/2 (p-ERK1/2) and Phospho-c-Jun N-terminal kinase (p-JNK1/2). The Yu-Shen-Zhu-Yun formula delays ovarian aging and improves ovarian function in DOR rats, suggesting a potential mechanism of reducing p-ERK1/2 and p-JNK1/2 protein activations, decreasing granulosa cell apoptosis, and inhibiting ovarian tissue atrophy [41].

3.3 Regulation of Ovarian Peroxidative Stress

Oxidative stress can trigger apoptosis of female germ cells, aging of reproductive organs, and inflammatory responses in the reproductive system, ultimately leading to damage in the female reproductive system [42]. Under normal ovarian physiological conditions, reactive oxygen species (ROS) mediates redox processes, regulating oocyte growth, meiosis, ovulation, and other physiological processes, with ROS involvement [43]. Excessive ROS production and stimulation lead to mitochondrial dysfunction in oocytes, abnormal changes in follicular development and ovulation, and accelerated decline in ovarian function [44, 45]. The cause of POF is kidney deficiency, and kidney deficiency and essence are highly consistent with aging. TCM can improve the oocyte quality of kidney tonifying, which may be related to the improvement of oxidative stress damage and inhibition of granulosa cell apoptosis. The Sheng-Di-Huang decoction, which nourishes kidney yin, can enhance the antioxidant function of POF rats, increase E2 and P levels, significantly upregulate ER expression in endometrial stromal cells and granulosa cells of POF rats, improve ovarian tissue and function, and thereby delay ovarian aging [46].

The method of tonifying kidney and promoting blood circulation can reduce the expression of malondialdehyde (MDA) in ovarian lipids, while enhancing the activities of superoxide dismutase (SOD) and catalase (CAT) [47]. The kidney-tonifying and menstruation-regulating formula can enhance the activities of Mn-superoxide dismutase (Mn-SOD) and glutathione peroxidase (GSH-Px), which are located in ovarian granulosa cells and follicular fluid, regulating oxidative stress and improving mitochondrial function [48]. The kidney-tonifying and blood-activating decoction can significantly increase the contents of antioxidant enzymes SOD, heme oxygenase 1 (HO-1), and quinone NADH dehydrogenase 1 (NQO1), suggesting that it can enhance the antioxidant capacity of autoimmune POI mice. As SOD, HO-1, and NQO1 are antioxidant enzymes downstream of the Keap1/Nrf2/ARE signaling pathway, the mechanism of action of the kidney-tonifying and blood-activating decoction may be related to the Keap1/Nrf2/ARE signaling pathway [49]. Based on the method of tonifying kidney and promoting blood circulation, the He's Ovary-Nourishing formula can improve oocyte quality and enhance embryonic development potential. The mechanism is that the flavonoid compounds in the compound formula have significant antioxidant activity, which can reduce the ROS level in oocytes through the ROS/JNK/p53 pathway [50].

Er-Zhi-Wan can reduce the elevated ROS level in rat insulinoma cells (INS-1) induced by H2O2, enhancing antioxidant stress capacity [51]. Its mechanism may involve reducing MDA, increasing GSH-Px and SOD activities, thereby delaying the aging process of renal cells in D-galactose-induced rats [52].

3.4 Regulation of the Ovarian Microcirculation and Angiogenesis

Traditional Chinese medicine believes that kidney is the by essence and blood. Kidney-tonifying Chinese medicine can benefit essence and produce blood, and provide sufficient blood material basis for the ovary. With blood activating drugs, it can promote the operation of blood in the ovary, ensure that the blood flow is needed, and then improve the ovarian artery blood flow, regulate the local microcirculation, and play a positive role in the prevention and treatment of POF.

Through color Doppler flow imaging (CDFI), the blood flow distribution of the ovaries, uterus, etc. can be visually observed, revealing that kidney-tonifying and menstruation-regulating traditional Chinese medicines can increase the peak systolic velocity (PSV) of the uterine and bilateral ovarian arteries, decrease the resistance index (RI) and pulsatile index (PI), improve uterine and ovarian circulation, and thereby enhance ovarian function [53]. Yu-Lin-Zhu optimizes ovarian blood supply, reduces blood flow resistance, and thereby improves the microcirculation environment of POI mouse ovaries by regulating the balance of antioxidant and hypoxia-related factors, creating favorable conditions for follicle development and maturation [54].

Angiogenesis is a prerequisite for abundant blood supply to the ovary, and the normal growth and development of follicles play an important role in ovarian physiological functions. Kidney-tonifying and blood-activating traditional Chinese medicine compounds can regulate VEGF-mediated neovascularization, improve ovarian tissue microcirculation, and increase ovarian blood supply, thereby enhancing ovarian sensitivity and embryonic development potential. The receptors VEGFR1 and VEGFR2 of VEGF can promote angiogenesis when binding to VEGF, and kidney-tonifying and blood-activating traditional Chinese medicine can enhance angiogenesis through the VEGF signaling pathway [48]. The Bu-Shen-Tian-Jing formula can effectively improve ovarian reserve function and promote angiogenesis in POF rats, and the upregulation of VEGF signaling pathway in ovarian tissue may be related to its mechanism [55]. The Bu-Shen-Yi-Qi-He-Xue formula can elevate the levels of VEGF and its receptor proteins, promote neovascularization within the ovary, enhance ovarian blood circulation, thereby maintaining normal follicle growth and preventing premature exhaustion [56]. The method of kidney-tonifying and menstruation-regulating can improve ovarian function and ovarian reserve capacity in patients with premature ovarian failure by regulating sex hormones, angiogenesis-related factor levels, and uterine artery blood flow [57].

Zuo-Gui-Wan may improve the functional status of reproductive organs in prematurely aging rats by stimulating angiogenesis through enhancing the expression of placental growth factor (PLGF), hepatocyte growth factor (HGF), and their receptor proteins and mRNA in reproductive organs [58]. You-Gui-Wan can promote ovarian angiogenesis and improve ovarian function in rats by downregulating the mRNA and protein expression levels of chemokine CXCL8, chemokine receptors CXCR1, and CXCR2, and upregulating the mRNA and protein expression levels of angiotensin I (Ang-1) and angiotensin II (Ang-2) in ovarian tissue [59].

4. Summary and Outlook

POF, a complex condition with escalating incidence, gravely threatens women's well-being. Hormone replacement therapy in modern medicine, though prevalent, faces scrutiny over its efficacy and safety. In contrast, TCM's natural and varied approach gains favor, drawing on the theory of "kidney reproduction." Modern studies reveal TCM can harmonize Yin and Yang, balance qi and blood, regulate hormones, hinder granulosa cell apoptosis, unblock ovarian meridians, and rejuvenate ovarian function. It effectively alleviates menopausal symptoms, boosts fertility prospects, and alleviates liver stress, emotional imbalance, depression, and anxiety. TCM's comprehensive benefits enhance patients' quality of life, fostering physical and mental equilibrium.

In the quest for treating premature ovarian failure (POF), apoptosis inhibition stands as a critical approach. Western drugs, such as imatinib, while inhibiting apoptosis, increase DNA damage risks, compromising oocyte quality. Animal studies exploring rapamycin for primordial follicle activation are in early stages, necessitating further confirmation of safety and efficacy. In contrast, Traditional Chinese Medicine (TCM) demonstrates distinct benefits in POF management, particularly the kidney-tonifying method based on the theory of "kidney as the root of reproduction." This approach has yielded promising clinical outcomes. Nonetheless, rigorous clinical trials are crucial to evaluate its mechanisms and guarantee both efficacy and safety. TCM's personalized treatment strategies and vast clinical expertise offer robust support for POF therapy. The potential and importance of TCM in POF research are promising, deserving extensive promotion and in-depth exploration. Integrating TCM with modern medicine to refine treatment protocols remains a crucial research direction. The synergistic therapeutic effects of TCM compounds present new opportunities, requiring further scientific investigation to uncover their mechanisms and modernize treatment modalities. Integrated TCM-Western medicine approaches for POF treatment are emerging trends, outperforming monotherapy, yet effective combination strategies await further elucidation. In conclusion, future research should prioritize safer, longer - lasting, and efficacious POF therapies, harnessing TCM and modern medicine's strengths to provide optimal treatment options. Concurrently, early detection and preventive measures for POF are crucial, requiring collaborative efforts between women and medical professionals to uphold women's holistic health.

Acknowledgement

This study was funded by The Shaanxi Provincial Natural Science Basic Research Plan Project (No. 2023-JC-YB-733).

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