

Exploration on the Role and Mechanism of Chronic Inflammation on Polycystic Ovary Syndrome Based on Blood-Water Homoeopathy in Chinese Medicine

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Abstract: Polycystic ovary syndrome (PCOS), as a common gynaecological disease, has a variety of clinical manifestations and a lingering course. Modern medicine believes that chronic low-grade inflammation is involved in the development of PCOS, and the abnormal coagulation/fibrinolytic function of PCOS patients will aggravate and prolong the development of the disease. Chinese medicine believes that the basic pathogenesis of this disease lies in kidney deficiency, with qi, phlegm, and stasis as pathological products, which is the same as the pathogenesis analysed by modern medicine, and corresponds to the idea of treating blood and water together. Therefore, it is of great significance to summarize and elucidate the pathogenic mechanism of PCOS in both Chinese and Western medicine, and combine it with the theory of "if the blood is not favourable, then the water will be water" for the development of subsequent related research and clinical treatment. Therefore, summarising and elucidating the pathomechanisms of PCOS in Chinese and Western medicine, combined with the theory of "if the blood is not favourable, then the water will become water", is of great significance to the subsequent research and development of clinical treatment.

Keywords: PCOS; chronic inflammation; coagulation/fibrinolytic function; blood is not favourable to water

1. Introduction

Polycystic ovary syndrome (PCOS), as one of the most common female reproductive endocrine disorder syndromes, has a prevalence of 6% to 21% in women of reproductive age ^[1]. The etiology of PCOS has not yet been clearly defined, but the heterogeneity of the symptoms and constitution suggests that it has a complex aetiology and pathogenesis, and the main clinical manifestations of patients with PCOS include menstrual disorders, gonadal axis dysfunction, persistent anovulation, hyperandrogenemia, insulin resistance, etc., and they have increased long-term health risks such as cardiovascular disease, type 2 diabetes mellitus, and endometrial cancer.

In recent years, a large number of studies have found that inflammatory factors are significantly elevated in the peripheral blood and in the local ovaries of PCOS patients, suggesting that the ovarian microenvironment in PCOS patients is a low-grade chronic inflammatory state. Chronic low-grade inflammation and immune dysfunction can interact with each other, which can directly affect the ovary, hinder follicular development or lead to ovulation abnormality, and even cause infertility; and chronic inflammation also induces IR, HA, and obesity through related pathways, which play an important role in the development of PCOS.

2. Western medicine's understanding of PCOS and chronic inflammatory factor

2.1. NF- κ B

NF- κ B is a key nuclear transcription factor that initiates and regulates inflammation and plays an important role in the pathogenesis of PCOS. In normal cells, NF- κ B exists in the cytoplasm in an inactive form bound to the inhibitory I κ B protein. Under the stimulation of inflammatory factors in the follicular fluid of the ovaries of PCOS patients, the kinase upstream of I κ B protein kinase (IKK) is

activated, activating IKK, which phosphorylates I κ B, changes the original state of binding to NF- κ B and releases NF- κ B, thus mediating the regulation of the synthesis and release of related inflammation, exacerbating the inflammatory state of patients with PCOS, and the large amount of inflammatory factors generated can further activate the IKK. IKK, forming a vicious circle. At the same time, NF- κ B pathway is also involved in apoptosis of PCOS ovarian granulosa cells; Caspase protein kinase family, as the centre of apoptosis, can induce apoptosis after its overexpression, and anti-apoptosis gene BCL-2 can inhibit apoptosis after over-activation by combining with NF- κ B, so that there is a bi-directional regulation of cell apoptosis by NF- κ B, which can either promote or inhibit apoptosis [2]. The NF- κ B pathway can induce apoptosis in polycystic ovarian granulosa cells by positively regulating the expression of Caspase-3 and BCL-2 [3]; some studies have also shown that high mobility group protein 1 (HMGB1) may promote apoptosis of granulosa cells in rats by activating NF- κ B, which may in turn lead to PCOS [4]. In addition, the NF- κ B pathway is also involved in pathological processes such as abnormal glucose metabolism, which contributes to the development of PCOS; the NF- κ B pathway activates downstream immune receptors, releasing a large amount of inflammatory factors, and a large amount of inflammatory factors promote the phosphorylation of IRS-1 serine, which inhibits its normal tyrosine phosphorylation, leading to the impairment of insulin signaling pathway, and ultimately causing hyperinsulinemia and IR.

2.2. *TNF- α*

TNF- α is a cytokine released by adipocytes, monocytes-macrophages, etc., and plays an important role in promoting inflammatory responses. On the one hand, it can reduce IRS-1 tyrosine phosphate and thus inhibit the insulin signal transduction pathway; on the other hand, it can promote lipolysis, increase free fatty acids, reduce insulin sensitivity, or down-regulate the expression of many important signalling molecules or proteins in adipocytes, all of which can cause IR. TNF- α is also an important factor in the triggering of HA. Elevated TNF- α induces apoptosis of follicular granulosa cells, activates mitotic activity of follicular mesenchymal stromal cells, leading to a decrease in follicular granulosa cells and an increase in follicular mesenchymal stromal cells, and also increases the number of steroid-producing cells, which leads to a blockage of estrogen synthesis, and an increase in the androgen content that ultimately contributes to the development of PCOS and its complications. In addition, TNF- α expression and its receptor change throughout the menstrual cycle and can be involved in the endometrial remodelling and proliferation process. Increased levels of TNF- α systematically affect the process of fertilised egg implantation, resulting in low fertility in PCOS patients [5].

2.3. *CRP*

CRP is the most important member of acute acidic heat-sensitive proteins synthesized by liver cells, and the content of CRP increases significantly when stimulated by serum TNF- α , IL-6 and other intra-serum factors, so it can be used as a non-specific marker for acute and chronic inflammation [6]. CRP damages the vascular endothelium and activates the inflammatory response system by mediating the production of endothelial adhesion molecules by endothelial cells, and promotes the secretion of a large number of inflammatory factors by monocytes and phagocytes. CRP activates the inflammatory response system by mediating the production of endothelial cell adhesion molecules by endothelial cells, damaging the vascular endothelium, promoting the secretion of monocytes and phagocytes to produce a large number of inflammatory factors, and the generated inflammatory factors can activate lymphocytes and phagocytes at the same time, aggravating inflammatory response, and then affecting the transmission and transformation of signals of insulin pathway, resulting in IR. Lymphocytes in the blood also infiltrate the ovarian tissue, resulting in PCOS lymphocytes are also significantly elevated in the ovarian tissue, and these lymphocytes may inhibit follicular development through the secretion of inflammatory factors. CRP induces an increase in the production of reactive oxygen radicals, which act on the ovaries to cause oxidative damage to the body, leading to impaired conversion of androgens to oestrogens, and can promote the secretion of gonadotropins to further exacerbate HA [7]. Zhao Wenhui et al. [8] used the method of tonifying the kidney and activating the blood to treat PCOS, CRP and LH/FSH decreased significantly, and the menstrual cycle gradually became regular, which showed a positive correlation between CRP and LH and FSH. CRP is not only one of the strongest predictors of cardiovascular disease risk, but also can be used to predict and evaluate the risk of cardiovascular disease in PCOS patients in the future [9].

2.4. Interleukin Factors

The imbalance between pro-inflammatory and anti-inflammatory cytokines in the interleukin community is a key reason for the maintenance of a chronic subclinical low-grade inflammatory state in PCOS patients.

IL-6, an immunomodulatory multi potent adipocytokine with both pro-inflammatory and anti-inflammatory effects, is abnormally expressed at elevated levels in PCOS patients, and is closely associated with IR, obesity, and HA, and affects normal physiological functioning of the ovaries and pregnancy and childbirth in patients [10-11]. High levels of IL-6 can damage pancreatic islet β -cells or interfere with insulin signalling pathways by decreasing the activation of insulin receptor substrate-1 (IRS1), reducing the transmembrane sites of glucose transporter protein 4 on the cell surface, and decreasing the synthesis of glycogen, which can lead to the development of IR. In addition, the elevated level of IL-6 is associated with hyperandrogenism in the body, and IL-6 can up-regulate the expression of testosterone (T) receptor in ovarian tissues, which indirectly promotes the secretion and production of androgens, and thus participates in the pathogenesis of PCOS; at the same time, HA will also be sustained due to the high level of circulating IL-6 expression, which regulates the IL-6 signalling pathway mediated by various pro-inflammatory factors. Finally, the high level of IL-6 and androgens in PCOS patients can directly or indirectly regulate the STAT3 signalling pathway to induce adipocyte proliferation and promote the release of free fatty acids (FFAs), resulting in persistent chronic inflammation of the patient's ovaries, and making the patient more prone to abdominal obesity. more than 50% of the patients with PCOS are obese, and most of them are predominantly abdominal-type obesity (central obesity). The metabolic homeostasis of adipose tissue is regulated by immune cells and cytokines. Excess adipose tissue secretes pro-inflammatory factors, and elevated levels of lipids can lead to the accumulation of inflammatory factors, resulting in the accumulation of impaired intracellular insulin signalling, interfering with normal follicular development and ovulation dysfunction, which not only results in anovulation, but also in the secretion of more androgens, which exacerbates the onset and development of PCOS. High-fat and high-sugar diets can easily cause intestinal flora disorders and imbalance of intestinal homeostasis, and the intestinal flora produces lipopolysaccharide (LPS) mediated damage to the intestinal mucosal barrier, which in turn mediates the TLR4/NF- κ B signalling pathway and initiates the transcription and expression of relevant inflammatory factors [12]. IL-10 is an anti-inflammatory factor, which is secreted by Th2 cells, monocytes-macrophages and other cells, and it establishes a balance between pro-inflammatory and anti-inflammatory, and has been shown to be expressed at a lower level in PCOS [13], which regulates the onset and development of the disease process of PCOS; this is of great significance for the prevention and treatment of PCOS-related diseases.

3. Western medicine's understanding of PCOS and coagulation/fibrinolytic function

The blood state of PCOS patients is often in a hypercoagulable and hypofibrinolytic state, and there is often a prothrombotic state. Inflammatory factors can increase endothelial permeability and promote leukocyte aggregation and adhesion on the endothelium, which have the effect of enhancing thrombus formation and delaying thrombus dissolution. In patients with hyperglycaemia and hyperinsulinism, vascular endothelial cells are damaged, platelet reactivity and adhesion are increased, coagulation factor expression is promoted, and the concentration of PAI-1, the main physiological inhibitor of fibrinogen activator, is increased, resulting in the upstream stage of thrombus formation [14]. The presence of viscous, running blood in obese PCOS patients is also a high risk factor for the prethrombotic state. Obesity leads to higher risk of IR, HA and CVD etc. and also more prone to coagulation abnormalities. Hyperhomocysteinemia (HHcy) is closely associated with obesity, abnormalities of glucose and lipid metabolism, IR, etc. and is an independent risk factor for distant cardiovascular complications in PCOS [15]. During female reproduction, high levels of HHcy cause oxidative stress by increasing the production of reactive oxygen species (ROS) in vascular endothelial cells, damaging vascular endothelial cells, activating pro-coagulant factors, promoting fibrin deposition, leading to impaired blood flow, and stimulating the proliferation of vascular smooth muscle cells, activating the unfolded protein response (UPR). The unfolded protein response (UPR) induces apoptosis in vascular endothelial cells [16-17], thereby decreasing oocyte maturation rate, impairing meconium and chorionic villus angiogenesis, and affecting endometrial tolerance [18], leading to a variety of obstetrics and gynaecology complications such as recurrent miscarriage, gestational diabetes mellitus, hypertensive disorders of pregnancy and intrauterine foetal developmental delay, resulting in poor pregnancy outcomes.

4. Chinese medicine's understanding of PCOS

The ancient Chinese medical literature does not involve the name of PCOS and its monographs, the study of Chinese medicine over the years of ancient texts found that the "broken threads", "menstruation breaks do not come", "menstrual cycle delay" and other gynecological diseases are similar to this symptom. Modern scholars have classified PCOS as "obstruction in the abdomen", "late menstruation", "menorrhagia", "amenorrhoea", "amenorrhoea" and "amenorrhoea" in traditional Chinese medicine according to the characteristics of the polycystic ovary pattern and the main clinical manifestations of PCOS. PCOS is classified as belonging to the categories of "obstruction", "late menstruation", "scanty menstruation", "amenorrhoea", "disintegration" and "infertility" in Chinese medicine. The disease is not limited to the kidney, spleen and liver, and the pathogenesis mainly revolves around qi, phlegm and blood stasis, with the root cause lying in deficiency.

4.1. Kidney deficiency

The Yellow Emperor's Classic of Internal Medicine - Su Wen - Theory of the Ancient Heavenly Truth says: "When a woman is seven years old, her kidney qi flourishes and her teeth grow long; at the age of two or seven, the heavenly decanter arrives, the Ren vein passes through, and the Taichong vein flourishes, and the menstrual cycle begins at the right time, so that there are children. Kidney is the source of tiankui and the origin of Chongren, which is the basis of menstruation and conception, and dominates the female reproductive axis of "kidney-tiankui - Chongren - uterus". The fundamental mechanism of this disease lies in the deficiency of the kidneys. Kidney yin is the material basis of menstruation, and the prevalence of kidney qi is a prerequisite for menstruation. The egg is the "essence of reproduction" stored in the kidney, which is the material basis for conception, and kidney yang can warm and warm the blood and generate kidney qi to promote the blood flow, which is the driving force for the development and maturation of the egg. If the kidney essence is insufficient, Yin deficiency, the blood generation is insufficient, viscosity increases, coupled with Yin deficiency generates internal heat, tormented blood and become fatigue blood. Kidney yang deficiency is drumming without power, qi and chemical failure, yin loss of constraints, it is difficult to transform the gas line water, water and dampness stagnation, gathered as phlegm, gas line is not smooth, long time the blood stagnation is stagnant, stagnation of the Chong Ren; or the blood by the cold and cohesion, the blood vessel are not smooth; kidney qi is strong, the yin and yang balance of the kidney is a prerequisite for the regulation of blood and qi, stagnation of blood stagnation together with the action in the uterus, the meridian does not come, the blockage of the network, the ovum shall not come out.

4.2. Spleen deficiency and phlegm-dampness

Spleen is the root of the body, the source of qi and blood biochemistry, spleen health and qi transport, qi and blood flourish, the blood follows the blood vessel, menstruation is naturally harmonious. Weakness of the spleen and stomach is trapped by dampness, easy to gather dampness into phlegm, phlegm and dampness congestion of the Chong Ren and the uterus, the blood does not run smoothly, the hair for the blood stasis, phlegm and stasis of each other, resulting in amenorrhoea, infertility, and other diseases, spleen deficiency phlegm aggregation into the water dampness and fat, stagnation of the internal organs and the skin is manifested in the form of obesity, phlegm and stasis flooding in the face is seen in the acne hairy skin, sticky skin. Phlegm stasis stagnation, internal stagnation of dampness and turbidity, and the accumulation of heat, heat burns the fluids and internal heat, resulting in thirst.

4.3. Liver Depression

Liver stores blood, the main excretion, so that the normal operation of blood and qi, Chongren and harmony, the cell blood vessel can be nourished and can take in the essence of pregnancy. Liver and kidney reside in the lower burner, if liver qi is stagnant and unfavourable, then qi and blood will be stagnant, blocking Chong Ren and the uterus, which can lead to late menstruation, amenorrhoea and infertility; qi is easy to be transformed into fire after a long period of depression, and the liver fire will consume the kidney yin and heat the Chong Ren, which can be seen in early menstruation, excessive menstruation, abnormal bleeding during non-menstrual period, and the fire fumigates the face, which will lead to facial sores, thick hair, rough skin and other manifestations. In addition, when the liver is not nourished, the spleen and earth are affected, the spleen is not healthy, the water and liquid transport is not normal, and phlegm and dampness are generated within the body, resulting in amenorrhoea and

obesity.

4.4. Blood stasis and obstruction

Blood is the basis for women, and female reproductive function cannot be separated from sufficient blood and essence. Because of the cold, heat, dampness, or because of the generation of the lack of source can lead to blood in the blood vessel flow slowly, and gradually into stasis, generated stasis will aggravate the blood run poorly, stasis of blood once formed, internal organs and organs and meridians physiological functions will be blocked, stasis in the uterus and cytoplasmic blood vessel will affect menstruation and fertility. □

5. Chinese medicine's understanding of the modern pathogenesis of PCOS

There is no such thing as "inflammation" in Chinese medicine, and Chinese medicine mostly adopts the therapeutic features of "holistic view" and "diagnosis and treatment" to study it from multiple angles. Inflammatory response is a process in which inflammatory factors activate the body's immune system after injury to form a defence and stabilising effect to ensure the elimination of harmful stimuli and the repair of damaged tissues. Traditional Chinese medicine believes that this reaction process is the same as "positive and evil struggle", "positive qi stored inside, evil cannot be dry" and "where the evil is, its gas must be weak", the kidney is the root of qi, kidney deficiency is positive qi deficiency, so kidney deficiency is intrinsic to the occurrence of chronic inflammatory states. Chronic inflammation is the inner foundation of the state, kidney yin and yang imbalance, easy to lead to the essence of blood and fluid operation is not smooth, blood flow is not smooth, phlegm stasis, that is, the inflammatory substances gathered, adherence. The defense and warming effects of the human body mainly rely on Wei Qi, which originates from Promordial Qi. The Wei Qi also originates from cereal essence transformed by the spleen and stomach, aggressive and smooth of which transmute into whole-body Wei Qi. Patients with PCOS have spleen and kidney deficiency, which leads to a lack of solidity in the Wei Qi and a chronic inflammatory state over time. Spleen deficiency leads to a lack of fluid distribution in the body, which turns into water dampness and phlegm retention, blocking the blood vessel and causing poor circulation of qi and blood, and stagnation of blood stasis. In addition, PCOS patients are in a pre-thrombotic state, which is equivalent to the concept of "Blood Stasis Syndrome" in traditional Chinese medicine. Blood stasis in the blood vessel can cause stagnation or overflow of water and qi, which can mix body fluid and blood, phlegm and blood stasis together to cause diseases, aggravating and prolonging the development of this disease.

6. Chinese medicine on the blood is unfavourable for the understanding of water

Body fluid and blood come from the same source, which both are the basic substance that maintains the life activities of the body. Blood is located in the blood vessels, extending outward to the skin, passing through the orifices, providing nutrients throughout the body, and maintaining the normal function of the internal organs. Sanjiao is the ascending channel of body fluid in the human body, which nourishes the skin and hair through internal organs such as the lungs, spleen and kidneys. Body fluid and blood interact under physiological and pathological conditions. Blood is unfavourable to water" is from "The Essentials of the Golden Chamber - Water and Gas Disease Pulse Evidence and Treatment XIV": "The Shaoyang pulse is low, the Shaoyin pulse is fine, the man is not in a good position to urinate, and the woman is not able to pass the menstrual flow. The menstruation is blood, and when blood is unfavourable, it is water, which is called blood division. "Youyi believed that Shaoyin and Shaoyang qi originated from the middle jiao of the spleen and stomach, and that a weakened middle jiao qi would be insufficiently infused, resulting in a weak Shaoyin pulse, and that a malfunction of qi in the lower jiao would lead to lower jiao illnesses; all of which were attributed to a lack of yang qi. Tang Rongchuan believes that qi is born from water, summarising the intrinsic connection between qi, blood and water, stating that "qi is water", and that the normal functioning of water and blood cannot be separated from qi, and in the subsequent application of the method of treating blood and water together in the diagnosis and treatment of various illnesses, he emphasised that the treatment of water should be based on qi, and that the blood and water are of the same origin, and that the three are not separated from qi, blood and water. Fu Qingzhu emphasised the three organs of the liver, spleen and kidneys in the diagnosis and treatment of gynaecological diseases. The Four Sacred Sources of the Heart - Blood Stasis: "Blood is warm and ascending in nature, and when the kidney water is revolving, it gives birth to liver blood; liver blood is born, and it holds the Yang Soul,

so its nature is mild and ascending and dispersing." Liver-qi, liver-blood, spleen-earth and kidney-qi are connected, which can promote the opening of ostium of uterus. Therefore, patients who are infertile with liver qi stagnation should adopt Kai Yu Zhong Yu Decoction, which can soothe the liver and relieve depression, connect heart and kidney, combine blood and water and regulate qi flow to result in the opening of ostium of uterus. Patients who are infertile with chest fullness and lack of diet should adopt Wentu Yulin Decoction, which can warm and nourish the spleen and stomach, while also nourish the fire of the vital gate and pericardium. It can protect the spleen and stomach from cold, enrich qi and blood to nourish the fetus. Obesity infertility formula with Buzhong Yiqi Decoction, smoothing the water transportation of spleen, regulating the yin and yang of the internal organs, so that the evil dampness is easy to disperse.

In modern medicine, there are also many medical doctors on the treatment of PCOS guidelines for the treatment of blood and water together. Xiao Xinchun concluded that Gui Zhi Fu Ling Wan can activate blood and promote water circulation and treat both symptoms and root causes, and used this formula with additions and subtractions in clinical PCOS patients in order to dissolve phlegm and promote dampness, activate blood circulation and dissipate blood stasis, which can effectively improve patients' glucose and lipid metabolism, ovulation rate and pregnancy rate [19]. Spleen and kidney treatment to resolve phlegm and eliminate blood stasis Chinese medicine (Cangzhu guiding phlegm pill plus reduction) combined with acupuncture treatment of PCOS patients 86 cases, the results show that the observation group hypercoagulable state and HA symptoms than the control group significantly improved, and the incidence of adverse reactions between the two groups were not significantly different [20]. Ding Yongfen [21] et al. used the formula of tonifying the kidney and activating blood to treat PCOS, and the experimental group was able to regulate and correct the level of sex hormones and improve the pregnancy rate of the patients relative to the control group which was only treated with western medicines. Chen Xufeng [22] and others prepared their own Zuo Gui Shuo Liver Tang plus reduction to treat PCOS infertility, serum LH, FSH, T and other levels were significantly reduced, to achieve the effect of ovulation to improve the pregnancy rate.

7. Summary

In summary, the chronic low-grade inflammation level in the organism of PCOS patients is closely related to the factors such as NF- κ B, TNF- α , CRP, and IL-6, and has an impact on IR, HA, and long-term cardiovascular complications in PCOS patients. According to TCM, the chronic inflammatory state of PCOS patients is equivalent to the body's positive qi fighting against evil energy, resulting in pathological products such as phlegm and blood stasis that further disrupt the balance of yin and yang. At the same time, the pre-thrombotic state of PCOS is the same as blood stasis, which can lead to phlegm dampness, lead to kidney deficiency and damage to Chongren. It can affect women's menstruation, pregnancy and childbirth ultimately. Through the analysis of the etiology and pathogenesis of this disease, the theory of "treating blood and water together" was proposed, namely tonifying the kidney, strengthening the spleen, soothing the liver. This method can enrich qi and blood, promote blood circulation and resolving phlegm. Some clinical studies have shown that it can improve the treatment efficiency of PCOS, provide more guidance for the diagnosis and treatment of this disease in TCM, which will provide us with new ideas in the future.

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