

Research Progress on the Treatment of Kidney Deficiency and Blood Stasis Type Infertility with Tonifying Kidney and Activating Blood

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ABSTRACT: In recent years, the incidence rate of infertility has been increasing. Chinese medicine has a significant effect in the treatment of infertility. Chinese medicine believes that kidney deficiency and blood stasis are the basic pathogenesis of infertility. The method of tonifying kidney and activating blood is the main method of treatment. It can play a therapeutic role by regulating reproductive endocrine function, improving the local blood supply of the ovary and regulating cytokines. The research progress of type I infertility in recent years is summarized as follows.

1. Introduction

Couples of childbearing age cohabit for more than one year, have normal sex life, and fail to get pregnant without taking any contraceptive measures, which is called infertility. This kind of fertility disorder is an adverse event in the reproductive health of couples of childbearing age, which is caused by a variety of reasons. It has been reported that infertility will become the world's third largest disease affecting human health, second only to malignant tumor and cardiovascular disease[1]. According to the latest information, about 9%-18% of the general population in the world are suffering from infertility[2], while the prevalence rate in China has risen to 10%-15%, and it is increasing, which is about 10 times higher than that in the 1970s[3], among which infertility caused by ovulation disorder accounts for about 20%-40%[4]. In recent years, Chinese medicine through the use of tonifying kidney and activating blood in the diagnosis and treatment of female infertility due to kidney deficiency and blood stasis, has achieved a more significant clinical effect, has been recognized by patients. Based on the theory of traditional Chinese medicine and relevant research data, this paper discusses the research progress of tonifying kidney and activating blood in the treatment of infertility of kidney deficiency and blood stasis type in recent years.

2. Understanding of Infertility in Traditional Chinese Medicine

Traditional Chinese medicine has a long history of understanding of female infertility. As early as the Western Zhou Dynasty, “Women have not become pregnant within three years” has been proposed in The book of changes, and “Du Channel's disease causes female infertility” also exists in Huangdi Neijing in the pre Qin period. Doctors of all dynasties have attached great importance to the diagnosis and treatment of infertility. For example, in the Zhubing Yuanhou Lun, Beiji Qianjin Yaofang and Fu Qingzhu Nvke, the causes, pathogenesis, treatment rules and prescriptions of female infertility are discussed in detail.

2.1 The Basic Pathogenesis of Infertility is Kidney Deficiency and Blood Stasis

According to the theory of traditional Chinese medicine, the kidney stores essence and controls reproduction, which is the foundation of Yin and Yang in the five organs of the human body, Tiangui originates from the kidney, Chong Channel and Ren channel depends on the kidney, Qi and blood is based on the kidney. The normal development of human reproductive organs, the maturity and maintenance of reproductive function, and the strength of reproductive capacity all depend on the rise and fall of kidney essence. Traditional Chinese medicine believes that Tiangui, the essence of human body, is produced by the essence of the kidney. When the kidney essence is full, Tiangui will arrive. When the kidney essence is depleted, Tiangui will exhaust. Tiangui dominates the menstrual cycle and stops. Suwen· Shanggu Tianzhen Lun says that “When a woman is 14 years old, Tiangui will come, Ren Channel will be smooth, Chong Channel will be full, menstruation can come on time, so she can get pregnant, and when a woman is 49 years old, Tiangui will dry up, Ren Channel will be blocked, menstruation will not come on time, so she will not be able to get pregnant”. Therefore, the essence of the kidney is sufficient, Tiangui comes as scheduled, and women's menstruation is normal, so they can get pregnant normally; if the female's qi of kidney is deficient, menstruation can't come on time, so can't normal pregnancy, just as the Furen Gui says, “The cause of irregular menstruation is all in the kidney”.

Egg cell, also known as egg, is a germ cell produced by female ovary, which belongs to the category of reproductive essence in traditional Chinese medicine. The production of reproductive essence is based on the innate essence stored in the kidney and the acquired essence transported by the spleen and stomach. It is generated through the promotion of Tiangui. Its essence also comes from the kidney essence and has the function of reproduction. The essence of kidney can be transformed into kidney yin and kidney yang, On the one hand, the development and maturity of the egg depends on the nourishing and nurturing of the kidney yin. If the kidney Yin is depleted and unable to nourish, the egg can not develop and mature normally, leading to infertility. On the other hand, the normal discharge of mature eggs depends on the stimulation of the kidney yang. If the kidney yang is weak and powerless, the egg can not be discharged normally, also leading to infertility[5].

Menstrual blood comes from the uterus, and the kidney is related to the uterus. Just as the Bingji Shazhuan says, “the source of blood is the kidney”. Kidney stores essence, essence generates marrow, and one of the basic substances of metaplasia blood is kidney essence. When kidney essence is full, blood metaplasia is active. Therefore, kidney is the basis of menstruation. Traditional Chinese medicine believes that Qi and blood are inseparable, and Qi can promote and regulate the normal operation of blood, just as “blood circulation, disease can not be born” in the biography of Hua Tuo in the Sanguo Zhi. The formation of blood stasis is not caused by kidney qi deficiency, kidney yin deficiency and kidney yang deficiency. Due to Qi deficiency, the push is weak, the blood circulation is sluggish, and the blood stasis is formed after staying for a long time; Yin deficiency, the ministerial fire is hyperactivity, and there is no kidney water to restrict it, so that the blood stasis is formed by burning Yin blood; Yang deficiency, the middle cold is endogenous,

the cold coagulation is stagnant, and the blood stasis is formed by losing the warmth. Finally, the blood stasis blocks the uterus, the blood stasis blocks the veins and collaterals, the Chong Channel and Ren channel can not communicate, and the male and female's germ cell can not match, which leads to infertility.

Kidney deficiency can lead to blood stasis, which in turn affects the nourishing of kidney essence and the metaplasia of kidney qi. They are the causes and influence each other. Therefore, kidney deficiency and blood stasis are the basic pathogenesis of infertility.

2.2 The Main Treatment of Infertility is Tonifying Kidney and Activating Blood Circulation

Huangdi Neijing once pointed out that the treatment of the disease needs to “observe the pathogenesis”, therefore, for infertility caused by kidney deficiency and blood stasis, tonifying the kidney and activating blood circulation is its right method. Tonifying the kidney is to nourish the egg according to the law of Yin and Yang in the kidney and the transformation of Yin and Yang, so that the egg can mature on schedule and be discharged smoothly, and then get pregnant; promoting blood circulation is to add the Chinese herbal medicine of activating blood circulation and removing blood stasis at the same time of Tonifying the kidney, remove blood stasis, communicate Chong Channel and Ren channel, new blood generation, and nourish the uterus, so as to obtain essence and pregnancy. In clinical treatment, according to the dynamic changes of Yin and Yang in a menstrual cycle, the method of invigorating the kidney and activating blood circulation should also be emphasized and appropriately adjusted. For example, in the later period of menstruation, the follicles enter the golden period of growth and development, the Yin grows and the Yang disappears, and the sea of blood is deficient. Therefore, the treatment should focus on nourishing the kidney and nourishing the Yin, and subsidizing the follicles to grow and mature; in the premenstrual period, it is the preparation before the sperm and egg implantation period, at this time, the female body Yin disappears and the Yang grows, Qi and blood with strong, treatment should be mainly kidney yang, to prepare for pregnancy; In the mid menstruation, this is the “Right time”, at this time, the transformation of Yin and Yang, many Yin turns into Yang, treatment should be mainly to promote the normal discharge of eggs[6]. Studies have pointed out that Chinese herbal medicine of kidney tonifying can improve the estrogen level or estrogen like effect of the body. For example, the total flavonoids of *Cuscuta chinensis* contained in *Cuscuta chinensis* has a significant effect on improving the ovarian quality and increasing the number of follicles in rats. At the same time, it also has a certain effect on the recovery of ovarian function and the increase of E2 level in rats[7]. Animal experiments show that *Rehmannia glutinosa* has phytoestrogen-like effects, It can effectively improve the uterus coefficient of young rats[8], *Lycium barbarum* has the effect of nourishing Yin, tonifying kidney and tonifying essence, which can significantly improve the hormone level in the body and help to improve the ovarian function[9]. *Angelica*, *Salvia*, *Chuanxiong*, *Caulis spatholobi* and other traditional Chinese herbal medicine can effectively improve the blood flow of ovarian artery, increase the local blood supply of ovary, and have a certain positive effect on the development and maturation of follicles[10]. In addition, experimental studies have found that traditional Chinese herbal medicine can also regulate the hormone level of the body to a certain extent, reduce oxidative stress injury, and improve the chances of pregnancy for infertile women[11].

3. Clinical Application of Tonifying Kidney and Activating Blood

Through clinical research, Li Xiaofei found that for patients with infertility caused by ovulation disorder, there was no significant difference in ovulation rate between the two groups after treatment with clomiphene and traditional Chinese medicine for invigorating kidney and activating

blood circulation, but the pregnancy rate of patients treated with traditional Chinese medicine for invigorating kidney and activating blood circulation reached 44.44%, which was significantly higher than 26.67% in the treatment group treated with clomiphene. At the same time, compared with clomiphene group, the total effective rate and endometrial thickness of the treatment group for invigorating kidney and activating blood circulation was higher than that of the treatment group treated with clomiphene, there were significantly different[12]; Zhang Xuemei and Tian Yan found that compared with clomiphene group, the total effective rate after treatment with Tonifying kidney and activating blood was significantly increased. In addition, traditional Chinese herbal medicine of Tonifying kidney and activating blood can effectively regulate LH, FSH and their ratio, improve E2 level and reduce the content of INS, PRL and T in the body, which is more conducive to the development and maturation of follicles, optimizes the endometrial capacity, and greatly increases the probability of ovulation and conception[13]; guided by the Method of Tonifying kidney and activating blood, Guo Yaning used the self-made formula combined with clomiphene to treat. According to the research results, the traditional Chinese herbal medicine of Tonifying kidney and activating blood combined with clomiphene can effectively stimulate the positive feedback effect of endogenous estrogen, improve the vitality of follicles, and at the same time increase the blood circulation in the uterus, thereby effectively increasing the ovulation rate and pregnancy rate; Yu Peiluo also found that the diameter of follicles and endometrial thickness of infertile patients treated with kidney invigorating and blood activating herbs combined with letrozole were significantly better than those treated with letrozole alone[15]; Chen Yanhua used the method of invigorating the kidney and regulating the menstrual cycle when treating ovulation disorder infertility caused by kidney deficiency and blood stasis. The treatment group was given Oral Huoxue Tiaojing Decoction during menstruation period, Cu Luanpao Decoction was given during the later period, Cu Pailuan Decoction was given during the menstrual period, and Huangti Decoction was given during the premenstrual period. The control group was given Oral Clomiphene and Progyal. After two consecutive menstrual cycles, it was found that the effective rate of the method of invigorating the kidney and regulating the menstrual cycle was 86.7%, while the effective rate of the control group was 70%, and the menstrual volume, color, quality and other TCM symptoms of the treatment group were also improved. Compared with the control group, especially in lumbosacral soreness, dizziness, tinnitus, libido, etc., the curative effect of the traditional Chinese medicine treatment group is much higher than that of the control group[16]. In recent years, studies have shown that for the treatment of infertility due to kidney deficiency and blood stasis, it has certain curative effect to take Tonifying kidney and activating blood Herbs Combined with acupuncture, After treatment, Zhong qiuzhu found that after combined acupuncture, the ovulation rate of patients reached 73.0%, and the clinical pregnancy rate reached 38.1%, which was significantly improved compared with 44.4% and 31.7% of the control group. Therefore, the method of Tonifying kidney and activating blood combined with acupuncture can effectively improve the patient's endocrine status, maintain the balance of sex hormones in the body, and increase the ovulation rate and pregnancy rate[17]. The clinical research of Li Huixin and Wang Yugang also confirmed that acupuncture therapy combined with Tonifying kidney and activating blood has a significant effect on improving the symptoms of patients with ovulatory infertility[18].

4. Mechanism of the Method of Tonifying Kidney and Activating Blood in the Treatment of Infertility

4.1 The Method Can Regulate Reproductive Endocrine Function

Pang Li'e and Wu Limin found through research that Chinese medicine for Tonifying kidney and activating blood can significantly increase the pituitary's response to the hypothalamus. While

reducing FSH levels in the body, it can increase E2 levels and pituitary gonadotropin levels, adjust the H-P-O axis, and improve the body's reproductive endocrine regulation function. Then adjust the level of reproductive hormones in the body, so as to realize the coordination of reproductive endocrine[19]. Through animal experiments, Hu Xingwen et al. found that Chinese medicine for Tonifying kidney and activating blood can regulate the pituitary gland and increase the secretion of FSH, and can increase the expression level of FSH receptors in ovarian granulosa cells to promote the secretion of more estrogen[20]; Miao Mengqi et al. used Bushen Huoxue Decoction to treat POI rats caused by high corticosterone and found that compared with the control group, the levels of CORT and FSH in rats treated with Bushen Huoxue Decoction were significantly reduced, while the AMH level increased. pathological observations also indicate that the ovarian granulosa cells are arranged regularly, the structure of the follicle is complete, the number of atresia follicles decreases, and the number of preantral follicles and antral follicles increases. The mechanism may be related to the down-regulation of the expression of Angptl4 and Np4 in ovarian tissue[21].

4.2 The Method Can Improve the Local Blood Supply of Ovary

Through sorting and research, Mo Qiong et al. found that Chinese medicines for promoting blood circulation and removing blood stasis contain chemical components such as flavonoids, terpenes, phenylpropanoids and steroids, which can improve blood viscosity, improve microcirculation disorders, prevent blood clotting, and relieve blood. Inflammation, regulating body immunity, etc.[22]. On the basis of using Chinese medicine for invigorating the kidney, combined with the product for promoting blood circulation and removing blood stasis, it can effectively increase the blood supply of the ovaries, improve the blood circulation of the ovaries and increase the responsiveness of the ovaries, thereby regulating ovarian function. Liang Rubi used Bushen Huoxue Tiaoqing Decoction to treat patients with PCOS infertility. Observing their ovarian interstitial pulsation index (PI) and resistance index (RI), they found that RI decreased and PI increased significantly after treatment. Compared with the control group, the treatment group ovulated Rates and pregnancy rates have increased.[23] Studies have pointed out that vascular endothelial growth factor (VEGF) can cause ovarian stromal hyperplasia, and the expression of VEGF mRNA in the isolated serum and ovarian tissue of PCOS women is higher than that of normal women of childbearing age[24]. Wang Ruijie, Wang Zichuang and others found through animal experiments that the expression of VEGF mRNA in the ovarian tissue of rats in the treatment group was significantly weaker than that in the control group, while the angiotensin II type 1 receptor (AT1) and The expression of type 2 receptor (AT2) and G protein-coupled receptor MAS mRNA increased, which suggests that Chinese medicine for invigorating the kidney and promoting blood circulation has a certain effect on improving the local blood supply of the ovary[25].

4.3 The Method Can Regulate Cytokines

Studies have shown that excessive atresia of follicles due to various reasons will lead to the development and maturation of follicles, which will further lead to ovulation disorders and infertility. One of the important factors leading to atresia of follicles is the apoptosis of granulosa cells[26]. Experimental studies by Zhang Lina and others have shown that Chinese medicine for invigorating the kidney and promoting blood circulation has a positive effect on reducing the apoptosis of ovarian granulosa cells. Pathological slices suggest that compared with the model group, the number of atresia follicles in the ovaries of rats is increased, the corpus luteum is not fully developed, and the number of apoptotic granulosa cells is obvious The ovarian condition of the rats in the treatment group was significantly improved[27]. Cai Jing found through animal

experiments that tripterygium wilfordii polyglycosides can inhibit the activity of the PI3K/AKT/mTOR signaling pathway by down-regulating the expression levels of p-AKT, p-mTOR, and p-p70S6, inhibit the proliferation of granulosa cells, and make follicular granulosa cells. The thickness is reduced, which affects the normal development and maturation of secondary follicles and antral follicles, leading to excessive atresia of follicles, and the treatment of Chinese medicine for tonifying the kidney and promoting blood circulation can promote the normal development of follicles. The mechanism may be the same as that of the Chinese medicine for tonifying the kidney and promoting blood circulation by up-regulating p-AKT and p-mTOR. The expression level of p-p70S6 activates the PI3K/AKT/mTOR signaling pathway and promotes the proliferation of granular cells[28]. Bai Jun's study on rat ovarian granulosa cells using the method of Tonifying kidney and activating blood found that triptolide (TP) caused a decrease in ovarian reserve. The expression of p-PI3K, p-AKT, p-mTOR and p62 in rat ovarian granulosa cells was significantly reduced. The expression of Beclin-1 and LC3 was significantly increased, while the related factors in the treatment group showed the opposite expression, which shows that the Chinese medicine for invigorating the kidney and promoting blood circulation can reduce the expression of autophagy effector molecules Beclin1 and LC3 by activating the PI3K/AKT/mTOR signaling pathway, While reducing the consumption of p62, thereby repairing the autophagy damage of rat ovarian granulosa cells caused by TP[29].

5. Conclusion

As a unique therapy for infertility of kidney deficiency and blood stasis type, the method of tonifying kidney and activating blood has been developed rapidly at this stage. It has also achieved significant effects in clinical treatment, mainly by regulating the reproductive endocrine function, improving the local blood supply of the ovary, and regulating cytokines. Play a therapeutic role. However, due to the complexity and flexibility of traditional Chinese medicine treatment, there is currently no standard and systematic prescription medication. At the same time, there is still a lack of systematic and in-depth research on the mechanism of the method of nourishing the kidney and promoting blood circulation. Therefore, there is still much room for improvement in the research of this method.

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