

REVIEW

Progress of Integrative Chinese and Western Medicine in Treating Polycystic Ovarian Syndrome Caused Infertility*

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ABSTRACT Polycystic ovarian syndrome (PCOS) is one of the most popular diseases that cause menstrual dysfunction and infertility in women. The present paper is a brief retrospection on the progress in treatment of PCOS caused infertility with integrative Chinese and Western medicine (ICWM). It can be seen from these materials that using traditional Chinese medicine (TCM) recipes formulated by Shen-replenishing herbs or acupuncture to reinforce Gan-Shen, regulate Chong-Ren Channels in treating PCOS, stable clinical efficacy could be obtained, with less adverse reaction, though the effect initiated somewhat late. Whereas, when Shen-replenishing recipe and acupuncture are combined with hormone or ovulation promoting drugs of Western medicine, the above-mentioned shortcomings would be overcome. So, this combined therapy is frequently used in clinical practice.

KEY WORDS polycystic ovarian syndrome, integrative Chinese and Western medicine therapy, traditional Chinese medicinal treatment, drug therapy

Polycystic ovarian syndrome (PCOS) is an endocrine metabolic disturbance disease of multiple causes with multifarious clinical features, characterized by hyperinsulinism, hyperandrogenism and insulin resistance, etc., and manifested as menstrual disturbance, infertility, hirsutism, acne, acanthosis nigricans syndrome, etc. It is the most common cause for menstrual disturbance and infertility in women. This paper sums up the progress of drug and acupuncture therapy of integrative Chinese and Western medicine (ICWM) in treating PCOS caused infertility as follows.

TRADITIONAL CHINESE MEDICINE TREATMENT

Traditional Chinese medicine (TCM) has no special descriptions and records on PCOS in the ancient literatures, yet according to its main clinical features, it can be categorized into “amenorrhea”, “infertility”, “metrorrhagia and metrorrhagia”, etc. It is considered that PCOS is related to Shen (肾), and mainly belongs to Shen deficiency and blood stasis with phlegm and dampness as well as Gan (肝)-qi stagnation. Therefore the key of treatment is replenishing Shen, which is assisted with activating blood circulation to remove stasis (ABCRS), getting rid of phlegm and dampness and soothing Gan-qi and clearing heat. Modern pharmacological study has also confirmed that herbs for replenishing Shen could play an endocrine hormone-like effect, showing bidirectional regulatory action on gonadal axis of women, and might elevate the receptivity of endometrium to the fetus. It has been confirmed by lots of clinical and experimental studies that herbs for replenishing Shen combined with those of ABCRS could improve local blood circulation of the ovary, increase the blood flow of the ovary to promote follicular

development, induce ovulation and promote luteum formation⁽¹⁾.

TCM Empirical Recipe

Hua, et al.⁽²⁾ used the empirical TCM recipe of veteran doctor CHAI Hao-yan, consisting of dodder seed 12 g, plaintain seed 10 g, epimedium 10 g, eucommia bark 10 g, Chinese angelica 10 g, peach kernel 10 g, fresh Job's-tears seed 10 g, chuanxiong 3 g, etc. to treat 76 PCOS patients of Pi (脾)-Shen Yang-deficiency type, and also enrolled 31 patients treated by orally taken clomifen (CC) as control. The results showed that both the treatments could reduce serum levels of luteum hormone (LH) and testosterone (T), but the TCM recipe was obviously superior to CC in aspects of recovery of oral glucose tolerance test (OGTT), body mass index (BMI), pregnancy rate, and Ferriman-Gallwey scoring. The pregnancy rate in the group treated with TCM recipe was 65.7% and the change of F-G scoring was significant, while in the CC treated group, the pregnancy rate was 25.0% and F-G scoring was insignificantly changed.

*Supported by the National Nature Science Foundation of China (No. 30572404); The Nature Science Foundation of Heilongjiang Province (No. ZJY0506-01); Heilongjiang Oversea Scholars Project (No. 1151HZ010); Heilongjiang Postdoctoral Financial Assistance (No. LBH-Z05230) and Sino-Finish Scientific and Technological Cooperation (11th Session for 2004-2006)

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Hou, et al.⁽³⁾ observed 22 patients of PCOS, who had been earlier treated in vain by CC. The enrolled patients were randomly assigned to two groups, one receiving Tiangui Recipe (天葵方, TGR, consisting of anemarrhena rhizome, tortoise shell, lilyturf root, solomonseal rhizome, Chinese angelica, psoralea, grass-leaved sweetflag, polygonum cuspidatum, European verbena, epimedium, rehmannia rhizome, peach kernel, etc.), the other receiving metformin therapy. After three months of treatment, it was discovered that the levels of insulin (Ins), waist : hip ratio (WHR) and BMI got somewhat lowered in the TGR treated patients, and $\log T/E_2$ significantly decreased, with menstruation recovered in 6 patients who were also accompanied with emergence of biphasic basic body temperature (BBT). While in those who received metformin the levels of Ins and $\log T/E_2$ got apparently reduced, but the changes of WHR and BMI were insignificant, and the recovery of regular menstruation and biphasic BBT appeared in 4 patients. Statistical analysis showed that TGR was superior in ovulation promotion and metformin was superior in lowering Ins. The mechanisms of the two drugs were quite different. That of metformin was to increase the sensitivity of peripheral tissues to Ins so as to lower the blood Ins level and block the vicious cycle in hyperinsulinism and hyperandrogenism to some extent. Besides, it can improve the local condition of ovary and regulate gonadal axis to help follicle maturation. There was no need of contraception during the time of metformin administration, and to the pregnant PCOS women, metformin could even reduce the spontaneous abortion rate, lessen the occurrence of diabetes mellitus without increasing the incidence of fetus malformation. Metformin could elevate the ovulation rate without any risk of inducing multiple pregnancy. The action of TGR is mainly to recover the function of ovary and improve the outcome of insulin resistance, suggesting that the two drugs used together could improve the clinical efficacy.

Artificial Periodic Therapy with Chinese Medicinal Herbs

Since artificial periodic therapy of “replenishing Shen-ABCRS-replenishing Shen-activating blood circulation to regulate menstruation” for treatment of PCOS was created, clinical studies have been carried out in treatment of PCOS by this therapy and certain effect won.

Hao⁽⁴⁾ used Chinese herbs with artificial periodic therapy to treat 46 PCOS patients. The basic recipe used consisted of epimedium herb 30 g, curculigo rhizome 10 g, dodder seed 30 g, degelatinated deerhorn 30 g, eclipta herb 30 g, grossy privet 30 g, Chinese angelica 15 g, chuanxiong 10 g, motherwort 15 g, milkvetch 15 g and licorice 6 g. It was modified on schedule in the following 4

stages: in the post-menstrual stage (the 6th-10th day of the menstrual cycle) the principle being mainly nourishing Shen-yin, and regulating Chong (冲)-Ren(任) Channels, wolfberry 30 g, solomonseal 30 g were added; in the pre-ovulation stage (the 11th-14th day), herbs for regulating qi and activating blood circulation such as red sage root, bugleweed and cyperus tuber were added; in the post-ovulation stage (the 15th-23rd day), herbs for replenishing Shen-yang such as eucommia bark, teasel root, mulberry mistletoe and ass-hide gelatin should be added in proper proportion; and in the pre-menstrual stage (the 24th-28th day), treatment should be improving the occasion to make the menstrual blood outflow smoothly, and so the addition of such drugs as cyanthula root, peach kernel, safflower, zedoary tumeric and burreed tuber was appropriate. Besides, in case that the size of ovary should expand by 1-3 times, some drugs for softening and resolving hard mass, such as prunella, kelp and pleione are necessary; and if the amenorrhea lasts for quite a long time with dark purple tongue proper, thin and white fur, and uneven pulse, drastic drugs for breaking blood stasis such as leech, gladfly and groundbeetle should be added. After treatment, 10 out of the 46 patients got pregnant, 30 were cured who had spontaneous menstruation accompanied with biphasic BBT as well as obviously lowered levels of BMI, WHR and T, and increased E_2 . Pharmacological study indicates that this therapy could regulate endocrinological mechanism, elevate the response of ovary to LH to regulate the function of hypothalamus-pituitary-ovary axis, promote the growth, development, maturation and ovulation of follicles, restore the menstrual cycle and ameliorate pregnancy disturbance.

Acupuncture Therapy

Modern studies proved that owing to its regulatory effect on hypothalamus-pituitary-ovary axis, acupuncture could normalize the secretion of follicle stimulating hormone (FSH), LH, E_2 and progesterone (P), etc. so as to improve the ovulation function.

Yang, et al.⁽⁵⁾ treated 126 patients who conformed to the criteria of PCOS by randomly assigning them to the treated group (66 cases) and the control group (60 cases). The treated group was treated by acupuncture therapy. It was started on the 10th day of the menstrual cycle or on the 10th day of the withdrawal bleeding induced by intramuscular injection of progesterone, and lasted for 5-10 consecutive days, with uniform reinforcing-reducing manipulation, and 30 min of needle retaining. Used in the treatment were three groups of acupoints: Group 1: Sanyinjiao (SP6), Guanyuan (CV4), Diji (SP8), Shuidao (S28); Group 2: Guilai (S29), Dahe (K12), Qugu (CV2), Xuehai (Sp10); Group 3: Zhongji (CV3), Shuidao (S28), Guilai (S29), Sanyinjiao (SP6), with one group used per

day alternately. On the 12th day of the menstrual cycle, vaginal ultrasonography B for monitoring the size of follicle was performed, and when the diameter of follicle reached 16-18 mm, acupuncture therapy was stopped and the patient was required to have sexual intercourse. Then abdominal B ultrasonographic monitoring on the condition of ovulation was performed within 48 h. The control group was treated with CC plus human chorionic gonadotropin (HCG) to induce ovulation. It started on the 5th day of menstrual cycle or on the 5th day after the withdrawal bleeding induced by intramuscular injection of progesterone. Patients began to orally take CC 100 mg per day for 5 successive days, and their condition of ovulation was monitored with vaginal ultrasonography B on the 12th day. When the diameter of follicle reached 18 mm, HCG 5 000-10 000 IU was injected and the patient was required to have sexual intercourse, with the same B ultrasonographic monitoring performed as in the treated group. Results showed promising clinical efficacy was obtained in the treated group, with ovulation rate reaching 83.2%, pregnancy rate 60.6% and less complication, and with the incidence of luteinized unruptured follicle (LUF) merely 4.8%. While the ovulation rate in the control group was 70.5%, and pregnancy rate was 31.7%, both lower than those in the treated group, suggesting that the efficacy of acupuncture in treating PCOS to elevate ovulation rate was significantly superior to that of conventional CC plus HCG treatment. Since TCM holds that systemic yin meridians are controlled by Ren channel, and pregnancy can only take place when Chong-Ren channels are concerted and menstruation runs smoothly, the authors selected the three groups of acupoints, based on the principle of replenishing Gan-Shen and regulating Chong-Ren Channels, to function mutually in coordination in supplementing Shen essence, regulating qi-blood of Chong-Ren Channels, nourishing uterus and regulating the balance of yin-yang and qi-blood of the body, thus to recover the normal ovulatory function. Moreover, acupuncture could also promote ovulation by inducing some reactions of nucleus or changes of transmitter in the brain and by regulating the hypothalamus function.

Other TCM Therapies

Some scholars formulated some recipes, on the basis of the principle of replenishing Shen, activating blood circulation, soothing Gan-qi, and invigorating Pi, and when these recipes were applied in treating PCOS induced infertility confirmative results were also obtained. But some problems still remain to be solved. For example: (1) Most of the recipes concentrated on syndrome differentiation and modifications, and so they were hardly repeatable; (2) The studies on therapeutic mechanism and pharmacological action were far from enough depth; (3) Single TCM herb was inadequately studied; (4) Only

few studies were conducted with advanced equipment and modern medical approaches from microscopic view. Further studies are necessary to provide more efficient and safer measures to solve all these problems in treating PCOS caused infertility.

ICWM TREATMENT

In the past, when gonadotropic hormone (GTH) was used for treatment of PCOS, strict monitoring on ovarian function was necessary during administration, because it might cause ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy. Therefore it is seldom used clinically so far. At present, CC is the first choice among the ovulation-promoting drugs, but it has such adverse reactions as low pregnancy rate, high ovulation rate, and insufficient estrogen secretion. ICWM treatment displays its superiority not only in that Chinese herbal medicine could coordinate with the action of Western medicines to promote follicle development, but also alleviate their adverse reactions and reduce the occurrence of luteum function insufficiency, lower threatened abortion rate, so as to elevate pregnancy rate.

Combination of Shen-replenishing Herbs/Recipes and Ovulation-promoting Agents

TCM and Western medicine each has its own advantages and shortcomings in treating PCOS caused infertility, with better efficacy and less adverse reactions, but with later initiating time and poor patients' compliance for Chinese drugs; whereas Western medicine is comparatively rapid in initiating time, but with adverse reactions more apparent. For this reason, most modern doctors advocate applying ICWM therapy by getting benefit from each one's strong points to offset each one's weakness.

Xia, et al⁽⁶⁾ randomly assigned patients with confirmed PCOS to two groups. To the 46 patients in the treated group, Chinese herbal recipe consisting of epimedium 15 g, desertliving cistanche 15 g, dluoritum 12 g, psoralea 12 g, degelatineated deerhorn 12 g, morinda root 12 g, dodder seed 12 g, Siberian solomonseal 12 g, glossy privet 12 g, two-teethed achyrantes 12 g, tortoise plastron 12 g, eupatorium 12 g, zedoary 12 g, tumeric root 12 g, sweetgum root 30 g, dogwood fruit 12 g, Chinese yam 15 g and peony bark 15 g, began to be given orally firstly one dose a day on the 5th day of menstruation. After 2 months of treatment with TCM, CC 50-100 mg was given additionally once per day from the 5th day to the 18th day of menstrual cycle, with 6 consecutive months as one therapeutic course. The 40 patients in the control group were treated with 50-100 mg of CC once a day from the 5th day to the 9th day of menstrual cycle. For those

with amenorrhea, artificial menstrual cycle was established at the beginning. The total course of therapy would last for 6 successive months. B ultrasonographic monitoring on the condition of ovulation was performed in all patients on the 10th day of menstrual cycle. Result showed that in the treated group ovulation rate was 82.8% and pregnancy rate 52.2%, both significantly higher than those in the control group (40.0% and 22.5%, respectively).

Ren⁽⁷⁾ reported that 58 PCOS patients had been treated in vain with CC 50-100 mg, orally taken once a day for 5 consecutive days, altogether 6 months, and no ovulation was found. They were randomly assigned to two groups, to whom, besides CC, one was given tamoxifen (TMX) additionally, and the other Zhuyun Recipe (助孕方) additionally, which was a Chinese herbal recipe consisting of dogwood fruit 6 g, prepared rehmannia glutinosa 12 g, Chinese yam 12 g, poria cocos 12 g, morinda root 6 g, Siberian solomoneal 12 g and peony bark 6 g. It was found that the pregnancy rate in the two groups was 35.71% and 63.33% respectively, and that in the latter were obviously higher than that in the former. Moreover, the occurrence of luteal phase defect (LPD) and LUF was lower in the Zhuyun Recipe group, and no OHSS occurred in either group.

Shao, et al.⁽⁸⁾ used Bushen Huoxue Oral Liquid (补肾活血口服液), which consisted of prepared rehmannia glutinosa, grossy privet, eclipta, fluoritum, psoralea, dodder seed and wolfberry each 30 g, Chinese angelica, white peony, chuanxiong and cyperus tuber each 10 g, and honeylocust thorn 20 g, combined with CC 100 mg per day for 5 successive days to treat patients and obtained effects more efficient and safer than that of CC alone, with the ovulation rate of 86.7% vs 65.8% and the pregnancy rate of 65.6% vs 36.7%, both higher in the group treated by TCM combined with CC. Besides, hormonal level was also improved, and OHSS and LUF did not occur.

Combined Treatment of Acupuncture with Western Medicine (WM)

Acupuncture shows unique efficacy in treating many diseases. Li, et al.⁽⁹⁾ adopted acupuncture and Western drugs to treat 79 PCOS patients and obtained excellent therapeutic effect. The following two groups of acupoints were used alternatively, namely: (1) Qihai (CV6) and bilateral Guilai (S29), Fuliu (K7), Zusanli (S36); (2) Guanyuan (CV4) and bilateral Dahe (K12), Zusanli (S36), Taixi (K9). Acupuncture therapy was started from the 6th day of menstrual cycle once daily for 7-9 consecutive days, with filiform needles used in the reinforcing method, moxibustion added when needling sensation happened, and the needles were retained for 20-30 min. Besides, for patients with poor endogenous estrogen, CC and

HCG were given; and for those with low gonadotropin level, human menopausal gonadotropin (HMG) and HCG were given additionally. B ultrasonography confirmed that ovulation recovered in 59 patients (74.7%) and 12 patients (15.2%) got pregnant, with the effect better than that in those treated with WM (ovulation rate 40.5%, pregnancy rate 5.1%).

Staging Treatment by ICWM

Ninety patients were treated by Lin⁽¹⁰⁾, by randomly assigning them to the treated group (48 cases) and the control group (42 cases). The treatment for the treated group was the so-called artificial cycle sequential method conducted in 4 stages: follicle promoting decoction—ovulation promoting decoction—luteum promoting decoction—menstruation regulating decoction, that is: during the 5th-10th day of the menstrual cycle, CC was administered in combination with follicle-promoting decoction; during the 12th-16th day when the follicle was almost mature, the ovulation promoting decoction was orally taken; when the matured follicle was seen under B ultrasonographic monitoring, intramuscular injection of HCG and needling of Sanyinjiao (SP6), Zhongji (CV3), Zigong (EX-CA1), and Guanyuan (CV4) were performed to promote ovulation; during the 17th-24th day the luteum promoting decoction for warming and replenishing Pi-Shen was administered; and during the 25th-30th day the menstruation regulating decoction, a recipe formed by modifying Taohong Siwu Decoction (桃红四物汤) was given. The treatment for the control group was: CC 50 mg, once per day, was given for 5 consecutive days starting from the 5th day of menstrual cycle or the 5th day of withdrawal bleeding, and when mature follicle was seen under B ultrasonographic monitoring, HCG 5 000-10 000 IU was injected intramuscularly. Three months was taken as one treatment course, and the number of course applied to patients was limited within 1-2. After treatment the pregnancy rate in the treated group was 70.83%, while that in the control group was merely 28.57%. The authors held that elevating levels of FSH and E₂ and lowering of LH/FSH ratio may be the mechanism of ICWM in promoting the primary follicles to develop into dominant follicles thus to elevate pregnancy rate.

Besides, marked efficacy was also obtained by other doctors using their self-formulated Chinese medical recipes in combination with ovulation agents or hormone in treating PCOS caused infertility. But it should be particularly stressed that contraception is necessary when androgen antagonist is used, otherwise, male external genitalia feminization (bisexual organ) and hermaphroditism are likely to take place. The action of dexamethasone in lowering adrenogenous androgen is confirmed, but it should be prohibited in early stage of pregnancy, though

application of dexamethasone in the late pregnant stage might benefit fetus' s lung maturation.

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(Received January 4, 2006)