

PERSPECTIVE

Chinese Medicine as Complementary Therapy for Female Infertility*

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ABSTRACT Chinese medicine (CM) has been used in clinical treatment for thousands of years in China, Japan, Korea, and other countries. CM is at present attracting many attentions around the world for reproductive health care and disease prevention, including treatment of female infertility. This review focuses on the CM treatment for female infertility patients, and supplies a summary on the efficacy, safety, and mechanism of some Chinese herbal medicines, herbal medicine-derived active compounds, and acupuncture. A large number of researches have reported that CM could alleviate or even cure female infertility by regulating hormone, improving reproductive outcome of *in vivo* fertilization, affecting embryonic implantation, curing polycystic ovarian syndrome, endometriosis, pelvic inflammatory disease, relieving mental stress, and regulating immune system. Meanwhile, a few studies claimed that there was little adverse reaction of CM in randomized controlled trials. However, up to present there is a lack of adequate evidences with molecular mechanistic researches and randomized controlled trials to prove the CM as an effective and safe treatment for infertility. Thus, utility of CM as a complementary medicine will be a feasible method to improve the outcome of female infertility treatment.

KEYWORDS female infertility, complementary medicine, Chinese medicine, combination therapy

Infertility is the inability of a person to reproduce by natural ways. It is normally not the natural status of a healthy adult.^(1,2) Usually, female infertility is defined as a woman being unable to get pregnant after one year of frequent unprotected sexual intercourse.⁽³⁾ Risk factors, such as biological factor, genetic factor, infection, lifestyle and environmental factor, are connected with infertility.⁽⁴⁾ Common causes of infertility of women include polycystic ovarian syndrome (PCOS), pelvic inflammatory disease caused by infections like tuberculosis, endometriosis, tubal blockage, age-related factors, uterine problems, previous tubal ligation, advanced maternal age, and so on.⁽⁵⁾

Common therapeutic methods for infertility may include medical treatments and alternative and complementary medicine (ACM).⁽⁶⁾ Medical treatment methods for infertility usually contain the utility of fertility medication, surgery, *in vitro* fertility (IVF) or other assisted reproductive technologies (ART).⁽⁷⁻¹⁰⁾ Medications used in clinic commonly include clomiphene citrate (CC), human chorionic gonadotropin (hCG), follicle-stimulating hormone (FSH), human menopausal gonadotropin (hMG), gonadotropin-releasing hormone (GnRH), GnRH analogs, bromocriptine, and cabergoline.⁽¹¹⁻¹⁷⁾ However, these medications have various adverse reactions, such as breast tenderness, swelling, rash, mood swings, depression, nausea, vomiting, headache, bone

density loss and so on.^(3,18) IVF treatment is expensive, emotionally and financially, for both the patients and the public. Thus, there is an urgent need for an ACM. Chinese medicine (CM) contains a series of traditional therapeutic methods that have been utilized in China for more than five thousand years, such as acupuncture, herbal medicine, moxibustion, and massage.⁽¹⁹⁻²⁴⁾ Acupuncture is a form of ACM involving different thickness of the needles inserted into the body at acupuncture points for various treatments, especially in managing pain. Herbal medicine is another important form of ACM, for the utility of herbal

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medicine is not strictly based on evidences being collected by scientific methods. As there are deficiencies of modern medicine, CM has been gradually focused on by more and more physicians and researchers.

CM Regulating Hormones

Shortfall of GnRH, stimulated by the hypothalamus, will commonly lead to infertility in both women and men, for GnRH plays a role of initiating ovulation and sperm production.⁽²⁵⁾ CM could increase the production of GnRH. A recent study suggests that acupuncture could promote endorphin generation to lead to analgesia, which can be neutralized by the narcotic antagonist, naloxone.⁽²⁶⁾ Because the localization of both the β -endorphin and the GnRH are existed in the arcuate nucleus, acupuncture which affects β -endorphin expression levels in the locus could accordingly regulate GnRH production and subsequently influence the menstrual cycle.^(27,28) Thus, electrical stimulation is desirable candidate as an effective method to affect hypothalamus-pituitary-gonad axis. Besides electrical stimulation, the materials, which could affect above locations, also will be candidates as medications.

Moreover, a few other researches also have discussed the function of neuropeptides, such as β -endorphin, in the regulation of GnRH production.⁽²⁹⁾ The *in vivo* researches of neuroendocrine signaling system of rats and rabbits validated the significance of acupuncture method in increasing GnRH and affecting peripheral gonadotropin level.⁽³⁰⁾ In a clinical research, the plasma level of follicle-stimulating hormone/luteinizing hormone (FSH/LH) and estradiol/progesterone (E₂/P) were revealed to be regulated in women accepting the treatment of acupuncture or Chinese herbal medicine.^(31,32) The results further suggested that CM could regulate the hypothalamic-pituitary-ovarian axis of women, further affecting ovulation. In above papers, authors suggested that the mammalian target of rapamycin (mTOR) might be a target in CM treatment, and mTOR had been reported to be associated with sexual maturity and hormones secretion. Thus, the signaling pathways involved in sexual maturity may be potential targets for infertility therapy. A research team reported that their laboratory, animal and clinical studies indicated that the herbal medicines *Vitexagnus-castus*, *Cimicifuga racemosa* and *Tribulus terrestris* regulated endocrine levels in the pituitary as measured by down-regulated prolactin and LH and upregulated FSH. Four kinds of herbal medicines, *Tribulus*

terrestris, *Cinnamomum cassia*, *Glycyrrhiza* spp., (alone or in combination with *Paeonia lactiflora*), and *Paeonia lactiflora* (in combination with *Cinnamomum cassia*) validated morphological changes in polycystic ovaries and steroidogenesis, including decreased ovarian volume and cysts, downregulated androgens, increased insulin sensitivity and up-regulated oestradiol.^(33,34) Meanwhile, these herbal medicines showed no adverse reactions in clinical investigations. Above all, in treatment of infertility hormone supplementing is an important method, but there were quite a few of adverse reactions in conventional treatments. CM could be a kind of complementary medication for it would efficiently increase hormone levels without significant adverse reactions.

CM Improving Reproductive Result of IVF

In the recent years, CM is employed as a complementary medicine in assisted reproduction. In a research, acupuncture was used in IVF and intracytoplasmic sperm injection (ICSI) with a randomized controlled trial (RCT) and was found to play a good role on the outcome of IVF/ICSI in the luteal phase.⁽³⁵⁾ Another research showed that acupuncture during the period of embryo transfer (ET) obviously improved the reproductive result of IVF/ICSI, compared with no acupuncture.⁽³⁶⁾ A research reported that there is no significant difference in the pregnancy ratios of women undergoing ET between the acupuncture group and the control group.⁽³⁷⁾ However, the acupuncture group had 1.5-fold higher pregnancy ratios than placebo group. They also reported that acupuncture might be a safe form for women undergoing ET. The mechanisms of acupuncture to improve the result of IVF could be summarized as four reasons: regulating neuroendocrinological factors, strengthening blood flow to the uterus and ovaries, regulating cytokines, and decreasing mental stress, such as anxiety and depression.⁽³⁸⁾ In addition, in above researches, researchers also considered that psychological effects of acupuncture could improve the therapeutic effects. In treatment, psychologic status of patient is directly related to the outcomes and prognosis and some CMs were reported to be able to activate endogenous opioids in the central nervous. Thus, improving patients' moods should be an important aspect of fertility studies in the future. In a research, Erzhi Tiangui Recipe (二至天葵方, ETR) was used to increase the ovarian function in elderly sterile women.⁽³⁹⁾ This research validated that ETR combining with FSH could significantly reduce the dosage of FSH administrated, strengthen ovarian

function, increase pregnancy rate and activity of oocytes. A few researchers reported that macrophage-activating Chinese mixed herbs (MACH), a mixture of seven crude drugs such as *Angelicae radix*, *Rehmanniae radix*, *Plantaginis semen*, *Lonicerae flos*, *Carthami flos*, *Ginseng radix*, and *Cucurbita moschata* Duch, could significantly increase the percentage of good quality early stage blastocysts and have no obvious adverse events.⁽⁴⁰⁾ Cao, et al⁽⁴¹⁾ reported that in a series of clinical tests during 2002 and 2011 a few herbal medicine such as Wenshen Yangxue Antai Decoction (温肾养血安胎汤), Xiaoyao Powder (逍遥散), Erzhi Tiangu Granules (二至天葵颗粒), Zishen Yutai Pills (滋肾育胎丸) significantly improved IVF success. However, the standard of clinical trials of CM is not as strict as the one of Western medicine (WM), such as uncompleted informed consent, unreasonable grouping criteria, and improper drug administration. Thus, the results of clinical trials are still arguable.

Effect of CM on Human Embryonic Implantation

The conditions of artery uterine blood flow, endometrial thickness, and morphology are thought to be important parameters for the success of IVF and ET.⁽⁴²⁻⁴⁴⁾ Sufficient endometrial thickness and adequate blood flow to the uterus will improve the pregnancy rate. Therefore, how to improve the activity of uterus blood flow is a challenge for the therapy of infertility. In a research, it was testified that electroacupuncture method performed to ten infertile women led to a decreasing of GnRH to prevent from the affection of endogenous hormones to retard uterine blood flow.⁽⁴⁵⁾ Researchers also employed the rat model to reveal that low-frequency electroacupuncture (2 Hz) could improve ovarian blood flow.⁽⁴⁶⁾ Some Chinese herbs such as *Salvia miltiorrhiza*, *Ligusticum chuanxiong* and *Artemisiaanomale* also have effects in improving blood and regulating menstrual flow by upregulating the plasma concentration of estradiol and prostaglandin $F_{2\alpha}$ of the ovary, meanwhile conversely downregulating the concentration of ovarian prostaglandin E_2 .⁽⁴⁷⁾ In another study, CM was combined with salpingostomy to improve the infertility through promoting the follicular development and increasing the endometrial thickness.⁽⁴⁸⁾ Thus, the effect of CM in optimizing uterine artery blood flow and endometrial thickness could supply assistance to improve its outcome of embryonic implantation. In a mice model research, extracts from the herbal medicine called Zhuyun Recipe (助孕方) were reported to be able to reverse the expression levels of endometrial leukemia inhibitory factor (LIF) and integrin $\beta 3$ subunit, increase

the uterine receptivity in model and improve pregnant rate and embryonic implantation.⁽⁴⁹⁾ So far, the researches on CM to improve implantation did not make the molecular mechanisms clearly, thus the study of further molecular signaling network is need.

Treatment of CM for PCOS

PCOS is a health problem that can affect a woman's hormone levels, periods, and ovulation and causes infertility. In a study, researchers performed a series of PCOS researches including both clinical trials and animal model experiments to explore the potential mechanisms. In their investigation, repeated low-frequency electroacupuncture treatment of patients revealed a better outcome in ovulation.⁽⁵⁰⁾ The low-frequency electroacupuncture regulates the sympathetic system via the upregulation of β -endorphin, immune responses, and the activity of autonomic nervous system.⁽⁵¹⁾ The researchers employed the steroid-induced PCOS rat model to reveal upregulated β -endorphin concentrations in the hypothalamus after low-frequency electroacupuncture.⁽⁵²⁾ Meanwhile, repeated electroacupuncture treatments changed the neuroendocrinological status by down-regulating concentrations of corticotropin-releasing factor in the brain, the adrenal glands, and the ovaries of rat model.⁽⁵³⁾ The sympathetic nerve function in the ovaries stemming from an alternation in the neuroendocrinological status could be regulated by therapy of repeated electroacupuncture to decrease endothelin-1 and nerve growth factor (NGF).⁽⁵⁴⁾ In another research, CM combined with WM utilized in clinical practice showed encouraging outcome on the women with PCOS and anovulation, but with no obvious adverse reactions.⁽⁵⁵⁾ Lee, et al⁽⁵⁶⁾ reported that two herbal formulae, Changbudodam Tang (Cangfu Daotan Decoction, 苍附导痰汤) and Yongdamsagan Tang (Longdan Xiegan Decoction, 龙胆泻肝汤), significantly downregulated the increased NGF staining in the ovaries without influencing the brain tissues significantly. Xie, et al⁽⁵⁷⁾ suggested that Bushen Tongmai Recipe (补肾通脉方) could improve PCOS by decreasing the phosphorylation level of insulin receptor substrate-1 Ser307 and then increasing insulin signal transduction in rat model. In another rat model, a research team reported that *Aloe barbadensis* Mill. Formulation treated PCOS rats showed obvious decrease in plasma triglyceride and low-density lipoprotein (LDL) cholesterol levels, with an increase in high-density lipoprotein (HDL) cholesterol.⁽⁵⁸⁾ PCOS, as a well-known disease in the

field of female infertility, has been researched more thoroughly. Up to now, a few of evidences on molecular level have been reported and provided targets for further drug design and development. In addition, recently study of CM affecting metabolism to improve PCOS was reported.⁽⁵⁸⁾ In view of many POCS-related matters being associated closely with metabolic system, this research direction will be new gold ore in the field.

Treatment of CM for Endometriosis

Endometriosis is a kind of disease in which tissue that normally grows inside the uterus grows outside it. The main symptoms are pelvic pain and infertility. Fang, et al⁽⁵⁹⁾ reported that in Taiwan 90.8% (12,788 cases) of reproductive age women with endometriosis used CM and 25.2% of them sought CM with the intention of treating their endometriosis-related symptoms. Flower, et al⁽⁶⁰⁾ found that postsurgical delivery of CM might have better benefits to gestrinone but with fewer adverse effects. Oral CM may have a preferable curative effect than danazol and may be more impactful in alleviating dysmenorrhoea and shrinking adnexal masses. In another clinical research, Zhao, et al⁽⁶¹⁾ suggested that Chinese herbal medicines might suppress the recurrence of endometriosis after a conservative surgery, advance the fertility rate and reveal fewer adverse effects than treatment with WM therapy such as gonadotropin-releasing hormone agonist. In a rat model study, it was revealed that three CM-derived active compounds, ferulic acid, ligustrazine and tetrahydropalmatine, could suppress the growth of ectopic endometrial tissue in endometriosis rats. It might be associated to the decreasing of hypothalamic-pituitary-ovarian axis and the increasing of peritoneal macrophage activities.⁽⁶²⁾ Zou, et al⁽⁶³⁾ reported that Chinese herbal medicine Sanjie Zhentong Capsule (散结镇痛胶囊) and its two main components *Draconis sanguis* and saponin could inhibit the development of endometriosis by downregulating levels of vascular endothelial growth factor (VEGF) and tumor necrosis factor α (TNF- α) in the peritoneal focus compared with the control group, the anastrozole group, loureirin A group, ginsenoside Re group. In a former study, Cao, et al⁽⁶⁴⁾ found that *Caulis Sargentodoxae* Granule could significantly decrease the endometrial volumes in the treated groups through downregulating the expressions of VEGF and its receptor fetal liver kinase 1 in ectopic endometrium. Li, et al⁽⁶⁵⁾ reported that Quyu Jiedu Granule (祛瘀解毒颗粒) played a role of improving the quality of oocytes

by decreasing the TNF- α and interleukin-6 expression levels in ovarian granulose cells of endometriosis rat model. CM could cure endometriosis through influencing NGF, inducing apoptosis of endometriotic cells, and inhibiting growth of endometriotic cells. Taking together, these researches may indicate that combination of various compounds will reach more effective and comprehensive therapeutic effects.

Treatment of CM for Pelvic Inflammatory Disease

Pelvic inflammatory disease, also called pelvic inflammatory disorder (PID), is an infection of the upper part of the female reproductive system such as the womb, fallopian tubes, and ovaries.^(66,67) PID without treatment for a long term can lead to several complications such as infertility.⁽⁶⁸⁾ Now, many investigators suggest that inflammatory injury is a critical pathological change of PID. Sustained releasing of inflammatory factors and activation of inflammation-related cells cause inflammatory autoimmune injury and subsequently affect the initiation, progression and prognosis of PID. Persistent inflammation results in blood stasis. In turn, blood stasis promotes inflammation. The therapeutic principle of CM for chronic PID is to increase blood flow and decrease blood stasis. A number of Chinese herbal medicines with the action of increasing blood circulation and decreasing blood stasis have worked successfully in clinical practice. Su, et al⁽⁶⁹⁾ reported that in two RCTs Guizhi Fuling Capsules (桂枝茯苓胶囊) showed obvious effect in the treatment of 255 patients with PID. Liu, et al⁽⁷⁰⁾ suggested that another CM, Shaofu Zhuyu Decoction (少腹逐瘀汤), had significant effects on reducing genital infectious and decreasing pelvic inflammation by inhibiting cytokine production and excessive infiltration of inflammatory cells. In 2015, a combination therapy of Lichong Decoction (理冲汤) and moxibustion were reported to be an effective treatment for chronic PID.⁽⁷¹⁾ In rat model, Zou, et al⁽⁷²⁾ performed a research that *Patrinia scabiosaefolia* Fisch has inhibitory effect on infections-induced PID and systematic interventional effect on PID-related metabolomic changes such as alterations in tricarboxylic acid (TCA) cycle, sugar metabolism, and amino acid metabolism. In addition, Liu, et al⁽⁷³⁾ found that Danzhi Decoction (丹蛭汤) may alleviate PID by suppressing the expression level of VEGF in the blood microenvironment of PID by affecting the cytoplasm of endometrial glandular epithelial cell. Although acupuncture has been used in clinic for treating PID

for many years, there is a lack of direct evidences of mechanism. Thus, it is unclear whether acupuncture worked as a placebo in treatment for PID.

CM Improving Treatment of Stress-Associated Infertility

Many kinds of stress including physiological and psychological factors which could lead to infertility have been reported.^(74,75) In fact, infertility problems and the infertility treatment itself are stressful enough to patients. Thus, infertility and stress are two key factors causing a vicious circle. High levels of stress in women will change hormone levels and lead to abnormal ovulation via its affection on the hypothalamic-pituitary-ovarian axis. Besides, stress may also lead to fallopian tube spasm in female.⁽⁷⁶⁾ Female patients tended to have much stress before undergoing treatment for infertility. Thus, how to relieve the stress is important for a successful treatment. Acupuncture has been testified to relieve stress such as anxiety and depression via the regulation of the autonomic nervous system by suppressing sympathetic tone and regulating vagal tone.^(77,78) Besides, CM can lead to fewer adverse effects and showed anxiolytic and antidepressant effects to decrease stress level in female patients during the treatment of infertility.

CM Affecting Treatment of Immune-Related Infertility

Immunological abnormality may also lead to infertility at different reproductive stages. The cause of immunological infertility has not been studied intensively; nevertheless, there are various elements which are thought to contribute to immunological infertility. In a report by Lian, et al,⁽⁷⁹⁾ combination therapy of Zhenqi Zhuanyin Decoction (贞芪转阴汤) and intrauterine insemination lead to a better outcome in the female patients with anti-sperm antibody than those administrated with Zhenqi Zhuanyin Decoction or intrauterine insemination respectively.

Conclusion

Female infertility differentiates widely by geographical position in the world. In 2010, there was an assessed 48.5 million couples suffering from infertility around the world, and in recent twenty-five years there was almost no fluctuation in levels of infertility in most of the world. Female infertility has been a significant disease for a long time and will be in the future. Physicians and researchers around the world

have continuously tried to work our way through this. CM has been adopted by Chinese physicians in clinical treatment for thousands of years. A large number of researches have reported that CM could alleviate or even cure female infertility by regulating hormone, improving reproductive outcome of *in vivo* fertilization, affecting embryonic implantation, curing polycystic ovarian syndrome, endometriosis, pelvic inflammatory disease, relieving mental stress, and regulating immune system. In Table 1, the herbal medicines and CM-derived compounds are summarized. However, CM has not been widely used in the world for the reason that CM has not adequate evidences with molecular mechanistic researches and RCTs to be highly approved by the WM community. Thus, accumulation of these evidences could promote the widespread use of CM in more nations. In the present circumstances, the combination treatment of CM and WM could be an encouraging way for the treatment of female infertility. In addition, infertility diseases and futile treatment will bear heavy psychological and physiological burdens on patients. Emotional support could encourage patients to adhere to treatment and to maintain hope for future treatment. During the CM treatment, many patients reported feeling hope, confidence and even a sense of responsibility for their treatment. A previous study reported that patients treated with CM continued to receive treatment for up to twenty-four months.⁽⁸⁰⁾ Thus, psychology affection of CM should be considered as an important aspect in treatment for female infertility.

Conflict of Interest

The authors declared that they have no conflicts of interest to this work.

Electronic Supplementary Material

Supplementary material (Table 1) is available in the online version of this article at <http://dx.doi.org/10.1007/s11655-016-2510-5>

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