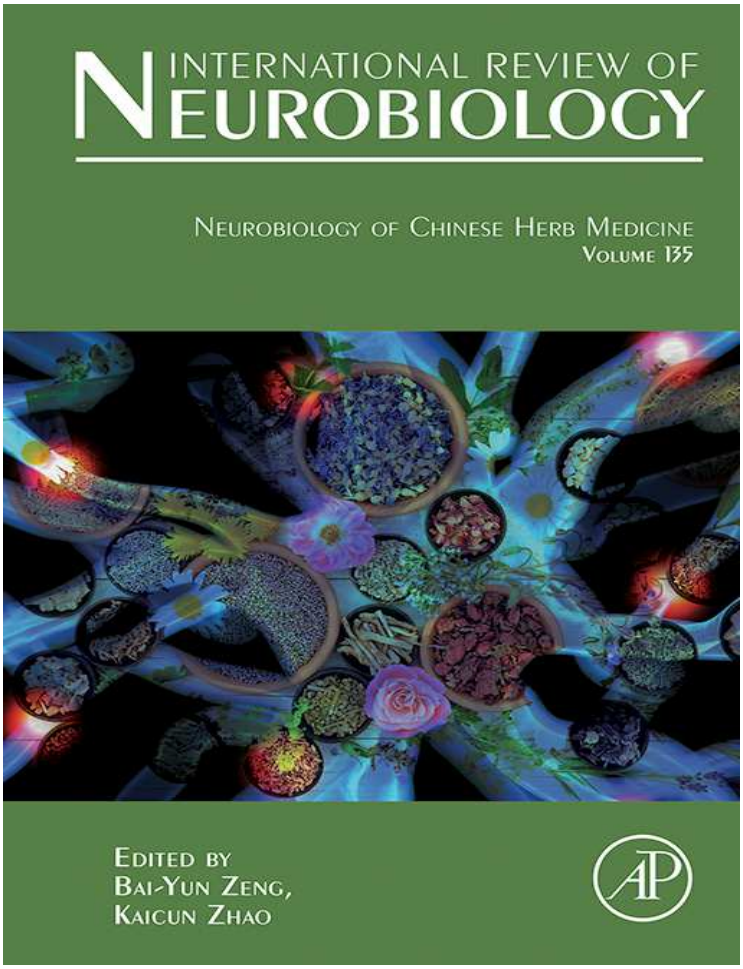

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CHAPTER TEN

Treatment of Chinese Herbal Medicine for Female Infertility

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Contents

Abstract

Female infertility is when a woman of reproductive age and sexual active, without contraception, cannot get pregnant after a year and more or keeps having miscarriages. Although conventional treatments for infertility such as hormone therapy, in vitro fertilization and many more, helped many female patients with infertility get pregnant during past a few decades, it is far from satisfactory with prolonging treatment time frames and emotional and financial burden. In recent years, more patients with infertile problems are seeking to alternative and complementary medicines to achieve a better outcome. In particular, Chinese herbal medicine (CHM) is increasingly popular for treating infertility due to its effectiveness and complimentary with conventional treatments. However, the mechanisms of action of CHM in treating female infertility are not well

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understood. In this chapter authors reviewed research development of CHM applied in many infertile models and CHM clinical studies in many conditions associated with female infertility, published in past 15 years. The data of review showed that CHM has either specific target mechanisms of action or multitarget mechanisms of action, via regulating relevant hormone levels in female reproductive system, improving ovary function, enhancing uterine receptivity. More studies are warranted to explore the new drugs from CHM and ensure safety, efficacy, and consistency of CHM.

1. INTRODUCTION

Infertility in general, is defined as not being able to get pregnant (conceive) after 1 year of unprotected sex (NICE Clinical Guideline, 2013; WHO Infertility, 2013). Fertility decreases with age. Estimated infertility from 782 couples recruited from seven European centres is 8% for women aged 19–26 years, 13%–14% for women aged 27–34 years, and 18% for women aged 35–39 years (Dunson, 2004). Common reasons causing female infertility are tubal blockage, pelvic inflammatory diseases caused by infections such as tuberculosis, uterine problems, previous tubal ligation, endometriosis, and advanced maternal age (Corbett & Morin-Papunen, 2013; Matzuk & Lamb, 2008; Vercellini, Viganò, Somigliana, & Fedele, 2014). Up to 20% of infertile couples have unexplained infertility. In these cases, abnormalities are likely to be present but not detected by current methods, or only functional disorders are apparent (Gurunath, Pandian, Anderson, & Bhattacharya, 2011; Pandian, Gibreel, & Bhattacharya, 2015). Conventional treatments of infertility generally involve the use of fertility medication, e.g., follicle-stimulating hormone (FSH), human chorionic gonadotropin, gonadotropin-releasing hormone analogues, ovarian stimulating medication such as clomiphene citrate, human menopausal gonadotropin, and many more (Williams, Mortada, & Porter, 2016), and surgery including tuboplasty, salpingectomy, oophorectomy, unilateral or bilateral salpingo-oophorectomy (Lang, Dunaway, & Roniger, 1990; Sotrel, 2009), or assisted reproductive technologies such as in vitro fertilization (IVF) and related techniques (Pandian et al., 2015). These therapies can treat some causes of infertility, but results are not always satisfactory. Although the overall live birth rate per embryo transfer has increased from 19.2% in 2002 to 23.3% in 2013 (Chambers et al., 2016), the result still falls short of the expectations of the infertile woman/couple. Furthermore, side effects from hormonal treatment are not without risk, such as over stimulated ovaries (Rashidi,

Najmi, & Mobasseri, 2015) or psychiatric disorders (Freeman, Toth, & Cohen, 2013).

Due to the lack of a satisfactory outcome from conventional medical treatments for many women with infertility, they are increasingly seeking to alternative therapies to improve their results. During past 15 years, Chinese herbal medicine (CHM), as a holistic approach to many conditions, has been increasingly used to treat infertility in many Western countries (Coulson & Jenkins, 2005; Smith et al., 2010; Stankiewicz, Smith, Alvino, & Norman, 2007). Further, CHM treatment increased fertility rate and played an important role in supporting conventional infertility treatments (Ried, 2015; Ried & Stuart, 2011; Zhou & Qu, 2009). However, the mechanisms of action of CHM in treating infertility are not well understood. In this chapter we reviewed recent research development of CHM treatment with female infertility from both basic research and clinical studies, in particular, focusing on the underlying mechanisms of action of CHM.

2. EFFECT OF CHM ON FEMALE INFERTILITY MODELS

There are many studies which aim to elucidate the mechanism of CHM in treating female infertility in animal models of common diseases associated with infertility.

2.1 Promoting Endometrial Receptivity in the Uterus

It is believed that a receptive uterine state is essential for successful conceive either naturally or using an assisted pregnancy technique. Poor endometrial receptivity is one of the most common reasons for infertility and prevents embryo implantation into the uterus. Many studies showed that CHM promoted a receptive uterine state (Guo, Wang, & Li, 2011). In a mouse model of infertility, effect of extracts from a CHM remedy (Zhuyun recipe, 助孕) on improving endometrial receptivity in mice with embryonic implantation dysfunction and ovulation stimulation was conducted (Yu, Yang, & Liang, 2011). Female pregnant kunming mice were randomly divided into six groups: A control group; B ovulation stimulation (OS) group; C OS + CHM formula group; D embryo implantation dysfunction (EID) group; E, EID + CHM formula; and F CHM-only group. Uterine samples were collected at gestation day 4 and detected with immunohistochemistry and real-time PCR analyses for expression of endometrial leukemia inhibitory factor (LIF) and integrin β3 subunit, markers of endometrial receptivity (Bhatt, Brunet, & Stewart, 1991; Illera et al., 2000). It was found, at the

end of study, that OS group and EID group showed a significant decrease in pregnancy rate and the lower level expression of both endometrial LIF and integrin β3 subunit during the implantation window compared with control group. The OS + CHM formula and EID + CHM formula groups showed a higher pregnant rate and higher level of endometrial LIF and integrin β3 subunit expression compared to the OS and EID groups. The number of implanted embryos in EID group was lower than in the control group; in contrast, the number of implanted embryos in EID + CHM formula group was significantly higher than in the EID group and control group. However, no significant difference was found in the measured indices between the CHM-only group and control group. The studies showed that CHM helped reverse the expression of endometrial LIF and integrin β3 subunit, improved the uterine receptivity in mice, and increased pregnancy rate and the number of embryonic implantations (Yu et al., 2011). In another study, Bu Shen Huo Xue Decoction (BSHXD, 补肾活血饮), prescribed to aid in preparing the endometrium for implantation in China, was recently investigated for its mechanism of actions in a rat model with controlled ovarian hyperstimulation (COH) treatment (Gong, Lou, Lu, Huang, & Jin, 2015). BSHXD treatment markedly increased the number of live births and enhanced the implantation capacity in the rat model by restoring protein expression of endometrial LIF, and without affecting expression of Ang-2 protein, which tends to destabilizing quiescent endothelium (Fiedler et al., 2006), compared with COH alone group (Gong et al., 2015). This suggested that BSHXD treatment could help patients with an impaired endometrium following COH treatment.

2.2 Improving Ovarian Function

Premature ovarian failure (POF) and insufficient storage function of the ovaries are both common reasons for female infertility and result from a variety of hormonal disorders (Matzuk & Lamb, 2008). Established formulas of CHM have been found to effectively stimulate ovaries and raise the low hormone level. Li and Luo (2010) used rat model where ovulation was inhibited by hydroxyl urea, which matched kidney deficiency and dampness accumulation patterns in TCM theory. They showed that Luo's established recipe (罗氏促排卵汤) increased ovulation, modified serum levels of FSH, LH, and estrogen, and promoted pregnancy rate when compared to the control groups (Li & Luo, 2010). In another study, Fu et al. (2012) investigated the underlying mechanism of therapeutic effect of CHM formula Tongmai

Danshen Tablet (TMDST, 通脉丹参片) in tripterygium glycosides-induced POF rat model. They found that TMDST treatment significantly restored normal estrous cycle and promoted near or above normal ovarian index such as, serum estradiol and, serum inhibin B level in comparison with those of normal controls. Further, TMDST significantly elevated expression of estrogen receptor, vascular endothelial growth factor (VEGFR), and VEGFR-2, markedly lowered intracellular TNF-α and Caspase-3, improved ovarian vascular structure, thinner vascular wall, and larger vascular lumen compared with control groups (Fu et al., 2012). This suggested that therapeutic effect of TMDST in treating POF was through improving angiogenesis and antiapoptosis pathway.

2.3 Preventing Spontaneous Abortion

Spontaneous abortion also known as miscarriage is a common complication of pregnancy that affected about 5% of child-bearing women (Rai & Regan, 2006). CHM such as Zhuyun No. 3, an established formula for preventing miscarriage, showed that it could help prevent miscarriage. Study of mechanism behind Zhuyun No. 3 (ZY3, 助孕3号) was conducted in rat models of abortion using hydroxyurea and mifepristone, to mimic kidney deficiency and spleen deficiency, respectively (according to TCM theory), to understand the underlying mechanisms of ZY3 (Luo et al., 2003). It was found that ZY3 formula significantly increased the expression of progesterone receptors in deciduas of models of both types compared with respective control groups. The water extract and drug serum of ZY3 lowered the potency of uterus contractility in vivo and in vitro isolated uterine smooth muscle, respectively (Luo et al., 2003). The study showed that by reinforcing kidney and strengthening Pi, ZY3 protected pregnancy via elevating the target cell progesterone receptors and relaxing the uterine smooth muscle.

2.4 Reregulating Luteum Inhibition and Immune Function

Transforming growth factor beta 1 (TGF-β1) plays the important role in promoting the embryo embedding at the surface of uterus via modulating immune tolerance (Ayatollahi, Geramizadeh, & Samsami, 2005). Alterations in TGF-β1 were linked to pregnancy failure. Zhao, Luo, Ni, and Zhou (2008) studied the effect of CHM formula Zhuyun No. 3 (ZY3, 助孕3号) on serum TGF-β1 in luteum inhibition abortion rat model and explored its mechanisms in preventing abortion from the perspective of immune regulation. The rat model was produced by feeding pregnancy rats with

hydroxyurea for 7 days, then feeding with mifepristone for 1 day. Results showed that treatment with Zhuyun 3 dose-dependently increased in the serum levels of TGF-β1 compared with control groups (Zhao et al., 2008), indicating that Zhuyun 3 participated immune regulation via modifying TGF-β1expression which might lead to prevent abortion.

Taken together, CHM formulas mentioned earlier increased fertility rates in the infertility models by improving uterine embedding conditions and rebalance hormonal levels in the uterus.

3. CHM INCREASES CLINICAL PREGNANCY RATE

3.1 Improving Fallopian Tube Obstruction

Blocked fallopian tubes are unable to let the ovum and sperm converge, thus making fertilization impossible. Study of CHM formula for fallopian tube obstruction was conducted (Jiang, Liang, & Liu, 2006) in which patients with salpingostomy were treated with CHM formula Bu Shen Huo Xue decoction (BSHXD, 补肾活血饮), starting from the 5th day of menstrual cycle for 14 days, with salpingostomy alone as a control. Three-month treatment was taken as one therapeutic course and total treatment lasted for four courses. It was demonstrated at the end of treatment that the condition of follicular development, thickness of endometrium, and level of serum estradiol in the preovulatory phase were all markedly improved in both BSHXD plus salpingostomy and salpingostomy alone groups compared with respective baseline evaluation. However, the improvement was significantly superior in BSHXD plus salpingostomy group compared with that in salpingostomy group. Moreover, the pregnancy rate was also higher in the former than in the latter (Jiang et al., 2006). An earlier study with fallopian tube obstruction reported that the fallopian tube patency rate was 86.7% and the pregnant rate 85.0% in the CHM-Western medicine (WM) group, respectively, while 66.7% and 63.3% in the CHM alone group, respectively, and 53.3% and 50.0% in the WM alone group, respectively, in comparison with their respective baseline assessments. The levels of serum C-reactive protein and interleukin-1 beta were all lowered after three courses of treatment, and the effect was more evident in the CHM-WM group, indicating rebalance of immune system might be one of factors enhancing pregnant rate (Kang, Xia, & He, 2001). However, there was no mention about the names and treatment regimes of either CHM formula or Western medicine.

3.2 Improving Ovarian Function

Lin'erlai (LEL, 琳儿来) prescription, an established CHM recipe for treating infertility, was used to treat patients with anovulatory infertility, in comparison with patients control group treated with clomiphene, a nonsteroidal fertility medicine that stimulates ovulation (Huang, 2007). The total effective rate in the LEL group was 96.7%, which was significantly higher than 53.3% in the control group. The abortion rate was 10.0% in the LEL group, which was significantly lower than 54.6% in the control group. The symptom scores decreased significantly in the LEL group but remained unchanged in control group. The study demonstrated that LEL had a better effect than clomiphene in treating anovulatory infertility (Huang, 2007). Further, Tan et al. (2012) reported a meta-analysis where 1659 participants were involved in 15 studies showing the efficacy of CHM treatment of infertility caused by anovulation as compared to clomiphene treatment. Analysis data indicated that CHM significantly improved the cervical mucus score, increased the ovulation rate leading to higher the pregnancy rate, and reduced the miscarriage rate compared to clomiphene. No significant adverse effects were identified from the use of CHM in this review (Tan et al., 2012). Similarly, a Cochrane review found that the addition of CHM to clomiphene is associated with improved clinical pregnancy outcomes compared with clomiphene alone (Zhang et al., 2010).

Effect of CHM formula on improving ovulation failure and on incidence rate of luteinized unruptured follicle syndrome (LUF) and luteal phase defect (LPD), by tonifying kidney and activating blood (according to TCM theory), was assessed in patients with ovulation disorder (Zhou & Li, 2006). CHM formula (for details, see Table 1) was adjusted at different stages of menstrual cycle. At the end of treatment, it was revealed that CHM formula treatment significantly increased ovulation rate, markedly decreased the occurrence rates of LUF and LPD, raised the conception rate compared with control group (Zhou & Li, 2006). Similar therapy, using several of herbal formulas at different stages of the menstrual cycle, according to the cyclical hormonal changes, improved ovarian function and enhanced pregnant rate in patients with infertility in Western countries (Jiang, 2014).

3.3 Improving Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is one of the most common causes of female infertility, resulting in abnormal follicular development and ovulation dysfunction partially due to imbalance of steroid hormone releasing

Table 1 Details of CHM Formulas Administered in Different Stages of Menstrual Cycle in Zhou and Li (2006)

Periodic Stage	Treating Principle	Chinese Herbal Formula Elements
During menstruation	To move Qi's stagnation and activity blood for supporting follicle's growth	Cangzhu/Xanthium Sibiricum part
		Xiangfu/Cyperus Rotundus L.
		Mudanpi/Paeonia Suffruticosa Andr.
		Danshen/*Salviae miltiorrhizae* Bge.
		Chishao/Paeonia Lactiflora Pall.
		Wulingzhi
		Zelan/Lycopus Lucidus Turcz var.
		Hirtus Regel
		Zishiying/
		Shanzha/Crataegus Pinnatifida Bge.
		Yimucao/Leonurus Japonicus Hoult
		Fuling/Poria Cocos (Schw.) Wolf
Post of menstruation	To nourish Yin and blood for promoting essence (egg)'s growing up and bursting out	Danggui/Angelica Sinensis (Oliv.) Diels
		Chishao/Paeonia Lactiflora Pall.
		Shudihuang/Radix *Glutinosa Libosch*
		Mudanpi/Paeonia Suffruticosa Andr.
		Fuling/Poria Cocos (Schw.) Wolf
		Shanyao/Dioscorea Opposita Thunb.
		Shanyurou/Cornus Officinalis Sieb et.
		Zucc
		Zhizi/Gardenia Jasminoides Ellis
		Chuanduan/Dipsacus Asperoides C.Y.
		Cheng et
		Tusizi/Cuscuta Glabra Roxb
		Fupenzi/Rubus Chingi Hu
Ovulation	To tonify kidney Yang and to nourish Yin essence and blood for preparing a pregnancy	Danggui/Angelica Sinensis (Oliv.) Diels
		Danshen/*Salviae miltiorrhizae* Bge.
		Chishao/Paeonia Lactiflora Pall.
		Zelan/Lycopus Lucidus Turcz var.

Table 1 Details of CHM Formulas Administered in Different Stages of Menstrual Cycle in Zhou and Li (2006)—cont'd

Periodic Stage	Treating Principle	Chinese Herbal Formula Elements
		Hirtus Regel
		Chongweizi/Leonurus Heterophyllus
		Sweet
		Honghua/Carpesium Tinctorins L.
		Xiangfu/Cyperus Rotundus L.
Before of menstruation	To move liver Qi stagnation and nourish blood for feeding embryo and preventing a miscarriage	Chaihu/Bupleurum Chinense DC.
		Xiangfu/Cyperus Rotundus L.
		Aiye/Artemisisia Argyi Levl. et Vant.
		Xuduan/Dipsacus Asperoides C.Y.
		Cheng et
		Duzhong/Eucommia Ulmoides Oliv.
		Ejiao/Asini Gelatinum, Comi Asini Colla
		Sangjisheng/Taxillus Chinensis (DC.) Danser

(Corbett & Morin-Papunen, 2013; Williams et al., 2016). Recently, some CHM formulas showed beneficial effect on PCOS. For example, CHM formula Erzhi Tiangui Granule (ETG, 二至天癸颗粒) was found to significantly improve oocyte quality of patients with PCOS, via regulating the anti-Müllerian hormone levels in the serum and in the follicular fluid, adjusting the androgen level, improving the pathophysiological changes of PCOS, and activating the ovarian microenvironment (Lian & Zhao, 2012). Another CHM formula Bushen Huatan formula (BHF, 补肾化痰汤) was reported to ameliorate insulin resistance and also to improve the function of ovarian ovulation in patients with PCOS (Lee et al., 2006). In another report, a metabolomics approach was used to investigate the mechanism of action of CHM formula BHF on improving PCOS (Lu et al., 2016). Following BHF intervention for three menstrual cycles, body weight, Body Mass Index (BMI), waist circumference, and Hip circumference of all patients with PCOS significantly decreased compared to baseline assessment. Then, patients were divided into normoinsulinemic (NI) group and hyperinsulinemic (HI) group for serum metabolic studies. There were significant changes in serum metabolic following treatment compared with baseline in

NI group and HI group, respectively. In NI group, significant phospholipid metabolism improvement was observed. In HI group, changes in amino acid metabolism were observed (Lu et al., 2016). The results suggested that BHF was effective in treating patients with PCOS by reduced inflammatory reaction and oxidative stress in both NI group and HI group.

3.4 Improving Mycoplasma Infection

Female mycoplasma genitalium infection can cause infertility. Relevant tests showed an increased in cytokines (IL-1beta, IL-2, TNF-α) in the peripheral blood and in the cervical mucus, and positive culture of mycoplasma from genital tracts of infertile women with mycoplasma infection (Lis, Rowhani-Rahbar, & Manhart, 2015). Recently, a randomized study was conducted to evaluate antimycoplasma effect of CHM formula Xiaozhi decoction in 72 patients with positive genital mycoplasma cultures (Lou, Yang, & Liu, 2012). The patients were randomly divided into a CHM group and a Western medicine group. The TCM group was treated with Xiaozhi decoction twice every day for 6 weeks. The Western medicine group was treated with azithromycin for 3 days consecutively and underwent six courses of treatment. At the end of treatment, CHM group showed a significant decrease in serum cytokines such as IL-1beta, IL-2, TNF-α, and in the cervical mucus compared with baseline and with end value of Western medicine group. This suggested that Xiaozhi decoction could be used to treat infertile women with mycoplasma infection (Lou et al., 2012).

In a series of studies of CHM treatment for female infertility, Ried et al. first (Ried & Stuart, 2011) identified 8 randomized controlled trials (RCTs), 13 cohort studies, 3 case series, and 6 case studies involving 1851 women with infertility. Meta-analysis of the RCTs suggested a 3.5 greater likelihood of achieving pregnancy with CHM therapy over a 4-month period compared with clomiphene therapy alone. They suggested that management of female infertility with CHM could improve pregnancy rates twofold compared with clomiphene alone (Ried & Stuart, 2011). Then, they found that the quality of the menstrual cycle, integral to TCM diagnosis, appears to be fundamental to successful treatment of female infertility (Ried & Alfred, 2013). Recently, the same group published an updated review of the same topic, where they collected data from 40 RCTs involving 4247 women with infertility into a systematic review. Meta-analysis study suggested a 1.74 higher probability of achieving pregnancy with CHM therapy than with clomiphene alone. In addition, the authors concluded that fertility indicators

such as biphasic basal body temperature, ovulation rates, cervical mucus score, and appropriate thickness of the endometrial lining are positively influenced by CHM therapy, implicating an alleviating physiological effect for viable pregnancy (Ried, 2015).

4. ENHANCING THE SUCCESS RATE OF IVF AND EMBRYO TRANSFER

4.1 Promoting Uterus Receptivity

ETG (二至天癸颗粒) not only was used to treat PCOS, improving ovarian function, but also used to improve efficacy of in vitro fertilization–embryo transfer (IVF-ET). In a series studies, Lian, Teng, and Zhang (2007) and Lian et al. (2013) assessed the effect and mechanisms of ETG on infertile women who undergo IVF-ET. First, in a randomized study, ETG treatment distinctively increased the amount of oocyte, elevated the quality of embryo, and raised the successful rate of IVF-ET, and this was correlated to the increase of leukemia inhibitory factor levels in follicular fluid compared with Western drug group (Lian et al., 2007). Then, a randomized, double-blinded, and placebo-controlled clinical trial was conducted to explore the effects of ETG on DNA methyltransferases (DNMT) 1 protein expression in endometrium of infertile women who were to undergo IVF-ET. DNMT 1protein has regulatory effects on genes associated with shedding of endometrium in the menstrual cycles and was decreased in patients with infertility (Yamagata et al., 2009). Treatment with ETG significantly improved syndrome scores, decreased dosage, and duration of gonadotropin compared with placebo treatment group. Further, the high-quality oocyte and embryo rates, and clinical pregnancy rate were all higher in the ETG group than those in placebo group. The DNMT1 protein expression in the endometrium was much more abundant in the ETG group than that in the placebo group, which might lead to enhanced endometrial receptivity and improvement in clinical pregnancy rate (Lian et al., 2013).

4.2 Improving Pregnant Rate in Patients With Failure of IVF Treatment

Recently, a study exploring the effect of traditional Chinese comprehensive therapy (TCCT), consisting of both Chinese herbs and ear acupuncture, on promoting gestation in patients with previously failure IVF-ET was conducted (Xu et al., 2015). Sixty-seven patients were enrolled in this study and divided into two groups: a treatment group with 35 patients and a control group with 32 patients. The treatment group was given TCCT for 3

months, and then administered IVF-ET or natural pregnancy was awaited. The control group was administered IVF-ET without TCCT 3 months after the previous IVF-ET or natural pregnancy attempt. The natural pregnancy rate of the two groups was calculated after treatment. After treatment with TCCT, seven patients in the treatment group became pregnant, while there were no successful conceptions in the control group, showing that TCCT treatment group had a significantly higher conception rate (20%) than the control group (0%). The study suggested that TCCT could increase the number of fertilized eggs, the fertilization rate, pregnancy rate, and clinical pregnancy rate after another IVF-ET treatment and could promote natural pregnancy rate in patients with previously failed IVF-ET (Xu et al., 2015). A systematic review and meta-analysis of RCTs were conducted to evaluate the effectiveness of CHM with concurrent IVF vs IVF alone on the outcomes of IVF (Cao et al., 2013). Twenty trials involving 1721 women were included in the study, and three trials were evaluated as having an unclear risk of bias. The remaining trials were evaluated as having a high risk of bias. Despite the consideration the authors found that the combination of CHM and IVF significantly increased clinical pregnancy rates and ongoing pregnancy rates. The study indicated that combination of IVF and CHM in the included trials improved IVF success, however, due to the high risk of bias observed with the trials; the significant differences found were felt to be likely inaccurate. The authors also mentioned that no conclusion could be made with respect to the reproductive toxicity of CHM (Cao et al., 2013).

5. CONCLUSION

The quality of the environment in the body is considered as important as the quality of eggs, sperm, and embryo for a successful pregnancy. The fundamental principle of TCM therapy, in particular CHM, is to restore balance within the body, which affects hormonal regulation of the menstrual cycle, and provides a physiological environment to facilitate conception, implantation, and maintenance of a viable pregnancy. Studies reviewed here showed CHM helped infertile female patients in many ways to achieve a successful pregnancy. Further, CHM can complement with Western medicine and fertility treatment to improve pregnancy rates while reducing treatment time frames and emotional and financial burden. Although CHM in particular its formulas has been increasingly used to treat female infertility, more studies concerning its efficacy, consistency, and safety are still needed.

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REFERENCES

Ayatollahi, M., Geramizadeh, B., & Samsami, A. (2005). Transforming growth factor beta-1 influence on fetal allografts during pregnancy. *Transplantation Proceedings*, *37*, 4603–4604.

Bhatt, H., Brunet, L. J., & Stewart, C. L. (1991). Uterine expression of leukemia inhibitory factor coincides with the onset of blastocyst implantation. *Proceedings of the National Academy of Sciences of United States of America*, *88*, 11408–11412.

Cao, H., Han, M., Ng, E. H., Wu, X., Flower, A., Lewith, G., et al. (2013). Can Chinese herbal medicine improve outcomes of in vitro fertilization? A systematic review and meta-analysis of randomized controlled trials. *PloS One*, *12*, e81650.

Chambers, G. M., Wand, H., Macaldowie, A., Chapman, M. G., Farquhar, C. M., Bowman, M., et al. (2016). Population trends and live birth rates associated with common ART treatment strategies. *Human Reproduction*, *31*, 2632–2641.

Corbett, S., & Morin-Papunen, L. (2013). The polycystic ovary syndrome and recent human evolution. *Molecular and Cellular Endocrinology*, *373*, 39–50.

Coulson, C., & Jenkins, J. (2005). Complementary and alternative medicine utilisation in NHS and private clinic settings: A United Kingdom survey of 400 infertility patients. *Journal of Experimental & Clinical Assisted Reproduction*, *2*, 5.

Dunson, D. B. (2004). Increased infertility with age in men and women. *Obstetrics and Gynaecology*, *103*, 51–56.

Fiedler, U., Reiss, Y., Scharpfenecker, M., Grunow, V., Koidl, S., Thurston, G., et al. (2006). Angiopoietin-2 sensitizes endothelial cells to TNF-alpha and has a crucial role in the induction of inflammation. *Nature Medicine*, *12*, 235–239.

Freeman, M. P., Toth, T. L., & Cohen, L. S. (2013). Assisted reproduction and risk of depressive relapse: Considerations for treatment. *Annals of Clinical Psychiatry*, *25*, 283–288.

Fu, Y., Zhao, Z., Wu, Y., Wu, K., Xu, X., Liu, Y., et al. (2012). Therapeutic mechanisms of Tongmai Dasheng tablet on tripterygium glycosides induced rat model for premature ovarian failure. *Journal of Ethnopharmacology*, *139*, 26–33.

Gong, X., Lou, J. Y., Lu, Q. D., Huang, H. T., & Jin, Z. (2015). Bu Shen Huo Xue decoction restores endometrial leukemia-inhibitory factor but not Angiopoietin-2 expression, and improves uterine receptivity in the controlled ovarian stimulation rat model. *Experimental and Therapeutic Medicine*, *9*, 751–756.

Guo, J., Wang, L. N., & Li, D. (2011). Exploring the effects of Chinese medicine in improving uterine endometrial blood flow for increasing the successful rate of in vitro fertilization and embryo transfer. *Zhong Xi Yi Jie He Xue Bao*, *9*, 1301–1306.

Gurunath, S., Pandian, Z., Anderson, R. A., & Bhattacharya, S. (2011). Defining infertility—A systematic review of prevalence studies. *Human Reproduction Update*, *17*, 575–588.

Huang, Y. (2007). Clinical observation on anovulatory infertility of blood and essence asthenia type treated by Lin'erlai Prescription. *Chinese Journal of Integrated Traditional and Western Medicine*, *27*, 1028–1030.

Illera, M. J., Juan, L., Stewart, C. L., Cullinan, E., Ruman, J., & Lessey, B. A. (2000). Effect of peritoneal fluid from women with endometriosis on implantation in the mouse model. *Fertility and Sterility*, *74*, 41–48.

Jiang, D. (2014). Treating female infertility by strengthening the natural menstrual cycle with acupuncture and Chinese herbal medicine. *The European Journal of Oriental Medicine*, *7*, 28–35.

Jiang, Y. C., Liang, R. N., & Liu, R. T. (2006). Effects of combined therapy of salpingostomy and Bushen Huoxue drugs on fallopian tube obstructive infertility. *Chinese Journal of Integrated Traditional and Chinese Medicine*, *26*, 325–328.

Kang, J. L., Xia, W., & He, Q. Y. (2001). Clinical study on treatment of oviduct obstruction by integrative traditional Chinese and western medicine. *Chinese Journal of Integrated Traditional and Western Medicine*, *21*, 416–418.

Lang, E. K., Dunaway, H. E., Jr., & Roniger, W. E. (1990). Selective osteal salpingography and transvaginal catheter dilatation in the diagnosis and treatment of fallopian tube obstruction. *American Journal of Roentgenology*, *154*, 735–740.

Lee, Y. S., Kim, W. S., Kim, K. H., Yoon, M. J., Cho, H. J., & Shen, Y. (2006). Berberine, a natural plant product, activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistant states. *Diabetes*, *55*, 2256–2264.

Li, S., & Luo, S. (2010). Study on kidney tonifying of CHM to the rat models with ovulated inhibition. *Chinese Journal of Basic Medicine in Traditional Chinese Medicine*, *16*, 567–569.

Lian, F., Teng, Y. L., & Zhang, J. W. (2007). Clinical study on effect of Erzhi Tiangui granule in improving the quality of oocytes and leukemia inhibitory factor in follicular fluid of women undergoing in vitro fertilization and embryo transfer. *Chinese Journal of Integrated Traditional and Western Medicine*, *27*, 976–979.

Lian, F., Wang, R. X., Feng-Mei, M., Zhen-Gao, S., Li-Hong, W., & Lei, S. (2013). Effects of Chinese medicines for tonifying the kidney on DNMT1 protein expression in endometrium of infertile women during implantation period. *Journal of Alternative and Complementary Medicine*, *19*, 353–359.

Lian, F., & Zhao, S. (2012). Effects of Shen invigorating and Chong-channel regulating method on anti-Müllerian hormone and oocyte quality in polycystic ovarian syndrome patients. *Chinese Journal of Integrated Traditional and Western Medicine*, *32*, 9–12.

Lis, R., Rowhani-Rahbar, A., & Manhart, L. E. (2015). Mycoplasma genitalium infection and female reproductive tract disease: A meta-analysis. *Clinical Infectious Diseases*, *61*, 418–426.

Lou, Y. F., Yang, X. F., & Liu, L. C. (2012). Study on changes in cytokines of infertile women with mycoplasma infection and intervention with traditional Chinese medicines. *China Journal of Chinese Materia Medica*, *37*, 3158–3160.

Lu, C., Zhao, X., Li, Y., Li, Y., Yuan, C., Xu, F., et al. (2016). Serum metabolomics study of traditional Chinese medicine formula intervention to polycystic ovary syndrome. *Journal of Pharmaceutical and Biomedical Analysis*, *20*, 127–133.

Luo, S. P., Liang, G. Z., Zhang, Y. Z., Xu, L. M., Deng, G. P., & Ouyang, H. Q. (2003). Study of mechanism on Zhuyun No. 3 in preventing and treating spontaneous abortion. *Chinese Journal of Integrated Traditional and Western Medicine*, *23*, 522–525.

Matzuk, M. M., & Lamb, D. J. (2008). The biology of infertility: Research advances and clinical challenges. *Nature Medicine*, *14*, 1197–1213.

NICE Clinical Guideline CG156. (2013). *Fertility: Assessment and treatment for people with fertility problems*. London, United Kingdom: National Institute for Health and Care Excellence.

Pandian, Z., Gibreel, A., & Bhattacharya, S. (2015). In vitro fertilisation for unexplained subfertility. *The Cochrane Database of Systematic Reviews, 11*, CD003357 http://dx.doi.org/10.1002/14651858.

Rai, R., & Regan, L. (2006). Recurrent miscarriage. *Lancet*, *368*, 601–611.

Rashidi, M., Najmi, Z., & Mobasseri, A. (2015). *Advantages of recombinant follicle-stimulating hormone over human menopausal gonadotropin in intrauterine insemination: A randomized clinical trial in polycystic ovary syndrome-associated infertility*. Gynaecological and Obstetric Investigation. PMID: 26228499.

Ried, K. (2015). Chinese herbal medicine for female infertility: An updated meta-analysis. *Complement Therapy Medicine*, *23*, 116–128.

Ried, K., & Alfred, A. (2013). Quality of life, coping strategies and support needs of women seeking Traditional Chinese Medicine for infertility and viable pregnancy in Australia: A mixed methods approach. *BMC Women's Health*, *13*, 17–19.

Ried, K., & Stuart, K. (2011). Efficacy of traditional Chinese herbal medicine in the management of female infertility: A systematic review. *Complement Therapy Medicine*, *19*, 319–321.

Smith, J. F., Eisenberg, M. L., Millstein, S. G., Nachtigall, R. D., Shindel, A. W., Wing, H., et al. (2010). The use of complementary and alternative fertility treatment in couples seeking fertility care: Data from a prospective cohort in the United States. *Fertility and Sterility*, *93*, 2169–2174.

Sotrel, G. (2009). Is surgical repair of the fallopian tubes ever appropriate? *Review Obstetrics and Gynaecology*, *2*(3), 176–185.

Stankiewicz, M., Smith, C., Alvino, H., & Norman, R. (2007). The use of complementary medicine and therapies by patients attending a reproductive medicine unit in South Australia: A prospective survey. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, *47*, 145–149.

Tan, L., Tong, Y., Sze, S. C., Xu, M., Shi, Y., & Song, X. Y. (2012). Chinese herbal medicine for infertility with anovulation: A systematic review. *Journal of Alternative and Complementary Medicine*, *18*, 1087–1100.

Vercellini, P., Viganò, P., Somigliana, E., & Fedele, L. (2014). Endometriosis: Pathogenesis and treatment. *Nature Review Endocrinology*, *10*, 261–275.

Williams, T., Mortada, R., & Porter, S. (2016). Diagnosis and treatment of polycystic ovary syndrome. *American Family Physician*, *94*, 106–113.

World Health Organization. (2013). *Health topics: Infertility*. Available http://www.who.int/topics/infertility/en/.

Xu, X., Jia, W., Cheng, S., Zhong, Y., Xia, W., & Zeng, Q. (2015). Effect of traditional Chinese comprehensive therapy on gestation in patients with previously failed in vitro fertilization and embryo transfer. *Journal of Traditional Chinese Medicine*, *35*, 428–433.

Yamagata, Y., Asada, H., Tamura, I., Lee, L., Maekawa, R., Taniguchi, K., et al. (2009). DNA methyltransferase expression in the human endometrium: Downregulation by progesterone and estrogen. *Human Reproduction*, *24*, 1126–1132.

Yu, N., Yang, J., & Liang, T. (2011). Extracts from a traditional Chinese herbal remedy (Zhuyun recipe) improve endometrial receptivity in mice with embryonic implantation dysfunction and ovulation stimulation. *Journal of Ethnopharmacology*, *137*, 389–395.

Zhang, J., Li, T., Zhou, L., Tang, L., Xu, L., Wu, T., et al. (2010). Chinese herbal medicine for subfertile women with polycystic ovarian syndrome. *Cochrane Database of Systematic Reviews, 9*, CD007535 http://dx.doi.org/10.1002/14651858.

Zhao, H. Y., Luo, S. P., Ni, Y. C., & Zhou, Y. (2008). Effects of Zhuyun No. 3 serum TGF-β1 in abortion rats of kidney deficiency and luteum inhibition. *Shanghai Journal of Traditional Chinese Medicine*, *42*, 71–73.

Zhou, J., & Li, D. J. (2006). Tonifying kidney and activating blood method in treating ovulation failure of 32 cases: B ultrasonic evaluation. *Chinese Journal of Clinical Rehabilitation*, *10*, 114–116.

Zhou, J., & Qu, F. (2009). Treating gynaecological disorders with traditional Chinese medicine: A review. *African Journal of Traditional, Complementary, and Alternative Medicines*, *6*, 494–517.