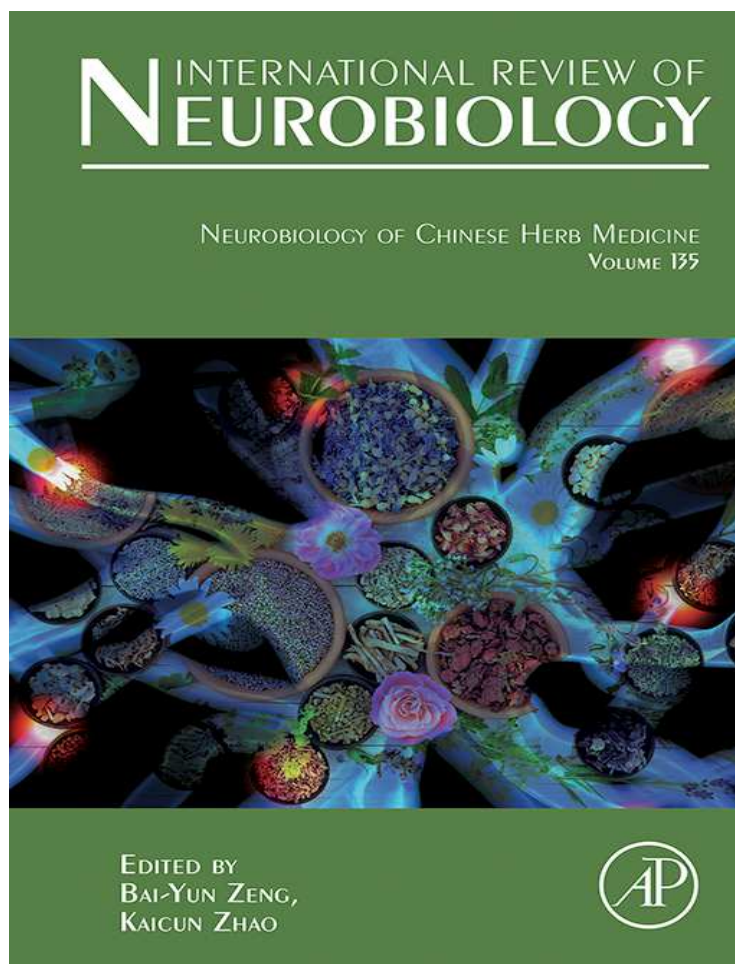


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From Dan Jiang, Alberto Coscione, Lily Li and Bai-Yun Zeng, Effect of Chinese Herbal Medicine on Male Infertility. In: Bai-Yun Zeng and Kaicun Zhao, editors, *International Review of Neurobiology, Vol. 135*, Burlington: Academic Press, 2017, pp. 297-311.

ISBN: 978-0-12-811779-8

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Academic Press



Effect of Chinese Herbal Medicine on Male Infertility

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Abstract

Male infertility normally refers a male's inability to cause pregnancy in a fertile female partner after 1 year of unprotected intercourse. Male infertility in recent years has been attracting increasing interest from public due to the evidence in decline in semen quality. There are many factors contributing to the male infertility including abnormal spermatogenesis; reproductive tract anomalies or obstruction; inadequate sexual and ejaculatory functions; and impaired sperm motility, imbalance in hormone levels, and immune system dysfunction. Although conventional treatments such as medication, surgical operation, and advanced techniques have helped many male with infertility cause pregnancy in their female partners, effectiveness is not satisfactory and associated with adverse effects. Chinese herbal medicine (CHM) has been used to improve male infertility in China for a very long time and has now been increasingly popular in Western countries for treating infertility. In this chapter we summarized recent

development in basic research and clinical studies of CHM in treating male infertility. It has showed that CHM improved sperm motility and quality, increased sperm count and rebalanced inadequate hormone levels, and adjusted immune functions leading to the increased number of fertility. Further, CHM in combination with conventional therapies improved efficacy of conventional treatments. More studies are needed to indentify the new drugs from CHM and ensure safety, efficacy, and consistency of CHM.



1. INTRODUCTION

Infertility is defined by the World Health Organization as a disorder of reproductive system, characterized by failure to achieve a clinical pregnancy after ≥ 12 months of regular unprotected intercourse (Mascarenhas, Flaxman, Boerma, Vanderpoel, & Stevens, 2012; Zegers-Hochschild et al., 2009). Although much attention has been focused on issues related with infertility in women, male infertility, in recent years, has been attracting increasing interest due to evidence in decline in semen quality among young health men and public awareness (Alrabeeh et al., 2014). More than 90% of male infertility cases are due to low sperm counts, poor sperm quality, or both (Bensdorp, Cohlen, Heineman, & Vandekerckhove, 2007; Levine & Grifo, 2008). The remaining cases of male infertility can be linked with a number of factors including ejaculation dysfunction, immunological factor, hormonal imbalances, and genetic defects (Corona et al., 2015; Pitteloud & Dwyer, 2014; Ray et al., 2017; Zhao, Zhu, Xue, & Han, 2014). In addition, obesity and varicocele are believed to have adverse impacts on male fertility (Evers & Collins, 2003; Sallmén, Sandler, Hoppin, Blair, & Baird, 2006). Conventional treatments such as drug therapy, surgical approaches, intrauterine insemination, and intracytoplasmic sperm injection (ICSI) helped many men with fertility problems achieve clinical pregnancy (Dorjpurev et al., 2011; Ho & Tan, 2013; Johnson, Sasson, Sammel, & Dokras, 2013; Pisipati & Percy, 2010; Valenti et al., 2013). However, those treatments are sometimes ineffective, invasive, and expensive or associated with adverse effects and high risks (Cissen et al., 2016; Palomba, Homburg, Santagni, La Sala, & Orvieto, 2016).

Chinese herbal medicine (CHM), as an important part of traditional Chinese medicine (TCM), has been used to treat infertility for both women and men in China for a long time (Xu, Yin, Tang, Zhang, & Gosden, 2003). CHM helped improving sperm quality (Liao et al., 2013; Zeng et al., 2003) and rebalance immune system (Yu, Zhang, & Zhang, 2004). When used in combination with conventional medicine, CHM enhanced the

efficacy of conventional medicine and reduced its side effect (Ma & Jia, 2011). However, the mechanism of action underlying the therapeutic effect of CHM is not fully understood. In this chapter, we reviewed the published studies that concerned effect of CHM on male infertility from online databases including PubMed, Medline, EMBASE, CNKI, CIAHL, and Wanfan for the past 20 years and summarized the development of basic research and clinical studies of CHM on the male infertility.



2. PRECLINICAL RESEARCHES BY ANIMAL MODELS

A number of studies looked at established animal models of sexual dysfunction, or sperm disorders, or in particular TCM differentiation patterns relevant to infertility; and assessed the effect and the underlying mechanism of action of CHM on these models.

2.1 Improving Sperm Abnormalities and Quality

Recently, adenine (6-amino-purine), a nitrogen-containing heterocyclic purine compound, was used to develop male infertility model in rat (Wang, Chen, Zhou, Cao, & Jia, 2008; Wang, Huang, & Liang, 2008). Adenine may reduce spermatogenesis and testosterone synthesis through the large amount of free radicals generated by the xanthine oxidase reaction; or may be related to transforming growth factor-beta (TGF- β)'s inhibition of spermatogenesis and promotion of spermatocyte apoptosis (Huang, Xia, & Ren, 2003). Adenine-induced male infertile rat model was used to investigate the effect and mechanisms of some CHM formulas, because the symptoms adenine-induced is similar to the human Shen-yang (kidney-Yang) deficiency pattern according to TCM theory (Yue, Chen, & Dai, 1997). Bushen Shengjing Decoction (BSSJD 补肾生精汤) was one of the CHM formulas earlier used in the male infertile model to explore its mechanism of therapeutic effect in treating infertility (Yue et al., 1997). Administration of BSSJD to adenine-treated rats for 30 days significantly increased the number of sperm, improved quality of sperm, and normalized serum levels of luteinizing hormone (LH), testosterone compared with non-treatment group (Yue et al., 1997). This indicated that BSSJD formula could improve testicular function.

Ma, Wang, and Lu (2006) investigated the effect of Wenyang Shengjing Decoction (WSD 温阳生精汤) on Smads proteins and the relevant genes expression. Smads are intracellular signal transduction molecules, belonging

to the TGF- β family, in the testis of adenine-induced male infertile rats. It was observed that in the normal rats, Smad 1 and Smad 2 were expressed in cytoplasm of spermatogenic cells in rats' testis. Positive Smad 2 expression could be found in cytoplasm of Sertoli's cell. Both Smad 1 and Smad 2 were not expressed in Leydig's cell. On the other hand, Smad 4 was positively expressed in cytoplasm of Leydig's cell but not expressed in spermatogenic cell and Sertoli's cell (Ma et al., 2006). Compared with the normal control, in adenine-induced male infertile rats, Smad 1 expression was markedly lower, but expression of Smad 2 and Smad 4 was markedly higher; WSD treatment significantly reversed these abnormal changes. Further, WSD treatment significantly neutralized adenine-induced changes in body weight, sperm number and serum testosterone level, and levels of follicle-stimulating hormone and LH (Ma et al., 2006). In another study, Liu, Wang, and Nan (2012) assessed the effects of WSD containing serum on the estradiol (E2) secretion, the synthesized cytochrome P450 aromatase (P450arom) activities, and the expression of its encoding gene CYP19 in Leydig cells of adenine-induced male infertility rats. The results showed that the E2 secretion of Leydig cells obviously decreased accompanied with the inhibition of P450arom activities and significantly reduced protein and mRNA expressions of CYP19 in the model groups. Following administration of WSD containing serum to adenine-induced infertile model, the E2 secretion in the Leydig cells significantly increased, the P450arom activities upregulated, and the CYP19 expressions partially upregulated at the protein and mRNA in a dose-dependent manner (Liu et al., 2012). Together, those studies showed that WSD formula could improve male infertility via multiple action mechanisms. It could increase the sperm number through elevating serum testosterone level, and adjust the levels of sex hormones via regulating Smads genes expression to promote the production of sperm; or could effectively elevate the E2 secretion in Leydig cells, through upregulating P450arom expression.

Using the same model, Wang, Li, Zhang, and Dang (2014) studied the influence of Yougui Capsule (右归胶囊) on Kidney Yang deficiency-related reproductive dysfunction in infertile rats. They found that administration of Yougui Capsule to adenine-treated rats partially reversed decrease in the weight of reproductive organs, with increasing spermatogenic cells and mesenchymal cells compared with control group. The morphology of seminiferous tubules of testis improved in Yougui Capsule group compared with control group. This implied that reproductive function might be improved although no data were presented.

2.2 Modulating Immune Function

Antisperm antibody is believed to prevent fertility by reducing sperm concentration, sperm motility, and sperm liquefaction (Cui et al., 2015). Lai, Song, and Liu (1997) investigated whether CHM formula Tai-bao (胎宝) could inhibit antisperm antibody in an infertile mouse model. Treatment with Tai-bao dose dependently and significantly increased pregnant rates and implantation rates compared with control group. Detection of cytotoxic antibody with enzyme-linked immunosorbent assay showed that Tai-bao formula significantly reduced the level of cytotoxic antibody to sperm compared with control group (Lai et al., 1997). In a rabbit model of immune infertility, CHM formula Yi Kang Ling (YKL 抑抗灵) was used to test its effect on serum and seminal plasma antisperm antibody. Results showed that YKL dose dependently and significantly reduced the levels of antisperm antibody in both serum and seminal plasma compared with prednisone-treated and nontreatment groups (Cui et al., 2003). The studies from both of the CHM formulas suggested that they may exert a regulatory effect on immune system function via inhibition of expression of antisperm antibody in serum and seminal plasma, leading to improved sperm quality and mobility.

2.3 Improving Blood Supply

Arteriogenic erectile impotence (AED) also known as erectile impotence is caused by insufficient arterial blood supply to the cavernous bodies regardless of the arterial disease or abnormality responsible for the insufficiency (Ghanem & Shamloul, 2008). Wang et al. (2012a) and Wang et al. (2012b) conducted a series of studies to investigate the underlying mechanism of CHM formula Shugan Yiyang capsule (SGYY 疏肝益阳胶囊) in treating AED in a rat model. First, they investigated the effect of SGYY on the expression of nitric oxide synthase (NOS)/cyclic guanosine monophosphate (cGMP) molecules in AED rat model and found that the gene and protein expression of three subtypes of NOS-neuropathic (nNOS), inducible (iNOS), and endothelial (eNOS) and cGMP concentrations in cavernous tissue were significantly decreased in the model. Following SGYY treatment expression of NOS/cGMP and nNOS, iNOS and eNOS levels were significantly elevated compared with nontreatment control group (Wang et al., 2012a). Then, authors studied the effect of SGYY on the expression of cytokines, such as vascular endothelial growth factor (VEGF), insulin-like growth factors (IGFs), and Akt1 (a serine-threonine

protein kinase) and found that SGYY dose dependently elevated the decrease in the mRNA level and plasma concentrations of VEGF and IGF in treated group compared with nontreatment group (Wang et al., 2012b). These results suggested that the therapeutic effect of SGYY seen in clinical studies (Wang, Jixiang, & Li, 2004) may be due to its synergetic effect by increasing the expression of NOSs and cGMP, modulating the NOS–cGMP pathway, and upregulating the expressions of VEGF, IGF, and Akt1 in the corpus cavernosum penis of AED rats, leading to improve the function of blood vascular endothelium.

2.4 Antiinfection

Escherichia coli is the most common cause of urogenital infection and is implicated in the genesis of male infertility (Pellati et al., 2008). Recently an in vitro study was conducted to assess effect of CHM formula Qinglishengjing pills (清淋生精片) on spermatozoa infected with *E. coli* (Yu et al., 2011). It was observed that *E. coli* infection caused significant detrimental changes in sperm motility parameters, phosphatidylserine externalization, and morphology of spermatozoa. Treatment of Qinglishengjing pills to infected cells almost normalized all changes caused by *E. coli* compared with control groups (Yu et al., 2011). This study supported the clinical effect of Qinglishengjing pills as an anti-*E. coli* agent.



3. CLINICAL OBSERVATION ON MALE INFERTILITY TREATED WITH CHM

3.1 Improving Blood Supply

Cui et al. (2007) conducted a clinical study to assess the therapeutic effect of CHMs Danshen (丹参) and Chaihu (柴胡) acupoint injection therapy on functional and mild arterial low-level blood supply erectile dysfunction (ED). A total of 150 patients with functional and arterial low-level blood supply ED were recruited for randomized controlled trial and divided into three groups, a Chinese herbs acupoint injection group, a saline acupoint injection group, and a HuichunRuyi capsules group as a control group, 50 patients in each group. The acupoints used for injection were Guanyuan (CV 4), Zuwuli (LR 10), and Huiyin (CV 1). The changes of the International Index of Erectile Function (IIEF) questionnaire, symptoms and signs, serum sexual hormones, and corpus spongiosum peak systolic velocity (PSV) before and after the treatment were monitored. Results revealed that acupoint injection of Danshen injection and Chaihu injection had a definite

beneficial effect on functional and arterial low-level blood supply ED. This therapy raised IIEF Questionnaire II score and improved corpus spongiosum PSV. The overall effect of Chinese herb acupoint injection group was better than that of saline acupoint injection or oral HuichunRuyi capsule group (Cui et al., 2007).

3.2 Treating Sperm Disorders—Severe Oligospermatism and Azoospermi

Zhang, Zhao, and Zhang (2007) investigated the pregnancy-promoting effect of Bushen Shengjing Decoction (BSSJD 补肾生精汤) combined with ICSI in treating male infertile patients with severe oligospermatism and azoospermia (SOA). ICSI was applied on 164 patients; among them, 82 patients were assigned for additional BSSJD treatment for 2–3 months before ICSI, and the other 82 were assigned as the control group and received ICSI alone. The density, motility, viability, and deformity of sperm; semen level of reactive oxygen species (ROS); number of eggs retrieved, Metaphase II eggs, and mean transplanted fetus; rates of fertilization, cleavage, available embryo, and clinical pregnancy in the two groups were monitored before and after treatment. It was found that compared with those in the control group, the density, motility, and viability of sperm were higher, and the deformity rate and ROS level were lower in ICSI plus BSSJD group. Moreover, rates of fertilization and clinical pregnancy were higher in ICSI plus BSSJD group than those of ICSI alone (Zhang et al., 2007). This suggests that BSSJD helped decrease semen ROS levels and improve the quality of sperm. This combined therapy could be helpful for enhancing the natural fertilization ability of patients with SOA and improving the viability of their sperm to increase the ovarian fertilization and clinical pregnancy rate in ICSI cycles.

Wang, Chen, et al. (2008) and Wang, Huang, and Liang (2008) compared the therapeutic effects of Chinese herb formula WuziYanzong Pill (五子衍宗片) alone with that of combined treatment with acupuncture in patients with oligospermia and asthenospermia. Two hundred and thirty-one patients with infertile conditions were divided into three groups: WuziYanzong Pill group ($n=82$), acupuncture alone group ($n=71$), and WuziYanzong Pill plus acupuncture group ($n=78$). Acupuncture was applied at acupoints Qihai (CV 6), Guanyuan (CV 4), Zhongji (CV 3), and other optional acupoints. Semen routine test and the acrosome enzyme activity were observed before and after treatment. The data showed that the effective rate was 68.3% in the WuziYanzong Pill, 67.6% in the acupuncture group, and 84.6% in the WuziYanzong Pill plus acupuncture group. The

semen density, vitality, and the acrosome enzyme activity were increased in all three groups, with more obvious increase in the WuziYanzong Pill plus acupuncture group (Wang, Chen, et al., 2008; Wang, Huang, & Liang, 2008). This showed that combined treatment of Chinese herbal formula WuziYanzong Pill with acupuncture was more effective than acupuncture or herb therapy alone in improving the semen quality and pregnancy rate of male interfile patients with oligospermia and asthenospermia.

3.3 Improving Sperm Quality

Liao et al. (2013) evaluated the effect of short-course kidney-invigorating therapy on near-term semen quality in patients with asthenozoospermia (reduced sperm motility). A total of 121 patients with asthenozoospermia were divided into groups A (kidney-yin deficiency), B (kidney-yang deficiency), and C (spleen and kidney deficiency), and treated with Yougui Decoction (右归饮) plus WuziyanzongPills (五子衍宗丸) for group A, Jinkuishenqi Pills (金匮肾气丸) plus Wuziyanzong Pills (五子衍宗丸) for group B, and ShiziPills (十子丸) for group C once daily for 4 weeks. Sperm parameters of the patients were analyzed with the computer-assisted sperm analysis system before and after treatment and compared among the three groups. All the three groups showed significant increase in sperm motility after treatment as compared with the baseline levels. The cure rate and total effectiveness rate were significantly higher in group B than in A, but had no significant difference between either A and C or B and C. No adverse effect was reported (Liao et al., 2013). This suggested that CHM formulas with short-term kidney-invigorating property could significantly improve near-term semen quality in patients with asthenozoospermia and kidney asthenia, especially in those with kidney-yang deficiency.

In an *in vitro* study Zeng et al. (2003) investigated the effect of Shouwu-Huanjing Decoction (SWHJR 首乌还精煎)-medicated serum on human sperm motility and fertility. Human sperm was cocultured with SWHJR-medicated serum *in vitro*. Data from computer-assisted semen analysis revealed that the cocultured sperm with SWHJR-medicated serum significantly increased the sperm motion velocity, the amplitude of lateral head movement and the beat frequency of flagellum, the density of progressive motility sperms, and the acrosome reaction rate. Further, the fertilization rate and the fertilization index in sperm penetration assay test were improved. The stimulation of SWHJR-medicated serum occurred in a dose-dependent manner (Zeng et al., 2003). This showed that SWHJR

could improve human sperm motility and fertility. In another study [Han, Liu, Wang, and Guo \(2015\)](#) investigated the effect of the YishenZhongzi Pill (益肾种子丸) on the sperm motility in patients with Shen-essence (kidney essence) deficiency syndrome (SEDS) according to TCM theory, in comparison with CHM formula WuziYanzong Pill (五子衍宗丸). A total of 134 patients were randomly assigned to YishenZhongzi Pill group ($n=67$) and WuziYanzong Pill group ($n=67$). The therapeutic course for both groups was 1 month. Changes in sperm motility, clinical efficacy, and symptoms scores were observed between the two groups before and after treatment. Results showed that percentages of sperm progressive motility were enhanced in the two groups after treatment in comparison with baseline. However, rate of rapid sperm progressive motility was higher in YishenZhongzi Pill group than in WuziYanzong Pill group. The total effective rate in YishenZhongzi Pill group was significantly higher than those of WuziYanzong Pill group. Scores for symptoms were improved in YishenZhongzi Pill group compared with WuziYanzong Pill group ([Han et al., 2015](#)). This suggested that YZP was more effect in treating patients with asthenospermia and classified as SEDS, and could effectively elevate the motility of sperm.

3.4 Therapeutic Effect on Male Immune Infertility

Autoimmune reaction against sperm cells is defined by [WHO \(2000\)](#) as one of the causes of infertility in men. Antisperm antibody (ASA) is believed to be a possible causative factor in infertility, with significant levels of ASA detected in the semen of 5%–15% of infertile men ([Adeghe, 1993](#)) but in only 1%–2% of fertile men ([Bates, 1997](#)). Studies of ASA showed that ASA has adverse effect on male fertility by influencing the sperm concentration, sperm motility, and sperm liquefaction ([Cui et al., 2015](#); [Garcia, Rubio, & Pereira, 2007](#)). Many CHM formulas have been used to treat immune infertility in men. [Sun and Bao \(2006\)](#) conducted a clinical study to assess a CHM formula, Yikang decoction (益抗汤) for male immune infertility, in which 100 patients with immune infertility were treated with Yikang decoction, while another 100 patients were treated with prednisone as control. At the end of the treatment, it was found that although both Yikang decoction and prednisone significantly decreased the levels of ASA in serum and semen, they markedly improved sperm density and semen liquidation compared with the baseline. The effect of Yikang decoction was more significant in all parameters tested compared with prednisone treatment ([Sun & Bao, 2006](#)). In another study, CHM

formula Huzhangdanshenyin (虎杖丹参饮) was used to treat patients with immune infertility (Lu et al., 2006). Sixty patients were treated with Huzhangdanshenyin and another 30 patients were treated with prednisone for 3 months. Improvement of clinical symptoms, immunologic indexes (anti-sperm antibodies in serum and seminal plasma), and sperm indexes (semen liquefied duration, motility, viability, density, and abnormal morphology rate) was monitored before and after the treatment. It was found that at the end of the treatment, ASA levels in serum and seminal plasma were significantly decreased, and sperm motility and viability and clinical symptoms were markedly improved in Huzhangdanshenyin-treated group compared with prednisone-treated group. However, there was no significant difference in sperm density and semen liquefied duration between the two groups (Lu et al., 2006).

CHM in combination with conventional therapies improved the efficacy of conventional treatment. For example, Yu et al. (2004) investigated the combined effect of CHM formula Zhuanyindan (ZYD 转阴丹) with hormone in treating infertile men with positive ASA and its influence on nitric oxide (NO) level in a randomized study. Eighty-two patients were divided into ZYD-alone group, hormone-alone group, and combined group (ZYD + hormone). It was found that all treatments significantly improved serum NO level, sperm motion parameters, such as linear motion speed, linearity, propulsion, sperm vitality, and mean moving angle, and quality of semen compared with pretreatment baseline. However, the total effective rate was significantly higher in combined group compared with ZYD-alone and hormone-alone treatment (Yu et al., 2004). In another study, Lian, Zhang, and Zhang (2002) compared the effect of combined therapy of CHM formula Zhenqi Zhuanyin decoction (ZQZYD 贞芪转阴汤) and timely intrauterine insemination (IUI) with that of using ZQZYD or IUI alone in treating patients with immune infertility. A total of 103 patients were randomly divided into three groups, group A (ZQZYD + IUI, $n = 34$), group B (ZQZYD alone, $n = 34$), and group C (IUI alone, $n = 35$). At the end of the treatment, it was shown that the negative conversion rate of ASA was 82.35% in group A, 76.47% in group B, and 8.57% in group C. Pregnancy rate was 41.18% in group A, 20.59% in group B, and 11.43% in group C. T-lymphocyte subsets CD4 and CD8 were significantly decreased in groups A and B compared with group C (Lian et al., 2002). Those studies showed that CHM formulas alone or in combination with conventional therapies reduced the expression of ASA, improved immunologic indexes and sperm indexes, and enhanced pregnancy rate.

3.5 Treating Disorders of Accessory Organs

3.5.1 Infertility Caused by Varicocele

Varicocele is an abnormally enlarged and twisted (varicose) vein in the spermatic cord that connects to the testicle. Varicoceles are found in about 15% of all men and in about 40% of infertile men (Jarow, 2001). Although it is not clear how much they affect fertility or by what mechanisms, they can raise testicular temperature, which may have adverse effects on sperm production, movement, and sperm shape. Qi, Lu, and Kan (2001) conducted a study to compare the effect of the CHM formula Tongjing granule (TJG 通精冲剂) in treating varicocele-induced infertility with surgical operation. A total of 75 infertile men caused by moderate or severe varicocele were divided into two groups: TJG group ($n = 44$) and surgery group (high ligation of spermatic vein and/or inferior epigastric venous bypass, $n = 31$). Data showed that there was no significant difference in the measurement of various parameters between the two groups (Qi et al., 2001). This indicated that TJG treatment achieved the same effect as that of surgery in treating the varicocele-caused infertility and might be an alternative therapy to surgery. In another study, Yan, Jiang, and Shao (2004) investigated the effect of Jingling oral liquid (JLOL 精灵口服液) in treating infertile patients with recurrent varicocele after varicocelectomy. Sixty patients were randomly divided into two groups: JLOL treatment group ($n = 30$) and injection group treated with intramuscular injection of human chorionic gonadotropine (hCG) ($n = 30$). Results revealed that in JLOL-treated group, levels of superoxide dismutase (SOD) and zinc in semen were significantly increased at the end of the treatment compared with baseline, and this was not found in injection group (Yan et al., 2004). Further, the quality of semen and the pregnant rate of the patient's partners were markedly higher in JLOL group than in injection group (Yan et al., 2004). This suggested that JLOL improved the quality of semen and sperm in infertile patients with recurrent varicocele after varicocelectomy, and increased the pregnancy rate of their spouses.

3.5.2 Male Infertility Caused by Accessory Gland Infection

Sun, Zhou, and Ding (2006) studied the effect of CHM formula QingreYulin Decoction (QYD 清热毓麟汤) on male infertility caused by accessory gland infection (AGI). Sixty infertile patients with AGI were divided into two groups: QYD-treated group and medication group treated with antibiotic plus vitamin E for 3 months. At the end of the treatment,

results showed that in QYD-treated group cure rate was 26.7%, the markedly effective rate was 43.3%, the effective rate was 16.7%, and the total effective rate was 86.7%, whereas in medication group it was 6.7%, 30.0%, 40.0%, and 76.7%, respectively. Data showed a higher cure rate and total effective rate in the QYD-treated group than in the medication group. Additionally, sperm quality, average liquefaction time, and survival rate and vitality of sperm were markedly improved in both groups, but the efficacy was better in the QYD-treated group than in the medication group (Sun et al., 2006). The study showed that CHM formula QYD not only has antiinfectious effect but also improved the quality of sperm, leading to enhance the pregnant rate of patient's spouses.



4. CONCLUSION

There have been many researches to investigate the scientific basis to understand the traditional uses of CHM formulas for male infertility. Our studies from literature review showed that CHM formulas could significantly improve sperm abnormalities and sperm quality, modify immune system, and treat many aspects of andrological conditions, via different action mechanisms depending on the formula compositions. CHM not only could treat many male infertile conditions and increase pregnancy rate but also improve the efficacy of conventional treatments. However, in addition to the need for more extensive pharmacological studies and randomized controlled trials to investigate the efficacy of promising CHM formulas for male infertility, evaluation of their safety is also needed. Other challenges for the investigation of CHM formulas for their relevance in male infertility include their standardization to known active constituents, understanding polyvalent and synergistic effects, which is particularly difficult to elucidate for CHM formulas composed of a mixture of different herb species. It is clear, under these circumstances, that the appropriate quantitative and qualitative chemical profiles of specific CHM formulas should be investigated to determine their safety and efficacy.

ACKNOWLEDGMENT

This work was partly supported by ATCM (The Association of Traditional Chinese Medicine and Acupuncture UK). Authors thank for the IT support from the King's College London.

REFERENCES

- Adeghe, J. H. (1993). Male subfertility due to sperm antibodies: A clinical overview. *Obstetrical and Gynecological Survey*, 48, 1–8.
- Alrabeeah, K., Yafi, F., Flageole, C., Phillips, S., Wachter, A., Bissonnette, F., et al. (2014). Testicular sperm aspiration for nonazoospermic men: Sperm retrieval and intracytoplasmic sperm injection outcomes. *Urology*, 84, 1342–1346.
- Bates, C. A. (1997). Antisperm antibodies and male subfertility. *British Journal of Urology*, 80, 691–697.
- Bensdorp, A. J., Cohlen, B. J., Heineman, M. J., & Vandekerckhove, P. (2007). Intra-uterine insemination for male subfertility. *Cochrane Database Systematic Review*, 17, CD000360.
- Cissen, M., Bensdorp, A., Cohlen, B. J., Repping, S., de Bruin, J. P., & van Wely, M. (2016). Assisted reproductive technologies for male subfertility. *Cochrane Database Systematic Review*, 26, CD000360.
- Corona, G., Rastrelli, G., Limoncin, E., Sforza, A., Jannini, E. A., & Maggi, M. (2015). Interplay between premature ejaculation and erectile dysfunction: A systematic review and meta-analysis. *Journal of Sexual Medicine*, 12, 2291–2300.
- Cui, Y., Feng, Y., Chen, L., Zhou, Y., Yang, X. Q., He, J., et al. (2007). Randomized and controlled research of Chinese drug acupoint injection therapy for erectile dysfunction. *Zhongguo Zhen Jiu*, 27, 881–885.
- Cui, D., Han, G., Shang, Y., Liu, C., Xia, L., Li, L., et al. (2015). Antisperm antibodies in infertile men and their effect on semen parameters: A systematic review and meta-analysis. *Clinica Chimica Acta*, 444, 29–36.
- Cui, Y. X., Huang, Y. F., Wang, Y. M., Hu, Y. A., Xu, J. P., Yao, B., et al. (2003). Chinese traditional medicine yi kang ling to treat immunity infertility caused by anti-sperm antibody: The experimental research. *Zhonghua Nan Ke Xue*, 9, 628–631.
- Dorjpurev, U., Kuwahara, A., Yano, Y., Taniguchi, T., Yamamoto, Y., Suto, A., et al. (2011). Effect of semen characteristics on pregnancy rate following intrauterine insemination. *Journal of Medical Investigation*, 58, 127–133.
- Evers, J. L., & Collins, J. A. (2003). Assessment of efficacy of varicocele repair for male subfertility: a systematic review. *Lancet*, 361, 1849–1852.
- Garcia, P. C., Rubio, E. M., & Pereira, O. C. M. (2007). Antisperm antibodies in infertile men and their correlation with seminal parameters. *Reproductive Medicine and Biology*, 6, 33–38.
- Ghanem, H., & Shamloul, R. (2008). An evidence-based perspective to commonly performed erectile dysfunction investigations. *Journal of Sexual Medicine*, 5, 1582–1589.
- Han, Q., Liu, D. C., Wang, F., & Guo, J. (2015). Treatment of asthenozoospermia men with Shen-essence deficiency syndrome by YishenZhongzi pill: A clinical study. *Zhongguo Zhong Xi Yi Jie He Za Zhi*, 35, 1050–1053.
- Ho, C. C., & Tan, H. M. (2013). Treatment of the hypogonadal infertile male—A review. *Sexual Medicine Reviews*, 1, 42–49.
- Huang, T., Xia, M., & Ren, K. (2003). The correlation research of adenine-induced male infertility and chronic renal failure in the rats. *Chinese Journal of Andrology*, 17, 171–173.
- Jarow, J. P. (2001). Effects of varicocele on male fertility. *Human Reproduction Update*, 7, 59–64.
- Johnson, L. N., Sasson, I. E., Sammel, M. D., & Dokras, A. (2013). Does intracytoplasmic sperm injection improve the fertilization rate and decrease the total fertilization failure rate in couples with well-defined unexplained infertility? A systematic review and meta-analysis. *Fertility and Sterility*, 100, 704–711.
- Lai, A. N., Song, J. F., & Liu, X. J. (1997). An experimental study on inhibitory effect of Chinese medicine tai-bao on antisperm antibody. *Zhongguo Zhong Xi Yi Jie He Za Zhi*, 17, 360–362.

- Levine, B. A., & Grifo, J. A. (2008). Intrauterine insemination and male subfertility. *Urologic Clinics of North America*, 35, 271–276.
- Lian, F., Zhang, N., & Zhang, J. W. (2002). Clinical observation on effect of zhenqizhuanyin decoction combined with intrauterine insemination in treating spleen–kidney deficiency type patients of sterility with positive anti-sperm antibody. *ZhongguoZhong Xi Yi Jie He Za Zhi*, 22, 95–97.
- Liao, Z. J., Zhou, J. F., Yin, Z. C., Zhang, J. J., Xiang, S. T., Wang, S. S., et al. (2013). Short-course kidney-invigorating therapy improves near-term semen quality in asthenozoospermic men with kidney deficiency. *Zhonghua Nan Ke Xue*, 19, 159–162.
- Liu, M. L., Wang, Z. R., & Nan, Y. Y. (2012). Effects of WenyangShengjing decoction containing serum on the estradiol secretion of Leydig cells of sterile rats of shen-yang deficiency. *ZhongguoZhong Xi Yi Jie He Za Zhi*, 32, 248–252.
- Lu, T. K., Ouyang, H. G., Jin, G. Y., Hong, Y. S., Zou, Q., Lin, Z. Y., et al. (2006). Clinical study on the treatment of male immune infertility by Huzhangdanshenyin. *Zhonghua Nan KeXue*, 12, 750–755.
- Ma, W. G., & Jia, J. M. (2011). The effects and prospects of the integration of traditional Chinese medicine and Western medicine on andrology in China. *Asian Journal of Andrology*, 13, 592–595.
- Ma, J., Wang, Z. R., & Lu, Z. F. (2006). Regulatory effect of WenyangShengjing decoction on Smads expressions in testis of sterile rats with Shen-yang deficiency. *ZhongguoZhong Xi Yi Jie He Za Zhi*, 26, 1107–1113.
- Mascarenhas, M. N., Flaxman, S. R., Boerma, T., Vanderpoel, S., & Stevens, G. A. (2012). National, regional, and global trends in infertility prevalence since 1990: A systematic analysis of 277 health surveys. *PLoS Medicine*, 9, e1001356.
- Palomba, S., Homburg, R., Santagni, S., La Sala, G. B., & Orvieto, R. (2016). Risk of adverse pregnancy and perinatal outcomes after high technology infertility treatment: A comprehensive systematic review. *Reproductive Biology and Endocrinology*, 14, 76.
- Pellati, D., Mylonakis, I., Bertoloni, G., Fiore, C., Andrisani, A., Ambrosini, G., et al. (2008). Genital tract infections and infertility. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 140, 3–11.
- Pisipati, S., & Percy, R. (2010). The role of urological surgery in male infertility. *Human Fertility*, 13, 233–241.
- Pitteloud, N., & Dwyer, A. (2014). Hormonal control of spermatogenesis in men: Therapeutic aspects in hypogonadotropic hypogonadism. *Annales d'Endocrinologie*, 75, 98–100.
- Qi, G. C., Lu, J. K., & Kan, Q. L. (2001). Comparative clinical study on treatment of varicocele caused infertility by tongling granule and surgical operation. *ZhongguoZhong Xi Yi Jie He Za Zhi*, 21, 412–415.
- Ray, P. F., Toure, A., Metzler-Guillemain, C., Mitchell, M. J., Arnoult, C., & Coutton, C. (2017). Genetic abnormalities leading to qualitative defects of sperm morphology or function. *Clinical Genetics*, 91, 217–232. <http://dx.doi.org/10.1111/cge.12905>. PMID: 27779748.
- Sallmén, M., Sandler, D. P., Hoppin, J. A., Blair, A., & Baird, D. D. (2006). Reduced fertility among overweight and obese men. *Epidemiology*, 17, 520–523.
- Sun, Z., & Bao, Y. (2006). TCM treatment of male immune infertility—A report of 100 cases. *Journal of Traditional Chinese Medicine*, 26, 36–38.
- Sun, J., Zhou, A. F., & Ding, C. F. (2006). Clinical observation of qingreyulin decoction in treatment of male infertility caused by accessory gland infection. *ZhongguoZhong Xi Yi Jie He Za Zhi*, 26, 877–880.
- Valenti, D., La Vignera, S., Condorelli, R. A., Rago, R., Barone, N., Vicari, E., et al. (2013). Follicle-stimulating hormone treatment in normogonadotropic infertile men. *Nature Review Urology*, 10, 55–62.

- Wang, J. H., Chen, D., Zhou, J. G., Cao, Y. G., & Jia, J. M. (2008). Construction of the male rat model of adenine-induced infertility with kidney-yang deficiency. *Zhonghua Nan Ke Xue*, *14*, 565–570.
- Wang, Z. Q., Huang, Y. Q., & Liang, B. (2008). Clinical observation on electroacupuncture and Chinese drug for treatment of oligospermia and asthenospermia of the male infertility patient. *Zhongguo Zhen Jiu*, *28*, 805–807.
- Wang, Q., Jixiang, Y., & Li, G. (2004). Multi-center and randomly controlled trial of shuganyiyang capsules for the treatment of erectile dysfunction (Chinese). *Journal of Beijing University of Traditional Chinese Medicine*, *27*, 72–75.
- Wang, X. J., Li, H. S., Zhang, H., & Dang, J. (2014). Influence of Yougui capsule on kidney Yang deficiency infertility rats' reproductive function. *Global Traditional Chinese Medicine*, *7*, 669–672.
- Wang, J., Wang, Q., Liu, B., Li, D., Yuan, Z., & Zhang, H. (2012a). A Chinese herbal formula, Shuganyiyang capsule, improves erectile function in male rats by modulating Nos-CGMP mediators. *Urology*, *79*, 241.e1–241.e6.
- Wang, J., Wang, Q., Liu, B. X., Li, D. H., Zhang, H. M., & Yuan, Z. J. (2012b). ShuganYiyang capsule increases the expressions of VEGF, IGF and Akt1 in the rat model of arteriogenic erectile dysfunction. *Zhonghua Nan Ke Xue*, *18*, 184–188.
- WHO. (2000). Manual for the standardized investigation and diagnosis of the infertile couple. In WHO (Ed.), (3rd ed., p. 83). Cambridge, United Kingdom: Cambridge University Press.
- Xu, X., Yin, H., Tang, D., Zhang, L., & Gosden, R. G. (2003). Application of traditional Chinese medicine in the treatment of infertility. *Human Fertility*, *6*, 161–168.
- Yan, L. F., Jiang, M. F., & Shao, R. Y. (2004). Clinical observation on effect of jingling oral liquid in treating infertile patients with varicocele after varicocelectomy. *Zhongguo Zhong Xi Yi Jie He Za Zhi*, *24*, 220–222.
- Yu, A., Li, X., Deng, W., Zhu, X., Zhuang, D., Liu, L., et al. (2011). Influence of traditional Chinese medicine on spermatozoa infected in vitro with Escherichia coli. *Andrologia*, *43*, 321–326.
- Yu, A. L., Zhang, F. Z., & Zhang, F. X. (2004). Clinical observation on effect of combination of zhuan'yindan and hormone in treating male infertility with positive antisperm antibody. *Zhongguo Zhong Xi Yi Jie He Za Zhi*, *24*, 223–226.
- Yue, G. P., Chen, Q., & Dai, N. (1997). Experimental study on effect of bushen shengjing decoction on kidney yang and testicular dysfunction in rats. *Zhongguo Zhong Xi Yi Jie He Za Zhi*, *17*, 289–291.
- Zegers-Hochschild, F., Adamson, G. D., de Mouzon, J., Ishihara, O., Mansour, R., Nygren, K., et al. (2009). International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009. *Fertility and Sterility*, *92*, 1520–1524.
- Zeng, J. X., Dai, X. H., Liu, J. H., Yang, J. H., Chen, J. F., & Lin, M. N. (2003). Effects of shouwu-huanjing recipe on human sperm motility and fertility in vitro. *Zhonghua Nan Ke Xue*, *9*, 476–479.
- Zhang, H. Q., Zhao, H. X., & Zhang, A. J. (2007). Male infertility with severe oligospermism and azoospermia treated by Bushen Shengjing Decoction combined with intracytoplasmic sperm injection. *Zhongguo Zhong Xi Yi Jie He Za Zhi*, *27*, 972–975.
- Zhao, S., Zhu, W., Xue, S., & Han, D. (2014). Testicular defense systems: Immune privilege and innate immunity. *Cellular & Molecular Immunology*, *11*, 428–437.