

# Effect of chinese herbal medicine on female infertility

## Abstract

Infertility is the inability of a sexually active, non-contracepting couple to achieve pregnancy in one year. In recent years, more couples are looking to alternative and complementary medicine (CAM) to achieve a satisfactory result, although conventional treatment possesses many effective therapies to treat infertility. Chinese Herbal Medicine (CHM) can be a very effective treatment. Through combining multiple therapies from within this traditional medical system, such as CHM and acupuncture together, CHM, otherwise known as TCM, can enhance the natural pregnancy rate two-fold, which is remarkably higher than through routine hormonal treatment. Evidence has also shown that CHM can increase the success rate of Assisted Reproductive Techniques (ART) from 33% to 60%. Authors here have reviewed CHM research papers from China, Asia, Europe and America which explain how to treat infertility using CHM based on clinical experience, how CHM supports ART, and also pre-clinical research which seeks to prove CHM's effectiveness, and demonstrate its mechanism of action from laboratory and animal tests. The key techniques of CHM are either using a tried-and-tested formula composed of a mixture of several herbs according to classical theory or clinical experience of a famous doctor, or by using a combination of multiple traditional therapies together. Some researchers advocate integrating CHM with surgery to encourage post-operative healing and promote early patient recovery.

**Keywords:** Infertility; Chinese Herbal Medicine; TCM

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## Introduction

Infertility is defined as an absence of successful pregnancy in a couple where the woman is 35 years and younger, with at least one year of regular intercourse without using birth control methods. Fertility decreases with age.<sup>1</sup> 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.<sup>2</sup> women aged 15-44 in the USA with impaired fertility is 12.3%.<sup>3</sup> Common reasons causing female infertility are tubal blockage, pelvic inflammatory disease caused by infections such as tuberculosis, uterine problems, previous tubal ligation; endometriosis, and advanced maternal age.<sup>4</sup> 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.<sup>5</sup>

Medical treatment of infertility generally involves the use of fertility medication [follicle-stimulating hormone (FSH), human chorionic gonadotropin (hCG), gonadotropin-releasing hormone (GnRH) analogues], ovarian stimulating medication [clomiphene citrate, human menopausal gonadotropin (hMG), Letrozole],<sup>6</sup> surgery (tuboplasty, salpingectomy, oophorectomy, unilateral or bilateral salpingo-oophorectomy (USO)).<sup>7,8</sup> or assisted reproductive technology (ART) techniques such as in vitro fertilization (IVF) and related techniques (ICSI, ZIFT, GIFT).<sup>9</sup>

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 (21.9-24.3% for fresh embryo transfers and 14.6-23.3% for frozen/thaw embryo transfers).<sup>9,10</sup> 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 overstimulated ovaries.<sup>11</sup> or psychiatric disorders.<sup>12</sup>

Due to the lack of a perfectly satisfactory outcome from standard medical treatment, patients are looking to alternative therapies to

improve their results. Acupuncture has been proven by many different studies from both laboratory and clinic to play an important role in supporting infertility treatment.<sup>13-15</sup> Chinese Herbal Medicine is an integral part of Traditional Chinese Medicine, in which acupuncture, diet, exercise (Taiji) and Qigong are involved together as a whole system of health maintenance. Do they play an important role in supporting infertility treatment? As a traditional medical system, how can this system of TCM be used to give the best result or infertility treatment? In this chapter we perform a thorough review of papers.

Key words "Chinese Herbal Medicine, or TCM, and Infertility" were used in the Pubmed, Cochrane, Medline, Google Scholar, CINAHL and Wanfang databases to search for papers published between 2001-2016. The resultant papers were evaluated closely and summarised below. In general most of research on the mechanism of infertility treatment using CHM or TCM have come from research teams in China, as well as other Asian countries such as Japan.<sup>17,18</sup> Korea.<sup>19</sup> and Taiwan.<sup>20</sup> However increasingly more papers are being published from Western countries such as Australia, the USA, and Europe.. Below is a summary of the findings from literature review:

### Pre-clinic and laboratory research:

There are many studies which aim to elucidate the mechanism of Chinese Herbal Medicine in treating infertility in rat models of common diseases associated with infertility.

**To promote endometrial receptivity in the uterus:** To conceive either naturally or using an assisted pregnancy technique, a receptive uterine state is required. Poor endometrial receptivity is the commonest reason for infertility and prevents embryo implantation into the uterus. CHM has been found to promote a receptive uterine state.

In Y Nan's study using a mouse model, 163 female pregnant kunming mice were randomly divided into six groups, comprising the A control group; B ovulation stimulation (OS) group; C OS+TCM (Chinese herbal medicine Pregnancy-supporting Recipe – the Zhuyun Recipe, Table 1) group; D embryo implantation

dysfunction (EID) group; E, EID+TCM group; F TCM-only group. Uterine samples were collected at gestation day four and detected with immunohistochemistry and Real Time-PCR analyses. Uterine horns were excised to determine the number of pregnant mice and implantation sites on day eight post-coitus.

The study found that OS group and EID group showed a significant decrease in pregnancy rate and the expression of both endometrial leukaemia inhibitory factor (LIF) and integrin  $\beta 3$  subunit during the implantation window. The OS+TCM and EID+TCM groups showed a higher pregnant rate and endometrial LIF and integrin  $\beta 3$  subunit expression compared to the OS and EID groups. The number of implanted embryos in EID group was lower than in the control group, but higher in the EID+TCM group than in the EID group. Their research indicates that TCM appears to reverse the expression of endometrial LIF and integrin  $\beta 3$  subunit, improves the uterine receptivity in mice, and increases pregnancy rate and embryonic implantation.<sup>21</sup>

X Gong's team showed that Leukemia-inhibitory factor (LIF) and Angiopoietin-2 (Ang-2) are important factors in fertility. Bu Shen HuoXue Decoction (BSHXD, an established CHM recipe, Table 1) was investigated for its effect on the number of implantation sites and live births in rats. Uteri were collected on day (D) 3, 4 and 5 of pregnancy, and LIF and Ang-2 protein and mRNA expression were detected using Western blot analysis and quantitative polymerase chain reaction. On pregnancy D10, the average number of implantation sites was observed, and the number of live births from each group was recorded. The study found that BSHXD treatment markedly increased the number of live births by restoring endometrial LIF expression and the implantation capacity in the rat model. In addition, no association was identified between LIF and Ang-2 expression. The author's conclusion was that BSHXD may be useful in female reproduction.<sup>22</sup>

**To stimulate ovulated inhibition and to treat ovary failure, and to raise hormonal levels:** Premature ovarian failure and insufficient storage function of the ovaries are both common reasons for infertility. They can be a result of a variety of hormonal disorders. Established recipes of CHM have been found to effectively stimulate ovaries and raise low hormone level.

S Luo's research team used rat models where ovulation was inhibited (by hydroxyl urea), which matched Shen deficiency and dampness-accumulation patterns in TCM. They showed that Luo's established recipe (Table 1) increased ovulation, levels of FSH, LH and oestrogen, and promoted pregnancy rate when compared to the control group.<sup>23</sup>

X Teng's team gave 60 female rats *Tripterygium wilfordii* tablets orally to establish a rat model of premature ovarian failure. The rats were randomly divided into a control group (n=10), and model group (n=50). The latter group were given Yulin Formula which is a classical established CHM recipe for treating Shen deficiency and blood stasis (Table 1). The test group was also sub-divided into groups of low, middle, and high dose Yulin formula. Their results showed that Yulin formula increased ovarian wet weight in rats with premature ovarian failure and increased the ovarian index. The study also showed that Yulin formula reduced FSH and LH levels, and raised oestrogen levels. They found also that Yulin formula promoted follicle growth and repair, thus improving ovarian function.<sup>24</sup>

**To relax the uterus and to prevent spontaneous abortion:** Luo's team designed rat models of abortion using hydroxyurea and mifepristone to mimic Kidney deficiency and Spleen deficiency respectively for observing the effect of ZY3 (CHM recipe for Pregnancy-support: Zhuyun No3, an established formula for preventing

miscarriage, Table 1) on Progesterone (P) and Estradiol (E2) and their receptors (PR and ER). They found that ZY3 could significantly increase positive rates of PR in decidua models of two types: its water extract and drug serum can decrease the potency of contractility of the uterus in vivo, and isolated uterus smooth muscle in vitro respectively. They concluded that the major mechanism of ZY3 in reinforcing Kidney and strengthening Spleen in protecting pregnancy is to elevate target cell PR and relax uterine smooth muscle.<sup>25,26</sup>

**To comprehensive observation to embryo embedding condition of uterus for increase a natural pregnancy and IVF's successful rates which is supported by CHM:** H Du et al. [27] studied the effect of recipes for reinforcing Kidney and dredging Liver on strengthening endometrial receptivity to improve pregnancy rates. They found that two-thirds of pregnancy failure was caused by poor uterine receptivity. They designed a mouse model with recurrent failure of IVF-ET. After giving injection of hCG to the test and control groups of mice, they observed levels of E2, LH, and progesterone, the thickening of the endometrium, and expression of angiogenic proteins at the endometrial surface. They found that the Bushenzhuyun Recipe (Table 1) increased hormone levels and thickened the endometrium. It also down-regulated the expression of ER, PR, and up-regulated expression of VEGF, VEGFR-2, eNOS, PCNA, MMP-9, and CyclinD1, which are involved in promoting cellular growth, increasing vasculogenesis, and increasing vascular permeability. They concluded that CHM could correct uterus receptivity.<sup>27</sup>

**Chinese Herbal Medicine can increase pregnancy rate in clinical research:** K Ried's team performed a systematic review in 2011 looking at Chinese herbal medicine in infertility. They identified eight randomised controlled trials (RCTs), 13 cohort studies, three case series, and six 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 four-month period compared with Western drug (clomiphene) therapy alone. They suggested that management of female infertility with Chinese Herbal Medicine could improve pregnancy rates two-fold.<sup>28</sup> They also found that assessment of the quality of the menstrual cycle, integral to TCM diagnosis, appears to be fundamental to successful treatment of female infertility.<sup>29</sup>

The same group published an updated review of the same topic in 2015, where they collected data from 40 RCTs involving 4247 women with infertility into a systematic review. Meta-analysis suggested a 1.74 higher probability of achieving pregnancy with CHM therapy than with Western therapy alone. In addition the authors concluded that fertility indicators such as ovulation rates, cervical mucus score, biphasic basal body temperature, and appropriate thickness of the endometrial lining are positively influenced by CHM therapy, indicating an ameliorating physiological effect for viable pregnancy.<sup>30</sup>

**To promote ovulation rate:** L Tan.<sup>31</sup> published 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. Analysis indicated that CHM significantly increased the pregnancy rate. There were also no significant adverse effects identified from the use of CHM in this review.<sup>31</sup>

Y Huang's team divided 60 patients with anovulatory infertility into a Chinese medicine treatment group and a Western medicine control group where the groups were equally matched in their general and anovulatory condition. The treatment group was treated with LEL (an established CHM recipe, Table 1), and the control group was given clomiphene. Ovulation rates and pregnant rates were observed and compared. They found that the total effective rate in the treatment group was 96.7%, which was significantly higher than that in the

control group (53.3%,  $p < 0.05$ ). The abortion rate was 10.0% in the treatment group, which was significantly lower than that in the control group (54.6%,  $p < 0.05$ ). The symptom score decrease significantly in the treatment group after treatment ( $P < 0.01$ ), but remained unchanged

in the control group. The authors were able to conclude that LEL had good effect in treating anovulatory infertility. Q Chen and X Li's team have made similar studies with positive results.<sup>32-34</sup>

**Table 1** The established CHM formulae mentioned in this review, and the constituent herbs.

Reference number & Author	Name of formula	Herbs in formula	Latin names of herbs	Pattern of TCM	Research form
X Gong. <sup>6</sup>	Bushenhuoxue Recipe (Tonifying Kid and Activating Blood Formula)	Sheng Di Huang Dan Shen Dang Gui ChuanDuan Du Zhong Shan Yao Mei Gui-hua ChuanXiong Yi Yi-ren	<i>Rehmannia Rehmanniae</i> <i>Salviaemiltiorrhizae</i> Bge. <i>Radix Angelica sinensis</i> (Oliv.) <i>DipsacusAsperoides</i> Diels., <i>Eucommiaulmoides</i> Oliv., <i>cRhizomaDioscorea</i> <i>FlosRosa rugosa</i> <i>Ligusticum</i> <i>Rhizomachuanxiong</i> <i>Semen Coicis</i>	Kidney Deficiency & Blood stasis	Rat Model
S Luo. <sup>7</sup>	Luo's recipe	Tuisizi Dangshen Gouqizi Bajitian Shudihuang Yinyanghuo Dangui Fuzi Zhigancao	<i>Semen Cuscutae</i> <i>Radix Codonopsis</i> <i>FructusLycii Chinensis</i> <i>Radix Morindae Officinalis</i> <i>Radix Glutinosa Libosch</i> <i>Herba Epimedi</i> <i>Radix Angelicae Sinensis</i> <i>Radix Aconiti Lateralis Preparata</i> <i>Angelica Sinensis</i> (Oliv.)Diels <i>Aconitum Carmichaeli</i> Debx <i>Radix Glycyrrhizae Preparata</i>	Kidney deficiency & Dampness accumulation	Rat Model
X Teng. <sup>8</sup>	Yulin Formula (A classical recipe 39)	Renshen, Baizhu, Fuling, Baishao, Chuanxiong, Danggui, Shudihuang, Tusizi, Duzhong, Lujiaoshuang Chuanjiao Zhigancao	<i>Ranax Ginseng</i> C.A.Mey <i>Atractylodes Macrocephala</i> Koidz <i>Poria Cocos</i> (Schw)Wolf <i>Paeonia Laciflora</i> Pall <i>Ligusticum ChuanxiongHort</i> <i>Angelica Sinensis</i> (Oliv.)Diels <i>Rehmannia Glutinosa Libosch</i> <i>Cuscuta Chinensis</i> Lam <i>Eucommia UlmoidesOliv</i> <i>Zanthoxylum Bungeanum Maximl</i> <i>Radix Glycyrrhizae Preparata</i>	Kidney deficiency & Blood deficiency	Rat Model
S Luo. <sup>9</sup>	Zhuyun Recipe No3 (Promoting conceive recipe)	Tusizi, Sangjisheng Hunagqi, Dangshen, Xuduan, Nvzhenzi	<i>CuscutaChinensis</i> Lam <i>Taxillus Chinensis</i> (DC.) Danser <i>Astragalus Membranaceus</i> (Fisch) <i>Codonopsis Pilosula</i> (Franch.) Nannf <i>Dipsacus Asperoides</i> <i>Ligustrum Lucidum</i> Ait.	Kidney& Spleen deficiencies, Blood stasis	
H Du. <sup>11</sup>	Bushenzhuyun recipe (Tonifying Kid & promoting conceive)	Shudihuang Dangui Baishao Shanyao Shanyurou Gouqizi Yinyanghuo Huangqi Tusizi	<i>Rehmannia Glutinosa Libosch</i> <i>Angelica Sinensis</i> (Oliv.)Diels <i>Paeonia Laciflora</i> Pall <i>Dioscorea Opposita</i> Thunb. <i>Cornus Officinalis</i> Sieb <i>Fructus LyciiChinensis</i> <i>Epimedium Brevicornum Maxim.</i> <i>Astragalus Membranaceus</i> (Fisch) <i>Cuscuta Chinensis</i> Lam	Kidney deficiency & Liver stagnation	Rat Model
Q Chen. <sup>16</sup>	Tiaojingyunyu Recipe (regulating menstrual circle and promoting conceive formula 39)	Dangui, Chuanxiong Shudihuang Fuling Chenpi Xiangfu Wuzhuyu Rougui Ganjiang Mudanpi, Yanhusuo, Aiye	<i>Radix Angelica sinensis</i> (Oliv.) <i>Ligusticum ChuanxiongHort</i> <i>Radix Glutinosa Libosch</i> <i>Poria Cocos</i> (Schw)Wolf <i>Citrus Reticulata Blanco</i> <i>Cyperus Rotundus</i> L. <i>Evodia Rutaecarpa</i> (Juss.) Benth. <i>Cinnamomum Cassia Presl</i> <i>Zingiber Officinale</i> Rosc. <i>Paeonia Suffruticosa</i> Andr. <i>Cordalis Vanhusuo</i> <i>Artemisia Argyi</i> Levl.	Blood deficiency & stasis	Clinic

Table Continued...

Reference number & Author	Name of formula	Herbs in formula	Latin names of herbs	Pattern of TCM	Research form
Y Huang. <sup>18</sup>	Lin' erlai Recipe	Guoqizi Tusizi Fupenzi Wuweizi Cheqianzi, Shudihuang Baishao Danggui Chuanxiong	<i>LyciumBarbarum L.</i> <i>CuscutaChinensis Lam</i> <i>RubusChingii Hu</i> <i>Schisandra Sphenanthera</i> <i>Plantago Asiatica L.</i> <i>Cuscuta Chinensis Lam</i> <i>Paeonia Laciflora Pall</i> <i>Angelica Sinensis (Oliv.)Diels</i> <i>Ligusticum ChuanxiongHort</i>	Kidney & Blood deficiencies	Clinic
J Zhou. <sup>20</sup> Y Jiang. <sup>23</sup> J Guo . <sup>32</sup>	Tonifying Kid and Activating blood Recipe	Huangqi Danshen Baizhu Sanyao Shanzhuyu Nvzhenzi Hanliancao Xianmao Yinyanghuo Chuanxiong Fuling Honghua Danggui Tusizi Chenpi Muxiang Zexie	<i>Astragalus Membranaceus(Fisch)</i> <i>Salviaemiltiorrhizae Bge.</i> <i>Atractyloides MacrocephalaKoidz</i> <i>Dioscorea OppositaThunb.</i> <i>Cornus Officinalis Sieb</i> <i>Ligustrum Lucidum Ait.</i> <i>Eclipta Prostrata L.</i> <i>Curculigo OrchioidesGaeth</i> <i>Epimedium Brevicornum Maxim.</i> <i>Ligusticum Chuanxion Hort.</i> <i>Poria Cocos (Schw.)Wolf</i> <i>CarpesiumTinctoris L</i> <i>Angelica Sinensis (Oliv.)Diels</i> <i>CuscutaChinensis Lam</i> <i>Citrus Reticulata Blanco</i> <i>Vladimiria Souliei (Franch.) Ling</i> <i>Alisma Orientalis (Sam) Juzep</i>	Kidney deficiency & Blood stasis	Clinic
F Liang. <sup>24</sup> F Lian. <sup>31</sup>	ErzhiTiangui Granule	Nvzhenzi Hanliancao	<i>Ligustrum Lucidum Ait.</i> <i>Eclipta Prostrata L.</i>	Kidney Yin deficiency	Clinic
C Lu. <sup>25</sup>	BushenHua tan Recipe (Tonifying Kid and Cleansing Phlegm formula )	Huangqi Canzhu Fuling Yinyanghuo Danshen	<i>Astragalus Membranaceus (Fisch)</i> <i>Xanthium Sibiricum Part.</i> <i>Poria Cocos (Schw.) Wolf</i> <i>Epimedium Brevicornum Maxim.</i> <i>Salvia MiltiorrhizaBge</i>	Kidney deficiency & Phlegm accumulation	Clinic
Y Chen. <sup>26</sup>	Bushenantai Recipe (Tonifying Kid to protect embryo )	Baishao Chuanduan Sangjisheng Longgu Muli Gancao Ejiao	<i>Paeonia Laciflora Pall</i> <i>Dipsacus Asperoides</i> <i>Taxillus Chinensis (DC.) Danser</i> <i>(Fossilised Bone)</i> <i>(Oyster Shell)</i> <i>Glycyrrhizae Uralensis Fisch</i> <i>Asini Gelatinun,</i>	Kidney &Spleen deficiency	Clinic
J Yu. <sup>28</sup>	Yupingfeng Recipe (A classical formula)	Huangqi Baizhu Fangfeng	<i>Astragalus Membranaceus (Fisch)</i> <i>Atractyloides MacrocephalaKoidz</i> <i>Saposhnikovia Divaricata (Turcz)</i> <i>Schischk</i>	Lung and Spleen deficiencies	Clinic

**Table 2** Periodic Herbal Managements from G Xia's experience.<sup>20,21,34,39,40</sup>

Periodic stage	Treating Principle	Xia's herbal management <sup>39,44</sup>
During Menstruation	To move Qi's stagnation and activity blood for supporting follicle's growth.	Cangzhu / <i>Xanthium Sibiricum Part.</i> Xiangfu / <i>CyperusRotundus L.</i> Mudanpi / <i>PaeoniaSuffruticosaAndr.</i> Danshen / <i>Salviaemiltiorrhizae Bge</i> Chishao / <i>PaeoniaLactiflora Pall.</i> Wulingzhi Zelan / <i>LycopusLucidusTurcz var.</i> Hirtus Regel Zishiyang / Shanzha / <i>CrataegusPinnatifidaBge</i> Yimucao / <i>LeonurusJaponicus Hoult</i> Fuling / <i>Poria Cocos (Schw.) Wolf</i>

Table Continued...

Periodic stage	Treating Principle	Xia's herbal management <sup>39,44</sup>
Post of Menstruation	To nourish Yin and blood for promoting essence (egg)'s growing up and bursting out	Danggui / Angelica Sinensis (Oliv.)Diels Chishao / PaeoniaLactiflora Pall Shudihuang / RadixGlutinosaLibosch Mudanpi /PaeoniaSuffruticosaAndr Fuling / Poria Cocos (Schw.)Wolf Shanyao / DioscoreaOppositaThunb Shanyurou / Cornus Officinalis Sieb et. Zucc Zhizi / Gardenia Jasminoides Ellis Chuanduan / DipsacusAsperoides C.Y. Cheng et Tusizi / CuscutaGlabraRoxb Fupenzi / RubusChingi Hu
Ovulation	To tonify Kidney Yang & to nourish Yin essence and blood for preparing a pregnancy	Danggui / Angelica Sinensis (Oliv.)Diels Danshen /Salviaemiltiorrhizae Bge Chishao / PaeoniaLactiflora Pall. Zelan / LycopusLucidusTurcz var. Hirtus Regel Chongweizi / LeonurusHeterophyllus Sweet Honghua / CarpesiumTinctorins L. Xiangfu / CyperusRotundus L
Before of Menstruation	To move Liver Qi stagnation & nourish blood for feeding embryo and preventing a miscarriage	Chaihu / BupleurumChinense DC Xiangfu / CyperusRotundus L Aiye / Artemisia Argyi Levl.et Vant Xudian / Dipsacus Asperoides C.Y. Cheng et Duzhong / EucommiaUlmoidesOliv. Ejiao / AsiniGelatinum, ComiAsiniColla Sangjisheng / TaxillusChinensis (DC.) Danser

However a review published by J Zhang,<sup>35</sup> indicated a different opinion that there is limited evidence that the addition of CHM to clomiphene is associated with improved clinical pregnancy outcomes, and found no evidence of any other effect.<sup>35</sup>

**To treat ovulation failure and insufficiency of stored ova:** J Zhou's team observed the curative effect of CHM of Tonifying the Kidney and Activating the Blood on improving ovulation failure, and the effect on incidence rate of luteinized unruptured follicle (LUF) and luteal phase defect (LPD). 52 patients with ovulation disorder were randomly divided into two groups; one group was treated with traditional Chinese medicine (n=32, Table 1), and the other group, as the control, was treated with Western drugs (n=20). In the treatment group, the patients were given various herbal formulae according to the patients' stages of the menstrual circle; the Western drug control group patients were given clomiphene 50-100 mg per day on day 5 of menstrual or withdrawal of flavolutan. The two groups were all treated for three to six cycles. All 52 patients completed the treatment. The authors found that during the 156 cycles of 32 patients in the TCM group, ovulation was found in 133 cycles, and the ovulation rate was significantly higher than in the Western drug control group (85.26% versus 58.7%, p<0.05). They found that the occurrence rates of LUF and LPD in the TCM group were lower than in the Western drug control group. The authors concluded that CHM, by the Tonifying kidney and Activating Blood method improved ovulation rate and lowered incidence rate of LUF and LPD when compared with clomiphene.<sup>36</sup> (Table 2).

Periodic treatment method of CHM is a particular TCM technique using various herbal formulae in different stages of the menstrual circle to promote ovarian function and following the cyclical hormonal changes. It has been observed to be more effective than the standard TCM treatment methods. This method was created by Prof G Xia,<sup>39</sup>

and was developed by D Jiang into a regime which is suitable to be used in the West.<sup>37</sup> (Table 2).

**To treat Fallopian tube obstruction:** J Kang's team studied an effective and practical treatment to Fallopian tube obstruction (OvO). 120 patients with OVO were randomly divided into three groups: the TCM-WM group, treated with integrative Chinese herbal medicine (an established CHM formula) and Western medicine (salpingectomy); the TCM group, treated with Chinese herbal medicine alone; and the WM group treated with Western medicine alone. The therapeutic effect as well as the effect of treatment on serum C-reactive protein (CRP) and interleukin-1 beta (IL-1 beta) were observed. The authors found that after treatment, Fallopian tube patency rate rose to 86.7% and pregnancy rate to 85.0% in the TCM-WM group, while in the TCM group rates were 66.7% and 63.3% respectively, and in the WM group 53.3% and 50.0% respectively. Comparison among the three groups show that the effect in the TCM-WM group was significantly superior to that in the other two groups (P < 0.01). The levels of CRP and IL-1 beta were all lowered after three courses of treatment, and the effect was more evident in the TCM-WM group (P < 0.01). They authors concluded that TCM-WM treatment was a good and practical method in treating Fallopian tube obstruction.<sup>38</sup>

Y Jiang's team also compared the effect of treatment of Fallopian tube obstructive infertility by salpingectomy alone and in combination with TCM drugs for BushenHuoxue (invigorating Shen and promoting blood circulation, an established CHM formula, Table 1). To all the patients, salpingostomy was performed three to seven days after menstruation, and hydrotubation with Xiangdan Injection (XI) was applied once in the next menstrual cycle. BushenHuoxue Decoction (BHD) was administrated additionally to patients in the treatment group, one dose every day starting from the fifth day of

menstrual cycle for 14 days. Three months' treatment was taken as one therapeutic course, and the observation lasted for four courses. The authors confirmed the combined therapy of salpingostomy and CHM was an effective therapy for Fallopian tube obstructive infertility by enhancing follicular development and increasing thickness of endometrium, and could elevate the pregnancy rate in patients.<sup>39</sup>

**To treat PCO□PCOS:** F Lian 's team found that CHM-Erzhitiangui Granule (Table 1) could increase anti-Müllerian hormone (AMH) and oocyte quality for patients with polycystic ovarian syndrome. The drug's mechanisms of action are correlated with regulating AMH levels in the serum and follicular fluid, adjusting androgen levels, improving the pathophysiological changes of PCOS patients, and activating the ovarian microenvironment.<sup>40</sup>

CLu' team divided 30 patients with PCOS into a normoinsulinaemic group (NI=13), and an hyperinsulinaemic group (HI=17). Both groups were treated for three menstrual cycles with the TCM Formula BushenHuatan Formula (an established CHM formula for tonifying kidney and activating blood, Table 1). A metabolomics-approach based on ultra-high-performance liquid chromatography (UPLC) coupled with linear ion trap Orbi-trap mass spectrometer (LTQ Orbi-trap MS) was used to investigate serum metabolic changes of TCM intervention to PCOS. After BHF intervention for three menstrual cycles, the serum levels of glycerophosphoryl ethanolamine (GPEA), creatine, and creatinine decreased in both NI and HI groups. Furthermore in the NI group, the main manifestation were changes in phospholipid metabolism. While in the HI group, lysine, phenol sulfate, phe-phe etc. were decreased, and ornithine, proline, betaine, acetylcholine etc. were increased. Combined with clinical biochemical data, BHF was proved effective in treatment of PCOS by reducing the inflammatory reaction and oxidative stress. This study also illustrated that the LC-MS-based metabolomics approach was a helpful tool to evaluate curative effect and to understand the mechanisms of TCM.<sup>41</sup>

**To reduce and to treat miscarriage:** Recurrent spontaneous miscarriage (RSM) is one of the commonest and complicated medical conditions amongst pregnant women. In recent years miscarriage rates have been progressively increasing, due to women trying to conceive later in life and the higher risk of pregnancy loss from in vitro fertilisation (IVF) and intrauterine insemination (IUI). TCM is often able to treat and prevent RSM.

Y Chen's team observed the effect produced by the Gushenantai recipe (a classical formula to prevent and treat miscarriage, Table 1) to women with recurrent spontaneous miscarriage without obvious cause, and its influence on T-lymphocytes. 90 patients were separated into two groups where routine treatment of Progesterone was given, and Gushenantai recipe given to the half in the treatment group. No herbs were given to the other half in the control group. The authors found that miscarriage was prevented and pregnancy proceeded in 71.1% in the control group, and 86.7% in the treatment group. The team also observed that B-HCG, HPL, P, CD4, CD8, CD4/CD8 levels were different before and after treatment. They were able to confirm that Gushenantai recipe was effective in reducing recurrent spontaneous miscarriage, and could correct immunological disorders and increase hormone levels.<sup>42</sup>

**To treat mycoplasma infection:** Y Lou's team investigated the changes in cytokines (IL-1beta, IL-2, TNF-alpha) in the peripheral blood and cervical mucus of infertile women with mycoplasma infection and the effect of intervention of TCM. 72 patients with positive genital mycoplasma cultures were randomly divided into a TCM group (38 cases) and a Western medicine group (34 cases). The Western medicine group was treated with 0.5 g azithromycin

for three days and consecutively underwent six courses of treatment, each course of treatment of four days' duration. The TCM group was treated with Xiaozhi decoction (an established CHM formula) twice every day for six weeks. Cytokines (IL-1beta, IL-2, TNF-alpha) in the peripheral blood and cervical mucus were found to increase, suggesting that TCM could effectively inhibit the levels of IL-1beta, IL-2, TNF-alpha in the peripheral blood, and IL-1beta, TNF-alpha in cervical mucus. The authors concluded that Xiaozhi decoction could be used to treat infertile women with mycoplasma infection.<sup>43</sup>

**To re-regulate immunology disorder:** J Yu studied the effect of Yupingfeng Formula (a classic CHM formula) to treat infertility in women with immunological disorders. Table 1). 72 patients with immunological infertility were randomly assigned into two groups of 36. The observed group was given Yupingfeng granule; the control group was given oral Prednisone. Levels of AsAb, AEmAb, AOVAb and AbCGAb were markedly more reduced in the observed group than in the controlled group ( $p < 0.05$ ). Yu concluded that Yupingfeng granule was able to significantly affect immunological infertility.<sup>44</sup>

**To treat many abnormal physical and psychiatric symptoms, Such as anxiety, stress, and insomnia:** K Ried et al.<sup>28</sup> designed questionnaires and interviewed women with infertility with the aim of identifying their quality of life. They found high level of distress, guilt, grief, and frustration caused by infertility. However, these women represented a highly motivated sample, who were actively seeking alternative support methods. Traditional Chinese Medicine addresses some of these. The group recommended that more peer-led and professional-led support groups were greatly needed for women experiencing infertility to help break isolation and raise awareness of integrative approaches to fertility management.<sup>45</sup>

### Chinese Herbal Medicine can increase the success rate of *in-vitro* fertilisation and embryo transfer (IVF-ET) outcomes

A review series by J Liu et al. found that CHM could increase success rates from 33% to 60% in IVF and IVF-ET treatment. The authors' results are summarised below: Twenty trials involving 1721 women were included in the meta-analysis. Three trials were evaluated as having an unclear risk of bias. The remaining trials were evaluated as having a high risk of bias. Despite this the authors found that the combination of CHM and IVF significantly increased clinical pregnancy rates (OR 2.04, 95%CI 1.67 to 2.49,  $p < 0.00001$ ), and ongoing pregnancy rates (OR 1.91, 95%CI 1.17 to 3.10,  $p = 0.009$ ). Use of CHM after embryo transfer had no better outcome in reducing the rate of ovarian hyperstimulation syndrome (OR 0.39, 95%CI 0.14 to 1.11,  $p = 0.08$ ). This meta-analysis showed that combination of IVF and CHM used in the included trials improve IVF success, however due to the high risk of bias observed with the trials, the significant differences found were felt to be unlikely to be accurate. The authors also mentioned that no conclusion could be made with respect to the reproductive toxicity of CHM. Further large randomized placebo controlled trials were recommended to confirm these findings before recommending women to take CHM to improve their IVF success.<sup>47</sup>

F Lian's team conducted a series of studies to confirm the effectiveness of CHM in promoting IVF and increasing pregnancy rates:

**To promote pregnancy uterus receptivity:** Lian et al.<sup>48</sup> found that for infertile patients undergoing IVF, the recipe for tonifying the Kidney (Table 1) as an adjunct to standard Western treatment could reduce Gn dosage and treatment duration, alleviate clinical symptoms, and

improve pregnancy rate. The authors felt that the improvement could be explained by an increased level of DNMT1 protein expression after treatment, leading to enhanced endometrial receptivity.<sup>48</sup>

**To improve the quality of oocytes and leukemia inhibitory factor in follicular fluid:** The established CHM formula Erzhiangui Granule ETG (Table 1) was found to distinctively increase the amount of oocytes, elevate the quality of embryos, and raise the success rate of IVF-ET. The authors speculated that the mechanism maybe correlated to the increase of LIF level in FF and the activating of microenvironment for its full expression.<sup>49</sup>

**To improve endometrial blood flow in the uterus:** Endometrial blood flow is directly related to endometrial receptivity, thereby affecting in-vitro fertilization and embryo transfer (IVF-ET) outcomes. J Guo team's studies confirmed that CHM formulae (Table 1) based on reinforcing kidney and activating blood can promote the formation of uterine endometrial blood vessels by adjusting expression of a variety of angiogenic growth factors, and regulating nitric oxide levels for the inhibition of vascular smooth muscle contraction of the uterus. Treatments based on differentiation of syndromes are key to the theory of TCM. Differentiation of syndromes should be combined with biomedical disease diagnosis. The authors also felt that it was necessary to further clarify other endometrial blood flow disorders using TCM diagnostic methods.<sup>50</sup>

**To decrease FSH level for making a good preparation to IVF treatment:** Elliott reported that Follicle stimulating hormone (FSH) levels are routinely tested during biomedical investigations into female fertility. An appropriately low FSH level is frequently required by fertility clinics as an entry requirement for women wishing to receive assisted reproductive technology (ART) treatment such as *in-vitro* fertilisation (IVF). The author asserts that with the appropriate treatment using acupuncture and Chinese herbal medicine, the proper functioning of the ovaries and anterior pituitary gland, in cases where they have been pathologically affected, can be restored. This process does not, however, necessarily imply that treatment has reversed the ageing process or affected the quality of eggs produced.<sup>49</sup>

**To support patients who have failed IVF treatment:** X X's team explored the effect of traditional Chinese comprehensive therapy (TCCT) on promoting gestation in patients with previously failed in-vitro fertilisation and embryo transfer (IVF-ET) because of kidney deficiency, liver stagnation, and blood stasis (KLB). 37 patients were enrolled in this study and divided into two groups: a trial group with 35 patients, and a control group with 32 patients. The trial group was given TCCT for three months, then administered IVF-ET or natural pregnancy was awaited. The control group was administered IVF-ET without TCCT three months after the previous IVF-ET or natural pregnancy attempt. The patterns of KLB were observed both before and after treatment. The natural pregnancy rate of the two groups was calculated after treatment.

After treatment with TCM comprehensive therapy, seven patients in the treatment group became pregnant, while there were no successful conceptions in the control group. The difference in clinical pregnancy rate in the initial cycle and transfer cycle of IVF were significantly different ( $p < 0.05$ ). The trial group had a significantly higher conception rate than the control group ( $P < 0.05$ ). The authors concluded that TCCT can promote natural pregnancy rate in patients with previously failed IVF-ET. TCCT could increase the number of fertilised eggs, the fertilisation rate, pregnancy rate, and clinical pregnancy rate after another IVF-ET treatment.<sup>50</sup>

## Whole Systematic TCM Treatment for Infertility and IVF Treatment

TCM is a traditional medical system with a thousand years of experience which should be combined with herbal medicine and acupuncture together. From the evidence it appears that using whole TCM treatment may achieve the best results for both natural pregnancy and IVF.

K Sela et al.<sup>51</sup> observed the effect of combining acupuncture and medicinal herbs as a therapeutic adjuvant to ovulation induction with intrauterine insemination (IUI) procedures, and evaluated its contribution to pregnancy and "take-home baby" rates. The retrospective study was carried out in a university – affiliated municipal hospital. All women undergoing artificial insemination by donor spermatozoa (AID) and concomitantly treated with TCM were invited to participate. The enrolled women underwent weekly TCM in parallel with standard Western therapy. The treatment lasted between two and 36 cycles (equivalent to a time period ranging from one month to one year). The control group was comprised of women who underwent AID without TCM and whose data were retrospectively retrieved from hospital files. Pregnancy was assessed by human chorionic gonadotropin findings in blood 12–14 days after IUI. The birth rate was calculated during follow-up. A total of 29 women aged 30–45 years were enrolled in the study. The historical control group include 94 women aged 28–46 years. The results showed that women who combined TCM with procedures for undergoing IUI had significantly higher pregnancy (OR=4.403, 95% CI 1.51–12.835,  $p=0.007$ ) and birth rates (OR=3.905, 95% CI 1.321–11.549,  $p=0.014$ ) than the control group. The group concluded that TCM appeared to be beneficial as an adjunctive treatment in IUI procedures. They called for randomised controlled trials to further assess the role of acupuncture and herbs in this setting.<sup>51</sup>

E Lee et al.<sup>52</sup> observed that whole-systems traditional Chinese medicine (WS-TCM) was a multi-dimensional intervention that could include any combination of modalities classified under the system of TCM. They describe these as including any combination of acupuncture (the insertion of sterile, filiform needles in the body), moxibustion (the burning of the processed herb *Artemesia argyi* on or near the body), and Chinese herbal medicine (granule, powder or dry herbal forms). The authors compared the reproductive outcomes of women who elected for WS-TCM treatment in addition to their usual IVF care, and compared them with those who received the usual IVF care alone, and to those who received two standardised acupuncture treatments on the day of embryo transfer acupuncture only. They compared the three groups on the outcome of live birth, and found evidence that the addition of WS-TCM to non-donor IVF cycles increased the odds of achieving a live birth over usual IVF care alone or two standardized treatments administered around embryo transfer. They found that the effects of WS-TCM were less clear compared with usual donor IVF care alone but showed a non-significant trend towards increased odds of a live birth in this cycle type. This retrospective cohort study suggested that WS-TCM as an adjuvant IVF treatment may be associated with improved live birth rates.<sup>52</sup>

## Conclusion

From searching and reviewing the above information, some conclusions can be drawn:

- i. Chinese Herbal medicine is an effective therapy which appears to be show ability to support infertility treatment. Much research has been done in China to explain the mechanism of action of CHM in treating Infertility, and some utilise very modern techniques and high levels of expertise.<sup>21-27</sup> However they are limited in circulation and impact due to being in Chinese only.
- ii. A mature and established CHM formula may be the key to high efficacy, and effective and experienced herbal formulae should be designed according to diagnostic patterns within TCM.<sup>53,54</sup> No paper described effects produced by a single herb to treat Infertility.
- iii. Combining the whole system of TCM together, such as combining acupuncture and CHM, acupuncture, moxibustion and CHM, massage and CHM, gives better treatment power than individual therapy modalities.<sup>55,56</sup>
- iv. The shortcoming of CHM may still be its weaker treatment level. Some researchers observe that combining CHM with Western medical technology or drugs can give better effects than either CHM or Western drug alone.<sup>38,39,42</sup>

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## Conflicts of Interest

None.

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