



Chinese herbal medicine for female infertility: An updated meta-analysis



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KEYWORDS

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Summary

Objectives: To assess the effect of Traditional Chinese herbal medicine (CHM) in the management of female infertility and on pregnancy rates compared with Western medical (WM) treatment and update previous meta-analyses.

Methods: We searched the Medline and Cochrane databases until December 2013 for randomized controlled trials and meta-analyses investigating Chinese herbal medicine therapy for female infertility and compared clinical pregnancy rates achieved with CHM versus WM drug treatment. **Results:** Forty RCTs involving 4247 women with infertility were included in our systematic review. Meta-analysis suggested a 1.74 higher probability of achieving a pregnancy with CHM therapy than with WM therapy alone (risk ratio 1.74, 95%CI: 1.56–1.94; $p < 0.0001$; odds ratio 3.14; 95%CI: 2.72–3.62; $p < 0.0001$) in women with infertility. Trials included women with PCOS, endometriosis, anovulation, fallopian tube blockage, or unexplained infertility. Mean pregnancy rates in the CHM group were 60% compared with 33% in the WM group.

Conclusions: Our review suggests that management of female infertility with Chinese herbal medicine can improve pregnancy rates 2-fold within a 3–6 month period compared with Western medical fertility drug therapy. In addition, fertility indicators such as ovulation rates, cervical mucus score, biphasic basal body temperature, and appropriate thickness of the endometrial lining were positively influenced by CHM therapy, indicating an ameliorating physiological effect conducive for a viable pregnancy.

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Introduction

Fertility problems are encountered by about 15% of couples in Western countries.¹ Impaired fecundity, or the impaired ability to get pregnant or to carry a baby to term, affected about 6.7 million (10.9%) of women in the USA.¹

While 80% of infertility might be related to conditions such as endometriosis or polycystic ovary syndrome (PCOS), 20% are ‘unexplained’ in the Western Medicine model.² However, diagnosis of a specific disease/condition and subsequent treatment with surgery, drugs, in vitro-fertilisation (IVF) or other assisted reproductive technologies (ART) does not always result in a viable pregnancy and live birth. In 2011, for example, more than 170,000 ART cycles were recorded in the USA, and of these 29% resulted in live births.³

Moreover, ART treatment is costly for both governments and individuals. In 2011, for one IVF cycle costs

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were between US\$10–15,000, and individual couples' out-of-pocket expenses were on average US\$5300 and up to US\$19,000 for the first IVF cycle, and on average US\$7000 for subsequent cycles.⁴

Holistic approaches to infertility management, such as Traditional Chinese Medicine (TCM) might address some of the needs of women experiencing infertility, not met in the Western medical approach.^{5,6}

In the last decade, herbal medicines including Chinese herbal medicines are being used for fertility by a small proportion of women in Western countries, e.g. 5% of those surveyed at an infertility clinic in South Australia, 10% in the UK, or 18% in the USA.^{7–10}

Our previous meta-analysis of eight randomized controlled trials reported a doubling in the pregnancy rate in subfertile women using Chinese herbal medicine (CHM) within a 4-month treatment period compared with Western medical drug therapy.¹¹

Here we updated our previous meta-analysis on the effect of CHM on female infertility and pregnancy rates.¹¹ In addition, we summarize the effect of CHM therapy on ovulation rates and other fertility indicators. Furthermore we introduce the principles of TCM diagnosis and therapy, and provide examples of herbal formulae used in Traditional Chinese Medicine conducive to improving fertility.

Methods

Search strategy

We searched the Medline and Cochrane databases until December 2013 for randomized controlled trials and meta-analyses investigating Chinese herbal medicine therapy for female infertility using the following search terms: 'medicine, Chinese traditional' AND 'infertility'. In addition, we checked reference lists of relevant articles.

Study selection

We included randomized controlled trials with women of reproductive age with primary or secondary infertility. Infertility may have been associated with PCOS, anovulation, endometriosis, amenorrhea, fallopian tube blockage, or unexplained infertility.

Types of intervention

Chinese herbal medicine (CHM) treatment was defined as treatment with Chinese Herbs according to TCM pattern diagnosis. We included studies which used CHM alone or in combination with Western Medicine (WM) in the form of drugs or surgery. The control group in RCTs received WM treatment only. We excluded studies using acupuncture alone or TCM therapy in combination with assisted reproductive technologies (ART).

Types of outcome measures

The primary outcome was clinical pregnancy. We also summarized reported ovulation rates, basal body temperature

pattern, endometrial thickness, cervical mucus score, pain, adnexal mass reduction in patients with endometriosis, and restoration of tubal patency in women with blocked fallopian tubes. In addition, we report on the effect of CHM therapy on the continuation of pregnancy in women with threatened miscarriage.

Assessment of trial quality

To assess trial quality, the Cochrane Collaboration recommends the use of the risk-of-bias-tool which includes assessment of the adequacy of random sequence generation, allocation concealment, blinding, attrition/follow-up, and evidence of unselective reporting.¹² The quality of trials is then rated as adequate, unclear, or inadequate for these types of bias. The Jadad score is another commonly used assessment tool, including randomization, blinding, and attrition with a maximum score of five.¹³ A score of one is provided for each adequate method reported.

Data abstraction and analysis

Data from trials fitting the inclusion criteria were abstracted independently by two researchers.

Analysis of trials with sufficient quality was conducted using the Cochrane Review methodology and the Review Manager program.¹² A random effects model and the Mantel–Haenszel method were used to calculate the risk ratio between groups while accounting for heterogeneity. For comparison of results reported in some previous meta-analyses, we also calculated the odds ratio using the inverse variance method and a random effects model. Publication bias was assessed by funnel plot.

Results

Characteristics of included studies

In addition to our previous meta-analysis,¹¹ we identified a further three meta-analyses and one trial on the effect of Chinese herbal medicine compared to Western medical drug treatment for infertility, and reporting pregnancy rates (Fig. 1).^{14–16}

In summary, 40 trials involving 4247 women were included in our meta-analysis, comprising 8 trials^{17–24} from the meta-analysis by Ried,¹¹ 13 trials^{25–37} from the meta-analysis by See,¹⁴ 14 different trials^{38–51} from the meta-analysis by Tan,¹⁵ 4 trials^{52–55} from the meta-analysis by Zhang,¹⁶ and one RCT.⁵⁶ Only one trial²⁰ was reported in two reviews,^{14,15} but included only once in our meta-analysis. Characteristics of included trials are summarized in Table 1.

The majority of trials involved women with anovulation ($n=24$) and PCOS ($n=8$), while two trials studied women with endometriosis, one with immunological infertility, and one with blocked fallopian tubes (Table 1). About half of the trials compared CHM only with Western medical treatment ($n=21$), 40% used CHM plus clomiphene (CC) versus CC, and four trials combined CHM with other WM treatment and compared to WM treatment. In the control groups, two-thirds of the trials used CC as the only WM drug therapy, seven

Table 1 Characteristics of trials included in the meta-analysis on the effect of CHM on female infertility compared with WM.

Study	Infertility problem	CHM treatment	Control – WM treatment	Duration (months)	Trial quality (risk of bias)
In Ried 2011¹¹ (review)					CRB tool
Hua 2003 ¹⁷	PCOS	8 herb formula	CC	6	1
Wu 2006 ¹⁸	Endometriosis	2 herb formula	Gestrinone	3	1
Lin 2005 ¹⁹	PCOS	Periodic CHM + Acu + CC	CC, HCG	3–6	1
Xia 2004 ^{a,20}	PCOS	16 herb formula (2mths) + CC (1mth)	CC (1 mth)	1–3	1
Chen 1995 ²¹	Immunological	8 herb formula	Prednisolone, Vit E	1–3	1
Shao 2004 ²²	PCOS, anovulation	10 herb formula (15 days) + CC (5 days)	CC (5 days)	1–3 weeks	1
Ren 2002 ²³	PCOS	7 herb formula + CC	CC, Tamoxifen	2–3	1
Zhang 2006 ²⁴	Endometriosis	4 diff formulae containing 10–17 herbs by underlying TCM pattern	Danazol	ng	1
In See 2011¹⁴ (review)					Jadad score
	All: anovulation, incl due to PCOS		All: CC	All: 3–6	
Tang 2002 ²⁵		14 herb formula + CC			1
Cui 2003 ^{a26}		20 herb formula + CC			1
Huang 2001 ²⁷		10 herb formula + CC			1
Hu 2003 ²⁸		31 herb formula + CC			1
Wu 2000 ²⁹		12 herb formula + CC			1
Liu 2002 ³⁰		20 herb formula + CC			1
Ma 2005 ³¹		12 herb formula + CC			1
Li 2002 ³²		20 herb formula + CC			1
Fan 2006 ³³		15 herb formula + CC			1
Wang 2000 ³⁴		9 herb formula + CC			1
Xia 2004 ^{b,35}		10 herb formula + CC			1
Li 2004 ³⁶		26 herb formula + CC			1
Qiu 2001 ³⁷		7 herb formula + CC			1
In Tan 2012¹⁵ (review)					Jadad score
	All: anovulation				
Yin 2006 ³⁸		Periodic CHM	CC	6–9	1
Luo 2007 ³⁹		Periodic CHM	CC	3	1
Xu 2009 ⁴⁰		Periodic CHM	CC	3	1
Liu 2010 ⁴¹		Periodic CHM	CC	3	2
Cui 2003 ^{b, 42}		Mixed herb formula	CC	6	2
Qiu FL 2004 ⁴³		12 herb formula	CC	3	1
Chu 2006 ⁴⁴		Mixed herb formula	CC	3	1
Huang 2006 ⁴⁵		Mixed herb formula	CC	6	2
Pang 1997 ⁴⁶		Mixed herb formula	CC	ng	1
Huang 2002 ^{b, 47}		Mixed herb formula	CC	6	1
Yin 2004 ⁴⁸		Periodic herbs	CC	3–6	1
Huang 2007 ⁴⁹		Mixed herb formula	CC	6	2
Xia 2004 ^{b,35}		Mixed herb formula	CC	3	1
Qiu MY 2004 ⁵⁰		11 herb formula, Ki tonifying	CC, diethylestrol, medroxyprogesterone	3–6	1
Fu 2007 ⁵¹		Mixed herb formula	CC, HCG	1	1
In Zhang 2010¹⁶ (review)					CRB tool
	All: PCOS				
Li 2007 ⁵²		Group 1: CHM only: 6 + 7 herb formulae; Group 2: CHM + CC	CC	6	2

Table 1 (Continued)

Study	Infertility problem	CHM treatment	Control – WM treatment	Duration (months)	Trial quality (risk of bias)
Ye 2007 ⁵³		Periodic CHM + LOD	CC + LOD	6	1
Ma 2009 ⁵⁴		Periodic CHM + Diane-35 + CC, HCG	Diane-35 + CC, HCG	6	1
Liang 2008 ⁵⁵		14 herb formula + FA + HMG, HCG	FA + HMG, HCG	6	1
Pang 2012 ⁵⁶ (RCT)	Blocked fallopian tubes	10 herb formula (oral)	Intrauterine infusion of 3 drugs ^a 3 times	3	1

CC, clomiphene; CHM, Chinese herbal medicine; CRB; Cochrane Risk-of-Bias-Tool, Diane-35, ethinyloestradiol cyproterone actate; FA, follicle aspiration; HCG; human chorionotropic gonadotropin; HMG, human menopausal gonadotropin; LOD, laparoscopic drilling; PCOS, polycystic ovary syndrome; ng, not given; WM, Western Medicine.

Periodic CHM, formula changes according to phase in menstrual cycle.

^a Dexamethasone sodium phosphate (corticosteroid), chymotrypsin (digestive enzyme), gentamicin sulphate (antibiotic).

^b Same trial included in reviews by See (2011)¹⁴ and Tan (2012).¹⁵

trials combined CC with another WM treatment, and five trials used other drug therapy or WM treatment options (Table 1). The intervention in most trials was given between 3 and 6 months in most trials.

Included women were of reproductive age (18–45 years), with a mean of about 30 years.^{11,14–16,56} Two meta-analyses^{11,16} and the trial by Pang (2012)⁵⁶ reported the duration of infertility experienced by participating women prior to their involvement in a trial, ranging between 3 and 7 years.

Quality of included trials

Trial quality was assessed using the Cochrane-risk-of-bias-tool¹² in the reviews by Ried¹¹, and Zhang,¹⁶ and for the

RCT by Pang,⁵⁶ while the Jadad score¹³ was used in the reviews by See¹⁴ and Tan.¹⁵ The majority of trials included in this meta-analysis did not report on specifics of trial methodology, therefore assessment of trial quality was often unclear, resulting in a low quality score and considered high-risk-of-bias (Table 1).

Meta-analysis of RCTs

Effect of CHM on pregnancy rates

Our meta-analysis of 40 RCTs with more than 4200 women revealed a 1.74 higher probability of achieving a pregnancy with CHM therapy than with WM therapy alone (risk ratio (RR)=1.74, 95%CI: 1.56–1.94; $p < 0.0001$; odds ratio (OR)=3.14; 95%CI: 2.72–3.62; $p < 0.0001$) in women with

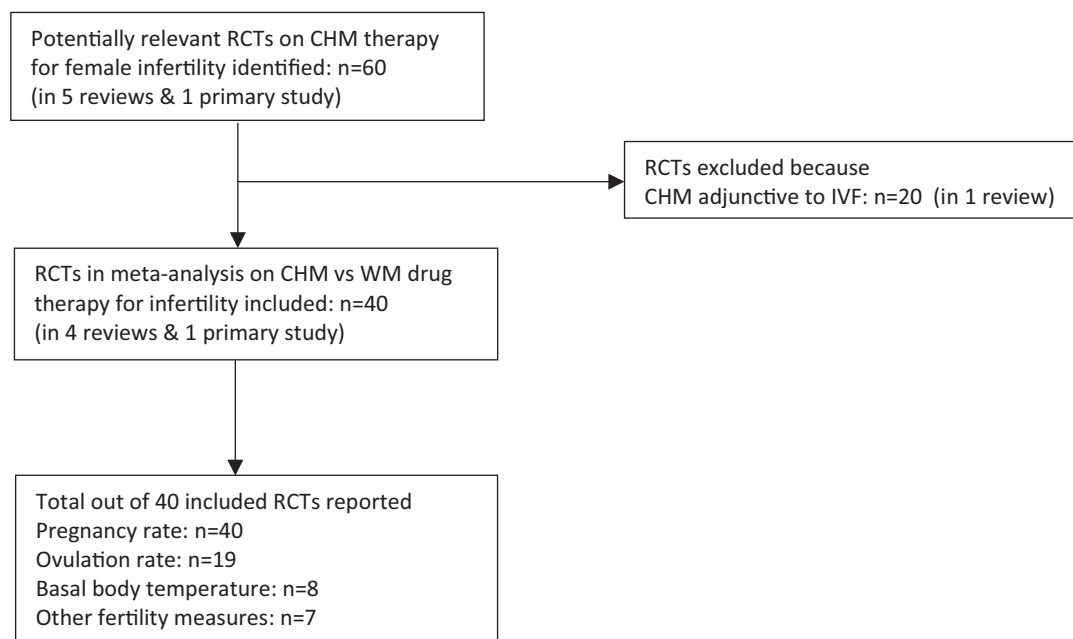


Figure 1 Flow diagram of study selection for meta-analysis. Abbreviations: CHM, Chinese herbal medicine; IVF, in vitro fertilization; n, number; RCTs, randomized controlled trials; WM, Western medicine.

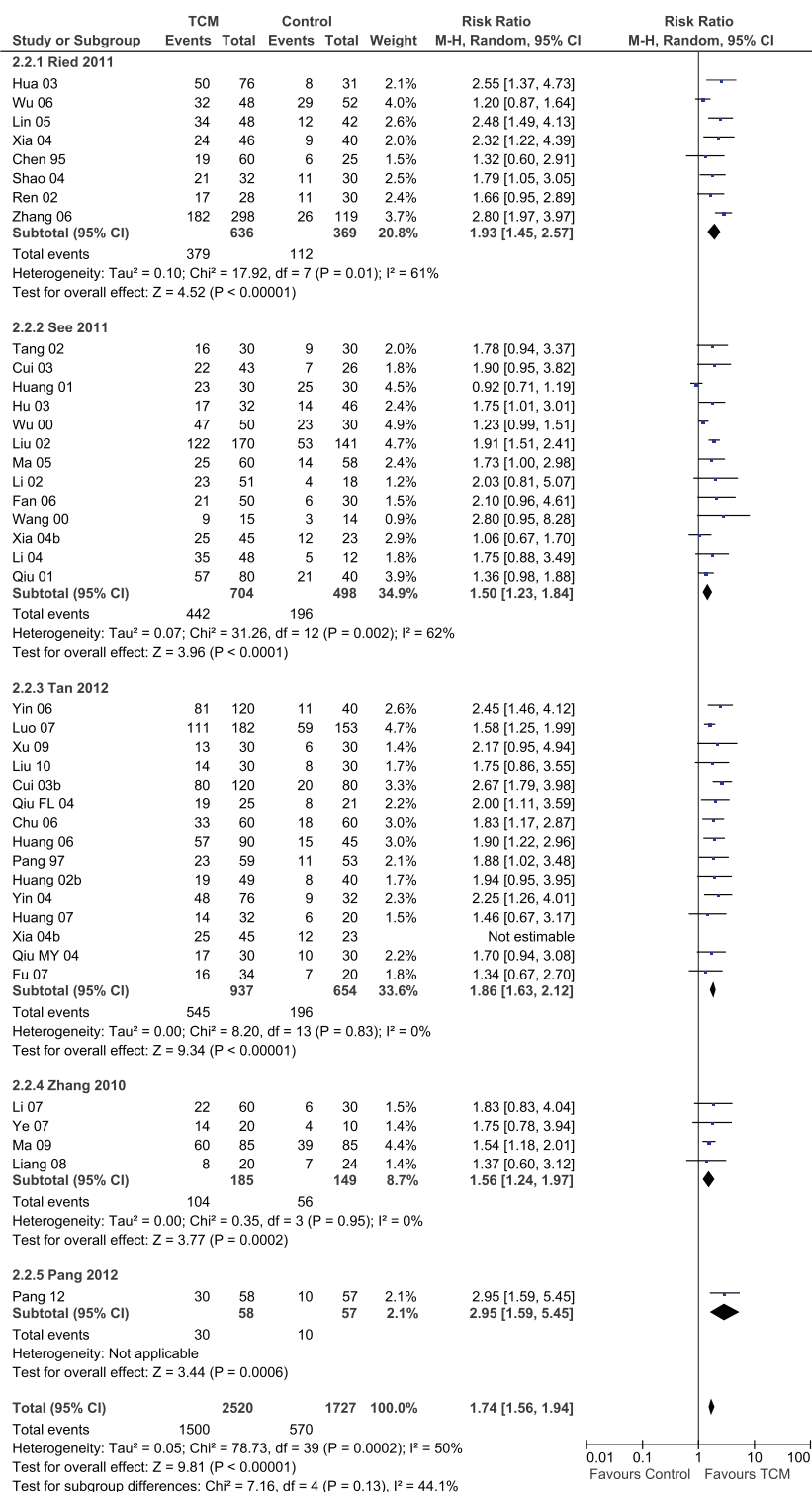


Figure 2 Meta-analysis of RCTs investigating pregnancy rates of infertile women treated with Chinese herbal medicine (CHM) compared with WM fertility medications.

Abbreviations: TCM, Traditional Chinese Medicine; CI, confidence interval; event, number of pregnancies; total, number of women.

infertility. Mean pregnancy rates in the CHM group were 60% compared with 33% in the WM group (Fig. 2).

A sensitivity analysis of trials including only women with PCOS or anovulation did not appreciably change results (RR = 1.71; 95%CI: 1.53–1.90; $p < 0.0001$, $n = 35$ trials).

This result is in line with our previous meta-analysis of 8 RCTs.¹¹ In fact, each of the 4 published meta-analyses comprising different trials, different infertility problems, and different CHM formulae reported similar probabilities of achieving a pregnancy (RR range between 1.50 and 1.93, Fig. 2).^{11,14–16,56}

Table 2 Summary of effects of Chinese herbal medicine (CHM) compared with Western Medicine (WM) treatment on fertility indicators.

Outcome	Study ID	Infertility problem	No. of studies	No. of women	CHM n/N	Control n/N	Treatment	RR	95% CI	p
Ovulation rate	All studies		19	2059	958/1205 (80%)	573/854 (67%)		1.18	1.12–1.25	<0.001
	Ye 2007 ⁵³	PCOS	1	30	17/20	8/10	CHM: 10 herb formula WM: CC Time: 6 months	1.42	0.19–10.49	0.73
	See 2011 ¹⁴	Anovulation	6	604	288/341	166/263	CHM: Diff formulae + CC WM: CC Time: 1–4 months	1.34	1.21–1.48	<0.001
	Tan 2012 ¹⁵	Anovulation	11 + 1	1425	653/844	399/581	CHM: Diff formulae WM: CC ± other drugs Time: 3–6 months	1.13	1.05–1.20	<0.001
Basal body temp biphasic	See 2011 ¹⁴	Anovulation	4	315	ng	ng	As above	1.14	1.00–1.29	0.05
	Tan 2012 ¹⁵	Anovulation	3 + 1	650	242/373	175/277	As above	1.03	0.91–1.15	0.66
Endometrial lining >6 mm	See 2011 ¹⁴	Anovulation	2	138	ng	ng	As above	1.78	1.22–2.60	0.003
Cervical mucus score	Huang 2006 ⁴⁷	Anovulation	1	130	59/86 (69%)	16/44 (36%)	CHM: Herb formula WM: CC Time: 6 months	1.89	1.24–2.86	0.003
Pain reduction	Wu 2006 ⁵⁷	Endometriosis	1	95	44/46 (96%)	46/49 (94%)	CHM: oral or oral + enema WM: gestrinone	1.02 ^a	0.93–1.12	0.07
	Wu 2006 ⁵⁷	Endometriosis	1	58	24/40 (60%)	2/18 (11%)	CHM: oral or oral + enema WM: danazol Time: 3 months	5.40	1.43–20.44	0.01
Adnexal mass reduction	Wu 2006 ⁵⁷	Endometriosis	1	48	28/33 (85%)	8/15 (53%)	CHM: oral or oral + enema WM: danazol Time: 3 months	1.59	0.97–2.61	0.07
Effective elimination of tubal obstruction	Pang 2012 ⁵⁶	Blocked fallopian tubes	1	115	45/58 (78%)	18/57 (32%); incl. 2 ectopic pregn.	CHM: 10 herb formula (oral) WM: Intrauterine infusion of 3 drugs ^a , 3 times Time: 3 months	2.46	1.64–3.69	<0.001
Continuing pregnancy >28 weeks gestation	Li 2012 ⁵⁸	Problem in pregnancy: Threatened miscarriage	5	553	287/304 (94%)	181/249 (73%)	CHM: diff formulae WM: Vit E, folic acid, progesterone (<i>n</i> = 4) ^b , and/or HCG (<i>n</i> = 2)	1.28	1.18–1.38	<0.001

CC = clomiphene; diff = different; HCG = human chorionic gonadotropin; ng = not given; Vit = vitamin.

^a Dexamethasone sodium phosphate (corticosteroid), chymotrypsin (digestive enzyme), gentamicin sulphate (antibiotic).^b One study used in the WM treatment group Salbutamol (beta₂ antagonist) and MgSO₄ in addition to Vit E, folic acid, progesterone.

The greatest difference of CHM therapy compared to WM treatment was found in the Pang⁵⁶ trial, which achieved a three-fold higher probability of pregnancy in women with fallopian tube blockage (as confirmed by hysterosalpingography), using a 10 herb vine-derived herbal oral formula (Jiu Teng Zhu Yu) over 3 months compared to intrauterine injections of a cocktail of three drugs (RR = 2.95, 95%CI 1.59–5.45; $p < 0.0001$, Fig. 2). Pregnancy rates were boosted to 52% in the CHM group compared to 18% in the WM group, and tubal patency was restored in 78% of women in the CHM group compared to 32% in the WM group, with 2 out of 10 women suffering an ectopic pregnancy in the WM group and none in the CHM group (Table 2).⁵⁶

Effect of CHM on fertility indicators

In addition to pregnancy rates, a number of trials assessed the effect of CHM on other fertility indicators compared to WM treatment. About half of the trials ($n = 19$) involving 2059 women reported on ovulation rates. A meta-analysis of these trials revealed a 18% increased chance of improved ovulation with CHM compared to standard WM therapy in women with previously anovulatory cycles (RR = 1.18; 95%CI: 1.12–1.25; $p < 0.001$) (Table 2).

Additional outcomes assessed in some of the trials include restoration of biphasic basal body temperature, reestablishment of thickness of the endometrial lining of more than 6 mm, and increase in cervical mucus score in anovulatory women with ovulation problems, all indicators of an environment conducive to a viable pregnancy (Table 2). Treatment with CHM achieved a more favorable environment for pregnancy than WM treatment. Reduction in pain and adnexal mass was assessed in two trials of women with endometriosis. Compared to the WM treatment with danazol, women reported less pain, and a reduction of adnexal mass was observed when treated with CHM, while the WM drug gestri-one had similarly favorable outcomes compared with CHM (Table 2).⁵⁷

Effect of CHM on threatened miscarriage

A Cochrane review by Li (2012)⁵⁸ investigating the effect of CHM on threatened miscarriage in pregnant women using CHM compared to WM drug therapy found a 28% increase in the continuation of pregnancy beyond 28 weeks gestation (RR = 1.28; 95%CI 1.18–1.38; $p < 0.001$, $n = 5$ trials, $n = 553$ women) (Table 2). Continuing pregnancy rates improved to 94% with CHM compared to 73% using WM. As this review looked into the effect of CHM during pregnancy, it was not included in our meta-analysis of the effect of CHM on infertility. However, the review illustrated that CHM therapy can be beneficial beyond conception, and may contribute to improving viable pregnancy and live birth.⁵⁸

Principles of TCM diagnosis and treatment

TCM pattern diagnosis refers to whole body systems such as meridians and involves the Kidney, Liver (Blood), Spleen, Heart, and Lung systems, excess or deficiency patterns, heat or cold patterns. The fundamental treatment principle in TCM is to treat imbalance and restore balance within the body.^{59–63} Observable signs and symptoms, including pulse and tongue diagnosis and menstrual cycle

characteristics, signify a specific TCM pattern diagnosis. Common TCM patterns in women with infertility include Kidney Jing deficiency, Spleen Qi deficiency, Liver Qi stagnation, Phlegm-Dampness, or Blood deficiency. Our previous meta-analysis provided an overview of common TCM pattern in infertility and their manifestations.¹¹

TCM therapy is based on the individual's underlying TCM pattern diagnosis. Conditions associated with infertility, such as PCOS, endometriosis, idiopathic infertility, recurrent miscarriage or unexplained stillbirth, may have similar underlying TCM pattern (e.g. Kidney deficiency Heat), and vice versa, one condition might be caused by different underlying TCM pattern (e.g. PCOS might be due to Kidney Yang deficiency, Blood stasis, or Phlegm-Dampness). Depending on the individual's combination of TCM pattern decoctions of herbal mixtures are formulated.

Examples of Chinese herbal formulae in infertility

TCM pattern diagnosis guides the practitioner toward a treatment with appropriate herbal formulae. A Chinese herbal medicine formula usually contains an average of 10–15 herbs, each of which is characterized by a main action/property, and includes principal, supporting, directing and correcting herbs.

Herbs are categorized by their main actions, e.g. tonify Yang, tonify Yin, tonify Blood, tonify Qi, warm and expel cold, warm and transform Phlegm-Cold (Table 3). Some examples of herbal formulae used to treat conditions associated with infertility and their underlying TCM pattern are provided in Table 4.

For instance, if PCOS is caused by an underlying Kidney Yang and Spleen Qi deficiency, the treatment with a herbal formula will mainly consist of Yang tonifying herbs, as well as other supporting herbs (Table 4). On the other hand, if PCOS is associated with an underlying Blood Qi and Kidney Jing deficiency, the herbal treatment formula would consist of mainly Blood tonifying herbs, as well as other supporting herbs (Table 4).

Similarly, Endometriosis is associated with the TCM pattern of Blood stasis, which has manifested due to other long-term underlying problems, e.g. Blood stasis due to Liver Qi stagnation, Blood stasis due to Kidney Yang deficiency, or Blood stasis due to accumulation of cold. Herbal formulae to resolve Blood stasis contain herbs which invigorate (move) blood and remove stasis, and are combined with herbs addressing the additional associated underlying TCM pattern.

Further examples are listed in Table 4, e.g. the effective formula 'Jiu teng zhu yu' used to resolve fallopian tube blockage (see also Table 2: CHM vs WM effective rate 78% vs 32%)⁵⁶ as well as a popular formula 'Wen jing tang' or 'Un-kei-to' or 'warm the menses decoction') often given to patients with anovulatory problems, e.g. luteal phase defect.

Long-term treatment with Chinese herbal medicine may be approached using different strategies. Some TCM practitioners resort to 'periodic therapy' by using different herbal formulas during different parts of the menstrual cycle (the follicular phase, the ovulation phase, the luteal phase, the menstrual phase), other TCM practitioners prescribe a

Table 3 Glossary.

Blood (xue)	Part of the Organ/Fluid system in TCM. While it refers to the blood, as understood in Western Medicine, Blood is interconnected with other organ systems, e.g. In TCM, Blood is the material form of Qi, it nourishes the body as the substance of Qi.
Damp	Dampness in TCM is a pathogenic condition involving accumulation of fluid in the tissues of the body, manifesting in a feeling of heaviness and swelling, such as in edema.
Phlegm	Accumulated Body Fluids may amass in the creation of Phlegm, e.g. Lung congestion, lumps under the skin, numbness, gall or bladder stones.
Qi	Life force, energy
Stagnation/stasis	Lack of movement, often associated with pain. In TCM, one distinguishes between Blood stasis and (Liver-) Qi stagnation. Stagnant qi manifests as pain and distention and is dull, crampy or colicky. Long-term Qi stagnation can give rise to Blood stasis. Blood stasis is associated with stabbing, sharp, fixed pain, clots in the menstrual discharge.
Yin/Yang	The qualities of Yin are cooling, fluid, nourishing, and material. The qualities of Yang are warming, active, expanding, moving. Yin and Yang should be in a balanced relationship.
Wind	Indicates its exterior origin, can manifest as Wind-Cold or Wind-Heat pattern, e.g. Wind-Cold: sinusitis with runny clears mucus; Wind-Heat: sinusitis with fever and thick yellow mucus
Eight guiding principles of TCM therapy	
Hot/cold	Overall energy of the patient. Cold conditions may be characterized by slow metabolism and chills, cold hand and feet; while hot conditions may have symptoms such as a fast metabolism, higher body temperature, and feelings of heat within the body.
Interior/exterior	Location of the imbalance/disharmony. Exterior conditions are usually short lasting and are caused by germs entering the body. Interior conditions may result from emotional reason or exterior pathogens which have penetrated the inside of the body and affect the internal organs. Diseases caused by an exterior pathogen may begin in the exterior, but in time they may affect the interior, and would be treated as Interior regardless of its etiology.
Deficiency/excess	This principle is used to describe the strength of an illness. A deficient condition is the lack of blood, energy, heat or fluid. An excess condition is where the body has too much of something. Deficient conditions are usually chronic while excess conditions are acute.
Yin/Yang	These are the generalization of all of the above principles and conditions are categorized according to the dominance of the yin or the yang. In general, yin is cold and represents the solid organs, while yang energy is hot and represents the hollow organs.
Eight common therapeutic methods	
Diaphoretic	Dispersion of pathogens from the body's surface
Emetic	Expelling toxic substances via the mouth
Purgative	Relieving the bowels
Regulating	Building the body's resistance to pathogens by controlling body functions
Warming	Eliminating cold and boosting yang
Heat-removing	Diminishing fever and quenching bodily thirst
Tonifying	Nourishing and boosting qi or life energy
Resolving	Invigorate, disperse, move – elimination of accumulated and stagnated qi, blood, phlegm, retained food and fluids that have hardened into lumps

particular herbal formula which addresses underlying TCM pattern for an extended time, adjusting the formula on a 2-weekly, monthly or 3-monthly basis depending on the individual's response to treatment and the formula's main properties.

For example, switching to an ovulation-stimulating herbal formula (Wen-jing-tang also known as Un-kei-to, Table 4) for 8 weeks in a subgroup of 60 Japanese women with PCOS resulted in a marked increase in their ovulation rate (59%) compared to a subgroup of women which did not switch the formula (7%) (RR=8.0, 95%CI: 2.03–31.48; $p=0.0036$).⁶⁴ Clinical studies demonstrated that the Wen-jing-tang formula had definite

endocrinological effects on FSH, LH and estradiol favorable for ovulation.⁶⁵

Standard Chinese Materia Medica list the most common Chinese herbal medicines and list each herb's properties, main actions, contraindications including information about its safety in pregnancy, as well as potential herb-drug interactions.^{66,67}

A large proportion of the contraindicated herbs during pregnancy fall into the TCM category of 'herbs that are invigorating blood and removing stasis', and herbs with a strong descending action, as these can interfere with the woman's ability to "hold" the embryo/fetus. In addition, self-prescription of herbal medicines, in

Table 4 Examples of herbal formulae for conditions associated with female infertility.

WM condition	TCM pattern	Formula	Herbs pinyin	Herbs latin	Herbs main action	Reference
PCOS	Kidney Yang & Spleen Qi def		Tu si zi	Semen cuscuta chinensis	Tonifies yang	Hua 2003 ¹⁷
			Yin yang huo	Herba epimedium grandiflorum	Tonifies yang	
			Du zhong	Cortex eucommia ulmoides	Tonifies yang	
			Tao ren	Semen prunus persica	Invigorates blood, remove stasis	
			Chuan xiong	Rhizoma ligusticum chuanxiong	Invigorates blood, remove stasis	
			Yi yi ren	Semen coicis lachyrma-jobi	Regulates water, drains dampness	
			Che qian zi	Semen plantaginis	Regulates water, drains dampness	
			Dang gui	Radix angelica sinensis	Tonifies blood	
PCOS	Blood Qi & Kidney Jing def		Gou qi zi	Fructus lycium chinensis	Tonifies blood	Shao 2004 ²²
			Dang gui	Radix angelica sinensis	Tonifies blood	
			Bai shao	Radix paeonia lactiflora alba	Tonifies blood	
			Shu di huang	Radix rehmannia glutinosa	Tonifies blood	
			Bu gu zhi	Fructus psoralea corylifolia	Tonifies yang	
			Tu si zi	Semen cuscuta chinensis	Tonifies yang	
			Nu zhen zi	Fructus ligustrum lucidum	Tonifies yin	
			Han lian cao	Herba eclipta prostrata	Tonifies yin	
			Chuan xiong	Rhizoma ligusticum chuanxiong	Invigorates blood, removes stasis	
Endometriosis	Blood Stasis due to Liver Qi stagnation		Zi shi ying	Fluoritum	Anchors, calms, settles spirit	Zhang 2006 ²⁴
			Chuan xiong	Rhizoma ligusticum chuanxiong	Invigorates blood, removes stasis	
			Dan shen	Radix salvia miltiorrhiza	Invigorates blood, removes stasis	
			Chuan niu xi	Radix cyathula officinalis	Invigorates blood, removes stasis	
			Yan hu suo	Rhizoma corydalis yanhusuo	Invigorates blood, removes stasis	
			Xue jie	Resina sanguis draconis	Invigorates blood, removes stasis	
			Mo yao	Resina commiphora myrrha	Invigorates blood, removes stasis	
			Dang gui	Radix angelica sinensis	Tonifies blood	
			Chi shao	Radix paeonia lactiflora rubra	Cools blood	
			Xiang fu	Rhizoma cyperus rotundus	Regulates qi	
			Gui zhi	Ramulus Cinnamomum cassia	Warms, releases the exterior	

Table 4 (Continued)

WM condition	TCM pattern	Formula	Herbs pinyin	Herbs latin	Herbs main action	Reference
Blocked fallopian tubes	Blood Stasis	Jiu teng zhu yu (Vine-derived)	Da xu teng	Caulis sargentodoxae	Clears heat, eliminates toxins	Pang 2012 ⁵⁶
			Ren dong teng	Caulis lonicera	Clears heat, eliminates toxins	
			Huang teng	Caulis fibraureau	Clears heat	
			Qing feng teng	Caulis sinomenii	Dispels wind-damp	
			Luo shi teng	Caulis trachelospermi	Clears wind-damp	
			Shou wu teng	Caulis polygoni multiflori	Dispels wind	
			Tong guan teng	Caulis mardeniae tenacissimae	Dispels phlegm	
			Ji xue teng	Caulis spatholobi	Invigorates blood, remove stasis	
			Tian ji xue teng	Caulis		
			Huang qi	Radix astragali	Tonifies qi	
Anovulation	Blood & Spleen Qi def	Wen jing tang = Unkeito = Warm the menses decoction	Bai shao	Radix paeonia lactiflora alba	Tonifies blood	Ushiroyama 2012
			Dang gui	Radix angelica sinensis	Tonifies blood	
			E zhao	Gelatinum corii asini	Tonifies blood	
			Gan cao	Radix glycyrrhiza uralensis	Tonifies blood	
			Ren shen	Radix ginseng	Tonifies qi	
			Mai men dong	Tuber ophiopogonis japonici	Tonifies yin	
			Gui zhi	Ramulus cinnamomum cassia	Warms, releases the exterior	
			Sheng jiang	Fresh rhizoma zingiberis	Warms, releases the exterior	
			Wu zhu yu	Fructus evodia rutaecarpa	Warms interior, expel cold	
			Ban xia	Rhizome pinellia temata	Transforms phlegm-cold	
			Mu dan pi	Cortex radices moutan	Cools blood	
			Chuan xiong	Rhizoma ligusticum chuanxiong	Invigorates blood, remove stasis	

Herbs in formulae are sorted by herbal action.

Definitions (latin): caulis, stem; cortex, bark; fructus, fruit; radix, root; resina, resin; rhizoma, rootstalk.

Abbreviations: def, deficiency.

particular during pregnancy, is strongly discouraged, and guidance should be sought by an experienced TCM practitioner.

Discussion

Our meta-analysis of 40 RCTs involving more than 4200 women suggests Chinese herbal medicine (CHM) taken over 3–6 months is more effective in the treatment of female infertility than Western medical (WM) drug treatment, achieving on average a 60% pregnancy rate with CHM

compared to 33% with WM. Trials included women with PCOS, endometriosis, anovulation, fallopian tube blockage, or unexplained infertility.

Fertility indicators such as ovulation rates, cervical mucus score, biphasic basal body temperature, and appropriate thickness of the endometrial lining were positively influenced by CHM therapy, creating an environment conducive for a viable pregnancy. Our meta-analysis of a subgroup of trials reporting on ovulation rates revealed a 18% increased chance of improved ovulation with CHM compared to standard WM therapy in women with previously

anovulatory cycles (RR = 1.18; 95%CI: 1.12–1.25; $p < 0.001$, $n = 19$ trial, $n = 2059$ women).

Findings of this updated meta-analysis of the effect of CHM on pregnancy rates including 40 trials and more than 4200 women are in line with our previous meta-analysis of 8 RCTs and 1005 women.¹¹ A number of meta-analyses investigating the effect of CHM on infertility have been published in the last 4 years independently by different authors and including independent RCTs.^{14–16} All meta-analyses found similar 2-fold higher pregnancy rates of CHM treatment compared to WM drug therapy alone, confirming the beneficial effect of CHM therapy on fertility.

Additionally, a recent meta-analysis has shown a supportive effect of CHM therapy as adjunct therapy to IVF, increasing the likelihood of clinical pregnancy two-fold (OR 2.04, 95% CI 1.67–2.49; $p < 0.0001$), as well as ongoing pregnancy (OR 1.91, 95% CI 1.17–3.10; $p < 0.009$).⁶⁸

A strength of this updated meta-analysis is the inclusion of a large number of relevant trials published in Chinese, whereas our previous meta-analysis comprised only trials which had abstracts published in English.¹¹

We were limited in checking data abstraction of primary trials in the three meta-analyses published by others.^{14–16} However, authors of all meta-analyses included in this updated review/meta-analysis stated to have abstracted data and checked trial quality independently by at least two of the researchers.^{11,14–16} Due to limited reporting on trial methodology, trials were rated with low quality scores and are therefore categorized as high-risk-of-bias. Future trials should improve reporting of trial methodology by following the CONSORT statement to facilitate the interpretation of findings with more confidence.⁶⁹

Furthermore, trial data was limited on information about ongoing pregnancy rates and live births, as trials were short-term and did not include follow-up. However, findings of case-series studies are suggesting CHM therapy for improved fertility to result in more stable and viable pregnancies and live births.¹¹

Results of this updated meta-analysis of randomized controlled trials are in line with the findings of relevant cohort studies. Ried¹¹ reported a pooled pregnancy rate of 49% (95%CI: 45–53; $p < 0.001$) in summarizing seven high quality cohort studies of 616 women treated with CHM therapy alone. Furthermore, a recently published cohort study testing an immune-stimulating Chinese herbal formula for one month reported a 1.9-fold increase in improved embryo quality in the early blastocyst stage (good quality: $18.7\% \pm 16.2$ improved to $36.1\% \pm 27.1$; $p < 0.01$) and a 1.4-fold increase in the late blastocyst stage (good quality: $14.8\% \pm 11.2$ improved to $21.1\% \pm 23.1\%$; $p < 0.05$), leading to pregnancy in 33% of cases.⁷⁰

Chinese herbal medicine therapy is based on the underlying TCM pattern diagnosis, which can be elucidated through observed manifestations including pulse and tongue diagnosis and menstrual cycle characteristics by a skilled TCM practitioner.

Observation of the menstrual cycle including basal body temperature, color and flow of the menstrual blood and clot formation, mucus changes, and any associated pain or distension, provide a window into the women's fertility status. A checklist of what constitutes a balanced fertile menstrual cycle has been summarized previously.^{6,59} A balanced

regular menstrual cycle provides a physiological environment conducive to conception, implantation and maintenance of a viable pregnancy. Any irregularities in the menstrual cycle and general wellbeing, often seen in conditions associated with infertility, are fundamental factors which can be optimized before conception is attempted.^{61,62,71} Chinese herbal medicine therapy addresses these imbalances, and therefore strengthens not just egg quality but also other 'environmental' factors, such as the quality of the endometrium.

In addition, to advice on a suitable herbal formula based on the underlying TCM pattern diagnosis, a TCM practitioner would also advise on diet and lifestyle, including healthy weight management, appropriate exercise, and a fertility conducive diet.^{72,73} Foods strengthening Kidney Jing, for example, important for reproductive health and fertility, include chicken, fish, eggs, full-cream milk, seeds, nuts, ghee, oats, and seaweed.⁷³

Diet can support therapy, in the case of Kidney Yang deficiency, for example, warming foods and food preparation methods would be recommended, e.g. warming spices such as ginger, garlic, cinnamon, or rosemary, and yang-increasing food preparation methods such as grilling, roasting, baking, and prolonged braising.⁷³

Conclusions

Our updated meta-analysis suggests Chinese herbal medicine to improve pregnancy rates two-fold compared to Western medical drug therapy in the treatment of female infertility, boosting pregnancy rates from 30% to 60% over 3–6 months. Diagnosis and treatment of underlying TCM pattern when experiencing infertility may reduce time and emotional and potential financial burden of those experiencing infertility.

While our meta-analysis intentionally focussed on the effect of Chinese herbal medicine for female infertility, a review investigating the effect of CHM on male infertility would be warranted.

Conflict of interest statement

The author declares no conflict of interest.

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