



Efficacy of Traditional Chinese Herbal Medicine in the management of female infertility: A systematic review

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KEYWORDS

Infertility;
Traditional Chinese
Herbal Medicine;
Menstrual health;
Pregnancy rate;
Meta-analysis

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.

Methods: We searched the Medline and Cochrane databases and Google Scholar until February 2010 for abstracts in English of studies investigating infertility, menstrual health and Traditional Chinese Medicine (TCM). We undertook meta-analyses of (non-)randomised controlled trials (RCTs) or cohort studies, and compared clinical pregnancy rates achieved with CHM versus WM drug treatment or in vitro fertilisation (IVF). In addition, we collated common TCM pattern diagnosis in infertility in relation to the quality of the menstrual cycle and associated symptoms.

Results: Eight RCTs, 13 cohort studies, 3 case series and 6 case studies involving 1851 women with infertility were included in the systematic review. Meta-analysis of RCTs suggested a 3.5 greater likelihood of achieving a pregnancy with CHM therapy over a 4-month period compared with WM drug therapy alone (odds ratio = 3.5, 95% CI: 2.3, 5.2, $p < 0.0001$, $n = 1005$). Mean (SD) pregnancy rates were $60 \pm 12.5\%$ for CHM compared with $32 \pm 10\%$ using WM drug therapy. Meta-analysis of selected cohort studies ($n = 616$ women) suggested a mean clinical pregnancy rate of 50% using CHM compared with IVF (30%) ($p < 0.0001$).

Conclusions: Our review suggests that management of female infertility with Chinese Herbal Medicine can improve pregnancy rates 2-fold within a 4 month period compared with Western Medical fertility drug therapy or IVF. Assessment of the quality of the menstrual cycle, integral to TCM diagnosis, appears to be fundamental to successful treatment of female infertility.

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Abbreviations: ART, assisted reproductive technologies; BBT, basal body temperature; CHM, Chinese Herbal Medicine; IVF, in vitro fertilisation; RCT, randomised controlled trial; PCOS, polycystic Ovary Syndrome; TCM, Traditional Chinese Medicine; WM, Western Medicine.

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Introduction

Infertility affects 15% or 3 million of couples in Australia and is defined as the inability to conceive or achieve a viable pregnancy after one year of regular unprotected intercourse. 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.^{1,2} 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 2008, for example, more than 61,900 ART cycles were recorded in Australia and New Zealand, and of these 22.6% resulted in clinical pregnancy, and 17.2% resulted in live births.³

IVF treatment is costly, emotionally and financially, for the treated couples and also for the public. The Australian Government's expenditure on ART was about A\$108 million in 2005 or A\$210 million in 2008 due to increasing demand. Costs of one IVF treatment cycle in addition to medications and consultations are about A\$6000–7000 with out-of-pocket costs estimated at A\$3000–4000.^{4,5}

Infertility causes emotional distress and grief for the affected couple.^{6,7} However, there is a dearth of recognition by organisations and the community for couples suffering infertility or recurrent miscarriages, and support services are inferior to those offered for a visible loss of pregnancy such as stillbirth.^{8–11}

Alternative holistic therapies, such as Traditional Chinese Medicine, offer less invasive and less costly physical and emotional treatment compared with standard Western Medical treatment. However, awareness of TCM therapy for infertility is generally low and often not suggested by Western Medical practitioners.^{11,12} The first port of call for most couples experiencing infertility in Australia is General

Practitioners, who routinely refer to infertility clinics for initial investigations and potential IVF treatment.¹³

Traditional Chinese Medicine searches for the individual's underlying imbalances causing the infertility using diagnostic tools such as pulse, tongue, complexion, general physical and emotional wellbeing, and menstrual history. TCM pattern diagnosis determines the specific individual treatment including Chinese Herbal Medicine (CHM) and acupuncture. 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 treatment principle in TCM is to balance any diagnosed imbalance.^{14–18}

A thorough assessment of menstrual history is embedded in standard TCM pattern diagnosis in female infertility, providing a visible window into the woman's (in-)fertility status. The combination of the basal body temperature (BBT) curve, menstrual flow, colour of the menstrual blood and clot formation, mucus changes, and any associated pain or distension are directly related to TCM pattern diagnosis and therefore therapy.^{16,19}

This review summarises current evidence on the efficacy of TCM herbal therapy for the management of female infertility and compares pregnancy rates to those achieved with Western Medical treatment. A practical guide of TCM pattern diagnostic is provided featuring common imbalances underlying infertility in relation to quality of the menstrual cycle and associated symptoms.

Methods

Search strategy

We searched the Medline and Cochrane databases and Google Scholar until February 2010 for abstracts in English

investigating infertility, menstrual health and Traditional Chinese Herbal Medicine therapy using the following search terms: 'Medicine, Chinese Traditional' AND ('Menstruation Disturbances' OR 'Menstrual Cycles' OR 'Menstrual Disorders' OR 'Infertility' OR 'Endometriosis' OR 'Polycystic Ovary Syndrome' OR 'Reproductive Techniques'). In addition, we sourced Google Scholar for books relevant to infertility and TCM and checked reference lists of relevant articles.

Study selection

Types of studies

We included randomised controlled trials (RCTs), controlled trials (CTs), cohort studies (C), case series (CS) and case studies (Case) that investigated treatment of infertility with TCM herbal therapy.

Types of participants

Women of reproductive age with primary or secondary infertility were included. Infertility may have been associated with endometriosis, PCOS, amenorrhea, advanced maternal age, or unexplained infertility. This review excluded studies of male infertility.

Types of interventions

Chinese Herbal Medicine (CHM) treatment defined as treatment with Chinese Herbs according to TCM pattern diagnosis. We included studies which used CHM alone, or in combination with acupuncture (Acu) or Western Medicine (WM) in the form of drugs or surgery. The control group in (R)CTs received WM pharmacological treatment only. In this review we excluded studies using acupuncture alone or TCM therapy (CHM ± Acu) in combination with assisted reproductive technologies (ART).

Types of outcome measures

The primary outcome was clinical pregnancy. We also assessed infertility status (number of years unsuccessful in achieving viable pregnancy), maternal age, CHM treatment duration, WM condition, and TCM pattern diagnosis, and – if available – live birth rate. In addition, we related common TCM pattern diagnosis in infertility to the quality of the menstrual cycle (colour, consistency and flow of blood, frequency, BBT, and associated symptoms including pain), and tongue and pulse appearance.

Data abstraction and quality assessment

Identified studies were assessed against the inclusion criteria and data abstracted independently by two authors, and consensus was reached by discussion. Reporting of study quality of RCTs was assessed using the risk of bias tool described in the Cochrane handbook for systematic reviews of interventions,²⁰ and the Newcastle-Ottawa Quality Assessment Scheme was used to assess quality of cohort studies.²¹ We included case series and case studies in this review for further illustration and reference.

Data analysis

Meta-analysis of RCTs was conducted using the Cochrane Program Review Manager version 5.0.25.²² A random effects model and the inverse variance method were used for comparison of odds ratios between trials while accounting for heterogeneity between trials. We explored robustness of results by sensitivity analysis excluding selected trials with potential risk of bias.

Meta-analysis of cohort studies was conducted using the program Stata version 11.²³ A pooled pregnancy rate of all studies was determined using a fixed model in the 'metan' package in Stata, with weighting of studies by sample size. Heterogeneity was explored by meta-regression analysis of the following variables: mean maternal age, mean length of infertility, mean CHM treatment duration and follow-up. We conducted sensitivity analysis excluding selected studies with potential risk of bias, and used this adjusted pooled estimate for comparison with the pregnancy rates of a cohort of women undergoing IVF.

Publication bias and small study effect for RCTs and cohort studies was assessed by funnel plot and Egger's test.^{24,25}

Case study data were analysed descriptively. Additionally, information on the menstrual cycle and associated symptoms was systematically summarised in relation to TCM pattern diagnosis in infertility.

Results

Study description

A total of 24 articles and 6 books were included in the review featuring 8 RCTs, 13 cohort studies, 3 case series and 6 cases (Fig. 1). The eight RCTs studied 1005 participants,^{26–33} (in 33–36) and the 13 cohort studies involved 793 participants.^{37–49} An additional 53 cases are described in the case series and case studies.^{15–17,19,41,50–52}

Characteristics of included studies are summarised in Table 1. Four of the eight RCTs investigated the effect of CHM alone in comparison to WM medication^{26,27,30,33} and four RCTs compared CHM plus WM medication with WM treatment alone.^{28,29,31,32} Ten cohort studies used CHM therapy alone,^{38,44–49} one combined CHM with acupuncture treatment,⁴² and two cohort studies combined CHM with either antibiotics, steroids³⁷ or standard medication for hyperprolactinaemia.⁴³ CHM alone or in combination with acupuncture was used in the treatment of infertility in the case studies.^{15,19,41,50–52}

Women who participated in the studies were between 18 and 45 years old, with a mean of 30 years. Infertility was experienced on average 4.5 years (range 1–20 years). Treatment duration with CHM was on average 4 months in the RCTs and cohort studies, and 5–6 months in the case studies, ranging from one up to 18 months for some individuals.

Methodological quality

RCTs were considered of sufficient quality to be included in the review if they reported detailed information on the

Table 1 Management of infertility and pregnancy rates using Chinese Herbal Medicine (CHM) therapy.

Study ID	Study design, treatment groups	Age	Infertility	Treatment duration	N	WM condition	TCM pattern diagnosis	Pregnancy outcome
1	Hua 03 ²⁶ RCT TCM: CHM Cont: CC	18–37 yrs (m25.5)	1–20 yrs (m7)	6 mths	107 TCM: 76 Cont: 31	PCOS	Spleen-Shen-Yang deficiency	TCM: 50/76 (66%) Cont: 8/31 (26%)
2	Wu 06a ²⁷ RCT TCM: CHM Cont: Gestrinone	23–45 yrs (m30)	–	3 mths 24 mths follow-up	100 TCM: 48 Cont: 52	Endometriosis, surgery on all before trial	Stagnation of Qi, Blood stasis, Kidney def	TCM: 32/48 (67%), m 7 mths Cont: 29/52 (56%), m 9.5 mths TCM: no side effects Cont: 13/52 (25%) acne, 19 (36.5%) increase in glutamic alanine transaminase, 31 (60%) oligomenorrhea
3	Lin 05 ²⁸ RCT TCM: CHM, Acu and CC, HCG Cont: CC, HCG	20–40 yrs	1–8 yrs	3–6 mths	90 TCM: 48 Cont: 42	PCOS, oligomenorrhea, amenorrhea	Blood stasis, Damp	TCM: 34/48 (71%) Cont: 12/42 (28.5%)
4	Xia 04 ²⁹ RCT TCM: CHM + CC Cont: CC 6 mths follow-up	18–36 yrs (m29)	1–10 yrs	CHM 2 mths + CC 1 mth Cont: CC 1 mth	86 TCM: 46 Cont: 40	PCOS	–	TCM: 24/46 (52.2%) Cont: 9/40 (22.5%)
5	Chen 95 ³⁰ RCT TCM: CHM Cont: prednisolone and Vit E	25–30 yrs (n = 31) 31–40 yrs (n = 49) >41 yrs (n = 5)	≥2 yrs	1–3 mths	85 TCM: 60 Cont: 25 1 yr follow-up	Immunological infertility	Kidney Yin def	TCM: 19/60 (32%) Cont: 6/25 (24%)
6	Shao 04 ³¹ RCT TCM: CHM + CC Cont: CC	23–38 yrs (m28)	2–10 yrs (m3.5)	CHM 15 days + CC 5 days Cont: CC 5 days	62 TCM: 32 Cont: 30	PCOS, Stein–Leventhal syndrome, anovulation PCOS	Blood stasis	TCM: 21/32 (65.5%) Cont: 11/30 (36.6%) Side effects lower in TCM group TCM: 18/28 (64%) Cont: 11/30 (36%)
7	Ren 02 ³² RCT TCM: CHM and CC Cont: TMX and CC	25–35 yrs (m27.8)	2–10 yrs (m3.5)	CHM 2–3 mths; all treated with CC for 6 mths prior	58 TCM: 28 Cont: 30	–	–	TCM: 18/28 (64%) Cont: 11/30 (36%)
8 CT	Zhang 06 ³³ Non-randomised controlled trial TCM: CHM Cont: Danazol (modified testosterone)	–	–	–	417 TCM: 298 Cont: 119	Endometriosis Dysmenorrhea Dyspareunia	Kidney def and Blood stasis	TCM: 182/298 (61%) Cont: 26/119 (22%) Side effects with Danazol: weight gain, acne and elevated liver enzymes Total: 136/343 (40.5%) 1a–d. 93/239 (69.9%) 1a. 42/61 (68.7%) 1b. 8/17 (47.1%) 1c. 2/8 (25%) 1d. 1/4 (25%) 2a. 448/75 (64%) 2b. 2/6 (33.3%) 2c. 2/6 (33.3%) 2c. 3/9 (33.3%) 3. 20/44 (45.5%) 4. 35/ 73 (48%) 5. 3/ 7 (43%) 6. 1/7 (14%) 7. 26/101 (25.7%) 8. 1/7 (14.3%)
C1	Luolan 86 ³⁷ Cohort study CHM and a) antibiotics, steroids (if inflammation); or b) and estrogen/progesterone, thyroxine, vitamins	<30 yrs (n = 164) 31–35 yrs (n = 121) >36 yrs (n = 60)	3–11 yrs (m6.6) 3–5 yrs (n = 164) 6–10 yrs (n = 118) >11 yrs (n = 61)	3 mths	343 incl. a–d: 253 a. 90 b. 17 c. 8 d. 4	1a–d. Functional primary infertility 2. Menses problems 2a. irregular menses, 2b. dysmenorrhea, 2c. amenorrhoea 3. Thin endometrial lining, underdeveloped follicles 4. Cervicitis 5. Vaginitis 6. Endometritis 7. Fallopian tube blockage (Adnexitis) 8. Ovarian mass	1a .Kidney def 1b. Blood stasis 1c. Phlegm-Damp 1d. Other	TCM: 182/298 (61%) Cont: 26/119 (22%) Side effects with Danazol: weight gain, acne and elevated liver enzymes Total: 136/343 (40.5%) 1a–d. 93/239 (69.9%) 1a. 42/61 (68.7%) 1b. 8/17 (47.1%) 1c. 2/8 (25%) 1d. 1/4 (25%) 2a. 448/75 (64%) 2b. 2/6 (33.3%) 2c. 2/6 (33.3%) 2c. 3/9 (33.3%) 3. 20/44 (45.5%) 4. 35/ 73 (48%) 5. 3/ 7 (43%) 6. 1/7 (14%) 7. 26/101 (25.7%) 8. 1/7 (14.3%)

C2	Zhang 01 ³⁸ⁱⁿ¹⁴	Cohort CHM	24–38 yrs	2–10 yrs	3 mths Follow-up 6–12 mths	94	Endometriosis, dysmenorrhea, antibodies against endometrium	Qi def, Blood def	55/94 (58%) 6–12 mths after conclusion of treatment; improvement: no antibodies (86%), no menses pain (72%) a. 18/32 (56%)
C3	Fang 91 ³⁹	Cohort CHM	25–37 yrs (m31)	1.5–8 yrs	3–6 mths	60 incl. 32 follow-up for pregnancy	Luteal phase defect a. Simple b. With complications fallopian tube, sperm antibodies Unexplained infertility	Kidney def	28/50 (56%) clinical pregnancy; 21/50 (42%) viable pregnancies incl. 11 births at end of study, +7/50 miscarriages (14%); preg rate not significantly different in two age groups; no reported side effects
C4	Wing 06 ⁴⁰	Cohort CHM	<35 yrs (n = 18) >35 yrs (n = 32)		6 mths >6 mths if not pregnant, follow-up 12 mths	50	Primary Inf (n = 34, 83%); secondary Inf (n = 7, 17%) Anovulation	No pattern given Qi def, Blood def, Yin def, vacuity cold	30/41 (73%)
C5	Tan 01 ⁴¹ⁱⁿ¹⁴	Cohort CHM	25–30 yrs (n = 28) 31–40 yrs (n = 13)	5–9 yrs (m6); 5 yrs (n = 26); 6–9 yrs (n = 15)	3–12 mths	41	Hyperprolactinaemia, with serum prolactin 30–50 ng/ml (n = 18) Amenorrhea (n = 6)	Kidney def	21/29 (72%); improved ovulation rate (89%) 12/27 (44.4%) 15/18 (83%) serum prolactin normalised 4/6 (67%) with amenorrhea, menses restored
C6	Tian 98 ⁴²	Cohort CHM + Acu	21–41 yrs (m29)	– CC treatment prior to CHM 3–6 mths unsuccessful	1–3 mths	29	PCOS, oligomen (n = 22), amenorrhea (n = 24)	(Artificial periodic therapy)	10/46 (22%); 30/46 (65%) menses restored with biphasic pattern
C7	Usuki 89 ⁴³	Cohort CHM ± bromocriptine	24–38 yrs (m29)	0.5–2 yrs	≥3 mths	27	Recurrent miscarriage (n = 31), endometriosis, pelvic inflammation, ovarian cyst	Blood stasis due to Qi def, Qi stagnation, Cold or Heat	34/41 (83%) ongoing pregnancy rate
C8	He 04 ⁴⁴	Cohort CHM	16–35 yrs (m26)	–	1 mth	46	Mild to medium fallopian tube blockage (21), uterine dysplasia (5), adnexi- tis = inflammation of ovaries (28) Primary Inf: 24 Secondary Inf: 16	Blood def, Qi stagnation, Kidney Yang def, Cold accumulation	37/40 (92.5%) Pregnant after 1 mth: 8; 2 mths: 10; 3 mths: 9; 4–6 mths: 10
C9	Jiang 97 ⁴⁵	Cohort CHM	25–40 yrs; <30 (n = 27), >30 (n = 14)		1–2 mths (m1.5)	41			
C10	Guo 01 ⁴⁶ⁱⁿ¹⁴	Cohort CHM All women received biomedical treatment for tubal patency before CHM	25–38 yrs	2–14 yrs	3–6 mths	40			

Table 1 (Continued)

Study ID	Study design, treatment groups	Age	Infertility	Treatment duration	N	WM condition	TCM pattern diagnosis	Pregnancy outcome
C11 Wang 91 ⁴⁷	Cohort CHM	21–44 yrs (m36)	1–10 yrs (m3)	3 mths	22 of 76 infertile, trying for pregnancy	Endometriosis, dysmenorrhea, nodules/cysts, dyspareunia	Blood stasis	Pregnancy secondary outcome: 3/22 (13.6%) Primary outcome: Improvement in 61/76 (80.3%) incl. dysmenorrhea (89%), dyspareunia (72%), pelvic pain (67%), diminished nodule/cyst size (22%)
C12 Dingling 82 ⁴⁸	Cohort CHM	24–34 yrs (m28)	1–10 yrs (m2.2) (n=15)	1–16 mths (m9)	18	a. Secondary amenorrhea (n=9), b. anovulation (n=3), c. luteal insufficiency (n=6)	Kidney Yin and Yang def	Pregnancy secondary outcome: 6/18 (33.3%) Primary outcome: 15/18 menses improvement (83%) b. 3 regained menses 6× menstrual cycle, flow, luteal function 3× no improvement (age 18, 30, 31 yrs)
C13 Liu 94 ⁴⁹	Cohort CHM	20–29 yrs (n=12); 30–39 yrs (n=21); ≥40 yrs (n=13)	3–13 yrs (m3.5)	6–9 mths	10 of 46 infertile, trying for pregnancy	Endometriosis, dysmenorrhea, nodules, dyspareunia, anal tenesmus	Blood stasis	Pregnancy secondary outcome: 6/10 (60%) Primary outcome: Improvement in 42/46 (91.3%) incl. reduction in dysmenorrhea (98%), anal tenesmus (94%), dyspareunia (87%), nodule size (87%) 22 births
CS1 Lyttleton 04 ¹⁶	Case series CHM + Acu	28–41 yrs (m35.5)	1–14 yrs (m4.5)	1–15 mths (m4)	22	e.g. 1. unexplained, irregular menses, PMS 2. advanced maternal age, 3. recurrent miscarriage, 4. PCOS, 5. endometriosis	1. Kidney Yin + Blood def, or Liver Qi stagn and heat, 2. Kidney Yin def, Heart Liver Fire, or Kidney Yang, Spleen def and Blood stasis, Blood def, 3. Kidney Yang def, 4. Spleen Qi def, Phlegm-Damp accumulation, 5. Blood stasis, Liver Qi stagnation	22 births
CS2 Lewis 04 ¹⁷	Case series CHM + Acu	28–43 yrs (m36)	1–9 yrs (m4)	2–18 mths (m6)	14	e.g. 1. advanced age/premature ovarian failure 2. unexplained, dysmenorrhea, endometriosis, 3. PCOS, 4. anovulation, thin endometrium	1. Spleen and Kidney Jing def, 2. Liver Qi stagn, Blood stasis, 3. Spleen def, Phlegm-Damp, 4. Liver Qi Excess and heat	14 births

CS3	Maciocia 98 ¹⁵	Case series CHM (n=4) CHM+Acu (n=4)	32–40 yrs (m30)	2–6 yrs (m3.4)	3–12 mths (m7.4)	8	e.g. 1. ovarian cysts, 2. recurrent miscarriage, stillbirth, 3. anovulation, coldness PCOS, amenorrhea, recurrent miscarriages PMS, delayed menses	1. Spleen + Kidney Yang def, dampness; 2. Kidney Jing, Spleen, Qi + Blood def; 3. Kidney Yang def, Blood def, cold uterus Liver Qi stagn, with Spleen, Kidney and Lung Qi deficiencies Kidney Yang def with Liver and Heart Fire Kidney Yin def with Blood Heat, Kidney Yang def, Blood stasis	8 births
Case1	Stone 09 ³⁰	Case CHM+Acu	32 yrs	–	12 mths	1			Birth
Case 2	Wood 99 ¹⁹	Case + Acu	34 yrs	5 yrs	10 wks	1			Birth
Case 3	Heese 06 ⁵¹	Case Previous 2 IVF unsuccessful	45 yrs	–	5 mths + during preg until 16 wks	1	Unstable follicular and luteal phase, advanced maternal age		Birth
Case 4	Tan 01 ⁴¹ m14	Case	25 yrs	3 yrs	3 mths	1	Dysmenorrhea	Qi stagn, Blood stasis, weakness of Qi and Blood	Birth
Case 5	Tan 01 ⁴¹ m14	Case	37 yrs	9 yrs	6 mths	1	Delayed menstrual cycle	Qi stagn, Blood stasis, Cold stagnation in Liver channel	Birth
Case 6	Hu 94 ³² m14	Case	28 yrs	3 yrs	6 mths	1	Irregular cycle 25–60 days	Qi stagnation, Blood stasis, Kidney exhaustion, Blood def, Cold in uterus	Birth

Studies are sorted by sample size. (RCTs (1–8) and cohort studies (C1–C7) are included in meta-analyses.

Acu, acupuncture; Cont, control; CC, clomifene; CHM, Chinese Herbal Medicine; Def, deficiency; HCG, human gonadotropin; HSPG, hysterosalpingogram; Inf, infertility; m, mean; mths, months; PCOS, Polycystic Ovary Syndrome; stagn, stagnation; TCM, Traditional Chinese Medicine; TMS, tamoxifen; TOS, time of study; Wks, weeks; Yrs, years; –, not provided

type of intervention (CHM, acupuncture, other intervention), length of treatment, and provided adequate follow-up (<10% loss-to-follow-up). We did not exclude any trials on grounds of inadequate reporting of randomisation procedures, allocation concealment or blinding in (R)CTs.

All cohort studies included in this review reported adequate selection, comparability and outcome assessment: participants were representative of women with infertility in the community; all participants in the intervention group received CHM treatment; and women were not pregnant at the start of all studies, but one trial investigating recurrent miscarriage and maintenance of viable pregnancy.⁴⁵ Cohorts were assessed by comparability of maternal age, length of infertility before treatment, CHM treatment duration, and whether pregnancy was the primary or secondary outcome measure.

Clinical pregnancy status was assessed using medical records. Follow-up in most cohorts was equivalent to treatment time (mean 4 months), which allowed assessment of pregnancy rates, but not birth rates, albeit one cohort study also reported birth rates.⁴⁰ Loss-to-follow up was negligible in all studies.

Meta-analysis of RCTs

The odds of achieving a pregnancy with CHM therapy over a 4-month period were 3.5 times higher (95% CI: 2.34, 5.24, $p < 0.0001$, $I^2 = 42\%$) than with WM drug therapy in women with infertility ($n = 1005$ in 8 RCTs; Fig. 2a). Mean (SD) pregnancy rates in the CHM group were 60% (59.9 ± 12.5) compared with 32% (31.6 ± 9.9) in the WM group.

Sensitivity analysis including seven trials of women diagnosed with PCOS or endometriosis revealed a mean pregnancy rate of 64% (63.9 ± 5.9) in the CHM group versus 33% (32.6 ± 10.3) in the WM group, and an odds ratio of 3.9 (95% CI: 2.65, 5.72, $p < 0.0001$, $I^2 = 31\%$), excluding the trial by Chen 95 of women with immunological infertility.³⁰ Sensitivity analysis of 7 RCTs excluding the non-randomised trial by Zhang 06³³ resulted in an odds ratio of 3.08 (95% CI: 2.01, 4.72, $p < 0.0001$, $I^2 = 28\%$).

Funnel plots and Egger's test of RCTs investigating the effect of CHM on women's infertility indicated no publication bias or small study effect (asymmetric coefficient = -2.28 , $p = 0.187$).

Meta-analysis of cohort studies

Most women participating in the cohort studies had primary infertility and had been diagnosed with a range of WM conditions including PCOS, endometriosis, oligomenorrhea, amenorrhea, dysmenorrhea, luteal phase defect, fallopian tube blockage, pelvic inflammation, hyperprolactinaemia, or unexplained infertility (Table 1).

The pooled pregnancy rate of all 13 cohort studies included in the systematic review involving 793 women treated with CHM therapy for 4.2 ± 2.5 months was 49.1% (95% CI: 45.7, 52.4, $I^2 = 93.5\%$).

Meta-regression analyses of mean maternal age ($p = 0.69$), mean length of infertility ($p = 0.15$), and mean CHM treatment duration ($p = 0.86$) did not explain heterogeneity amongst studies.

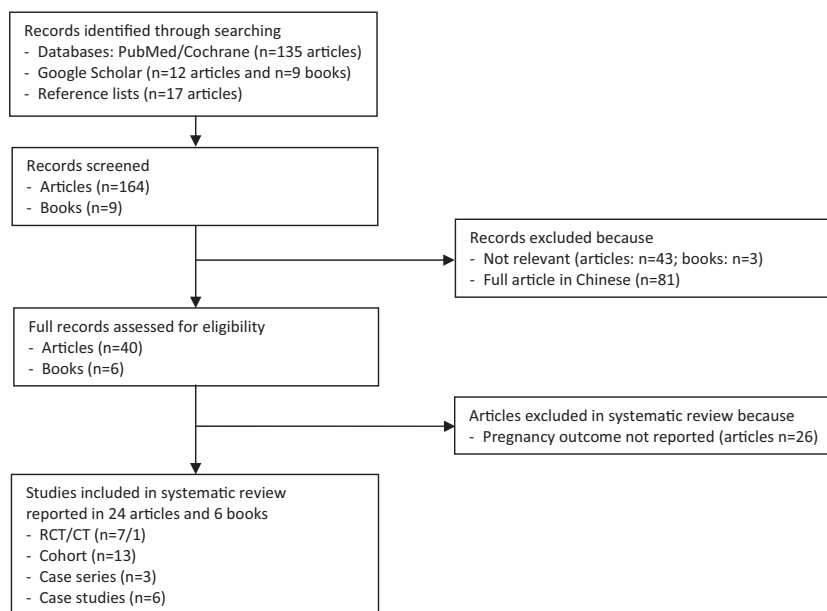


Figure 1 Flow diagram of resources included and excluded in the systematic review. *n*, number; (R)CT, randomised controlled trial.

In the sensitivity analysis we excluded the following six studies with potential risk of bias: pregnancy was a secondary outcome measurement in three studies,^{47–49} one study had a very short follow-up of 1 month,⁴⁴ all participants received biomedical treatment for tubal patency before CHM therapy,⁴⁶ and participants received treatment to avoid miscarriage.⁴⁵

The pooled pregnancy rate of seven cohort studies included in the adjusted meta-analysis involving 616 women treated with CHM therapy was 48.7% (95% CI: 44.7, 52.7, $I^2 = 82.8%$, Fig. 2b), similar to the pooled pregnancy rate of 13 cohort studies with slightly lower heterogeneity.

The adjusted odds of achieving a pregnancy with CHM therapy ranging between 1 and 12 months were 2.3 higher (95% CI: 1.6, 3.4, $p < 0.0001$) compared with the pregnancy rate of 30.4% a cohort of women ($n = 7439$) undergoing IVF in Australia in one year (2008/2009).⁵³

Case series and case studies

Case studies listed in Table 1 illustrate that individual infertility can often be associated with multiple TCM pattern. While there might be a dominating pattern, TCM treatment is dependent on the underlying combination of imbalances. In addition, Table 1 illustrates that a specific condition in WM, such as PCOS, might be associated with different TCM patterns in different individuals. While WM standardises the treatment to a specific illness/condition, TCM aligns the treatment with the underlying imbalance causing the condition.

TCM pattern diagnosis and the menstrual cycle

Common TCM pattern in infertility include Kidney Jing deficiency, Kidney Yin or Yang deficiency, Spleen deficiency,

Blood deficiency, Liver Qi stagnation, Blood stasis, Heat, Cold or Dampness (Tables 1 and 2). Imbalances underlying infertility are visible by observing the characteristics of the menstrual cycle, and are integrated with pulse and tongue diagnosis, and physical and emotional wellbeing (Table 2). The quality of the menstrual cycle is assessed by the appearance (colour, clots) and flow of the menstrual blood, the basal body temperature (BBT) curve, and the length and frequency of the menstrual cycle.

Discussion

Our meta-analyses of RCTs and cohort studies of 1621 women with infertility suggest that the odds of achieving pregnancy with Chinese Herbal Medicine (CHM) are about three times greater than with conventional WM treatment using standard medication or IVF.

Clinical pregnancy rates of about 60% were achieved with Chinese Herbal Medicine therapy over 4 months compared with 30% using WM fertility drug treatment, or IVF over 12 months.

Our review included English-only articles which might have introduced some bias. However, Juni et al. argue that generally there is little effect on summary treatment effect if non-English studies were included in meta-analyses, with effect size changes expected to be less than 5%.⁵⁴ Therefore the effect sizes in our meta-analyses are likely to be reasonably good estimates.

Here we compared approaches to diagnosis and treatment of infertility of two different medical systems (TCM versus WM). Available data did not allow meaningful direct comparison of specific interventions (e.g. a specific herbal formula versus a specific drug), due to fundamentally different diagnostic approaches.

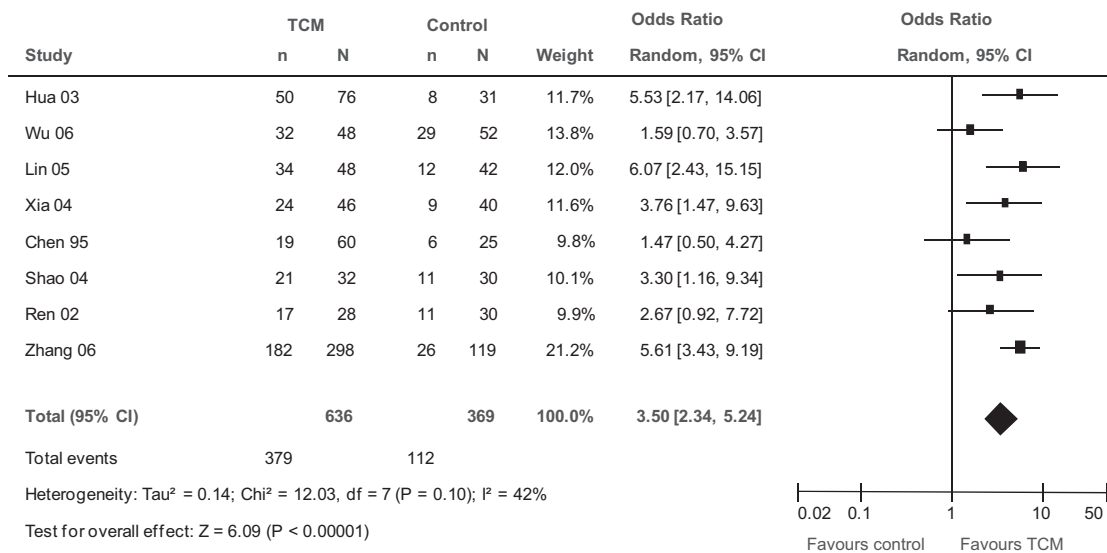
In addition to pulse and tongue diagnosis, TCM uses the characteristics of the menstrual cycle as an essential

Table 2 Common TCM pattern in infertility and manifestations.

TCM pattern	BBT	Quality of menses					Tongue	Pulse	Other symptoms	WM condition
		Colour	Clots	Flow	Frequency	Pain				
Kidney Jing Deficiency	Long follicular phase, low temp luteal phase; unstable; monophasic, little fertile mucus	Pink, watery	No	Scanty	Delayed	Lower back	Pale	Weak thready	Low energy/poor stamina, frequent urination, dark under eyes	Resistant ovary disease, ovarian failure, advanced ovarian age, amenorrhea
Kidney Yin deficiency	Short follicular phase, with higher temp (>36.5°C)	Bright red	No	Scanty	Irregular, shortened	Lower back, knees	Red with little coat, cracked	Thin, floating, rapid	Insomnia, dry throat/skin/hair	PMS, amenorrhea, mild PCOS, premature menopause
Kidney Yang deficiency	Long follicular phase, low temp (≤36.2°C); short luteal phase with low temp	Pale, light pink	Some times	Scanty	Irregular, delayed	Lower back, knees, legs	Pale, swollen	Deep, slow, weak	Pale complexion, fatigue, loose stools, feeling cold, low energy, low libido	Amenorrhea, insufficient progesterone
Spleen Qi deficiency	Slow-rise luteal phase (≥3 days, not usual 1–2 days); short luteal phase	Pink, watery	No	Scanty	Short	Mid-cycle pain	Swollen with white fur	Weak, slippery	Pale face, poor appetite, listlessness, loose stools	Amenorrhea, fibroids
Blood deficiency	Long follicular phase	Bright red	No	Scanty	Delayed	Mild lower abdominal, pressure relieves pain	Pale with little fur	Weak, deep, choppy	Dizziness, sallow complexion, fatigue, muscle spasm, brittle nails	Dysmenorrhea, amenorrhea, PCOS
Liver Qi Stagnation	Slow-rise unstable luteal phase	Dark red/purple	Yes	Scanty	Irregular	Abdominal cramps	Dark red with purple spots	Deep wiry/stringlike or choppy	Mood swings, irritability, headaches, breast distension	PMS, dysmenorrhea, irregular menstruation, amenorrhea
Heat, Kidney Yin deficiency	Follicular phase too short and temp too high	Dark red/purple	Often	Heavy	Irregular, mid-cycle bleeding	Thick itchy leukorrhea	Red, peeled (sides, tip) with yellow coating	Thin, rapid, wiry	Red cheeks, hot palms/soles, hot flushes, insomnia, agitation, weight loss, constipation, thirst, nosebleed	May be associated with hyperactive thyroid, essential hypertension, menopausal symptoms
Liver or Heart Fire	Unstable follicular + luteal phase, sawtooth or saddle pattern	Dark red	Some times	Thick, excessive	Shortened, intermittent bleeding	Abdominal	Red tip	Rapid	Irritability, thirst, restless sleep, headache, red complexion	Metorrhagia/mid-cycle bleeding, PMS
Damp-heat	Monophasic, little fertile mucus	Dark red	No	Scanty, sticky thick, often malodorous	Irregular	Lower abdomen, loins, bloating	Red with thick, greasy yellow fur	Slippery, full, rapid	Dysbiosis in digestive system, no appetite, nausea	Infection, inflammation, endometritis, PID
Phlegm-Damp or Cold-Damp	Long follicular phase, monophasic temp chart	Dark	Yes	Scanty	Delayed	Abdominal distension, pain	Pale with white fur	Deep, fine, slow	Cold limbs, poor appetite, overweight, dull-pale complexion, congested throat, heaviness	Fallopian tube blockage, PCOS, ovarian cysts, amenorrhea, dysmenorrhea
Blood stasis and Dampness	Slow fall of temp at start of cycle	Dark purple	Yes	Heavy	Irregular	Lower abdominal	Purple swollen sticky coating	Wiry, slippery	Low energy, feeling cold, emotional stress, anxiety	Endometriosis, ovarian cysts, fibroids
Cold uterus	Low temp	Dark brown spotting	Some times	Scanty	Irregular	Painful periods	Pale, or purplish	Deep, weak, slow, wiry	Cold limbs, loose stools, frequent urination	Recurrent miscarriage

Refs. 14–18,36.

(A) Meta-analysis of RCTs



(B) Adjusted meta-analysis of cohort studies

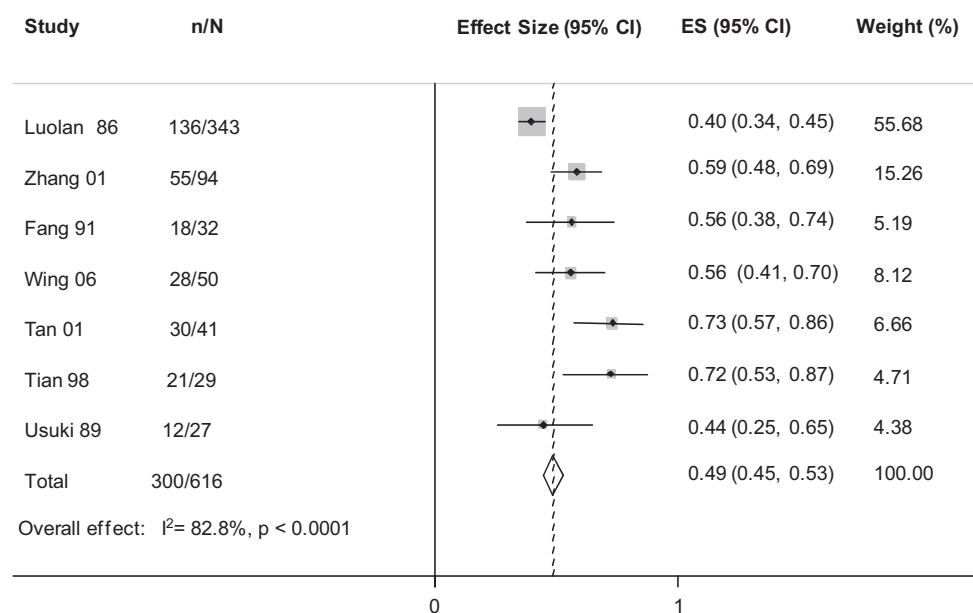


Figure 2 (a) Meta-analysis of RCTs investigating pregnancy rates of infertile women treated with Chinese Herbal Medicine (CHM) compared with WM fertility medications. (b) Adjusted meta-analysis of cohort studies investigating pregnancy rates of infertile women treated with CHM. TCM, Traditional Chinese Medicine; CI, confidence interval; n, number of pregnancies; N, number of women; ES, effect size.

diagnostic tool to ascertain underlying imbalances causing infertility. We have summarised common TCM pattern diagnosis in infertility in relation to the quality of the menstrual cycle and associated symptoms, providing a practical guide to a woman's fertility status for health professionals but also women and couples experiencing infertility.

The fundamental principle of TCM therapy is to restore balance within the body, which affects hormonal regulation

of the menstrual cycle, and provides a physiological environment to facilitate conception, implantation, and maintenance of a viable pregnancy. The quality of the environment in the body is considered as important as the quality of eggs, sperm and embryo. TCM practitioners often refer to the environment, including the endometrium, as the 'soil' and eggs/embryo as the 'seed' (Chinese proverb: "Cultivate the soil before planting the seed").^{14–18} Any irregularities in the menstrual cycle and general wellbeing,

often seen in conditions associated with infertility, including advanced maternal age and unexplained infertility, are fundamental factors which can be optimised before conception is attempted.^{16,17,51}

While the approach to infertility treatment might differ between the TCM and WM model, the desired outcome in both is the achievement of a viable pregnancy. In TCM, the diagnostic and treatment approach to conditions such as PCOS and endometriosis is not any different than to amenorrhea, dysmenorrhea, irregular menses or unexplained infertility.

PCOS, for example, is one of the most common female endocrine disorders affecting approximately 5–10% of women of reproductive age and is thought to be one of the leading causes of female subfertility.⁵⁵ PCOS is associated with amenorrhea or oligomenorrhea, irregular menses, hirsutism, obesity, insulin resistance, acne, hair loss, and infertility. The treatment of PCOS in the WM model involves prescription of the contraceptive pill, anti-diabetic drugs, gonadotropin (glycoprotein hormone), clomiphene (estrogen receptor modulator), sometimes surgery to destruct excess antral follicles, and IVF.⁵⁵ In contrast, TCM therapy uses herbal formulae or acupuncture treatment to restore, nourish, and resolve underlying imbalances associated with PCOS such as Kidney Jing deficiency, Phlegm-Damp accumulation, Liver Qi stagnation, Blood stasis, or Liver fire.^{14–16}

Additionally, 20–30% of women with fertility problems are diagnosed with endometriosis, which is associated with dispersed uterine tissue in the abdominal cavity causing inflammation and adhesions, and can lead to fallopian tube blockage, ovarian cysts and abdominal pain during bowel movements, urination, or sexual intercourse. WM therapy can involve invasive laparoscopy and removal of excess tissue or cysts.⁵⁶ There is no word for 'endometriosis' in TCM classical texts.^{14,33} Instead, the clinical picture is described as dysmenorrhea or abdominal masses. TCM therapy involves the treatment of Liver Qi stagnation, Blood stasis, accumulation of Phlegm, and other potential underlying imbalances.^{14–16}

Women and couples experiencing infertility may benefit from a holistic approach, inclusion of the menstrual cycle as a diagnostic tool, and integration of therapies such as TCM to improve fertility and pregnancy outcomes, shorten treatment time frames, and reduce the emotional and financial burden.

In 2010, a 3-month treatment period with TCM including diagnosis, consultation, herbal formulae and acupuncture cost about A\$600–800 (personal communication with TCM practitioners and TCM practice websites in Australia), whereas an IVF treatment cycle incurred an estimated fee of A\$6000–7000.⁵ Health fund rebates are available for TCM consultations and acupuncture, but not for herbal formulae.⁵⁷ TCM practice in Australia will become more transparent and consistent with the introduction of mandatory registration nationally in July 2012, as currently practiced in Victoria only.⁵⁸

Conclusions

Our meta-analyses suggest Traditional Chinese Herbal Medicine to be more effective in the treatment of female

infertility achieving on average a 60% pregnancy rate over 4 months compared with 30% achieved with standard Western Medical drug treatment, or IVF over 12 months.

The TCM approach to infertility treatment integrates the menstrual cycle as a simple, non-invasive, sensitive, motivational, diagnostic tool to understanding a women's fertility status.

Our findings suggest that the integration of TCM diagnostic tools and therapy in the current WM model of infertility treatment could improve pregnancy rates while reducing treatment time frames and emotional and financial burden.

In this review we focused on the TCM approach and diagnosis of infertility, a review of herbal formulae used in TCM therapy, and comparison of therapies combining TCM and ART/IVF were outside the scope of this review.

Author's contributions

KR conceptualised the study, and undertook data collection, extraction and quality assessment with KS. KR undertook data analysis and interpretation, and prepared the manuscript with contributions from KS. All authors approved the final version.

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