Chinese herbal medicines for unexplained recurrent miscarriage (Review)

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[Intervention Review]

Chinese herbal medicines for unexplained recurrent miscarriage

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ABSTRACT

Background

Recurrent miscarriage affects 1% to 3% of women of reproductive age and mostly occurs before the 10th week of gestation (and around the same gestational week in subsequent miscarriages). Although most pregnant women may not recognise a miscarriage until uterine bleeding and cramping occur, a repeat miscarriage after one or more pregnancy loss and the chance of having a successful pregnancy varies. To date, there is no universally accepted treatment for unexplained recurrent miscarriage. Chinese herbal medicines have been widely used in Asian societies for millennia and have become a popular alternative to Western medicines in recent years. Many clinical studies have reported that Chinese herbal medicines can improve pregnancy outcomes for pregnant women who had previously suffered recurrent miscarriage. This systematic review evaluated the efficacy of Chinese herbal medicines for recurrent miscarriage.

Objectives

To assess the effectiveness and safety of Chinese herbal medicines for the treatment of unexplained recurrent miscarriage.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (01 June 2015), Embase (1980 to 01 June 2015); Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to 01 June 2015); Chinese Biomedical Database (CBM) (1978 to 01 June 2015); China Journal Net (CJN) (1915 to 01 June 2015); China Journals Full-text Database (1915 to 01 June 2015); and WanFang Database (Chinese Ministry of Science & Technology) (1980 to 01 June 2015). We also searched reference lists of relevant trials and reviews. We identified and contacted organisations, individual experts working in the field, and medicinal herb manufacturers.

Selection criteria

Randomised or quasi-randomised controlled trials, including cluster-randomised trials, with or without full text, comparing Chinese herbal medicines (alone or combined with other intervention or other pharmaceuticals) with placebo, no treatment, other intervention (including bed rest and psychological support), or other pharmaceuticals as treatments for unexplained recurrent miscarriage. Cross-over studies were not eligible for inclusion in this review.

Data collection and analysis

Two review authors independently assessed all the studies for inclusion in the review, assessed risk of bias and extracted the data. Data were checked for accuracy.

Main results

We included nine randomised clinical trials (involving 861 women). The trials compared Chinese herbal medicines (various formulations) either alone (one trial), or in combination with other pharmaceuticals (seven trials) versus other pharmaceuticals alone. One study compared Chinese herbal medicines and other pharmaceuticals versus psychotherapy. We did not identify any trials comparing Chinese herbal medicines with placebo or no treatment, including bed rest.

Various Chinese herbal medicines were used in the different trials (and some of the classical the formulations were modified in the trials). The Western pharmaceutical medicines included tocolytic drugs such as salbutamol and magnesium sulphate; hormonal supplementation with human chorionic gonadotrophin (HCG), progesterone or dydrogesterone; and supportive supplements such as vitamin E, vitamin K and folic acid.

Overall, the methodological quality of the included studies was poor with unclear risk of bias for nearly all the 'Risk of bias' domains assessed.

Chinese herbal medicines alone versus other pharmaceuticals alone - the **live birth rate** was no different between the two groups (risk ratio (RR) 1.05; 95% confidence interval (CI) 0.67 to 1.65; one trial, 80 women). No data were available for the outcome of **pregnancy rate** (continuation of pregnancy after 20 weeks of gestation).

In contrast, the continuing **pregnancy rate** (RR 1.27 95% CI 1.10 to 1.48, two trials, 189 women) and **live birth rate** (average RR 1.55; 95% CI 1.14 to 2.10; six trials, 601 women, $Tau^2 = 0.10$; $I^2 = 73\%$) were higher among the group of women who received a combination of Chinese herbal medicines and other pharmaceuticals when compared with women who received other pharmaceuticals alone.

For Chinese herbal medicines and psychotherapy versus psychotherapy alone (one study) - there was a higher **live birth rate** (RR 1.32; 95% CI 1.07 to 1.64; one trial, 90 women) in the group of women who received a combination of Chinese herbal medicines and psychotherapy compared to those women who received psychotherapy alone. No data were available on the continuing **pregnancy rate** for this comparison.

Other primary outcomes (**maternal adverse effect and toxicity rate** and the **perinatal adverse effect and toxicity rate**) were not reported in most of the included studies. Two trials (341 women) reported that no maternal **adverse effects** were found (one trial compared (combined) medicines with other pharmaceuticals, and one trial compared combined Chinese herbal medicine alone versus other pharmaceuticals). One trial (Chinese herbal medicine alone versus other pharmaceuticals alone) reported that there were no abnormal fetuses (ultrasound) or after delivery.

There were no data reported for any of this review's secondary outcomes.

Authors' conclusions

We found limited evidence (from nine studies with small sample sizes and unclear risk of bias) to assess the effectiveness of Chinese herbal medicines for treating unexplained recurrent miscarriage; no data were available to assess the safety of the intervention for the mother or her baby. There were no data relating to any of this review's secondary outcomes. From the limited data we found, a combination of Chinese herbal medicines and other pharmaceuticals (mainly Western medicines) may be more effective than Western medicines alone in terms of the rate of continuing pregnancy and the rate of live births. However, the methodological quality of the included studies was generally poor.

A comparison of Chinese herbal medicines alone versus placebo or no treatment (including bed rest) was not possible as no relevant trials were identified.

More high-quality studies are needed to further evaluate the effectiveness and safety of Chinese herbal medicines for unexplained recurrent miscarriage. In addition to assessing the effect of Chinese herbal medicines on pregnancy rate and the rate of live births, future studies should also consider safety issues (adverse effects and toxicity for the mother and her baby) as well as the secondary outcomes listed in this review. This review would provide more valuable information if the included studies could overcome the problems in their designs, such as lacking of qualified placebo-controlled trials, applying adequate randomisation methods and avoiding potential bias.

PLAIN LANGUAGE SUMMARY

Chinese herbal medicines for unexplained recurrent miscarriage

Recurrent miscarriage has been defined as two, three, or more consecutive spontaneous miscarriages in early pregnancy, and affects a small number (1% to 3%) of women of reproductive age. Many pregnant women may not recognise a miscarriage until they experience uterine bleeding and cramping after the 10th week of pregnancy. There are risks of repeat miscarriages after the first pregnancy loss and the chance of having a successful pregnancy varies. Some recurrent miscarriages have underlying causes, including both maternal and fetal factors; specific treatments targeting these causes are effective. However, the underlying causes may not be identified and most recurrent miscarriage are unexplained. There is no universal recommendation for the treatment of unexplained recurrent miscarriage. Chinese herbal medicines have been widely used in Asian countries for centuries and have become a popular alternative therapy in Western countries in recent years. Many clinical studies have reported that Chinese herbal medicines can improve pregnancy and live birth rates by preventing miscarriage and promoting the continuation of pregnancy.

Different Chinese herbal medicine formulae (Shou Tai Pill, Yangxi Zaitai Decoction, Bushen Antai Decoction and some modified formulae) were used in the trials. The basic formula mostly contained some common Chinese herbal medicines (Chinese Dodder Seed, Chinese Taxillus Twig, Himalayan Teasel Root, Largehead Atractylodes Rhizome, Donkey-hide Glue, Eucommia Bark, Tangerine Peel, Szechwon Tangshen Root, White Paeony Root, Baical Skullcap Root, Mongolian Milkvetch Root, Chinese Angelica, etc). Western pharmaceutical medicines included tocolytic drugs such as salbutamol and magnesium sulphate, hormonal supplementation with human chorionic gonadotrophin, progesterone or dydrogesterone, and supportive supplements such as vitamin E, vitamin K and folic acid.

We searched for evidence on 1 June 2015 and found nine trials (861 women) to assess the effectiveness of the interventions. All trials were methodologically poor and at an unclear risk of bias overall. No trial used placebo, no treatment or bed rest as a control intervention. One trial studied the effectiveness of psychotherapy compared with Chinese herbs.

When Chinese herbal medicines were given in combination with other pharmaceuticals they were associated with higher rates of continuous pregnancy beyond 20 weeks (92.1% versus 72.0%, from two trials, involving 189 women) and live births (79.7% versus 44.2% from six trials, involving 601 women) compared to the other pharmaceuticals alone. Live birth rate was not different when comparing Chinese herbal medicines alone and other pharmaceuticals alone (in one trial, involving 80 women). A comparison of continuing pregnancy rate was not available in this trial. Compared with psychotherapy alone, the live birth rate was higher in the group of women who received a combination of Chinese herbal medicine and psychotherapy (91.1% versus 68.9%).

The majority of studies did not report any information about adverse effects for the mothers or the babies. Only two trials (involving 341 women) reported that no maternal adverse effects were found (one trial comparing (combined) medicines with other pharmaceuticals and one trial comparing combined Chinese herbal medicine alone versus other pharmaceuticals alone). Only one trial (comparing Chinese herbal medicine alone versus other pharmaceuticals alone) reported that there were no abnormal babies either before or after delivery.

No study recorded its limitations in the trial report. It is unclear which Chinese herbal medicines or their combinations are effective.

According to the unique diagnosis and classification of Chinese medicine, the preparations (formulae) may differ according to the subtype of recurrent miscarriage. Most Chinese medicine practitioners modify the classical prescriptions depending on the individual clinical presentations. Some herbal medicines were modified from the classical formula for treatment. Therefore, the conclusion on effectiveness in our study could only represent the overall effects of Chinese herbal medicines on recurrent miscarriage in general. In conclusion, combined Chinese herbal medicines and other pharmaceuticals appear more beneficial than other pharmaceuticals alone for unexplained recurrent miscarriage, but the evidence on the effectiveness and safety of Chinese herbal medicines alone as treatment is unclear.

We found no data to evaluate the safety and toxicity of this intervention for women and their babies and no data for all of our other maternal and infant outcomes. More high-quality studies are necessary to fully evaluate the utility of Chinese herbal medicines for unexplained recurrent miscarriage.

BACKGROUND

Description of the condition

Recurrent miscarriage has been defined as three or more consecutive spontaneous miscarriages in early pregnancy (Cunningham 2010). It affects 1% to 3% of women of reproductive age. Some experts have suggested that two consecutive pregnancy losses are sufficient to define recurrent miscarriage (Branch 2010; Kiwi 2006), because the risk of subsequent loss after two is similar to that following three (Cunningham 2010). The risk of repeat miscarriage after one or more pregnancy losses is still unknown. The best available data suggest that the pregnancy rate after one miscarriage is about 85% (Love 2010), and it significantly decreases to 70% after two miscarriages but remains approximately the same (67% to 70%) after three miscarriages (Ford 2009). The chance of having a successful pregnancy varies (Brigham 1999). Most recurrent miscarriages occur before the 10th week of gestation and around the same gestational week in subsequent miscarriages. However, most pregnant women may not recognise a miscarriage until uterine bleeding and cramping occurs after the 10th week of pregnancy (Wilcox 1988).

Major causes of recurrent miscarriage

The aetiology of recurrent miscarriage remains elusive; both maternal and fetal factors may contribute to underlying causes (ASRM 2008). The identified causes include chromosomal anomalies, mostly translocations (Tharapel 1985) and aneuploidy (ACOG 2001); anatomical defects, such as uterine and cervical abnormalities (Salim 2003); ovarian factors, such as reduced ovarian reserve and luteal phase defect (ACOG 2001); endocrinological factors (Arredondo 2006), such as thyroid disease, progesterone deficiency, polycystic ovarian syndrome, diabetes mellitus, and hypothyroidism; immunological factors (Yetman 1996), such as autoimmune and alloimmune factors; and inherited thrombophilia or abnormal clotting factors (ACOG 2001). Timing of the pregnancy losses may provide a clue to the underlying cause. For instance, genetic factors most frequently result in first-trimester losses, whereas autoimmune and anatomical abnormalities are more likely to result in second-trimester losses (Schust 2002). Physical or emotional trauma, such as depression (Sugiura-Ogasawara 2002), may lead to recurrent miscarriage. Advanced maternal age, history of previous miscarriages, habits such as smoking, caffeine, alcohol, drug abuse, and environmental toxin exposure are associated with an increased risk of recurrent miscarriage (ACOG 2001; Lyttleton 2004). Nevertheless, paternal age and increased DNA damage in sperm may also contribute to recurrent miscarriage (Vagnini 2007). Unfortunately, the underlying cause of more than 50% of recurrent miscarriages cannot be identified and they are classified as unexplained recurrent miscarriage (ASRM 2008). Infection has been associated with recurrent pregnancy loss, though the role of infection is still unclear (ACOG 2001).

Current treatment

For recurrent miscarriage with known cause, current treatments targeting the underlying cause are effective (Cunningham 2010). However, there is no universal recommendation for treatment of unexplained recurrent miscarriage (Cunningham 2010). If undetected or untreated, the affected women with an initial pregnancy loss are at increased risk not only of another miscarriage (Hathout 1982), but also of complications in the subsequent pregnancy, including preterm birth, induced labour, postpartum haemorrhage and maternal distress (Bhattacharya 2008). Current available treatments include weight reduction, caffeine avoidance (Christiansen 2005; van den Boogaard 2010), stress reduction (Craig 2001; Li 2012b), antenatal counselling and psychological support (Musters 2011a), folic acid and vitamin B supplements (Nadir 2007; Sikora 2007), progesterone (Sonntag 2012; Watanabe 2012), and low-dose aspirin (Alalaf 2012; Robinson 2010; Tan 2012). To avoid recurrent causes, pre-implantation genetic diagnosis (Musters 2011b), heparin, metformin (Tan 2012) and immunotherapy (Bansal 2012) have been applied successfully, whereas leucocyte immunisation (Szekeres-Bartho 2009) and immunoglobulin (IVIG) therapy (Kotlan 2009) have not proven to be beneficial.

Description of the intervention

Traditional Chinese Medicine is currently well accepted as a mainstream of medical care throughout East Asia and is considered as a complementary or alternative medicine in Western countries. Chinese medicine is a common name for Chinese Materia Medica which has therapeutic properties for medical treatment and healing. It is considered as a primary modality of internal medicine in Traditional Chinese Medicine.

Chinese medicines have been applied to pregnancy for more than 3000 years (Ma 2006). Chinese medicines are products mostly made of, or from plants, namely Chinese herbal medicines, principally used in China and some Asian countries, and have become popular worldwide to promote both mothers' and fetuses' health and treat common pregnancy disorders and complications, including recurrent miscarriage (Li 2012a). For recurrent miscarriage, Chinese herbal medicines have been used to prevent miscarriage and promoting the continuation of pregnancy. For example, some classical Chinese herbal medicine formulae are Bushen Guchong Pill (Deng 1971), Taishan Panshi San (Zhang 1959) and Liang Di Soup (Fu 1978). In recent decades, new formulae have been developed to improve effectiveness and reduce side-effects, for example, Bushen Gutai San, Jisheng Peiyu Soup, An Tai Pill, San Qing Decoction and Huoxue HuayYu Soup (He 2010). Chinese herbal medicines have also been commonly used as complemen-

tary to Western medicines in the treatment of recurrent miscarriage (Erman 2011).

How the intervention might work

Unlike Western medicine, Traditional Chinese Medicine has a unified theory in diagnosis and treatment of recurrent miscarriage. "Qi" and "Blood" are the two basic elements in the pathology of recurrent miscarriage (Ma 2006). "Qi" is equivalent to vital energy. "Blood" is sustenance of the body. The common causes of recurrent miscarriage in Traditional Chinese Medicine are "Qi" deficiency in "Kidney" or combined "Qi" and "Blood" deficiency (Ma 2006). "Kidney" is responsible for growth, development and reproduction as it stores the essential "Qi" that warms and activates all the other systems in the body (Li 2005). With sufficient "Qi" and "Blood" in "Kidney", the womb will be a warm, safe and comfortable environment where an embryo or fetus could survive and develop (Ma 2006). When "Qi" and/or "Blood" are insufficient, the embryo or fetus cannot be sustained and subsequently miscarried (Ma 2006).

The principle of Traditional Chinese Medicine to treat recurrent miscarriage is to correct the deficiency. Chinese herbal medicines such as Radix Codonopsis Pilosulae (Szechwon Tangshen Root), Rhizoma Atractylodis Macrocephala (Largeheaded Atractylodes Rhizome) and Radix Rehmanniae (Preserved Rehmania Root) are commonly used to correct "Qi" and "Blood" deficiency (He 2010; Ma 2006; Zhang 1959). Chinese herbal medicines are combined as formulae to enhance the therapeutic functions of individual herbs and which as a result, work together to create a more harmonious effect on the body for systemic treatment (Ma 2006; Zhang 1959).

Why it is important to do this review

So far, modern therapies have limited effectiveness in preventing and treating early pregnancy loss due to recurrent miscarriage (Cunningham 2010). Chinese herbal medicines have been used to prevent recurrent miscarriage in Asian countries for millennia and have become an alternative medicine in Western countries in recent years (Li 2011). Many clinical trials have been carried out to assess the therapeutic effects of Chinese herbal medicines as the prevention and treatment of recurrent miscarriage (Li 2011). A list of commonly used Chinese herbal medicines as treatment for recurrent miscarriage is given in Appendix 1. Despite its wide application, there are at present no systematic reviews evaluating the efficacy and safety of Chinese herbal medicines for recurrent pregnancy loss, in particular unexplained recurrent miscarriage.

OBJECTIVES

To assess the effectiveness and safety of Chinese herbal medicines for the treatment of unexplained recurrent miscarriage.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials, as well as cluster-randomised trials comparing Chinese herbal medicines (alone or combined with other intervention or other pharmaceuticals) with placebo, no treatment, other intervention (including bed rest and psychological supports) or other pharmaceuticals as treatments for recurrent miscarriage were eligible for inclusion. No language restrictions were applied.

Types of participants

All pregnant women diagnosed with unexplained recurrent miscarriage, regardless of maternal age, gestational age and parity, were studied. In this review, the definition of recurrent miscarriage used was two or more consecutive spontaneous miscarriages before 20 weeks of gestation. The inclusion criteria also stipulated that there had been no treatment given before the entry into the trials. Only recurrent miscarriage with unknown causes was studied. Trials involving recurrent miscarriage with identified causes were excluded. Any studies in which the prior miscarriages at $\leq$ 14 weeks are included and which cannot be separated from first trimester miscarriages were excluded, as only a minority of embryonic or fetal losses are after 14 weeks.

Types of interventions

All types of Chinese herbal medicines, either alone or in combination with other treatment for recurrent miscarriage, regardless of the dose, method of dosing or duration of administration; the composition of the formulae, were compared with other treatments. The following comparisons were studied.

1. Chinese herbal medicines versus placebo.
2. Chinese herbal medicines versus no treatment.
3. Chinese herbal medicines versus other intervention (including bed rest and psychological supports).
4. Chinese herbal medicines alone versus other pharmaceuticals (mainly Western medicines).
5. Combined Chinese herbal medicines and other pharmaceuticals versus other pharmaceuticals (mainly Western medicines).

Types of outcome measures

Primary outcomes

Effectiveness of intervention

1. Pregnancy rate.
2. Live birth rate.

Pregnancy rate was defined as successful continuation of pregnancy after 20 weeks gestation. It was presented as the percentage of pregnancies alive after 20 weeks of gestation over the total number of participants.

Live birth rate was defined as successful rate of pregnancy with live birth after 28 weeks of gestation. It was presented as the percentage of live birth after 28 weeks of gestation over the total number of participants.

Safety of intervention

1. Maternal adverse effect and toxicity rate.
2. Perinatal adverse effect and toxicity rate.

Adverse effect and toxicity refer to harmful and undesired side-effects and/or toxic effects resulting from the treatment. Specific outcomes of maternal adverse effect and toxicity included maternal death and all reported obstetric and other complications. The rate was presented as the percentage of maternal adverse or toxic events over the total number of participants.

Specific outcomes of perinatal adverse effect and toxicity included perinatal death and all reported complications, premature infant and congenital malformations. The rate was presented as the percentage of perinatal adverse or toxic events over the total number of newborns.

Secondary outcomes

Mother

1. Obstetric complications (haemorrhage, hypertension, etc).
2. Other complications (e.g. dry mouth, gastrointestinal discomfort, etc).

Child

1. Fetal death within 14 weeks of gestation.
2. Fetal death after 14 weeks of gestation.
3. Premature infant (< 37 weeks).
4. Perinatal complications (small-for-gestational age: birthweight < 10th percentile for gestational age, intrauterine growth restriction, physiopathological jaundice, etc).
5. Congenital malformations (e.g. limb anomaly such as polydactyly (congenital abnormality of having an extra finger), heart anomaly such as patent ductus arteriosus, nervous system anomaly for example, spina bifida, etc).

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (01 June 2015).

For full search methods used to populate the Pregnancy and Childbirth Group's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the Cochrane Pregnancy and Childbirth Group in *The Cochrane Library* and select the '***Specialized Register***' section from the options on the left side of the screen.

Briefly, the Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth Group review topic (or topics), and is then added to the Register. The Trials Search Co-ordinator searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that review authors then fully account for in the relevant review sections (Included, Excluded, Awaiting Classification or Ongoing).

In addition, we searched the following databases: Embase (1980 to 01 June 2015); Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to 01 June 2015); Chinese Biomedical Database (CBM) (1978 to 01 June 2015); China Journal Net (CJN) (1915 to 01 June 2015); China Journals Full-text Database (1915 to 01 June 2015); and WanFang Database (Chinese Ministry of Science & Technology) (1980 to 01 June 2015). *See* Appendix 2; Appendix 3 and Appendix 4 for search strategies.

Searching other resources

(1) References from published studies

We searched the reference lists of relevant trials and reviews identified.

(2) Unpublished literature

As some of the trials showed that there would be ongoing studies, we tried to contact the authors for more details if the studies were completed and results were available. We contacted the pharmaceutical companies for more information of the relevant medicines/products.

(3) Personal communications

We contacted organisations, individual experts working in the field, and medicinal herb manufacturers in order to obtain additional references.
We did not apply any language or date restrictions.

Data collection and analysis

Selection of studies

To determine which clinical trials to include, we screened the titles, abstracts, and keywords of the trials identified by the search. Two review authors (LL and LD) independently assessed each trial for inclusion and any disagreements were discussed. If the disagreements could not be resolved, we contacted the trial authors for clarification. We did not blind the review authors to the journal of origin or institution.

Data extraction and management

We designed a form to extract data, and two review authors (LL) and (LD) extracted the data using the agreed form for study eligibility. We resolved discrepancies through discussion or consulted the third review author (CCW). We entered data into Review Manager software (RevMan 2014), and checked for accuracy. We assessed the abstracts in the same way as full papers, then included them in the analyses. We excluded trials that did not meet our eligibility criteria (or as a result of the study authors' replies to our queries) and noted the reasons for exclusion in the Characteristics of excluded studies table. We planned that if authors of original reports did not immediately provide information, we would add these studies to 'Studies awaiting classification' and reconsider these studies for inclusion if the authors provided more information or once the full publications became available to confirm our queries.

Assessment of risk of bias in included studies

Two review authors (LL and LD) independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).Any disagreements were resolved by discussion or by involving the third assessor (CCW).

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at a low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods used to blind outcomes assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included the missing data in the analyses which we undertook.

We assessed the methods as:

- low risk of bias (e.g. no missing outcome data or less than 20% missing; missing outcome data balanced across groups);
- high risk of bias (e.g. number or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we have about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We planned to explore the impact of the level of bias through undertaking sensitivity analyses - see Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

Not applicable for this version of the review.

Unit of analysis issues

Only one multi-arm trial (Yuan 2013) (three arms Chinese herbal medicines alone, other pharmaceuticals alone, combined Chinese herbal medicines and other pharmaceuticals) was included and is described in the Characteristics of included studies table. We carried out comparisons between each arm. We did not undertake any subgroup analysis or pair-wise comparisons.

Dealing with missing data

For included studies, we noted levels of attrition. We planned to explore the impact of included studies with high levels of missing data for the overall assessment of treatment effect by using sensitivity analysis (*see* Sensitivity analysis below).

For all outcomes, we carried out analyses, on an intention-to-treat basis; we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the total number of participants randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if the T^2 was greater than zero and either an I^2 was greater than 30% or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

In future updates of this review, if there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials.

For random-effects analyses, the results were presented as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

Due to lack of data we were unable to carry out any of the prespecified subgroup analysis. In future updates of this review, if more data become available, we will carry out the following prespecified subgroup analyses:

1. maternal age: below 35 versus 35 and above;
2. gestational age at intervention with Chinese herbal medicines started: < 14 weeks versus ≧ 14 weeks;
3. numbers of prior recurrent miscarriage: two consecutive miscarriages versus more than two consecutive miscarriages;
4. type of herbal medicines: standard herbal medicines versus non-standard herbal medicines, according to the formulary stated in the Chinese Pharmacopeia;
5. timing of intervention: before pregnancy versus after pregnancy;
6. duration of intervention: short-term treatment (one course only) versus long-term treatment (more than one course);
7. study design: quasi-randomised clinical trials versus randomised clinical trials;
8. main types of recurrent miscarriage in Chinese medicine: "Qi" deficiency in Kidney versus combined "Qi" and "Blood" deficiency.

In future updates of this review, we will use the following outcomes in subgroup analysis:

1. pregnancy rate and live birth rate.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the X^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

It was not possible to carry out planned sensitivity analysis, all trials were at rated as unclear risk of bias for almost all 'Risk of bias' domains - apart from 'attrition bias' where we rated all studies as having a low risk of bias. In future updates, if appropriate, we will carry out sensitivity analysis to explore the effect of trial quality on important outcomes in the review. Where there is a high risk of bias in the allocation of participants to groups associated with a particular study or high levels of missing data, we will explore this by sensitivity analysis (Higgins 2011).

We will use the following outcomes in sensitivity analysis:

1. effectiveness of intervention: pregnancy rate and live birth rate;
2. pregnancy loss (before and after 14 weeks);
3. preterm delivery (less than 37 weeks);
4. multiple pregnancy;
5. obstetric complications (haemorrhage, hypertension, intrauterine growth retardation);
6. maternal morbidity;
7. prenatal morbidity.

RESULTS

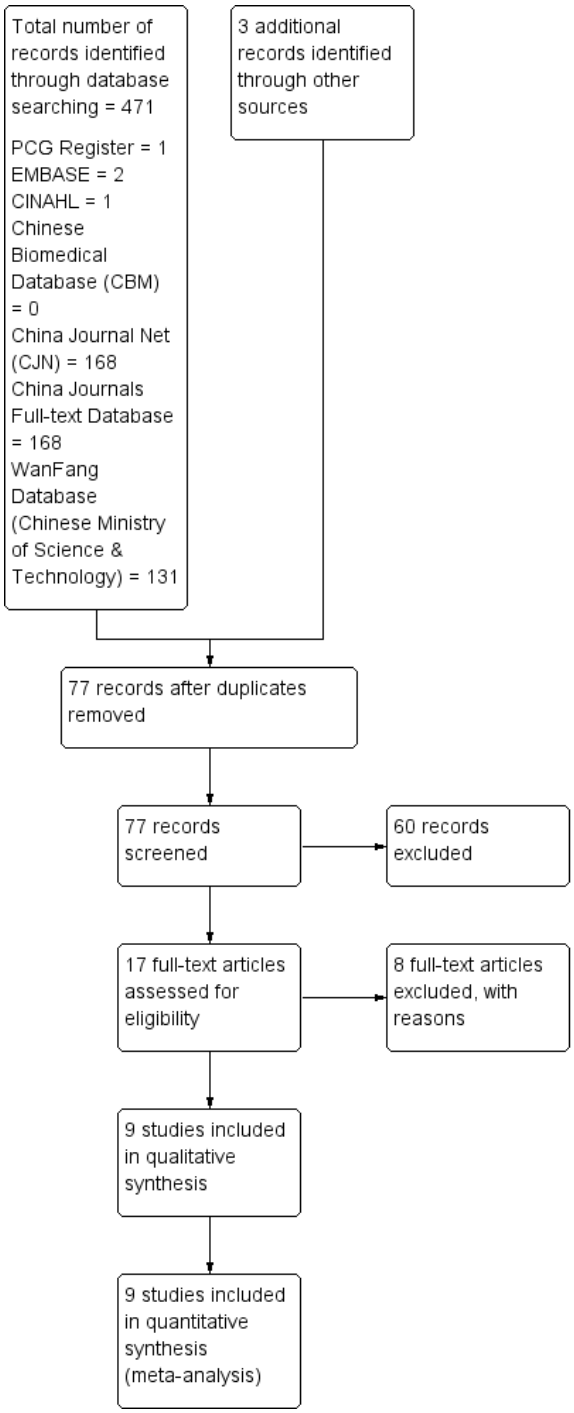
Description of studies

Seventy-seven clinical trials of Chinese herbal medicines for unexplained recurrent miscarriage were identified; only 17 trials were eligible for detailed review. Nine trials were included and eight trials were excluded.

Results of the search

Up to 01 June 2015, we identified 474 trial reports (see Figure 1). Most reports were obtained from China Journals Full-text Database, China Journal Net (CJN) and WanFang databases. There were 299 duplicate publications. After screening the titles and abstracts of the rest of the publications, we further excluded 60 reports. They were case reports, case series, commentary articles and other reviews. We assessed 17 full-text articles for eligibility, eight of which we excluded. In this review; we included nine studies for meta-analysis.

Figure 1. Study flow diagram.



Included studies

Nine trials (861 women) were included for assessment and meta-analysis. For more information see Characteristics of included studies

Study design

All of the included studies were declared as randomised controlled trials, but only one study reported the details of randomisation methods. Eight trials had two arms (Fan 2010; Guo 2013; Li 2000; Luo 2013; Qu 2012a; Qu 2012b; Wei 2013a; Zhang 2013), and one trial (Yuan 2013) had three arms.

Participants

All the study participants were pregnant Chinese women diagnosed with recurrent miscarriage (before 14 weeks of gestation) with a history of at least two spontaneous abortions (without any underlying cause being identified) and receiving no treatment before the study commenced. The studies were carried out in different cities in mainland China, mainly in provincial and municipal hospitals of the main cities.

Interventions and comparisons

Two trials compared Chinese herbal medicines alone with other pharmaceuticals alone (Wei 2013a; Yuan 2013), seven trials (Fan 2010; Guo 2013; Li 2000; Luo 2013; Qu 2012a; Yuan 2013; Zhang 2013) compared combined Chinese herbal medicines and other pharmaceuticals with other pharmaceuticals alone. One trial (Qu 2012b) compared Chinese herbal medicines alone with psychotherapy. We did not identify any trials comparing Chinese herbal medicines with placebo or no treatment, including bed rest. The formulae of Chinese herbal medicines were different in each study, but basic composition consisted of 12 common Chinese herbal medicines, including Chinese Dodder Seed; Chinese Taxillus Twig; Himalayan Teasel Root; Largehead Atractylodes Rhizome; Donkey-hide Glue; Eucommia Bark; Tangerine Peel, Szechwon Tangshen Root, White Paeony Root, Baical Skullcap Root, Mongolian Milkcetch Root, Chinese Angelica. Other pharmaceuticals were mainly common Western medicines including tocolytic drugs (e.g. magnesium sulphate and salbutamol), hormonal supplementations (e.g. human chorionic gonadotropin (HCG), progesterone and dydrogesterone tablets), and supportive supplements (e.g. vitamin E, vitamin K and folic acid).

Follow-up

All the included trials followed up the participants until the end of the treatments. Amongst these included trials, eight trials (Fan 2010; Guo 2013; Li 2000; Luo 2013; Qu 2012b; Wei 2013a; Yuan 2013; Zhang 2013) followed up the participants until delivery, two trials (Li 2000; Qu 2012a) followed up the participants until the 28^{th} week of gestation. Two trials (Guo 2013; Wei 2013a) studied and reported the safety of the interventions.

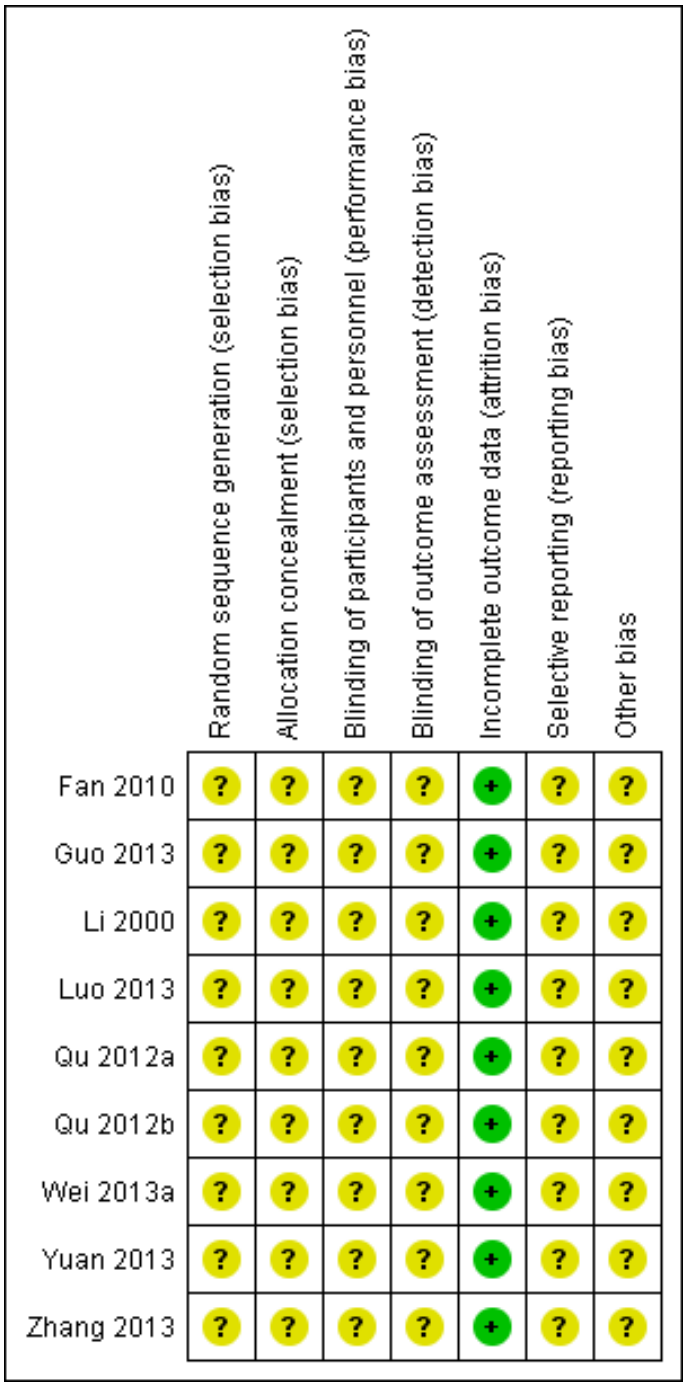
Excluded studies

Eight trials were excluded because the endpoint information was insufficient or inadequate for our meta-analysis in five trials (Wang 2013; Wei 2013b; Xu 2013; Zhang 2011; Zhang 2012); and different pharmaceuticals were used in the combined medicines and control in three trials (Chen 2013; Liu 2014; Yuan 2004). See Characteristics of excluded studies.

Risk of bias in included studies

Overall, the nine included studies were at an unclear risk of bias for almost all of the 'Risk of bias' domains (apart from attrition bias) due to insufficient information upon which to make a formal assessment. See Figure 2 for a summary of 'Risk of bias' assessments.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All the included studies reported that the participants were randomised to respective treatments without giving further details. One study (Li 2000), reported a detailed randomisation method; "2:1 ratio randomisation was applied". None of the included trials reported the details of the allocation methods. All studies were rated as 'unclear' risk of bias for sequence generation and allocation concealment.

Blinding

No information on blinding (of participants/personnel or outcome assessors) was provided in the trial reports and all studies were assessed as unclear of bias for performance bias and detection bias.

Incomplete outcome data

All of the nine studies were assessed as low risk of attrition bias. No exclusions or losses to follow-up were reported in the included studies. After checking the total number of participants and the patients included in each intervention group, there were no missing data in all the studies.

Selective reporting

All nine studies were assessed as unclear risk of reporting bias, since their protocols were not available.

Other potential sources of bias

All nine studies were assessed as unclear risk of other potential bias. All included studies followed up the participants until the end of treatment (which was pre-specified in the studies), some of which followed up the mothers after delivery and the newborn, but the data were not comprehensive. Six studies (Fan 2010; Guo 2013; Qu 2012a; Qu 2012b; Wei 2013a; Yuan 2013) reported that there were no significant differences amongst the groups before the interventions, and were considered to have good baseline similarity. However, other aspects of bias were still unclear.

Effects of interventions

Nine studies with 861 women were included in the review (Fan 2010; Guo 2013; Li 2000; Luo 2013; Qu 2012a; Qu 2012b; Wei 2013a; Yuan 2013; Zhang 2013). We did not find any studies that compared Chinese herbal medicines with placebo or no treatment (including bed rest). All included studies compared Chinese herbal medicines with other interventions (psychotherapy and pharmaceuticals, mostly Western medicines).

Three comparisons were available: Chinese herbal medicines alone versus psychotherapy alone; Chinese herbal medicines alone versus other pharmaceuticals alone; combined Chinese herbal medicines and other pharmaceuticals versus other pharmaceuticals alone.

Chinese herbal medicines alone versus other pharmaceuticals alone

Primary outcomes

1. Effectiveness of the intervention

1) Pregnancy rate

No information related to pregnancy rate was mentioned in all trials and no data could be extracted for further meta-analysis.

2) Live birth rate

There was no difference between Chinese herbal medicines and other pharmaceuticals (risk ratio (RR) 1.05; 95% confidence interval (CI) 0.67 to 1.65, one trial (Yuan 2013), 80 patients, P = 0.82, Analysis 1.1). No information related to live birth rate was reported in the other trial (Wei 2013a).

2. Safety of intervention

1) Maternal adverse effect and toxicity rate

Side-effects of drugs were not observed in both interventions groups in one trial (Wei 2013a) and relevant laboratory examinations of these pregnant women after treatments were reported to be normal. Harmful and undesired side-effects and/or toxic effects on the mother after treatment were not studied or reported in the other trial (Yuan 2013).

2) Perinatal adverse effect and toxicity rate

No abnormal fetuses were reported in the ultrasound examination at 18 to 24 gestational weeks and after delivery in Wei 2013a. Harmful and undesired side-effects and/or toxic effects on both fetuses and newborns or infants after treatment were not studied and reported in Yuan 2013.

Secondary outcomes

Due to the lack of detailed information on obstetric complications and other complications of the mother and fetal death, premature infant, perinatal complications and congenital malformations, it was not possible to carry out analyses on secondary outcomes.

Combined Chinese herbal medicines and other pharmaceuticals versus other pharmaceuticals alone

Primary outcomes

1. Effectiveness of intervention

1) Pregnancy rate

Combination of Chinese herbal medicines and other pharmaceuticals was more effective than other pharmaceuticals alone in terms of successful continuation of pregnancy until after 20 weeks of gestation, 92.1% versus 72.0%, respectively (RR 1.27 95% CI 1.10 to 1.48, two trials (Li 2000; Qu 2012a), 189 women, P = 0.002, Analysis 2.1).

2) Live birth rate

Combination of Chinese herbal medicines and other pharmaceuticals was more effective than other pharmaceuticals alone on the successful rate of pregnancy with live birth after 28 weeks of gestation, 79.7% versus 44.2%, respectively (average RR 1.55; 95% CI 1.14 to 2.10; six trials (Fan 2010; Guo 2013; Li 2000; Luo 2013; Yuan 2013; Zhang 2013), 601 women, $Tau^2 = 0.10$; $I^2 = 73\%$; P = 0.005, Analysis 2.2). Subgroup analysis was not possible due to insufficient information.

2. Safety of intervention

1) Maternal adverse effect and toxicity rate

Only one study (Guo 2013) reported the safety of interventions on the pregnant women. No complications or adverse effects were observed in both intervention groups, hence it was not possible to carry out any further analyses.

2) Perinatal adverse effect and toxicity rate

Harmful and undesired side-effects and/or toxic effects on both fetuses and newborns or infants after treatment were not studied and reported in these trials.

Secondary outcomes

Due to the lack of detailed information on obstetric complications and other complications of the mother and fetal death, premature infant, perinatal complications and congenital malformations, it was not possible to carry out analyses for any of this review's secondary outcomes.

Combined Chinese herbal medicines with psychotherapy versus psychotherapy alone

Primary outcomes

1. Effectiveness of intervention

1) Pregnancy rate

No information related to pregnancy rate was mentioned in this trial (Qu 2012b) and no data could be extracted for further meta-analysis.

2) Live birth rate

In the Qu 2012b study, effectiveness was defined as pregnancy sustained until term delivery. The live birth rate was higher among the women who received a combination of Chinese herbal medicines and psychotherapy compared with the group of women who received psychotherapy alone (91.1% versus 68.9%, respectively, RR 1.32; 95% CI 1.07 to 1.64, one trial (Qu 2012b), 90 patients, P = 0.01, Analysis 3.1).

2. Safety of intervention

1) Maternal adverse effect and toxicity rate

Harmful and undesired side-effects and/or toxic effects on both fetuses and newborns or infants after treatment were not studied or reported in (Qu 2012b).

2) Perinatal adverse effect and toxicity rate

Harmful and undesired side-effects and/or toxic effects on both fetuses and newborns or infants after treatment were not studied and reported in (Qu 2012b)

Secondary outcomes

Due to the lack of detailed information on obstetric complications and other complications of the mother and fetal death, premature infant, perinatal complications and congenital malformations, it was not possible to carry out analyses for any of this review's secondary outcomes.

DISCUSSION

Chinese herbal medicine is regarded by the public and some healthcare providers as effective, gentle and safe (Marcus 2005), and is also accepted as an alternative treatment for recurrent miscarriage in most Asian countries (Vidor 2011). The therapeutic effects of Chinese herbal medicine on the improvement of pregnancy and live birth rate by preventing miscarriage and promoting the continuation of pregnancy have been studied and reported (Li 2012). This review (nine studies, involving 861 women) was aimed to evaluate the effectiveness and safety of Chinese herbal medicines as a treatment for women who have unexplained recurrent miscarriage.

Summary of main results

Effectiveness

In all nine included clinical trials, the average effective rate (the live birth rate and the pregnancy rate) of Chinese herbal medicines treatment for unexplained recurrent miscarriages was recorded as around 88%. In seven trials, the birth rate was around 70% in five trials of the nine trials (Fan 2010; Guo 2013; Luo 2013; Yuan 2013; Zhang 2013). In three of the nine trials (Li 2000; Qu 2012a; Qu 2012b) the pregnancy rate was as high as 91%.

The most valuable and important comparison to evaluate a medicine (including Western medicines and Chinese herbal medicines) is with placebo or no treatment, but no such trial was identified in our review. The meta-analysis indicated that Chinese herbal medicine combined with other pharmaceutical approaches was associated with a higher rate of pregnancy than pharmaceuticals alone. In terms of the number of live births, a combination of Chinese herbal medicines with either other pharmaceuticals or psychotherapy was also associated with a higher rate of live births compared to other pharmaceuticals or psychotherapy alone. The results indicate that Chinese herbal medicines may enhance the therapeutic effects of other pharmaceuticals in the treatment of unexplained recurrent miscarriage.

Our analyses indicated that a combination of Chinese herbal medicines with other therapeutic approaches (psychotherapy or other pharmaceuticals) was associated with higher pregnancy live birth rate than other approaches as stand alone treatments (psychotherapy or other pharmaceuticals alone) for unexplained recurrent miscarriage. In contrast, the rate of live births was not different in two small studies (n = 151) comparing Chinese herbal medicines alone with other pharmaceuticals.

Safety

All medicines, including Chinese herbal medicines, may be associated with some risk. Chinese herbal medicines are claimed to be safe if used properly, but there was insufficient data to assess the safety of this intervention.

Furthermore, the active components in the Chinese herbs are also chemicals which are similar to prescribed pharmaceuticals. Some individual Chinese herbal medicines are associated with potential adverse effects. There are 31 Chinese herbal medicines that are classified as toxic and contraindicated during pregnancy, and these are listed in the Chinese Pharmacopeia. It is generally accepted by all Chinese medicine practitioners that the potential adverse effects and toxicity of Chinese herbal medicines can be reduced or eliminated by prescribing according to prescribed formulae and correctly adjusting the doses and constituent parts. Nevertheless, scientific evidence in relation to the safety Chinese herbal medicines in this condition is scant.

From the methodology applied in the included clinical trials, we found that safety issues were not considered. Our primary outcomes of maternal adverse effect and toxicity rate and perinatal adverse effect and toxicity rate were not reported in detail in any of the included studies (although two studies (Guo 2013; Wei 2013a) reported that there were no adverse effects or toxicity to mothers and fetuses in either of the groups.

There were no data available in relation to any of this review's secondary outcomes.

Overall completeness and applicability of evidence

For recurrent miscarriage with known causes, there are a variety of accepted treatments. However, for unexplained recurrent miscarriage, many approaches remain controversial. In this review, although we did not identify any controlled trials comparing Chinese herbal medicine with placebo or no treatment (including bed rest), our results suggest that combined Chinese herbal medicines with other approaches (psychotherapy and other pharmaceuticals) were more effective than other approaches alone but with a major caveat; the quality of the evidence is poor. Chinese herbal medicines may be useful as an alternative therapy or supplement

in the treatment of unexplained recurrent miscarriage. However, more high-quality studies are necessary to further elucidate the role and effectiveness and safety of Chinese herbal medicines as a treatment.

Quality of the evidence

Regarding to the quality of these included clinical trials as an evidence for this review, there are many limitations.

1. Quality of methodology

A well-conducted randomised controlled trial should follow the international standard, including sufficient details of randomisation method and adequate allocation concealment, double-blinded participants and clinicians or researchers and outcome assessors, participant classifications, and effects assessments. However, all the selected trials in this review had poor methodological quality. Some important demographic information was not provided. Many trials only generally mentioned "randomization was applied" in their studies, but no details of the randomisation, allocation and concealment methods were reported. Blinding is difficult to be applied in Chinese medicine studies, as most of the patients expected to receive Chinese medicine therapy if they decide to see a Chinese medicine doctor. Many would not accept the possibility of receiving placebos or Western medicines.

2. Study design

A well-designed clinical trial on Chinese medicine should describe or provide the information of the hypothesis, the baseline information of participants, the recruitment criteria, diagnosis criteria by Chinese medicine theory, clear information on study and control groups, the duration of interventions and the proper outcome measurements. However, the study designs of the included clinical trials failed this test of quality. For example, some of the studies did not follow up the pregnancy until delivery, which made the outcome parameters on live birth rate difficult to interpret or extract. Most trials did not assess or monitor the potential side-effects as a study outcome. This may be due to lack of awareness on the safety issue of Chinese herbal medicines in general. None of the secondary outcomes that were pre-specified in our protocol were reported in the included studies. Owing to the limited information, additional subgroup meta-analysis was not available. Furthermore, the lack of placebo-controlled trials made it impossible to draw any conclusion on the safety of Chinese herbal medicines as treatment for recurrent miscarriage.

3. Result report and analysis

Most of the included trials did not report drop-outs. We inferred there were no drop-outs by checking the numbers of participants from the beginning of the clinical trial to the end of the study. A well-reported result should include clear information and data of the drop-out rate. As the endpoints of clinical trials were not consistent, each individual clinical trial could still be analysed individually, but it is difficult to combine all the relevant data and perform a meta-analysis. However, registration of clinical trials is not yet widely implemented in China, and we could not obtain or access the original protocol of the clinical study.

4. Conclusions of the included studies

All studies reported the therapeutic effects of the intervention, but no study recorded its limitations in the discussion or conclusion section of the trial report. According to the unique diagnosis and classification of Chinese medicine, the formulae may differ according to the subtype of recurrent miscarriage. Most Chinese medicine practitioners would slightly modify the classical prescriptions depending on the individual clinical presentation. Some Chinese herbal medicines have been added to, or removed from, the classical formula during treatment. Therefore, the conclusion on effectiveness in our study could only be in general terms and not for individual Chinese herbal medicine or specific formula.

In summary, the selected clinical trials were eligible for this review, but the overall quality of the studies was poor. The studies varied considerably in methodology, so the scientific evidence for the effectiveness and safety of Chinese herbal medicines as treatment for recurrent miscarriage is limited. Standard workflows are necessary to lead to better clinical trial design for Chinese herbal medicine studies.

Potential biases in the review process

During the process of review, we tried to prevent and avoid any potential biases. In the literature search, we applied a very general term instead of specific term such as keyword or MeSH to include all the relevant studies on Chinese herbal medicines for recurrent miscarriage. In the study screening part, two review authors independently read all the full texts. All the full texts were in Chinese, and the review authors were fluent in Chinese, so no potential selection bias was likely. In order to obtain data for our review and meta-analysis, two review authors strictly followed the extraction form and extracted the data independently. For input of the data for meta-analysis in RevMan 2014, a third person who had no academic knowledge of both Chinese herbal medicines and miscarriage completed the work.

Agreements and disagreements with other studies or reviews

To date, there have been very few reviews on the application of Chinese herbal medicines for recurrent miscarriage. Most focus

on the types of recurrent miscarriage in Chinese medicines or give guidance on Chinese herbal medicines formulae as treatments for different types of recurrent miscarriage.

No other systematic review is available that has attempted to provide an overview of the effectiveness and safety of Chinese herbal medicines for recurrent miscarriage, especially unexplained recurrent miscarriage. This review provides a comparison between Chinese herbal medicines and other therapies for unexplained recurrent miscarriage. However, the poor quality of clinical trials has been previously documented.

AUTHORS' CONCLUSIONS

Implications for practice

We found limited evidence (from nine studies with small sample sizes and an unclear risk of bias) to assess the effectiveness of Chinese herbal medicines alone for treating unexplained recurrent miscarriage. A combination of Chinese herbal medicines and other pharmaceuticals (mainly Western medicines) appears to be more effective than Western medicines alone in terms of the rate of continuing pregnancy and the rate of live births. However, the quality of the included studies was generally poor. There was no evidence to fully evaluate the effect of the intervention on maternal and perinatal adverse effects and toxicity rates and we were unable to assess the impact of the intervention on any of this review's secondary outcomes due to lack of data. We found no randomised controlled trials that looked at Chinese herbal medicines versus placebo or no treatment (including bed rest).

More high-quality studies are urgently needed to fully evaluate the effectiveness and safety of Chinese herbal medicines for unexplained recurrent miscarriage.

Implications for research

There is a need for further, high-quality studies in this area. In addition to assessing the effect of Chinese herbal medicines on pregnancy rate and the rate of live births, future studies should also consider safety issues (adverse effects and toxicity for the mother and her baby), as well as this review's secondary outcomes (as listed in Types of outcome measures): maternal obstetric and other complications; fetal death within 14 weeks of gestation; fetal death after 14 weeks of gestation; premature infant < 37 weeks; perinatal complications and congenital malformations.

We strongly recommend standardisation and quality controls of clinical trials on the efficacy and safety of Chinese herbal medicines during pregnancy. This review would provide more valuable information if the included studies could overcome the problems in their designs, such as the lack of qualified placebo

-controlled trials, applying adequate randomisation methods and avoiding potential bias in interventions.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Fan 2010

Methods	Randomised controlled trial of combined medicines (Chinese herbal medicines + other pharmaceuticals) compared with other pharmaceuticals alone
Participants	56 inpatients and outpatients from Zhengzhou Municipal Hospital of Chinese Medicine were recruited (Aug 2006-Aug 2008). Participants were all diagnosed as unexplained recurrent miscarriage (2-3 abortion history)
Interventions	Treatment group received Chinese herbal medicines combined with Western medicines. 1) The Chinese medicine formula was Shou Tai Pill, including Chinese Dodder Seed; Chinese Taxillus Twig; Himalayan Teasel Root; Largehead Atractylodes Rhizome; Donkey-hide Glue; Barbary Wolfberry Fruit; Eucommia Bark; Tangerine Peel 2) Formula changes Yin deficiency: Baical Skullcap Root, Rehmannia Root were added Yang deficiency: Common Curculigo, Epimedium Herb, Palmleaf Raspberry Fruit were added. Vomitting: Perilla Stem, Bamboo Shavings, Villous Amomrum Fruit were added. Vaginal bleeding: Giant St.John's Wort Herb, Lotus Rhizome Node, Chinese Mugwort Leaf were added 3) Decoction: po, twice per day. 4) Western medicines were received at the same time, including vitamin E, 100 mg, po, twice per day, progesterone 20 mg, im, once per day, HCG 3000 U, im, every other day, until 10th gestational week or the week last abortion occurred. Control group was treated with Western medicines alone. Same as above, vitamin E, 100 mg, po, twice per day, progesterone 20 mg, im, once per day, HCG 3000 U, im, every other day, until 10th gestational week or the week last abortion occurred Both groups had standard care for pregnancy (having bed rest and prohibiting sexual activity)
Outcomes	Symptoms such as vaginal bleeding and abdominal pains stopped, and pregnancy maintained until term delivery (live birth rate) OR vaginal bleeding and abdominal pains subsided, and clinical examinations showed pregnancy maintained were considered as effective. The effectiveness rate reported in this study of combined medicines group was 89.28%, and Western medicines group was 78.57% ($P < 0.05$). However, according to our design of this review for meta-analysis, the live birth rate should be 57.14% and 42.85%, respectively
Notes	Randomised controlled trial with 2 arms.

Risk of bias

Bias	Authors' judgement	Support for judgement

Fan 2010 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	It only mentioned in the trial that "the patients were randomized divided into 2 groups"
Allocation concealment (selection bias)	Unclear risk	It only mentioned in the trial that "the patients were randomized divided into 2 groups"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The information was not reported in this study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The information was not reported in this study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions or losses were reported, but the number of participants remained the same at the endpoint of study ITT used.
Selective reporting (reporting bias)	Unclear risk	The protocol of the trial was not available, so the possibility of selective outcome reporting could not be examined by the review authors
Other bias	Unclear risk	The intervention groups were comparable, as it mentioned in the trial that "no significant difference was found between groups on age, abortion history, medical condition and complication". Other aspects of bias were unclear

Guo 2013

Methods	Randomised controlled trial of combined medicines (Chinese herbal medicines + other pharmaceuticals) compared with other pharmaceuticals alone
Participants	270 patients from People's Hospital of Fu Gou Xian were recruited. Participants were all diagnosed as unexplained recurrent miscarriage (>= 3 abortion history)
Interventions	Treatment group received Chinese herbal medicines combined with Western medicines. 1) The Chinese medicine formula was Yangxi Zaitai Decoction, including Szechwon Tangshen Root, Largehead Atractylodes Rhizome, Chinese Dodder Seed, Mantis Eggcase, White Paeony Root, Baical Skullcap Root, Danshen Root 2) Decoction: po, twice per day, 2 weeks treatment. 3) Western medicines were received at the same time, including HCG, Salbutamol, Carbazochrome Salicylate,vitamin K, 2 weeks.

	Control group was treated with Western medicines alone. Same as above, HCG, Salbutamol, Carbazochrome Salicylate,vitamin K, 2 weeks Both groups had standard care for pregnancy (having bed rest and prohibiting sexual activity)
Outcomes	Symptoms such as pregnancy maintained until term delivery OR vaginal bleeding and abdominal pains subsided, and clinical examinations showed pregnancy maintained were considered as effective. The effectiveness rate reported in this study of combined medicines group was 99.26%, and Western medicines group was 51.11% ($P < 0.05$) . However, according to our design of this review for meta-analysis, the live birth rate should be 98.50% and 41.48%, respectively. No complication or adverse effects were observed in both intervention groups
Notes	Randomised controlled trial with 2 arms.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It only mentioned in the trial that "the patients were randomized divided into 2 groups"
Allocation concealment (selection bias)	Unclear risk	It only mentioned in the trial that "the patients were randomized divided into 2 groups"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The information was not reported in this study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The information was not reported in this study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions or losses were reported, but the number of participants remained the same at the endpoint of study ITT used.
Selective reporting (reporting bias)	Unclear risk	The protocol of the trial was not available, so the possibility of selective outcome reporting could not be examined by the review authors
Other bias	Unclear risk	The intervention groups were comparable, as it mentioned in the trial that "no significant difference was found between groups on age and medical history". Other aspects

		of bias were unclear

Li 2000

Methods	Randomised controlled trial of combined medicines (Chinese herbal medicines + other pharmaceuticals) compared with other pharmaceuticals alone
Participants	90 inpatients and outpatients from Chinese Medicine Hospital of Xiang Xiang City were recruited (Aug 2006-Aug 2008). Participants were all diagnosed as unexplained recurrent miscarriage (3-6 abortion history)
Interventions	Treatment group received Chinese herbal medicines combined with Western medicines. 1) The Chinese medicine formula was Bushen Antai Decoction, including Szechwon Tangshen Root 15 g, Largehead Atractylodes Rhizome 12 g, Eucommia Bark 15 g; Himalayan Teasel Root 15 g; Donkey-hide Glue 12 g; East Asian Tree Fern Rhizome 15 g; Chinese Dodder Seed 12 g; Chinese Taxillus Twig 12 g; Chinese Mugwort Leaf 12 g; Sharpleaf Galangal Fruit 12 g; Malaytea Scurfpea Fruit 12 g 2) Formula changes Kidney deficiency: Common Macrocarpium Fruit 12 g, Wingde Yan Rhizome 12 g were added Qi deficiency: Mongolian Milkcetch Root 15 g was added. Blood deficiency: Steamed Rehmannia Root 15 g was added. Blood Heat: Baical Skullcap Root 9 g was added. Spleen deficiency: Villous Amomrum Fruit 6 g was added. Vaginal bleeding: Garden Burnet Root 9 g was added. 3) Decoction: po, twice per day. 4) Western medicines were received at the same time, including vitamin E, 100 mg, po, 3 times per day, progesterone 10-20 mg, im, once per day, until the month that last abortion occurred. Control group was treated with Western medicines alone. Same as above, vitamin E, 100 mg, po, 3 times per day, progesterone 10-20 mg, im, once per day, until the month that last abortion occurred
Outcomes	Symptoms such as vaginal bleeding and abdominal pains stopped or subsided, clinical examinations showed pregnancy maintained until term delivery were considered as effective. The effectiveness rate (live birth rate according to our design of this review for meta-analysis) reported in this study of combined medicines group was 91.60%, and Western medicines group was 76.66% ($P < 0.05$)
Notes	Randomised controlled trial with 2 arms.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It only mentioned in the trial that "the patients were randomized (2:1 ratio) divided into 2 groups.."

Li 2000 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	It only mentioned in the trial that "the patients were randomized (2:1 ratio) divided into 2 groups.."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The information was not reported in this study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The information was not reported in this study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions or losses were reported, but the number of participants remained the same at the endpoint of study ITT used.
Selective reporting (reporting bias)	Unclear risk	The protocol of the trial was not available, so the possibility of selective outcome reporting could not be examined by the review authors
Other bias	Unclear risk	No baseline information of the intervention groups was available

Luo 2013

Methods	Randomised controlled trial of combined medicines (Chinese herbal medicines + other pharmaceuticals) compared with other pharmaceuticals alone
Participants	33 patients from People's Hospital of Guangxi Luchuan were recruited (May 2009-May 2012). Participants were all diagnosed as unexplained recurrent miscarriage (3-5 abortion history)
Interventions	Treatment group received Chinese herbal medicines combined with Western medicines. 1) The Chinese medicine formula included Chinese Dodder Seed 10 g; Liquorice Root 6 g; Chinese Taxillus Twig 15 g; Villous Amomrum Fruit 9 g; Himalayan Teasel Root 10 g; Largehead Atractylodes Rhizome 9 g; Indian Buead 9 g; Szechwon Tangshen Root 30 g 2) Formula changes Dry mouth: Baical Skullcap 10 g, Rehmannia Root 10 g, Heterophylly Falsestarwort Root 15 g were added. Vaginal bleeding: Fineleaf Schizonepeta Herb 10 g, Giant St.John's Wort Herb 10 g, Glossy Privet Fruit 15 g were added 3) Decoction: po, 3 times per day. 4) Western medicines were received at the same time, including progesterone 20 mg, im, every other day / once per day, HCG 1000 U, im, once per day, until 8th gestational week or the week last abortion occurred.

	Control group was treated with Western medicines alone. Same as above, progesterone 20 mg, im, every other day / once per day, HCG 1000 U, im, once per day, until 8th gestational week or the week last abortion occurred Both groups had standard care for pregnancy (having bed rest and prohibiting sexual activity)
Outcomes	Symptoms such as vaginal bleeding and abdominal pains stopped, and pregnancy maintained until term delivery OR vaginal bleeding and abdominal pains subsided, and clinical examinations showed pregnancy maintained until 70 days were considered as effective. The effectiveness rate reported in this study of combined medicines group was 94. 12%, and Western medicines group was 68.75% (P < 0.05). However, according to our design of this review for meta-analysis, the live birth rate should be 70.59% and 50. 00%, respectively
Notes	Randomised controlled trial with 2 arms.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It only mentioned in the trial that "the patients were randomized divided into 2 groups"
Allocation concealment (selection bias)	Unclear risk	It only mentioned in the trial that "the patients were randomized divided into 2 groups"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The information was not reported in this study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The information was not reported in this study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions or losses were reported, but the number of participants remained the same at the endpoint of study ITT used.
Selective reporting (reporting bias)	Unclear risk	The protocol of the trial was not available, so the possibility of selective outcome reporting could not be examined by the review authors
Other bias	Unclear risk	No baseline information of the intervention groups was available

Qu 2012a

Methods	Randomised controlled trial of combined medicines (Chinese herbal medicines + other pharmaceuticals) compared with other pharmaceuticals alone
Participants	99 inpatients from The 5th Hospital of Zhang Jia Kou were recruited (Jan 2007-Jan 2011). Participants were all diagnosed as unexplained recurrent miscarriage (2-6 abortion history)
Interventions	Treatment group received Chinese herbal medicines combined with Western medicines. 1) The Chinese medicine formula included including Mongolian Milkcetch Root 20 g, Chinese Angelica 10 g, Szechuan Lovage Rhizome 10 g, Chinese Dodder Seed 10 g, Forbes Notopterygium Rhizome 12 g, Chinese Mugwort Leaf 12 g, Largehead Atractylodes Rhizome 10 g, Fineleaf Schizonepeta Herb 10 g, Liquorice Root 6 g, Medicated Leaven 10 g, Malt 10 g, Chinese Hawthorn Fruit 10 g, Szechuan-fritillary Bulb 10 g 2) Formula changes: the study did not report the details. 3) Decoction: po, twice per day. 4) Western medicines were received at the same time, including progesterone 100 mg, po, once per day, HCG 3000-5000 U, im, every other day/once per day, 25% magnesium sulphate injection, ivgtt. Control group was treated with Western medicines alone. Same as above, progesterone 100 mg, po, once per day, HCG 3000-5000 U, im, every other day/once per day, 25% magnesium sulphate injection, ivgtt Both groups had standard care for pregnancy (having bed rest and prohibiting sexual activity)
Outcomes	Pregnancy maintained until term delivery OR pregnancy maintained until 7 months were considered as effective. The effectiveness rate reported in this study of combined medicines group was 91.2%, and Western medicines group was 68.9% ($P < 0.05$). However, according to our design of this review for meta-analysis, the data could only be considered as the live birth rate The relief time of symptoms such as bleeding time, low back pain, abdominal pain, false contraction was significantly shorter in combined medicine group than control group ($P < 0.05$)
Notes	Randomised controlled trial with 2 arms.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It only mentioned in the trial that "the patients were randomized divided into 2 groups"
Allocation concealment (selection bias)	Unclear risk	It only mentioned in the trial that "the patients were randomized divided into 2 groups"

Qu 2012a (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The information was not reported in this study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The information was not reported in this study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions or losses were reported, but the number of participants remained the same at the endpoint of study ITT used.
Selective reporting (reporting bias)	Unclear risk	The protocol of the trial was not available, so the possibility of selective outcome reporting could not be examined by the review authors
Other bias	Unclear risk	The intervention groups were comparable, as it mentioned in the trial that "no significant difference was found between groups on age, education, pregnancy history, abortion history, abdominal pain, bleeding time". Other aspects of bias were unclear

Qu 2012b

Methods	Randomised controlled trial of combined medicines (Chinese herbal medicines + psychotherapy) compared with psychotherapy alone
Participants	90 inpatients from The 5th Hospital of Zhang Jia Kou were recruited (May 2007-Jan 2012). Participants were all diagnosed as unexplained recurrent miscarriage (2-7 abortion history)
Interventions	Treatment group received Chinese herbal medicines combined with psychotherapy. 1) The Chinese medicine formula was Bao Tai Decoction, including Mongolian Milkcetch Root 20 g, Chinese Angelica 10 g, Szechuan Lovage Rhizome 10 g, Chinese Dodder Seed 10 g, Forbes Notopterygium Rhizome 12 g, Chinese Mugwort Leaf 12 g, Largehead Atractylodes Rhizome 10 g, Fineleaf Schizonepeta Herb 10 g, Liquorice Root 6 g, Medicated Leaven 10 g, Malt 10 g, Chinese Hawthorn Fruit 10 g, Szechuan-fritillary Bulb 10 g 2) Decoction: po, firstly every other day from 1 month before the last abortion week, then once per day in the month of the last abortion week. 3) Psychotherapy was applied at the same time, including counselling to relieve the loss, fear, despair, guilt and other negative emotions of the habitual abortion patients and strengthen their positive emotions such as confidence, patience and perseverance; given relaxation training, advising on diet, nutrition, exercise and healthy life style.

Qu 2012b (*Continued*)

	Control group was applied with psychotherapy alone. Same as above, including counselling to relieve the loss, fear, despair, guilt and other negative emotions of the habitual abortion patients and strengthen their positive emotions such as confidence, patience and perseverance; given relaxation training, advising on diet, nutrition, exercise and healthy life style
Outcomes	Pregnancy maintained until term delivery was considered as effective. The effectiveness rate (which is considered as the live birth rate according to our design of this review for meta-analysis) reported in this study of combined medicines group was 91.1%, and psychotherapy group was 68.9% ($P < 0.05$)
Notes	Randomised controlled trial with 2 arms.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It only mentioned in the trial that "the patients were randomized divided into 2 groups"
Allocation concealment (selection bias)	Unclear risk	It only mentioned in the trial that "the patients were randomized divided into 2 groups"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The information was not reported in this study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The information was not reported in this study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions or losses were reported, but the number of participants remained the same at the endpoint of study ITT used.
Selective reporting (reporting bias)	Unclear risk	The protocol of the trial was not available, so the possibility of selective outcome reporting could not be examined by the review authors
Other bias	Unclear risk	The intervention groups were comparable, as it mentioned in the trial that "no significant difference was found between groups on age, education, pregnancy history, SCL-90 scores assessment and APGAR survey". Other aspects of bias were unclear

Wei 2013a

Methods	Randomised controlled trial of Chinese herbal medicines alone compared with other pharmaceuticals alone
Participants	71 outpatients from The Center Hospital of Gao Mi City Shan Dong Province were recruited (Feb 2007-Jan 2013). Participants were all diagnosed as unexplained recurrent miscarriage (2-4 abortion history)
Interventions	Treatment group received Chinese herbal medicines alone. 1) The Chinese medicine formula was Kun An Decoction, including Mongolian Milkcetch Root 6 g, Chinese Angelica 6 g, Donkey Hide Gelatin 1 g, Chinese Wolfberry fruit 5g, Pilose Asiabell Root 4 g, Ginseng 3 g, Eucommia Bark 3 g, Liquorice Root 3 g, Common Anemarrhena Rhizome 3 g, Sweet Wormwood Herb 3 g, Indian Bread 4 g, Rehmannia Root 5 g 2) Decoction: po, once per day, 10 days as one course. Control group was treated with Western medicines alone. Progesterone 20 mg, im, once per day, 10 days as one course Both groups had standard care for pregnancy (health education and having bed rest)
Outcomes	Symptoms relief after one course treatment was considered as effective, but no detail report on pregnancy rate and live birth rate in this study. Some patients were followed up till delivery Side-effects of drugs were not observed in both interventions groups and relevant laboratory examinations of these pregnant patients were reported normal. No abnormal fetuses were reported in the ultrasound examination at 18-24 gestational weeks and after delivery
Notes	Randomised controlled trial with 2 arms.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It only mentioned in the trial that "the patients were randomized divided into 2 groups"
Allocation concealment (selection bias)	Unclear risk	It only mentioned in the trial that "the patients were randomized divided into 2 groups"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The information was not reported in this study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The information was not reported in this study.

Wei 2013a (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions or losses were reported, but the number of participants remained the same at the endpoint of study ITT used.
Selective reporting (reporting bias)	Unclear risk	The protocol of the trial was not available, so the possibility of selective outcome reporting could not be examined by the review authors
Other bias	Unclear risk	The intervention groups were comparable, as it mentioned in the trial that "no significant difference was found between groups on age and pregnancy history". Other aspects of bias were unclear

Yuan 2013

Methods	Randomised controlled trial of comparisons amongst combined medicines (Chinese herbal medicines + other pharmaceuticals), Chinese herbal medicines and other pharmaceuticals groups
Participants	120 inpatients and outpatients from Chinese Medicine Hospital of Shen Zhen were recruited (Jan 2009-Aug 2012). Participants were all diagnosed as unexplained recurrent miscarriage (>= 2 abortion history)
Interventions	Treatment group 1 received Chinese herbal medicines combined with Western medicines. 1) The Chinese medicine formula included Mongolian Milkcetch Root 30 g, Chinese Angelica 10 g, Gordon Enryale Seed 18 g, Chinese Taxillus Twig 24 g, Largetrifoliolious Bugbane Rhizome 10 g, Glossy Privet Fruit 18 g, Largehead Atractylodes Rhizome 10 g, Eucommia Bark 15 g, Chinese Dodder Seed 15 g, Himalayan Teasel Root 15 g, Giant St.John's Wort Herb 15 g, Hairyvein Agrimonia Herb and Bud 30 g, Fortune Windmillpalm Petiole 15 g, Wingde Yan Rhizome 15 g, Common Macrocarpium Fruit 15 g 2) Formula changes Abdominal pain: White Paeony Root 15 g, Liquorice Root 10 g were added Yin deficiency: Baical Skullcap Root 10 g, Garden Mum 15 g, Rehmannia Root 15 g were added Dry stool: Tuber Fleeceflower Root 10 g, Platycladi Seed 30 g were added Low back pain: Palmleaf Raspberry Fruit, Sharpleaf Galangal Fruit were added. Vaginal bleeding: Chinese Angelica was removed, Garden Burnet Root was added 3) Decoction: po, twice per day. 4) Western medicines were received at the same time, including progesterone 10-20 mg, im, once per day, Dydrogesterone Tablets 10-20 mg, po, once per day, until 10th-12th week, vitamin E, 100 mg, po, twice per day, tranexamic acid tablets 1-2g, iv, once per day, until bleeding stopped Treatment group 2 received Chinese herbal medicines alone. Same as above, Mongolian Milkcetch Root 30 g, Chinese Angelica 10 g, Gordon Enryale Seed 18 g, Chinese

	Taxillus Twig 24 g, Largetrifoliolious Bugbane Rhizome 10 g, Glossy Privet Fruit 18 g, Largehead Atractylodes Rhizome 10 g, Eucommia Bark 15 g, Chinese Dodder Seed 15 g, Himalayan Teasel Root 15 g, Giant St.John's Wort Herb 15 g, Hairyvein Agrimonia Herb and Bud 30 g, Fortune Windmillpalm Petiole 15 g, Wingde Yan Rhizome 15 g, Common Macrocarpium Fruit 15 g. Control group was treated with Western medicines alone. Same as above, progesterone 10-20 mg, im, once per day, Dydrogesterone tablets 10-20 mg, po, once per day, until 10th-12th week, vitamin E, 100 mg, po, twice per day, tranexamic acid tablets 1-2 g, iv, once per day, until bleeding stopped
Outcomes	Symptoms such as pregnancy maintained until term delivery OR vaginal bleeding and abdominal pains subsided, and clinical examinations showed pregnancy maintained were considered as effective. The effectiveness rate reported in this study of combined medicines group was 90.0%, Chinese herbal medicines group was 75.0% and Western medicines group was 72.5% ($P < 0.05$). However, according to our design of this review for meta-analysis, the live birth rate should be 70.0%, 50.0% and 47.5%, respectively
Notes	Randomised controlled trial with 3 arms.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It only mentioned in the trial that "the patients were randomized divided into 3 groups"
Allocation concealment (selection bias)	Unclear risk	It only mentioned in the trial that "the patients were randomized divided into 3 groups"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The information was not reported in this study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The information was not reported in this study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions or losses were reported, but the number of participants remained the same at the endpoint of study ITT used.
Selective reporting (reporting bias)	Unclear risk	The protocol of the trial was not available, so the possibility of selective outcome reporting could not be examined by the review authors

Other bias	Unclear risk	The intervention groups were comparable, as it mentioned in the trial that "no significant difference was found between groups on age, education, gestational weeks, main symptoms"

Zhang 2013

Methods	Randomised controlled trial of combined medicines (Chinese herbal medicines + other pharmaceuticals) compared with other pharmaceuticals alone
Participants	72 inpatients and outpatients from People's Hospital of Wen Xian were recruited (Jun 2011-Aug 2012). Participants were all diagnosed as unexplained recurrent miscarriage (>= 3 abortion history)
Interventions	Treatment group received Chinese herbal medicines combined with Western medicines. 1) The Chinese medicine formula was Shou Tai Pill, including Chinese Dodder Seed 25 g; Chinese Taxillus Twig 15 g; Himalayan Teasel Root 15 g; Donkey-hide Glue 12 g; Mongolian Milkcetch Root 12 g; Largetrifoliolious Bugbane Rhizome 10 g; White Paeony Root 10 g; Common Macrocarpium Fruit 10 g 2) Formula changes Low back pain: Eucommia Bark, Sharpleaf Galangal Fruit were added. Vaginal bleeding: Garden Burnet Root, Chinese Mugwort Leaf were added Constipation: Desertliving Cistanche, Steamed Rehmannia Root were added 3) Decoction: po, twice per day, 2 weeks as 1 course. 4) Western medicines were received at the same time, including HCG 1000-2000 U, im, once per day, until 12th gestational week. Control group was treated with Western medicines alone. Same as above, HCG 1000-2000 U, im, once per day, until 12th gestational week
Outcomes	Symptoms such as vaginal bleeding and abdominal pains stopped, and pregnancy maintained over 28 weeks or term delivery OR vaginal bleeding and abdominal pains subsided, and clinical examinations showed pregnancy maintained were considered as effective. The effectiveness rate reported in this study of combined medicines group was 88.9%, and Western medicines group was 66.7% ($P < 0.05$). However, according to our design of this review for meta-analysis, the pregnancy rate should be 55.5% and 33.3%, respectively
Notes	Randomised controlled trial with 2 arms.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It only mentioned in the trial that "the patients were randomized divided into 2 groups"

Zhang 2013 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	It only mentioned in the trial that "the patients were randomized divided into 2 groups"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The information was not reported in this study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The information was not reported in this study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions or losses were reported, but the number of participants remained the same at the endpoint of study ITT used.
Selective reporting (reporting bias)	Unclear risk	The protocol of the trial was not available, so the possibility of selective outcome reporting could not be examined by the review authors
Other bias	Unclear risk	No baseline information of the intervention groups was available

HCG: human chorionic gonadotropin
im: intramuscular
ITT intention-to-treat
iv: intravascular
ivgtt: intravenously guttae, or IV drop referred to different administration methods
Po (per os): by mouth

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Chen 2013	Study group applied Combined Chinese herbal medicines (CHMs) and Western medicines (WMs), while control group applied CHMs+WMs+immunisation therapy, so the data could not be used for our meta-analysis
Liu 2014	Other pharmaceuticals were not the same in study group (combined medicines) and control group, so the data in this clinical trials could not be used for our meta-analysis
Wang 2013	The endpoint of this study included both < 12 weeks and 12-28 weeks, which cannot be separated, so the data could not be used for our meta-analysis

(*Continued*)

Wei 2013b	The endpoints of this study were 65 days and 12 weeks, so the data could not be used for our meta-analysis
Xu 2013	Information of gestational weeks (endpoint) is lacking, so the data could not be used for our meta-analysis
Yuan 2004	Other pharmaceuticals were not the same in study group (combined medicines) and control group, so the data in this clinical trial could not be used for our meta-analysis
Zhang 2011	Information of gestational weeks (endpoint) is lacking, so the data could not be used for our meta-analysis
Zhang 2012	The endpoint of this study was at the 12th gestational week, so the data could not be used for our meta-analysis

DATA AND ANALYSES

Comparison 1. Chinese herbal medicines versus other pharmaceuticals

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.67, 1.65]

Comparison 2. Combined medicines versus other pharmaceuticals

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy rate	2	189	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.10, 1.48]
2 Live birth rate	6	601	Risk Ratio (M-H, Random, 95% CI)	1.55 [1.14, 2.10]

Comparison 3. Combined medicines versus psychotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.07, 1.64]

Analysis 1.1. Comparison 1 Chinese herbal medicines versus other pharmaceuticals, Outcome 1 Live birth rate.

Review: Chinese herbal medicines for unexplained recurrent miscarriage

Comparison: 1 Chinese herbal medicines versus other pharmaceuticals

Outcome: 1 Live birth rate

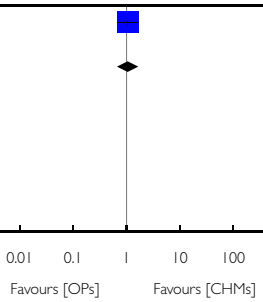
Study or subgroup	Chinese herbal medicines n/N	Other pharma-ceuticals n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Yuan 2013	20/40	19/40		100.0 %	1.05 [0.67, 1.65]
Total (95% CI)	**40**	**40**		**100.0 %**	**1.05 [0.67, 1.65]**

Total events: 20 (Chinese herbal medicines), 19 (Other pharmaceuticals)

Heterogeneity: not applicable

Test for overall effect: Z = 0.22 (P = 0.82)

Test for subgroup differences: Not applicable



Analysis 2.1. Comparison 2 Combined medicines versus other pharmaceuticals, Outcome 1 Pregnancy rate.

Review: Chinese herbal medicines for unexplained recurrent miscarriage

Comparison: 2 Combined medicines versus other pharmaceuticals

Outcome: 1 Pregnancy rate

Study or subgroup	Combined medicines	Other pharma-ceuticals	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Li 2000	55/60	23/30		47.6 %	1.20 [0.97, 1.48]
Qu 2012a	50/54	31/45		52.4 %	1.34 [1.09, 1.66]
Total (95% CI)	**114**	**75**		**100.0 %**	**1.27 [1.10, 1.48]**

Total events: 105 (Combined medicines), 54 (Other pharmaceuticals)

Heterogeneity: $Chi^2 = 0.59$, df = 1 (P = 0.44); $I^2 = 0.0\%$

Test for overall effect: Z = 3.17 (P = 0.0015)

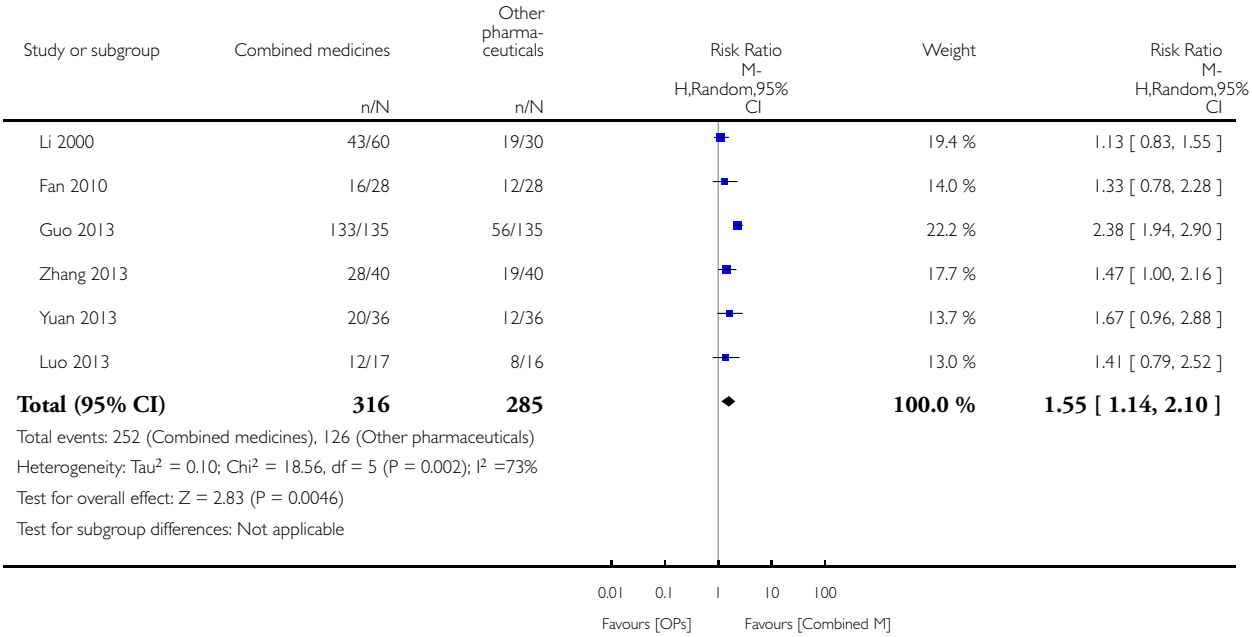
Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Combined medicines versus other pharmaceuticals, Outcome 2 Live birth rate.

Review: Chinese herbal medicines for unexplained recurrent miscarriage

Comparison: 2 Combined medicines versus other pharmaceuticals

Outcome: 2 Live birth rate

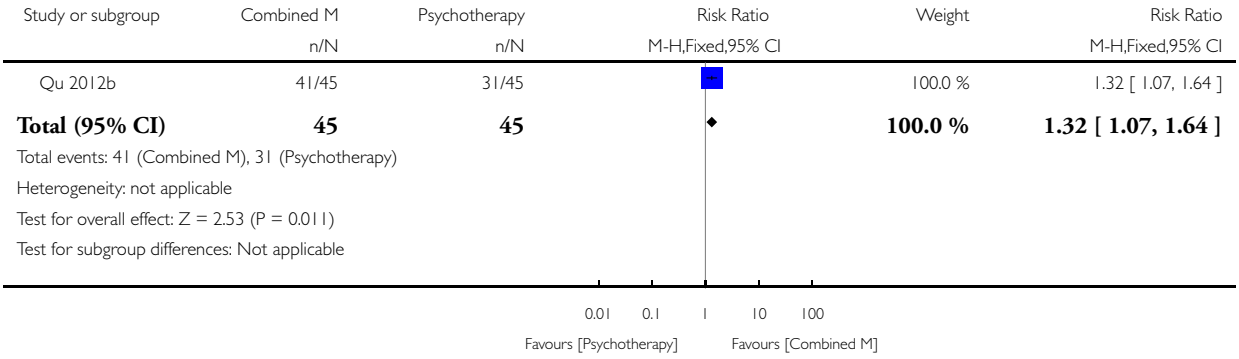


Analysis 3.1. Comparison 3 Combined medicines versus psychotherapy, Outcome 1 Live birth rate.

Review: Chinese herbal medicines for unexplained recurrent miscarriage

Comparison: 3 Combined medicines versus psychotherapy

Outcome: 1 Live birth rate



APPENDICES

Appendix 1. List of Chinese herbal medicines (CHMs) used as treatment for recurrent miscarriage*

No.	English names	Biological names	Chinese names (Pinyin)
1	Largehead Atractylodes Rhizome	*Rhizoma Atractylodis Macrocephalae*	Bai Zhu
2	Chinese Dodder Seed	*Semen Cuscutae*	Tu Si Zi
3	Himalayan Teasel Root	*Radix Dipsaci*	Xu Duan
4	Chinese Taxillus Twig	*Herba Taxilli*	Sang Ji Sheng
5	Liquorice Root	*Radix Astragali*	Huang Qi
6	Mongolian Milkcetch Root	*Radix Paeoniae Alba*	Bai Shao
7	White Paeony Root	*Radix Angelicae Sinensis*	Dang Gui
8	Chinese Angelica	*Radix Et Rhizoma Glycyrrhizae*	Gan Cao

(*Continued*)

9	Baical Skullcap Root	*Radix Scutellariae*	Huang Qin
10	Eucommia Bark	*Cortex Eucommiae*	Du Zhong
11	Steamed Rehmannia Root	*Radix Rehmanniae Praeparata*	Shu Di Huang
12	Szechwon Tangshen Root	*Radix Codonopsis*	Dang Shen
13	Common Yam Rhizome	*Rhizoma Diosscoreae*	Shan Yao
14	Villous Amomrum Fruit	*Fructus Amomi*	Sha Ren
15	Rehmannia Root	*Radix Rehmanniae*	Sheng Di Huang
16	Szechuan Lovage Rhizome	*Rhizoma Chuanxiong*	Chuan Xiong
17	Chinese Mugwort Leaf	*Folium Artemisiae Argyi*	Ai Ye
18	Tangerine Peel	*Pericarpium Citri Reticulatae*	Chen Pi
19	Danshen Root	*Radix Et Rhizoma Salviae Miltiorrhizae*	Dan Shen
20	Heterophylly Falsestarwort Root	*Radix Pseudostellariae*	Tai Zi Shen
21	Perilla Stem	*Caulis Perillae*	Zi Su Jin
22	Ramie Root	*Radix Boehmeriae*	Zhu Ma Gen
23	Gin Seng	*Radix Et Rhizoma Ginseng*	Ren Shen
24	Largetrifoliolious Bugbane Rhizome	*Rhizoma Cimicifugae*	Sheng Ma
25	Chinese Thorowax Root	*Radix Bupleuri*	Chai Hu
26	Red Paeony Root	*Radix Paeoniae Rubra*	Chi Shao
27	Glossy Privet Fruit	*Fructus Ligustri Lucidi*	Nv Zhen Zi
28	Hairyvein Agrimonia Herb and Bud	*Herba Agrimoniae*	Xian He Cao
29	Bamboo Shavings	*Caulis Bambusae in Taenia*	Zhu Ru
30	Chinese Angelica	*Radix Et Rhizoma Glycyrrhizae*	Zhi Cao
31	Common Macrocarpium Fruit	*Fructus Corni*	Shan Zhu Yu
32	Polished Glutinous Rice	*Abelia Chinensis*	Ruo Mi

(*Continued*)

33	Malaytea Scurfpea Fruit	*Radix Curcumae*	Yu Jin
34	Hiraute Shiny Bugleweed Herb	*Herba Lycopi*	Ze Lan
35	Indian Buead	*Poria*	Fu Lin
36	Barbary Wolfberry Fruit	*Fructus Lycii*	Gou Qi
37	Nutgrass Galingale Rhizome	*Rhizoma Cyperi*	Xiang Fu
38	Cassia Twig	*Ramulus Cinnamomi*	Gui Zhi
39	Fennel Fruit	*Fructus Foeniculi*	Xiao Hui Xiang
40	Garden Burnet Root	*Radix Sanguisorbae*	Di Yu
41	Yan Hu Suo	*Rhizoma Corydalis*	Yan Hu Suo
42	Dwarf Lilyturf Tuber	*Radix Ophiopogonis*	Mai Dong
43	Cape Jasmine Fruit	*Fructus Gardeniae*	Zhi Zi
44	Citron Fruit	*Fructus Citri*	Xiang Yuan
45	Sharpleaf Galangal Fruit	*Fructus Alpiniae Oxyphyllae*	Yi Zhi Ren
46	Spine Date Seed	*Semen Ziziphi Spinosae*	Suan Zao Ren
47	Chinese Magnoliavine Fruit	*Fructus Schisandrae Chinensis*	Wu Wei Zi
48	Round Cardamom Fruit/Java Amomum Fruit	*Fructus Amomi Rotundus*	Bai Dou Kou
49	Tuber Fleeceflower Root	*Radix Polygoni Multiflori*	He Shou Wu
50	Amur Corktree Bark	*Cortex Phellodendri Chinensis*	Huang Bai

*This is not an exhaustive list, and other CHMs will be supplemented in the future literature review.

Appendix 2. Search strategy for EMBASE

1. exp PREGNANCY/
2. (spontaneous adj2 abortion*).af
3. (recur* adj3 (pregnancy ADJ loss)).af
4. (habitual* adj3 (pregnancy ADJ loss)).af
5. (abortion* adj3 recur*).af
6. (abortion* adj3 habitual*).af
7. (spontaneous adj3 (pregnancy ADJ loss)).af
8. miscarriage*.af
9. exp CHINESE HERB/
10. (chin* adj6 herb*).af
11. ((china OR chinese) AND (tradition* adj4 medicine*)).af
12. 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
13. 9 OR 10 OR 11
14. 1 AND 12 AND 13

Appendix 3. Search strategy for CINAHL

1. exp PREGNANCY/
2. (spontaneous adj2 abortion*).af
3. (recur* adj3 (pregnancy ADJ loss)).af
4. (habitual* adj3 (pregnancy ADJ loss)).af
5. (abortion* adj3 recur*).af
6. (abortion* adj3 habitual*).af
7. (spontaneous adj3 (pregnancy ADJ loss)).af
8. miscarriage*.af
9. (chin* adj6 herb*).af
10. ((china OR chinese) AND (tradition* adj4 medicine*)).af
11. DRUGS, CHINESE HERBAL/
12. 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
13. 9 OR 10 OR 11
14. 1 AND 12 AND 13

Appendix 4. Search Strategies for other databases

Chinese Biomedical Database (CBM); China Journal Net (CJN); China Journals Full-text Database (Chinese)

1. (subject =miscarriage) OR (subject =abortion)
2. (subject= recurrent)
3. (subject =therapeutic) OR (subject = threatened) OR (subject = complete) OR (subject= incomplete) OR (subject= inevitable) OR (subject = missed)
4. 1 AND 2 NOT 3
5. (subject= Chinese medicine*(therapy application+ clinical use)) OR (subject= traditional medicine) OR (subject=TCM)
6. 4 AND 5

Search strategy for WanFang Database (Chinese)

1. TCM OR (traditional medicine) OR (Chinese medicine)
2. application OR (clinical use) OR therapy
3. 1 AND 2
4. miscarriage OR abortion

5. (recurrent abortion) OR (recurrent miscarriage)
6. 4 AND 5
7. 3 AND 6

CONTRIBUTIONS OF AUTHORS

Dr Li Lu and Prof Wang Chi Chiu both wrote the initial and final versions of the review. Dr Dou Li Xia, Prof Leung Ping Chung and Prof Chung Kwok Hung Tony commented on the final version of the review.

DECLARATIONS OF INTEREST

Lu Li: none known

Lixia Dou: none known

Ping Chung Leung: none known

Tony Kwok Hung Chung: none known

Chi Chiu Wang: none known

SOURCES OF SUPPORT

Internal sources

- Department of Obstetrics and Gynaecology, The Chinese University of Hong Kong. Shatin, Hong Kong.
- Institute of Chinese Medicine, The Chinese University of Hong Kong. Shatin, Hong Kong.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.