Chinese herbal medicine for endometriosis (Review)

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ABSTRACT

Background

Endometriosis is characterized by the presence of tissue that is morphologically and biologically similar to normal endometrium in locations outside the uterus. Surgical and hormonal treatment of endometriosis have unpleasant side effects and high rates of relapse. In China, treatment of endometriosis using Chinese herbal medicine (CHM) is routine and considerable research into the role of CHM in alleviating pain, promoting fertility, and preventing relapse has taken place.

This review is an update of a previous review published in the Cochrane Database of Systematic Reviews 2009, issue No 3.

Objectives

To review the effectiveness and safety of CHM in alleviating endometriosis-related pain and infertility.

Search methods

We searched the Menstrual Disorders and Subfertility Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library) and the following English language electronic databases (from their inception to 31/10/2011): MEDLINE, EMBASE, AMED, CINAHL, and NLH.

We also searched Chinese language electronic databases: Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chinese Sci & Tech Journals (VIP), Traditional Chinese Medical Literature Analysis and Retrieval System (TCMLARS), and Chinese Medical Current Contents (CMCC).

Selection criteria

Randomised controlled trials (RCTs) involving CHM versus placebo, biomedical treatment, another CHM intervention; or CHM plus biomedical treatment versus biomedical treatment were selected. Only trials with confirmed randomisation procedures and laparoscopic diagnosis of endometriosis were included.

Data collection and analysis

Risk of bias assessment, and data extraction and analysis were performed independently by three review authors. Data were combined for meta-analysis using relative risk (RR) for dichotomous data. A fixed-effect statistical model was used, where appropriate. Data not suitable for meta-analysis were presented as descriptive data.
Main results

Two Chinese RCTs involving 158 women were included in this review. Both these trials described adequate methodology. Neither trial compared CHM with placebo treatment.

There was no evidence of a significant difference in rates of symptomatic relief between CHM and gestrinone administered subsequent to laparoscopic surgery (95.65% versus 93.87%; risk ratio (RR) 1.02, 95% confidence interval (CI) 0.93 to 1.12, one RCT). The intention-to-treat analysis also showed no significant difference between the groups (RR 1.04, 95% CI 0.91 to 1.18). There was no significant difference between the CHM and gestrinone groups with regard to the total pregnancy rate (69.6% versus 59.1%; RR 1.18, 95% CI 0.87 to 1.59, one RCT).

CHM administered orally and then in conjunction with a herbal enema resulted in a greater proportion of women obtaining symptomatic relief than with danazol (RR 5.06, 95% CI 1.28 to 20.05; RR 5.63, 95% CI 1.47 to 21.54, respectively). Overall, 100% of women in all the groups showed some improvement in their symptoms.

Oral plus enema administration of CHM showed a greater reduction in average dysmenorrhoea pain scores than did danazol (mean difference (MD) -2.90, 95% CI -4.55 to -1.25; P < 0.01). Combined oral and enema administration of CHM also showed a greater improvement measured as the disappearance or shrinkage of adnexal masses than with danazol (RR 1.70, 95% CI 1.04 to 2.78). For lumbosacral pain, rectal discomfort, or vaginal nodules tenderness, there was no significant difference between CHM and danazol.

Authors’ conclusions

Post-surgical administration of CHM may have comparable benefits to gestrinone but with fewer side effects. Oral CHM may have a better overall treatment effect than danazol; it may be more effective in relieving dysmenorrhoea and shrinking adnexal masses when used in conjunction with a CHM enema. However, more rigorous research is required to accurately assess the potential role of CHM in treating endometriosis.

Plain Language Summary

Chinese herbs for endometriosis

Endometriosis is a common gynaecological condition causing menstrual and pelvic pain. Treatment involves surgery and hormonal drugs, with potentially unpleasant side effects and high rates of reoccurrence of endometriosis. This review suggests that Chinese herbal medicine (CHM) may be useful in relieving endometriosis-related pain with fewer side effects than experienced with conventional treatment. However, the two trials included in this review are of poor methodological quality so these findings must be interpreted cautiously. Better quality randomised controlled trials are needed to investigate a possible role for CHM in the treatment of endometriosis.
### Summary of Findings for the Main Comparison

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk of bias</th>
<th>Number of participants</th>
<th>Comparisons</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu SZ 2006a</td>
<td>B-moderate</td>
<td>100</td>
<td>CHM (oral + enema) versus gestrinone</td>
<td>RR 1.02 (95% CI 0.93 to 1.12)</td>
</tr>
<tr>
<td>Wu SZ 2006b</td>
<td>B-moderate</td>
<td>58</td>
<td>CHM oral versus CHM oral+enema versus danazol</td>
<td>RR 5.06 (95% CI 1.28 to 20.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>For 'symptomatic relief'</td>
<td>CHM oral+enema versus danazol</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>RR 5.63 (95% CI 1.47 to 21.54)</td>
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### Background

#### Description of the condition

Endometriosis is a disease characterized by the presence of tissue that is morphologically and biologically similar to normal endometrium in ectopic locations outside the uterine cavity. Hormonally stimulated cyclical bleeding from the endometriotic deposit appears to contribute to the induction of a local inflammatory reaction and fibrous adhesion; and, in the case of deep implants in the ovary, leads to the formation of an endometrioma or chocolate cyst.

Endometriosis classically presents with severe dysmenorrhea, pelvic pain, dyspareunia, menstrual irregularities, and infertility. Systemic symptoms may also occur, such as fatigue, increased incidence of allergies, and autoimmune disease (Ballweg 2004). Definitive diagnosis is usually made through laparoscopic investigation although recent research suggests that non-invasive symptom evaluation may have a greater positive prediction value (Ling 1999; Winkel 2003).

The precise prevalence of endometriosis is unclear but there is a broad consensus that between 5% to 15% of the female population will have signs and symptoms of the disease during their reproductive years (aged 15 to 50 years) (Eskenazi 1997; Stenchever 2001; Zondervan 2001).

Endometriosis is increasingly regarded as a complex, multi-factorial condition of uncertain aetiology where immunological (Ballweg 2004; Lebovic 2001; Sheng 1998), hormonal (Noble 1997), genetic (Bischoff 2004; Malinak 1980), environmental (Ballweg 2004; Ohtake 2003), and possibly even psychological (Low 1993; Strauss 1992) factors combine together to create a context for rogue endometrial cells to develop into a full-blown disease.

#### Description of the intervention

The treatment of endometriosis can be broadly divided into medical or surgical management. Medical treatment ranges from symptomatic control with non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics through to treatments that aim to suppress the normal ovarian production of estrogen by either hormonally simulating pregnancy (continuous oral contraceptives (COC) and progestins) or menopause (danazol and gonadotrophin-releasing hormone agonists (GnRH-a)). Surgical intervention can be either ‘conservative’, involving the removal of endometrial lesions or the severing of the nerve pathways responsible for the transmission of pelvic and uterine pain, or ‘definitive’, involving the removal of the uterus and ovaries.

Danazol, progestins, GnRH-a, and the COC have comparable short-term rates of success in alleviating the symptoms of endometriosis and in partially reducing the size of endometriosis-related lesions (GISG 1996; Moore 2004; Parazzini 2000; Prentice 2004; Selak 2007; Vercellini 1993). Unfortunately the benefits are poorly sustained over time with studies frequently reporting a high level of returning symptoms at six months post-treatment (Vercellini 1993). Even studies with more positive findings commonly demonstrate a return of symptoms in over a third of the women two to three years after stopping treatment (Biberoglu 1981; Dmowski 1998).

The short-term benefits of conventional medical treatment have to be balanced against the unpleasant and sometimes dangerous side effects resulting from these therapies. COC has been associated with increased thromboembolic risks (Anderson 2004). It is unsuitable for certain patient groups, such as women over the age of 35 years who smoke or who have a history of cardiovascular disease, and is obviously inappropriate for women trying to conceive. Danazol is associated with androgenic changes such as acne and weight gain, and menopausal symptoms such as flushing.
and fatigue. Concerns raised have highlighted its potential role in raising low-density lipoprotein (LDL) cholesterol levels (Hughes 2004) and in possibly contributing to ovarian cancer (Cottreau 2003). GnRH-a tend to produce a more hypo-estrogenic state than danazol with more severe menopausal side effects such as hot flushes, insomnia, reduced libido, and vaginal dryness (Prentice 1996). A common pattern of cardiovascular side effects such as thrombosis (Vasilakis 1999). The surgical management of endometriosis is also far from satisfactory. Two RCTs (Abbott 2004; Sutton 1994) and several observational studies (Abbott 2003; Fedele 2004; Wheeler 1983) demonstrate significant symptomatic relief after conservative laparoscopic surgery but in many cases these benefits were relatively short lived, with up to 44% of women experiencing a return of symptoms after one year (Lapp 2000). Surgery is also associated with the potential for serious side effects, with one study reporting that 2% to 3% of cases had post-operative bowel perforations with peritonitis (Koninckx 1996); an anonymous survey of 1951 gynaecologists revealed a significant number of unreported complications suggesting that the incidence of complications is higher than is commonly stated (Feste 1999).

In summary, current treatments all have high rates of reoccurrence and their short-term benefits have to be balanced with concerns over immediate and longer-term side effects.

How the intervention might work

Chinese herbal medicine (CHM) is a system of medicine with an unbroken written tradition stretching back over two thousand years. Although endometriosis as a distinct entity did not exist in the classical tradition, the symptoms of dysmenorrhoea, dysuria, dyschezia, menorrhagia, and so on, were systematically differentiated and apparently well treated (Wu 1997). A common pattern underlying these conditions is the presence of what is known as stagnation of the blood and Qi (vital energy) causing localised obstructions and leading to pain. This is interestingly similar to the modern biomedical understanding of the central role that endometrial lesions play in the symptomatology of the disease.

We have recently seen increasing integration of western medicine and CHM in China, and in the past 10 years the use of laparoscopic diagnosis has allowed some evaluation of the specific benefits of CHM in the treatment of endometriosis through a number of clinical trials. For example, one Chinese language review identified 13 randomised clinical trials on CHM treatment of endometriosis from Chinese literature published between 1994 and 2000 (Xu et al 2004). In these trials 1076 women were involved and Chinese herbal medicines were applied either alone or in combination with biomedical drugs. The suggested mechanism of Chinese medicine for endometriosis may involve regulation of endocrine and immune systems, improvement of blood circulation, and anti-inflammatory activity (Huang 2006; Xu et al 2004).

Whilst herbs might contain phyto-steroids these are considerably less potent than synthetic steroids. There are no reports of any androgenic or cholesterol raising adverse effects from herbs used in the treatment of endometriosis.

Why it is important to do this review

At present no other English language systematic review has been conducted to evaluate the results of these studies. We have reviewed the available Chinese and English language literature on the subject in an attempt to establish whether CHM has a valid role in the treatment of this common and disabling condition.

OBJECTIVES

To review the effectiveness and safety of CHM in alleviating endometriosis-related pain and infertility.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished randomised controlled trials (RCTs) were eligible for inclusion. We excluded non-randomised studies (for example studies with evidence of inadequate methods of sequence generation such as alternate days, patient numbers) as they are associated with a high risk of bias. If any crossover trials were found, it was planned to include only data from the first phase, as the crossover is not a valid design in this context.

Types of participants

Trials including women of reproductive age with a laparoscopically confirmed diagnosis of endometriosis were eligible for inclusion.

Types of interventions

Trials comparing the following interventions were eligible for inclusion:

CHM versus placebo;
CHM versus conventional biomedical treatment;
CHM plus conventional biomedical treatment versus conventional biomedical treatment alone;
One CHM strategy versus a different CHM strategy.

Types of outcome measures

Primary outcomes
- Relief of endometriosis-related pain (both in the long term and short term)

Secondary outcomes
- Improvement in fertility rates (live birth or pregnancy)
- Reduction in the size and extent of endometrial cysts
- Improvement in quality of life scores
- Improvement of endometriosis-related symptoms apart from pain (e.g. fatigue)
- Adverse effects resulting from the CHM intervention
- Rates of reoccurrence

It was our intention to investigate long-term outcomes (and several of the studies we had to reject reported on recurrence rates) but using the trials that were eligible for inclusion we were not able to fulfil this objective in terms of symptomatic relief. Wu SZ 2006a did have a 24 month follow up but this was to assess pregnancy outcomes.

Search methods for identification of studies

We searched for all published and unpublished RCTs of CHM for endometriosis, without language restriction and in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator:

Electronic searches

We searched the following on the 31/10/11:
1. Menstrual Disorders and Subfertility Group Trials Register;
2. Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library) using the keywords: endometriosis, Chinese herbal medicine;
3. MEDLINE, EMBASE, AMED, CINAHL, and NLH English language electronic databases (from inception to the present); for a detailed search string see Appendix 1;
4. Chinese language electronic databases Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chinese Sci & Tech Journals (VIP), Traditional Chinese Medical Literature Analysis and Retrieval System (TCMLARS), and Chinese Medical Current Contents (CMCC) using the following terms: Zigong Neimo Yiwei Zheng (endometriosis), Chuantong Yiyao (traditional medicine), Zhong Yao (Chinese medicine), Cao Yao (herbal medicine), Tiqu Yao (plant extract), Buchong Yiyao (complementary medicine).

Searching other resources

JPL searched the Chinese language databases to identify trials that could be considered for inclusion in this review. AF did the same in the English language databases. We handsearched reference lists of articles retrieved by the search.

Data collection and analysis

Selection of studies
AF and SC (in the UK) and JPL (in China) independently reviewed the studies retrieved by the search and identified those eligible for inclusion. Owing to some confusion over the term 'randomised' in Chinese research papers, the authors of all papers considered suitable for inclusion were telephoned by JPL to confirm that proper randomisation procedures had been applied. GL and PL acted in an advisory capacity during this process. Any differences of opinion were resolved through discussion.

Data extraction and management

Two review authors independently extracted data from eligible studies, resolving any disagreements by discussion. Data extracted included study characteristics and outcome data.

Assessment of risk of bias in included studies
AF and SC (in the UK) and JPL (in China) independently reviewed the studies retrieved by the search and rated them using the Cochrane risk of bias assessment tool (www.cochrane-handbook.org) to assess: selection bias (random sequence generation and allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessors); attrition bias (incomplete outcome data); reporting bias (selective reporting); and other sources of bias. Disagreements were resolved by discussion or by a third review author. GL and PL acted in an advisory capacity during this process.

See Figure 1; Figure 2.
Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.
Trials were assessed to determine how successfully selection, performance, detection, attrition, reporting and other biases were minimized.

**To minimize bias related to random sequence generation and allocation concealment (selection bias)**
- A clear and acceptable method of randomisation
- Quality of allocation concealment

**To minimize bias related to blinding (performance and detection bias)**
- Were the participants blinded?
- Were the outcome assessors blinded to the assignment status?

**To minimize bias related to incomplete outcome data (attrition bias)**
- A record of the number of randomised participants excluded or lost to follow up
- A record of treatment compliance
- An intention-to-treat analysis

**To minimize selective reporting (reporting bias)**
- Were the outcome measures used clearly defined and clearly and consistently reported?

**To minimize other bias**
- Comparable treatment and control groups at entry
- Confirmation that the care programmes, apart from the trial options, were identical

For each domain of bias, we assigned one of the following three judgements: low risk of bias, unclear risk of bias, or high risk of bias.

**Measures of treatment effect**

For dichotomous data we used the numbers of events in the control and intervention groups of each study to calculate risk ratios (RRs) and 95% confidence intervals (CIs). For continuous data (for example quality of life), if all studies reported exactly the same outcomes we planned to calculate mean difference (MDs) between treatment groups; or, if similar outcomes were reported on different scales, to calculate the standardised mean difference (SMD). However, no continuous data were reported by the included studies.

**Unit of analysis issues**

Analysis was per woman randomised.

**Dealing with missing data**

The data were analysed on an intention-to-treat basis as far as possible and attempts were made to obtain missing data from the original trialists. Where data were unobtainable, it was planned that only the available data would be analysed.

**Assessment of heterogeneity**

We considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. If pooling was undertaken we planned to assess statistical heterogeneity by the measure of the I² statistic. An I² measurement greater than 50% would be taken to indicate substantial heterogeneity (Higgins 2003; Higgins 2008). If we detected substantial heterogeneity, we planned to explore possible explanations in sensitivity analyses and to take any statistical heterogeneity into account when interpreting the results, especially if there was any variation in the direction of effect.

Only two trials (testing CHM against different conventional biomedical interventions) were eligible for this review so no assessment of statistical heterogeneity was undertaken (Higgins 2003).

**Assessment of reporting biases**

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, the authors aimed to minimize their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. If there were 10 or more studies in an analysis, it was planned to use a funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

**Data synthesis**

If the studies were sufficiently similar, we planned to combine the data using fixed-effect models in the following comparisons:
- CHM versus placebo;
- CHM versus conventional biomedical treatment;
- CHM plus conventional biomedical treatment versus conventional biomedical treatment alone;
- CHM strategy versus another CHM strategy.

Only two trials (testing CHM against different conventional medical interventions) were eligible for this review so no meta-analysis was undertaken (Higgins 2003).

**Subgroup analysis and investigation of heterogeneity**

If data were available, we planned to undertake subgroup analysis according to the type of intervention (for example type of biomedical treatment, type of CHM).
Sensitivity analysis

If there were sufficient studies, we planned to conduct sensitivity analyses for the primary outcome to determine whether the review conclusions would have differed if eligibility were restricted to studies without high risk of bias.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

One hundred and ten trials were initially identified in the 2009 review. A further 39 were identified for the updated review in November 2010, and an updated search identified an additional 47 clinical trials in October 2011 using the search strategy described above. All of these trials took place in China and were reported in Chinese. However, no new trials were eligible to be included based on the previous inclusion criteria (see table ‘Characteristics of excluded studies’).

Included studies

Only two trials (Wu SZ 2006a; Wu SZ 2006b) were able to be included in this review. The trials took place in a hospital outpatient department in China and were reported in Chinese. They were presented in four publications: one trial was reported in three publications each describing different outcome measures (Wu SZ 2006b). The review authors were able to confirm adequate randomisation and they acquired more information about methods and data via telephone discussion.

Participants

In total, 158 women were included in the two trials. The average age was 30 years (SD 4.5 years) with an age range of 23 to 45 years.

Diagnostic criteria

Laparoscopic diagnosis and American Fertility Society (AFS) staging
Vaginal or rectal B-ultrasound
All participants were diagnosed according to traditional Chinese medicine as having Qi and blood stagnation with an underlying kidney deficiency.

Herbal intervention

In one trial (Wu SZ 2006b), women were randomised into three groups: CHM endometriosis pills (Nei Yi Wan) (n = 16), CHM endometriosis pills (Nei Yi Wan) plus CHM enema (n = 24), or danazol (n = 18). In another trial, women were randomised into two groups: Nei Yi Wan plus herbal enema (n = 48) or gestrinone (n = 52) (Wu SZ 2006a).

Herb formulation

Details of which herbs were used are included in the table Characteristics of included studies.

Comparisons and control groups

Chinese herbs were used in the active groups. Danazol or gestrinone were used in the control groups.

Outcomes measured

The included trials used the same Chinese validated outcomes (CAITWN 1991) and divided responses to treatment into four categories: ‘symptomatic relief’ described a complete resolution of all symptoms and signs and included pregnancy, when desired, within three years of stopping treatment; ‘significant improvement’ described when most symptoms resolved and pelvic masses were reduced in size; ‘improvement’ described symptomatic improvement and no worsening of symptoms within three months of stopping the treatment but only minor or no change in pelvic masses; and finally ‘no effect’ was where symptoms either remained unchanged or worsened during the intervention.

Fertility rates were reported in one trial (Wu SZ 2006a). The two trials reported the incidence of adverse effects as an outcome.

Data were also presented describing changes in the biochemical markers CA 125, a cancer antigen, and EmAb. Whilst these may reflect the measurable effects of an intervention and contribute to the biological plausibility of CHM, they are not considered in this review. Neither would they be considered as ‘objective disease markers’ in western gynaecological practice.

Excluded studies

In the first analysis, 85 trials were excluded from the review for the following reasons: 43 trials did not have equal numbers in the experimental and control groups and did not present a clear account of the randomisation procedures leading to this discrepancy; 13 trials combined CHM with several other non-herbal therapeutic interventions (such as acupuncture) as part of the experimental intervention; 10 trials used non-authorised or experimental treatments such as mifepristone or tamoxifen as the control intervention; six trials did not report results using validated diagnostic criteria or outcomes measures; five trials had insufficient or unclear
data to enable a reasonable assessment of the trial; four trials did not consider the primary or secondary outcomes defined for this review; three trials were not RCTs; and one was a duplicate report. This left 25 randomised trials for consideration. However, insistence on a laparoscopic diagnosis and a new Cochrane requirement to contact all authors of Chinese RCTs to check for adequate randomisation procedures resulted in a second analysis where 12 trials were excluded because they did not have a laparoscopically confirmed diagnosis. Of the remaining 13 trials, 11 were excluded because: for three the authors could not be contacted; two authors refused to respond to questions relating to randomisation; three trials allocated participants according to patient preference; and three trials were quasi-randomised, according to the time of their first visit.

An updated search completed in October 2010 identified another 39 trials for consideration. Only five of these trials reported details of laparoscopic confirmation or randomisation. After phone call confirmations it was apparent that three of these papers did not employ adequate randomisation and for the remaining two trials the authors could not be contacted. As a result there has been no amendment to the previous findings of this review. An further updated search in October 2011 identified 47 trials, and only four trials appeared eligible for inclusion. After checking against inclusion criteria, they were all excluded and the reasons were presented in the table ‘Characteristics of excluded studies’.

Risk of bias in included studies

See Figure 1; Figure 2

The included trials (Wu SZ 2006a; Wu SZ 2006b) described adequate (‘A’) randomisation and allocation concealment methods using a random numbers generated randomisation sequence which was transferred to sealed envelopes. The trials also reported single blinding for participants, and assessor blinding. Both trials were given an overall ‘B’ status with a moderate risk of bias.

Allocation

Both studies were rated as at low risk of this bias because they used acceptable methods of randomisation and allocation concealment.

Blinding

Both studies were rated as at high risk of these biases because of the use of an active herbal enema without any inert control.

Incomplete outcome data

Both studies were rated as at low risk of this bias because few or no participants were excluded from the analysis.

Selective reporting

Both studies were rated as at low risk of this bias because they reported the expected outcomes.

Other potential sources of bias

Both studies were rated as at low risk of other potential sources of bias.

Effects of interventions

See: Summary of findings for the main comparison CHM compared to gestrinone and danazol

Chinese herbal medicine versus gestrinone

Overall, 100% of women in both the CHM and the gestrinone groups showed some improvement in their symptoms. However, in some participants this may have been a relatively minor improvement in symptoms whilst in others it related to more substantial resolution of pelvic masses, disappearance of symptoms, and a successful pregnancy.

There was no significant difference between the CHM Nei Yi Wan (oral plus enema) and gestrinone for the symptomatic relief rate (95.65% versus 93.87%; RR 1.02, 95% CI 0.93 to 1.12) (Wu SZ 2006a). The intention-to-treat analysis also showed no significant difference between the groups for the symptomatic relief rate (RR 1.04, 95% CI 0.91 to 1.18). The study followed the patients for one to 24 months for pregnancy. The number of participants with confirmed pregnancy was 4 (at 3 months), 17 (at 4 to 6 months), 8 (at 7 to 12 months), 2 (at 13 to 24 months), and 1 (at over 24 months) in the CHM group; while it was 0, 12, 12, 3, and 2 in the gestrinone group, respectively. There was no significant difference between the two groups with regard to the total pregnancy rate (69.6% versus 59.1%; RR 1.18, 95% CI 0.87 to 1.59) (Wu SZ 2006a).

Chinese herbal medicine versus danazol

In total, 100% of women in the CHM and danazol groups showed some improvement in their symptoms.

The CHM Nei Yi Wan and Nei Yi Wan plus enema groups reported a greater proportion of women obtaining symptomatic relief than for danazol (56.3% versus 11.1%; RR 5.06, 95% CI 1.28 to 20.05; and 62.5% versus 11.1%; RR 5.63, 95% CI 1.47 to 21.54, respectively) (Wu SZ 2006b).

Oral plus enema administration of the CHM Nei Yi formulation showed a greater reduction in average dysmenorrhea pain scores than with danazol (MD -2.90, 95% CI -4.55 to -1.25; P < 0.01). There were no significant differences between either CHM Nei Yi pills and danazol (MD -1.01, 95% CI -3.11 to 1.09) or CHM oral plus enema and danazol (MD -1.89, 95% CI -3.89 to 0.11).
Combined administration of CHM Nei Yi, orally and by enema, showed a greater improvement measured as the disappearance or shrinkage of adnexal masses than did treatment with danazol (RR 1.70, 95% CI 1.04 to 2.78). For lumbosacral pain, rectal discomfort, or vaginal nodules tenderness there was no significant difference either between CHM Nei Yi pills and danazol or between CHM oral plus enema and danazol (Comparisons 2.3 to 2.6).

Adverse effects

No significant adverse effects were observed in the 46 participants who received CHM Nei Yi Wan plus CHM Nei Yi enema (Wu SZ 2006a). Thirteen out of 49 participants who received gestrinone developed acne, 19 developed increased glutamic alanine transaminase (GPT) levels (which returned to normal after termination of the treatment), and 31 had oligomenorrhoea (Wu SZ 2006a). In the second trial (Wu SZ 2006b), four patients had a dry mouth, and one patient had acne of the 16 patients who took CHM Nei Yi Wan; two patients had dry mouth, 11 had rectal tenesmus in the initial two weeks, and one had a weight gain of 3 kg in the 24 patients who received CHM oral plus enema. In contrast, in the danazol group 13/18 developed acne, 3/18 had a weight gain of 3 kg, 2/18 a weight gain of 2 kg, 1/18 a weight gain of 1.5 kg. 2/18 increased GPT levels, and 4/18 oligomenorrhoea.

Discussion

Summary of main results

There are only very limited data available from two small trials comparing the same CHM interventions with two conventional treatments for endometriosis, danazol and gestrinone. The comparison of CHM with gestrinone showed no evidence of a difference between the two groups in the rates of symptomatic relief and pregnancy. However, there were fewer side effects in the CHM group than in the gestrinone group. It should be noted that the shrinkage of adnexal masses reported in these trials was determined by ultrasound investigation and not via laparoscopy.

Overall completeness and applicability of evidence

There was an unexplained discrepancy in the rates of symptomatic relief between the two trials. Wu SZ 2006a reported a symptomatic relief rate for CHM of 95.65% and 93.87% for gestrinone; whilst Wu SZ 2006b reported symptomatic relief rates for oral CHM, oral plus enema CHM, and danazol of 56.3%, 62.5%, and 11.1%, respectively. Both trials used the same standardised assessment measures (CAITWN 1991), however discussion with the authors revealed that in Wu SZ 2006a laparoscopic investigation and confirmation of endometriosis was combined with active surgical treatment for both groups whilst in Wu SZ 2006b laparoscopy was solely for diagnostic purposes. This explains the substantial difference in rates of symptomatic relief between the two groups but introduces a new variable into the analysis. In effect we have one trial (Wu SZ 2006a) comparing laparoscopic treatment with either gestrinone or CHM as a post-surgical adjuvant treatment and a second trial (Wu SZ 2006b) comparing purely medical interventions. Both trials reflect treatment options that are relevant to the management of endometriosis.

The completeness of the available data is limited by the tendency of Chinese reports to be restricted to two to three pages in length. These reports do not have the same depth of information required by Western journals. With regard to fertility, the papers do describe how many women are married and how many are sexually active but there are no relevant data on fertility (duration, clinical investigations etc). Other symptoms such as dyspareunia may be included in the overall analysis of symptoms but are not described as a separate outcome.

Fundamental to the understanding of endometriosis in Chinese medicine is the notion of stagnation of Qi, or vital energy, as a prerequisite for the subjective experience of pain; and of blood, which tends to localise and intensify the experience of pain and can lead to the formation of distinctive, substantial lesions. Differential diagnosis is further refined into a number of single or complex syndromes on the basis of information derived from traditional methods of clinical assessment such as tongue and pulse diagnosis, investigation of aetiological factors, the subjective presentation of the symptoms of endometriosis (for example a description of the nature and location of the pain), and an evaluation of the general health of the patient as evidenced from sleep patterns, digestive status, and subjective sense of temperature for example. This complex and involved process is considered essential to the successful treatment of the disease.

For a comprehensive introduction to Chinese medicine see Maciocia (Maciocia 1998).

Quality of the evidence

There are no clear data on participant blinding during the trials. Although Wu SZ 2006a and Wu SZ 2006b claimed to be single blind trials, it is difficult to know how this was maintained in the group receiving the herbal enema. There was no evaluation of the success of blinding during the trials. This increased the risk of bias in the trials.

Many of the trials that were excluded due to poor methodology described the ability of CHM to act as an immunological and hormonal modulator, and to break down the fibrous adhesions that characterize endometriosis. These data are interesting and suggest biologically plausible mechanisms that could underpin the
effectiveness of CHM. However, a detailed analysis of this work is beyond the remit of this review.

Agreements and disagreements with other studies or reviews

Compared with danazol, both the CHM groups produced a greater rate of symptomatic relief. However, the confidence intervals for these outcomes were very large, which brings into question the reliability of the findings. The combined oral plus enema approach also led to women in the CHM group having a greater reduction of average dysmenorrhoea scores and more shrinkage of adnexal masses than for those taking danazol. There was no difference between the oral CHM group and the danazol group for any of these outcomes. There was no evidence of a difference between CHM and danazol in the relief of lumbosacral pain or rectal irritation. Women taking danazol exhibited considerably more adverse effects than did women taking CHM.

A U T H O R S ’ C O N C L U S I O N S

Implications for practice

The included trials suggest that following laparoscopic surgery, combined oral and enema administration of CHM has a comparable beneficial effect to gestrinone but with fewer adverse effects. Oral and enema administration of CHM may be more effective than danazol in providing extended relief of endometriosis symptoms and in shrinking adnexal masses, with fewer adverse effects. However, these are two very small trials and it may not be possible to generalize the results.

Further research, with larger numbers of participants, is required to substantiate these results and to explore the role of CHM as a stand-alone medical option or as a post-surgical adjuvant in the treatment of endometriosis.

Implications for research

Despite the large number of clinical trials exploring the role of CHM in the treatment of endometriosis, unequal group sizes, and a lack of validated outcomes. The most worrying shortcoming in the trial reports is a misunderstanding of what is required for a randomised controlled trial. The use of quasi-randomisation or allocation according to patient preference does not constitute adequate randomisation and allows an unacceptably high risk of bias in a trial. There is an urgent need for Chinese researchers to adopt rigorous standards of randomisation and allocation concealment and to present the data in a transparent fashion. The nature of CHM and herbal products make blinding problematic and CHM clinical trials may have to be more pragmatic. In addition, it was not clear from the trial reports that laparoscopy involved active treatment in one case whilst in the other it was used only for diagnostic purposes. This is poor quality reporting that has the potential to confuse and undermine CHM research.

It is important that transparent, pragmatic but rigorous clinical research methodologies are developed that accommodate the complex, individualised, and changing nature of CHM interventions. Future research should provide more detailed accounts of symptomatic changes to include, for example, dyspareunia and daily pelvic pain rather than amalgamating these symptoms into an overall measure of change. In addition, future research should incorporate quality of life outcome measures and qualitative research to provide a more detailed account of the effect of the CHM intervention on the lives of women suffering from this disease. Finally, it is also essential that any research investigating CHM for endometriosis incorporates an extended follow-up period to identify any long-term benefits and to make an accurate record of rates of recurrence after CHM treatment. This will be an important point of comparison between CHM and conventional medicine.

In the period between the original review in 2009 and the revised review in 2012 it appears that the methodological quality of clinical trials of CHM for endometriosis has not improved. This apparent lack of development is unfortunate as it continues to undermine the ability of CHM trials to contribute to rigorous systematic reviews.

A C K N O W L E D G E M E N T S

The authors wish to acknowledge the previous authors of this review title, Wang Hongjing, Dave Olive and Sisi Chen, and Yun Xia for helping with data extraction and analyses.
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**Wu SZ 2006b** {published data only}

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**Fan 2003** {published data only}

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**Fan HX 2004** {published data only}

**Fei 2004** {published data only}
Chinese herbal medicine for endometriosis (Review)

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He RZ 2004 [published data only]

Hou 2010 [published data only]

Hu 2000 [published data only]

Hu 2005 [published data only]

Huang 2000 [published data only]

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Huang 2010 [published data only]

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Chinese herbal medicine for endometriosis (Review)

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Leng 2009 [published data only]

Li 1999 [published data only]

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Li 2006 [published data only]

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Li 2007a [published data only]

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Liao 2010 [published data only]

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Lin 2006a [published data only]

Li QX 2009 [published data only]

Liu 1998 [published data only]

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Shen XJ 2011 [published data only]  

Shang 2005 [published data only]  

Si 2006 [published data only]  

Su CZ 2002 [published data only]  

Sun YZ 2003 [published data only]  

Tang 2009 [published data only]  

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Xu 2004 [published data only]

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Xue 2009 [published data only]

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Lapp 2000

Lebovic 2001

Ling 1999

Low 1993

Maciocia 1998

Malinak 1980

Moore 2004

Noble 1997

Ohtake 2003

Parazzini 2000

Prentice 2004

Selak 2007
Sheng 1998

Stenchever 2001

Strauss 1992

Sutton 1994

Vasilakis 1999

Vercellini 1993

Wheeler 1983

Winkel 2003

Wu 1997

Xu et al 2004

Zondervan 2001

* Indicates the major publication for the study
# Characteristics of included studies [ordered by study ID]

## Wu SZ 2006a

### Methods
- **Trial design:** parallel randomised controlled trial
- **Blinding:** single blinding
- **Study duration:** December 1999 to May 2005
- **Statistics:** adequate (Chi\(^2\) test used for ‘overall improvement’)
- **Funding source declared**

### Participants
- **100 cases of endometriosis complicated by infertility**
- **Experimental group:** 48
- **Control group:** 52
- **Drop-out rate:** 5% (2 from experimental group, 3 from control group)
- **Laparoscopic diagnosis:** yes
- **Other diagnostic criteria:** Chinese validated criteria
- **Baseline comparison:** adequate

### Interventions
- **Nei Yi pills** (10g twice daily) plus **Nei Yi enema** (70ml daily) versus gestrinone (0.25 mg twice a week) for 3 months
  - **Nei Yi pills** consisted of:
    - Dan Shen (Salviae multiorrhizae Radix), Xue Jie (Draconis Sanguis), San Leng (Sparganii Rhizoma), E Zhu (Curcumae Rhizoma), Tao Ren (Persicae Semen), San Qi (Notoginseng Radix), Dang Gui (Angelicae Sinensis), Gui Zhi (Cinnamomum Ramulus), Xiang Fu (Cyperi Rhizoma), Niu Xi (Achyranthis Bidentatae Radix)
  - **Nei Yi enema** consisted of:
    - Dan Shen (Salviae multiorrhizae Radix), Xue Jie (Draconis Sanguis), Chi Shao (Paeoniae Rubrae Radix), Hu Zhang (Radix et Rhizoma Polygoni Cuspidati), San Leng (Sparganii Rhizoma), E Zhu (Curcumae Rhizoma), Tao Ren (Persicae Semen)
- **Treatment duration:** 3 months

### Outcomes
- **A) Clinical outcomes:**
  1. symptomatic relief (defined as disappearance of symptoms, pelvic mass; pregnancy or birth within 3 years for those with infertility)
  2. significant improvement (almost complete disappearance of symptoms or shrinkage of pelvic mass by ultrasound; or pregnancy)
  3. improvement (relief of symptoms but not disappearance, no change or moderate shrinkage of pelvic mass)
  4. no effect (no change of symptoms or become worse)
  5. overall improvement (1+2+3)
- **B) Adverse effects**

### Notes
- Follow up from 1-24 months

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## Risk of bias

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<th>Support for judgement</th>
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</table>

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**Adequate sequence generation** | **Low risk** | Randomisation achieved using random number sequence from table in statistical textbook
---|---|---

**Allocation concealment** | **Low risk** | Allocation concealment achieved by sorting numbers into envelopes

**Blinding**  
All outcomes | **High risk** | Although described as patient and assessor blinded (and confirmed with author) there is no description of an attempt to match the herbal enema with an inert control, so it is very unlikely patients were not aware of which group they were allocated to

**Incomplete outcome data addressed**  
All outcomes | **Low risk** | Two cases in treatment group and three cases in control group were lost during follow up. Adequate outcomes data presented

**Free of selective reporting** | **Low risk** | Identified outcomes adequately reported as compared with the description in methods

**Free of other bias** | **Low risk** | No source of other bias noted

---

### Wu SZ 2006b

**Methods**

| Trial design: parallel randomised controlled trial  
| Blinding: described as single blinding  
| Study duration: December 1999 to October 2003  
| Statistics: adequate (Mann-Whitney test and Annova test used for data analyses)  
| Funding source declared

**Participants**

| 58 cases of endometriosis with clear inclusion and exclusion criteria  
| Experimental group 1: 16  
| Experimental group 2: 24  
| Control group: 18  
| Drop-out rate: 0  
| Laparoscopic diagnosis: yes  
| Other diagnostic criteria: Chinese validated criteria  
| Baseline comparison: adequate

**Interventions**

| Experimental group 1: Nei Yi pills (10g twice daily)  
| Experimental group 2: Nei Yi pills (10g twice daily) plus Nei Yi enema (70ml daily)  
| Control group: danazol (400mg/day)  
| Nei Yi pills consisted of:  
Nei Yi enema consisted of:
Dan Shen (Salviae multiorrhizae Radix), Xue Jie (Draconis Sanguis), Chi Shao (Paeonia rubra Radix), Hu Zhang (Radix et Rhizoma Polygoni Cuspidati), San Leng (Sparganii Rhizoma), E Zhu (Curcumae Rhizoma), Tao Ren (Persicae Semen)

Treatment duration: 3 months

Outcomes
A) Clinical outcomes:
1. symptomatic relief (defined as disappearance of symptoms, pelvic mass; pregnancy or birth within 3 years for those with infertility)
2. significant improvement (almost complete disappearance of symptoms, shrinkage of pelvic mass by ultrasound; or pregnancy)
3. improvement (relief of symptoms but not disappearance, no change or moderate shrinkage of pelvic mass)
4. no effect (no change of symptoms or become worse)
5. overall improvement (1+2+3)

B) Adverse effects

Notes

Risk of bias

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<th>Support for judgement</th>
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<td>Randomisation for allocation of three groups was generated through random number table</td>
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<td>Allocation concealment</td>
<td>Low risk</td>
<td>Allocation sequence was concealed through numbered, sealed, opaque envelopes</td>
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## Characteristics of excluded studies [ordered by study ID]

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<tr>
<td>Bian 2009</td>
<td>No laparoscopic confirmation</td>
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<tr>
<td>Cai 1999</td>
<td>Unequal group size with no account of randomisation process.</td>
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<td>Chai H 1996</td>
<td>Unequal group size with no account of randomisation process.</td>
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<td>Chai LS 2004</td>
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<td>Che 2006</td>
<td>Unequal group size with no account of randomisation process. Also non validated outcomes measures</td>
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<td>Chen 2003</td>
<td>Unequal group size with no account of randomisation process.</td>
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<td>Chen 2006</td>
<td>Uses an experimental treatment (oral provera) as part of the active and control intervention</td>
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<td>Chen 2006a</td>
<td>Combines CHM with therapeutic ultrasound.</td>
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<td>Chen 2010</td>
<td>Didn't consider pain as a primary outcome</td>
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<td>Chui YX</td>
<td>No clear data on diagnostic or outcomes criteria.</td>
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<td>Cui 2010</td>
<td>No clear data on diagnostic criteria. Didn't consider pain as a primary outcome</td>
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<td>Fan 2003</td>
<td>Combined TCM with experimental WM treatment (mifepristone).</td>
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<td>Group allocation according to patient preference</td>
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<td>Fu 2005</td>
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<tr>
<td>Mo 2010</td>
<td>Control group used experimental WM treatment(mifepristone)</td>
</tr>
<tr>
<td>Ou 2007</td>
<td>The trial did not use validated outcomes measures.</td>
</tr>
<tr>
<td>Pan XR 2003</td>
<td>No laparoscopic confirmation</td>
</tr>
<tr>
<td>Qi 2006</td>
<td>Unequal group size with no account of randomisation process.</td>
</tr>
<tr>
<td>Qi YH 2011</td>
<td>130 confirmed endometriosis patients were randomised into herbal treatment group (n=75) or no intervention control group (n=55) after laparoscopic surgery. After our telephone interview, we were told they used random number table to allocate patients. However, some patients (about 10) assigned to control group asked for herbal treatment and they were analysed in the herbal treatment group</td>
</tr>
<tr>
<td>Qian 2000a</td>
<td>No validated outcomes criteria.</td>
</tr>
<tr>
<td>Qian J 2000</td>
<td>No laparoscopic confirmation</td>
</tr>
<tr>
<td>Qiu L 2005</td>
<td>Authors could not be contacted to confirm randomisation details</td>
</tr>
<tr>
<td>Qiu YJ 2004</td>
<td>No laparoscopic confirmation</td>
</tr>
<tr>
<td>Quan 2010</td>
<td>Group allocation according to the time of the patients’ first visit</td>
</tr>
<tr>
<td>Ren YL 2005</td>
<td>Unequal group size with no account of randomisation process.</td>
</tr>
<tr>
<td>Ren YL2005</td>
<td>No laparoscopic confirmation</td>
</tr>
<tr>
<td>Shen XJ 2011</td>
<td>A clinical case series study without control group.</td>
</tr>
<tr>
<td>Shong 2005</td>
<td>Unequal group size with no account of randomisation process.</td>
</tr>
<tr>
<td>Si 2006</td>
<td>No validated outcomes criteria.</td>
</tr>
<tr>
<td>Su CZ 2002</td>
<td>No laparoscopic confirmation</td>
</tr>
<tr>
<td>Sun YZ 2003</td>
<td>No laparoscopic confirmation</td>
</tr>
<tr>
<td>Tang 2009</td>
<td>No laparoscopic confirmation</td>
</tr>
<tr>
<td>Year</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Tang 2010</td>
<td>Group allocation according to the time of the patients' first visit</td>
</tr>
<tr>
<td>Wang 1996</td>
<td>Unequal group size with no account of randomisation process.</td>
</tr>
<tr>
<td>Wang 1999</td>
<td>Too many treatment variables. CHM combined with penicillin, metronidazole + oral contraceptive compared with gestrinone</td>
</tr>
<tr>
<td>Wang 2001</td>
<td>No validated outcomes measures. Control group used experimental treatment (tamoxifen)</td>
</tr>
<tr>
<td>Wang 2002</td>
<td>Used tamoxifen as a control for CHM. This is not a standard Western medical treatment for endometriosis</td>
</tr>
<tr>
<td>Wang 2002a</td>
<td>No information on pain as a primary outcome.</td>
</tr>
<tr>
<td>Wang 2004</td>
<td>Unequal group size with no account of randomisation process.</td>
</tr>
<tr>
<td>Wang 2004a</td>
<td>Unequal group size with no account of randomisation process.</td>
</tr>
<tr>
<td>Wang 2005</td>
<td>Used experimental treatment (tamoxifen) as the control group</td>
</tr>
<tr>
<td>Wang 2006a</td>
<td>Too many treatment variables. Also use Tamoxifen with CHM as active treatment with unequal group size and no account of randomisation</td>
</tr>
<tr>
<td>Wang 2006b</td>
<td>Pain was not the primary outcome and the trial only provided data for pain reduction on 7/78 participants in the trial group and 12/78 in the control group</td>
</tr>
<tr>
<td>Wang 2009</td>
<td>Didn't consider pain as a primary outcome</td>
</tr>
<tr>
<td>Wang 2010</td>
<td>Didn't consider pain as a primary outcome</td>
</tr>
<tr>
<td>Wang LX 2006</td>
<td>Authors could not be contacted to confirm details of randomisation</td>
</tr>
<tr>
<td>Wang W 2009</td>
<td>Didn't consider pain as a primary outcome</td>
</tr>
<tr>
<td>Wang XR 2009</td>
<td>Didn't consider pain as a primary outcome</td>
</tr>
<tr>
<td>Wu 1999</td>
<td>Unequal group size with no account of randomisation process.</td>
</tr>
<tr>
<td>Wu 2000a</td>
<td>Confounding Comparison of Laparoscopy + CHM with CHM and with Danazol. Too many treatment variables</td>
</tr>
<tr>
<td>Wu 2003</td>
<td>No control group-not a randomised controlled trial.</td>
</tr>
<tr>
<td>Wu 2004</td>
<td>Unequal group size with no account of randomisation process.</td>
</tr>
<tr>
<td>Wu 2006c</td>
<td>Part of a series of reports on the same trial. However this report considered the endometriosis markers EmAb and CA125 and did not provide any new clinical data relevant to this review</td>
</tr>
<tr>
<td>Authors</td>
<td>Notes</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Wu 2009</td>
<td>Authors could not be contacted to confirm randomisation details</td>
</tr>
<tr>
<td>Wu HY 2009</td>
<td>Didn’t consider pain as a primary outcome</td>
</tr>
<tr>
<td>Wu SS 2000</td>
<td>No laparoscopic confirmation</td>
</tr>
<tr>
<td>Wu XJ 2009</td>
<td>Too many treatment variables</td>
</tr>
<tr>
<td>Xia 2010</td>
<td>No laparoscopic confirmation</td>
</tr>
<tr>
<td>Xiang 2001</td>
<td>Uses acupuncture as part of the active intervention.</td>
</tr>
<tr>
<td>Xiong 2004</td>
<td>Too many treatment variables (CHM combined with indomethacin or norethisterone or danazol)</td>
</tr>
<tr>
<td>Xu 2004</td>
<td>Unequal group size with no account of randomisation process.</td>
</tr>
<tr>
<td>Xu 2004a</td>
<td>Unequal group size with no account of randomisation process.</td>
</tr>
<tr>
<td>Xu 2004b</td>
<td>Unequal group size with no account of randomisation process.</td>
</tr>
<tr>
<td>Xu 2005</td>
<td>Unequal group size with no account of randomisation process.</td>
</tr>
<tr>
<td>Xu HX 2011</td>
<td>Trial was claimed to be randomised, but after we contacted with authors, we were confirmed that they did not implement real randomisation process to allocate patients</td>
</tr>
<tr>
<td>Xuan JS 2005</td>
<td>Quasi randomised according to the time of patient presentation</td>
</tr>
<tr>
<td>Xue 2009</td>
<td>Didn’t consider pain as a primary outcome</td>
</tr>
<tr>
<td>Yan 2004</td>
<td>Insufficient data about outcomes criteria and unequal group size with no account of randomisation process</td>
</tr>
<tr>
<td>Yang 2006</td>
<td>Quasi randomised according to the time of patient presentation</td>
</tr>
<tr>
<td>Yang 2006a</td>
<td>Uses experimental treatment (tamoxifen) as a control. Also unclear outcomes measures and no report on pain reduction</td>
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<tr>
<td>Yang 2006b</td>
<td>Unequal group size with no account of randomisation process and insufficient data for evaluation</td>
</tr>
<tr>
<td>Yang HY 2001</td>
<td>No laparoscopic confirmation</td>
</tr>
<tr>
<td>Yang Y</td>
<td>Included acupuncture in the active treatment group.</td>
</tr>
<tr>
<td>Ye LQ 2004</td>
<td>No laparoscopic confirmation</td>
</tr>
<tr>
<td>Yu 1996</td>
<td>Too many treatment variables—combined TCM plus hormonal treatment compared to a variety of hormonal control interventions. Also unequal group size with no account of randomisation process</td>
</tr>
<tr>
<td>Author/Year</td>
<td>Observations</td>
</tr>
<tr>
<td>------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Yu 2003</td>
<td>Not a randomised controlled trial.</td>
</tr>
<tr>
<td>Yu 2010</td>
<td>Control group used experimental WM treatment (mifepristone)</td>
</tr>
<tr>
<td>Yuan 2003</td>
<td>Unequal group size with no account of randomisation process. Also too many treatment variables including CHM, surgery, danazol and tamoxifen</td>
</tr>
<tr>
<td>Zhang 2004</td>
<td>Unequal group size with no account of randomisation process.</td>
</tr>
<tr>
<td>Zhang 2009</td>
<td>No validated outcomes criteria</td>
</tr>
<tr>
<td>Zhang 2010</td>
<td>Didn’t respond to questions relating to randomisation</td>
</tr>
<tr>
<td>Zhang HQ 2009</td>
<td>No laparoscopic confirmation</td>
</tr>
<tr>
<td>Zhao 2002</td>
<td>The trial did not use validated outcomes measures.</td>
</tr>
<tr>
<td>Zhao 2010</td>
<td>Randomised according to patient preference</td>
</tr>
<tr>
<td>Zhong 2009</td>
<td>Authors could not be contacted to confirm randomisation details</td>
</tr>
<tr>
<td>Zhou 2010</td>
<td>No clear data on diagnostic criteria</td>
</tr>
<tr>
<td>Zhu 2000a</td>
<td>Combined TCM with experimental WM treatment (mifepristone). Also unequal group size with no account of randomisation process</td>
</tr>
<tr>
<td>Zhu 2001</td>
<td>Unequal group size with no account of randomisation process.</td>
</tr>
<tr>
<td>Zhu FH 2011</td>
<td>Trial was claimed to be randomised, but no information on randomisation methods. Our telephone contacts failed after trying several times</td>
</tr>
<tr>
<td>Zhu HY 2002</td>
<td>No laparoscopic confirmation</td>
</tr>
<tr>
<td>Zhu L 2000</td>
<td>No laparoscopic confirmation</td>
</tr>
<tr>
<td>Zou 2010</td>
<td>No laparoscopic confirmation</td>
</tr>
</tbody>
</table>
## Data and analyses

### Comparison 1. CHM versus gestrinone

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Symptomatic relief</td>
<td>1</td>
<td>95</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.02 [0.93, 1.12]</td>
</tr>
<tr>
<td>2 Symptomatic relief rate (intention-to-treat)</td>
<td>1</td>
<td>100</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.04 [0.91, 1.18]</td>
</tr>
<tr>
<td>3 Pregnant rate (accumulated from 3-24 months of follow-up)</td>
<td>1</td>
<td>95</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.18 [0.87, 1.59]</td>
</tr>
</tbody>
</table>

### Comparison 2. CHM versus danazol

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Symptomatic relief</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 CHM Nei Yi pills vs Danazol</td>
<td>1</td>
<td>34</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>5.06 [1.28, 20.05]</td>
</tr>
<tr>
<td>1.2 CHM Nei Yi pills + CHM Nei Yi enema vs Danazol</td>
<td>1</td>
<td>42</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>5.63 [1.47, 21.54]</td>
</tr>
<tr>
<td>2 Dysmenorrhea score</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2.1 CHM Nei Yi pills vs Danazol</td>
<td>1</td>
<td>34</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-1.01 [-3.11, 1.09]</td>
</tr>
<tr>
<td>2.2 CHM Nei Yi pills + CHM Nei Yi enema vs Danazol</td>
<td>1</td>
<td>42</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-2.9 [-4.55, -1.25]</td>
</tr>
<tr>
<td>3 Lumbosacral pain relief</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>3.1 CHM Nei Yi pills versus Danazol</td>
<td>1</td>
<td>34</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.21 [0.86, 1.70]</td>
</tr>
<tr>
<td>3.2 CHM Nei Yi pills + CHM Nei Yi enema vs Danazol</td>
<td>1</td>
<td>42</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.15 [0.82, 1.62]</td>
</tr>
<tr>
<td>4 Rectal Irritation relief</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>4.1 CHM Nei Yi pills vs Danazol</td>
<td>1</td>
<td>24</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.67 [0.90, 3.10]</td>
</tr>
<tr>
<td>4.2 CHM Nei Yi pills + CHM Nei Yi enema vs Danazol</td>
<td>1</td>
<td>30</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.78 [0.99, 3.20]</td>
</tr>
<tr>
<td>5 Tenderness of vaginal nodules in posterior fornix</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>5.1 CHM Nei Yi pills vs Danazol</td>
<td>1</td>
<td>24</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.31 [0.87, 1.97]</td>
</tr>
<tr>
<td>5.2 CHM Nei Yi pills + CHM Nei Yi enema vs Danazol</td>
<td>1</td>
<td>29</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.26 [0.84, 1.90]</td>
</tr>
<tr>
<td>6 Adnexal masses disappearance or shrinkage</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>Outcome or subgroup title</td>
<td>No. of studies</td>
<td>No. of participants</td>
<td>Statistical method</td>
<td>Effect size</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------</td>
<td>---------------------</td>
<td>--------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>1 Symptomatic relief</td>
<td>1</td>
<td>40</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.11 [0.65, 1.89]</td>
</tr>
<tr>
<td>1.1 CHM Nei Yi pills + CHM Nei Yi enema vs Nei Yi pills</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Dysmenorrhea score</td>
<td>1</td>
<td>40</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-1.89 [-3.89, 0.11]</td>
</tr>
<tr>
<td>2.1 CHM Nei Yi pills + CHM Nei Yi enema vs Nei Yi pills</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Lumbosacral pain relief</td>
<td>1</td>
<td>40</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.95 [0.74, 1.23]</td>
</tr>
<tr>
<td>3.1 CHM Nei Yi pills + CHM Nei Yi enema vs Nei Yi pills</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Rectal Irritation relief</td>
<td>1</td>
<td>30</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.07 [0.79, 1.44]</td>
</tr>
<tr>
<td>4.1 CHM Nei Yi pills + CHM Nei Yi enema vs Nei Yi pills</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Tenderness of vaginal nodules in posterior fornix</td>
<td>1</td>
<td>27</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.96 [0.74, 1.25]</td>
</tr>
<tr>
<td>5.1 CHM Nei Yi pills + CHM Nei Yi enema vs Nei Yi pills</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Adnexal masses disappearance or shrinkage</td>
<td>1</td>
<td>33</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.21 [0.85, 1.72]</td>
</tr>
<tr>
<td>6.1 CHM Nei Yi pills + CHM Nei Yi enema vs Nei Yi pills</td>
<td></td>
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</tr>
</tbody>
</table>
### Analysis 1.1. Comparison 1 CHM versus gestrinone, Outcome 1 Symptomatic relief.

**Review:** Chinese herbal medicine for endometriosis  
**Comparison:** 1 CHM versus gestrinone  
**Outcome:** 1 Symptomatic relief

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>CHM n/N</th>
<th>Gestrinone n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight 100.0%</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu SZ 2006a</td>
<td>44/46</td>
<td>46/49</td>
<td>1.02 [0.93, 1.12]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI):** 46 49 1.02 [0.93, 1.12]  
Total events: 44 (CHM), 46 (Gestrinone)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.39 (P = 0.70)  
Test for subgroup differences: Not applicable

### Analysis 1.2. Comparison 1 CHM versus gestrinone, Outcome 2 Symptomatic relief rate (intention-to-treat).

**Review:** Chinese herbal medicine for endometriosis  
**Comparison:** 1 CHM versus gestrinone  
**Outcome:** 2 Symptomatic relief rate (intention-to-treat)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>CHM n/N</th>
<th>Gestrinone n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight 100.0%</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu SZ 2006a</td>
<td>44/48</td>
<td>46/52</td>
<td>1.04 [0.91, 1.18]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI):** 48 52 1.04 [0.91, 1.18]  
Total events: 44 (CHM), 46 (Gestrinone)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.54 (P = 0.59)  
Test for subgroup differences: Not applicable
**Analysis 1.3. Comparison 1 CHM versus gestrinone, Outcome 3 Pregnant rate (accumulated from 3-24 months of follow-up).**

Review: Chinese herbal medicine for endometriosis

Comparison: 1 CHM versus gestrinone

Outcome: 3 Pregnant rate (accumulated from 3-24 months of follow-up)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>CHM n/N</th>
<th>Gestrinone n/N</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
<th>Weight 100.0%</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu SZ 2006a</td>
<td>32/46</td>
<td>29/49</td>
<td>1.18 [0.87, 1.59]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>46</td>
<td>49</td>
<td>1.18 [0.87, 1.59]</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 32 (CHM), 29 (Gestrinone)

Heterogeneity: not applicable

Test for overall effect: Z = 1.05 (P = 0.29)

Test for subgroup differences: Not applicable

Favours gestrinone  
Favours CHM
Analysis 2.1. Comparison 2 CHM versus danazol, Outcome 1 Symptomatic relief.

Review: Chinese herbal medicine for endometriosis

Comparison: 2 CHM versus danazol

Outcome: 1 Symptomatic relief

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>1 CHM Nei Yi pills vs Danazol</td>
<td>9/16</td>
<td>2/18</td>
<td>5.06 [ 1.28, 20.05 ]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td>Wu SZ 2006b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>16</td>
<td>18</td>
<td>5.06 [ 1.28, 20.05 ]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td>Total events: 9 (Experimental), 2 (Control)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 2.31 (P = 0.021)</td>
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</tr>
<tr>
<td>2 CHM Nei Yi pills + CHM Nei Yi enema vs Danazol</td>
<td>15/24</td>
<td>2/18</td>
<td>5.63 [ 1.47, 21.54 ]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td>Wu SZ 2006b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>24</td>
<td>18</td>
<td>5.63 [ 1.47, 21.54 ]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td>Total events: 15 (Experimental), 2 (Control)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.52 (P = 0.012)</td>
<td></td>
<td></td>
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</tbody>
</table>
### Analysis 2.2. Comparison 2 CHM versus danazol, Outcome 2 Dysmenorrhea score.

**Review:** Chinese herbal medicine for endometriosis

**Comparison:** 2 CHM versus danazol

**Outcome:** 2 Dysmenorrhea score

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>CHM</th>
<th>Danazol</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 CHM Nei Yi pills vs Danazol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wu SZ 2006b</td>
<td>16</td>
<td>3.91 (3.44)</td>
<td>4.92 (2.71)</td>
<td>100.0%</td>
<td>-1.01 [-3.11, 1.09]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>16</td>
<td>18</td>
<td></td>
<td>100.0%</td>
<td>-1.01 [-3.11, 1.09]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 0.94 (P = 0.35)

2 CHM Nei Yi pills + CHM Nei Yi enema vs Danazol

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>CHM</th>
<th>Danazol</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wu SZ 2006b</td>
<td>24</td>
<td>2.02 (2.7)</td>
<td>4.92 (2.71)</td>
<td>100.0%</td>
<td>-2.90 [-4.55, -1.25]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>24</td>
<td>18</td>
<td></td>
<td>100.0%</td>
<td>-2.90 [-4.55, -1.25]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 3.44 (P = 0.00059)

Test for subgroup differences: Chi² = 1.92, df = 1 (P = 0.17), I² = 48%
**Analysis 2.3.** Comparison 2 CHM versus danazol, Outcome 3 Lumbosacral pain relief.

Review: Chinese herbal medicine for endometriosis

Comparison: 2 CHM versus danazol

Outcome: 3 Lumbosacral pain relief

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>1 CHM Nei Yi pills versus Danazol</td>
<td>Wu SZ 2006b</td>
<td>14/16</td>
<td>13/18</td>
<td>100.0 %</td>
<td>1.21 [ 0.86, 1.70 ]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>16</td>
<td>18</td>
<td>100.0 %</td>
<td>1.21 [ 0.86, 1.70 ]</td>
<td></td>
</tr>
<tr>
<td>Total events: 14 (Experimental), 13 (Control)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.10 (P = 0.27)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 CHM Nei Yi pills + CHM Nei Yi enema vs Danazol</td>
<td>Wu SZ 2006b</td>
<td>20/24</td>
<td>13/18</td>
<td>100.0 %</td>
<td>1.15 [ 0.82, 1.62 ]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>24</td>
<td>18</td>
<td>100.0 %</td>
<td>1.15 [ 0.82, 1.62 ]</td>
<td></td>
</tr>
<tr>
<td>Total events: 20 (Experimental), 13 (Control)</td>
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</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 0.83 (P = 0.41)</td>
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</table>
## Analysis 2.4. Comparison 2 CHM versus danazol, Outcome 4 Rectal Irritation relief.

### Review: Chinese herbal medicine for endometriosis

### Comparison: 2 CHM versus danazol

### Outcome: 4 Rectal Irritation relief

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>m/N</td>
<td>m/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>1 CHM Nei Yi pills vs Danazol</td>
<td>10/12</td>
<td>6/12</td>
<td>1.67 [ 0.90, 3.10 ]</td>
<td>100.0 %</td>
<td>1.67 [ 0.90, 3.10 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>12</td>
<td>12</td>
<td>100.0 %</td>
<td>1.67 [ 0.90, 3.10 ]</td>
<td></td>
</tr>
<tr>
<td>Total events: 10 (Experimental), 6 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.62 (P = 0.11)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2 CHM Nei Yi pills + CHM Nei Yi enema vs Danazol</td>
<td>16/18</td>
<td>6/12</td>
<td>1.78 [ 0.99, 3.20 ]</td>
<td>100.0 %</td>
<td>1.78 [ 0.99, 3.20 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>18</td>
<td>12</td>
<td>100.0 %</td>
<td>1.78 [ 0.99, 3.20 ]</td>
<td></td>
</tr>
<tr>
<td>Total events: 16 (Experimental), 6 (Control)</td>
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</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 1.91 (P = 0.056)</td>
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</table>
**Analysis 2.5. Comparison 2 CHM versus danazol, Outcome 5 Tenderness of vaginal nodules in posterior fornix.**

Review: Chinese herbal medicine for endometriosis

Comparison: 2 CHM versus danazol

Outcome: 5 Tenderness of vaginal nodules in posterior fornix

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
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<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed, 95% CI</td>
<td></td>
<td>M-H,Fixed, 95% CI</td>
</tr>
<tr>
<td>1 CHM Nei Yi pills vs Danazol</td>
<td>Wu SZ 2006b</td>
<td>10/11 9/13</td>
<td>100.0 % 1.31 [ 0.87, 1.97 ]</td>
<td></td>
<td>1.31 [ 0.87, 1.97 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>11 13</td>
<td>100.0 % 1.31 [ 0.87, 1.97 ]</td>
<td></td>
<td>1.31 [ 0.87, 1.97 ]</td>
<td></td>
</tr>
<tr>
<td>Total events: 10 (Experimental), 9 (Control)</td>
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<td></td>
<td>Heterogeneity: not applicable</td>
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<tr>
<td>Test for overall effect: Z = 1.31 (P = 0.19)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2 CHM Nei Yi pills + CHM Nei Yi enema vs Danazol</td>
<td>Wu SZ 2006b</td>
<td>14/16 9/13</td>
<td>100.0 % 1.26 [ 0.84, 1.90 ]</td>
<td></td>
<td>1.26 [ 0.84, 1.90 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>16 13</td>
<td>100.0 % 1.26 [ 0.84, 1.90 ]</td>
<td></td>
<td>1.26 [ 0.84, 1.90 ]</td>
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</tr>
<tr>
<td>Total events: 14 (Experimental), 9 (Control)</td>
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<td></td>
<td>Heterogeneity: not applicable</td>
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</tr>
<tr>
<td>Test for overall effect: Z = 1.13 (P = 0.26)</td>
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</tbody>
</table>
Analysis 2.6. Comparison 2 CHM versus danazol, Outcome 6 Adnexal masses disappearance or shrinkage.

Review: Chinese herbal medicine for endometriosis

Comparison: 2 CHM versus danazol

Outcome: 6 Adnexal masses disappearance or shrinkage

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CHM Nei Yi pills vs Danazol</td>
<td>Wu SZ 2006b</td>
<td>9/12</td>
<td>8/15</td>
<td>100.0%</td>
<td>1.41 [0.79, 2.50]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>12</td>
<td>15</td>
<td></td>
<td>100.0%</td>
<td>1.41 [0.79, 2.50]</td>
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<tr>
<td>Total events: 9 (Experimental), 8 (Control)</td>
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</tr>
<tr>
<td>Heterogeneity: not applicable</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.16 (P = 0.25)</td>
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<td></td>
</tr>
<tr>
<td>2 CHM Nei Yi pills + CHM Nei Yi enema vs Danazol</td>
<td>Wu SZ 2006b</td>
<td>19/21</td>
<td>8/15</td>
<td>100.0%</td>
<td>1.70 [1.04, 2.78]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>21</td>
<td>15</td>
<td></td>
<td>100.0%</td>
<td>1.70 [1.04, 2.78]</td>
</tr>
<tr>
<td>Total events: 19 (Experimental), 8 (Control)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.10 (P = 0.036)</td>
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</tbody>
</table>
Analysis 3.1. Comparison 3 CHM versus CHM, Outcome 1 Symptomatic relief.

Review: Chinese herbal medicine for endometriosis

Comparison: 3 CHM versus CHM

Outcome: 1 Symptomatic relief

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>CHM2</th>
<th>CHM1</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>I CHM Nei Yi pills + CHM Nei Yi enema vs Nei Yi pills</td>
<td>15/24</td>
<td>9/16</td>
<td>100.0%</td>
<td>1.11 [ 0.65, 1.89 ]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>24</td>
<td>16</td>
<td>100.0%</td>
<td>1.11 [ 0.65, 1.89 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 15 (CHM2), 9 (CHM1)

Heterogeneity: not applicable

Test for overall effect: Z = 0.39 (P = 0.70)

Analysis 3.2. Comparison 3 CHM versus CHM, Outcome 2 Dysmenorrhea score.

Review: Chinese herbal medicine for endometriosis

Comparison: 3 CHM versus CHM

Outcome: 2 Dysmenorrhea score

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>CHM2</th>
<th>CHM1</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>Mean(SD)</td>
<td></td>
<td>Mean(SD)</td>
</tr>
<tr>
<td></td>
<td>IV ,Fixed,95% CI</td>
<td>IV ,Fixed,95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I CHM Nei Yi pills + CHM Nei Yi enema vs Nei Yi pills</td>
<td>24</td>
<td>16</td>
<td>2.02 (2.7)</td>
<td>3.91 (3.44)</td>
<td>100.0%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>24</td>
<td>16</td>
<td>100.0%</td>
<td>-1.89 [ -3.89, 0.11 ]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 1.85 (P = 0.064)

Test for subgroup differences: Not applicable
Analysis 3.3. Comparison 3 CHM versus CHM, Outcome 3 Lumbosacral pain relief.

Review: Chinese herbal medicine for endometriosis
Comparison: 3 CHM versus CHM
Outcome: 3 Lumbosacral pain relief

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>CHM2</th>
<th>CHM1</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed, 95% CI</td>
<td></td>
<td></td>
<td>M-H,Fixed, 95% CI</td>
</tr>
<tr>
<td>Wu SZ 2006b</td>
<td>20/24</td>
<td>14/16</td>
<td>100.0 %</td>
<td>0.95</td>
<td>[0.74, 1.23]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>24</strong></td>
<td><strong>16</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.95</strong></td>
<td><strong>[0.74, 1.23]</strong></td>
</tr>
</tbody>
</table>

Total events: 20 (CHM2), 14 (CHM1)
Heterogeneity: not applicable
Test for overall effect: Z = 0.37 (P = 0.71)

Analysis 3.4. Comparison 3 CHM versus CHM, Outcome 4 Rectal Irritation relief.

Review: Chinese herbal medicine for endometriosis
Comparison: 3 CHM versus CHM
Outcome: 4 Rectal Irritation relief

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>CHM2</th>
<th>CHM1</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed, 95% CI</td>
<td></td>
<td></td>
<td>M-H,Fixed, 95% CI</td>
</tr>
<tr>
<td>Wu SZ 2006b</td>
<td>16/18</td>
<td>10/12</td>
<td>100.0 %</td>
<td>1.07</td>
<td>[0.79, 1.44]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>18</strong></td>
<td><strong>12</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.07</strong></td>
<td><strong>[0.79, 1.44]</strong></td>
</tr>
</tbody>
</table>

Total events: 16 (CHM2), 10 (CHM1)
Heterogeneity: not applicable
Test for overall effect: Z = 0.42 (P = 0.67)
### Analysis 3.5. Comparison 3 CHM versus CHM, Outcome 5 Tenderness of vaginal nodules in posterior fornix.

**Review:** Chinese herbal medicine for endometriosis  
**Comparison:** 3 CHM versus CHM  
**Outcome:** 5 Tenderness of vaginal nodules in posterior fornix

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>CHM2</th>
<th>CHM1</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>1 CHM Nei Yi pills + CHM Nei Yi enema vs Nei Yi pills</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wu SZ 2006b</td>
<td>14/16</td>
<td>10/11</td>
<td>0.96 [ 0.74, 1.25 ]</td>
<td>100.0 %</td>
<td>0.96 [ 0.74, 1.25 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>16</td>
<td>11</td>
<td>100.0 %</td>
<td>0.96 [ 0.74, 1.25 ]</td>
<td></td>
</tr>
<tr>
<td>Total events:</td>
<td>14 (CHM2), 10 (CHM1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.28 (P = 0.78)</td>
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</table>

### Analysis 3.6. Comparison 3 CHM versus CHM, Outcome 6 Adnexal masses disappearance or shrinkage.

**Review:** Chinese herbal medicine for endometriosis  
**Comparison:** 3 CHM versus CHM  
**Outcome:** 6 Adnexal masses disappearance or shrinkage

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>CHM2</th>
<th>CHM1</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>1 CHM Nei Yi pills + CHM Nei Yi enema vs Nei Yi pills</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wu SZ 2006b</td>
<td>19/21</td>
<td>9/12</td>
<td>1.21 [ 0.85, 1.72 ]</td>
<td>100.0 %</td>
<td>1.21 [ 0.85, 1.72 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>21</td>
<td>12</td>
<td>100.0 %</td>
<td>1.21 [ 0.85, 1.72 ]</td>
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<td>Total events:</td>
<td>19 (CHM2), 9 (CHM1)</td>
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<td>Heterogeneity: not applicable</td>
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<td>Test for overall effect: Z = 1.04 (P = 0.30)</td>
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APPENDICES

Appendix 1. Search strategies

AMED (Allied and Complementary Medicine)
1 Controlled study/ or Randomized Controlled Trial/
2 Placebo/
3 Random$.tw.
4 latin square.tw.
5 crossover.tw.
6 cross-over.tw.
7 placebo$.tw.
8 ((doub$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
9 (comparativ$ adj5 trial$).tw.
10 (clinical adj5 trial$).tw.
11 animal/ not (human/ and animal/)
12 alternative medicine/ or traditional medicine/ or chinese medicine/
13 Complementary Therapie$.ti,ab,hw,tn,mf.
14 Plant Extract/
15 phytodrug$.ti,ab,hw,tn,mf.
16 phytopharmaceutic$.ti,ab,hw,tn,mf.
17 (traditional adj medicine).ti,ab,hw,tn,mf.
18 alternative medicine.ti,ab,hw,tn,mf.
19 Complementary Therap$.ti,ab,hw,tn,mf.
20 plant extract$.ti,ab,hw,tn,mf.
21 herb$.ti,ab,sh.
22 or/1-10
23 22 not 11
24 or/12-21
25 Endometriosis/ or endometriosis.mp.
26 24 and 25
27 23 and 26
28 from 27 keep 1-2

EBM Reviews - Cochrane Central Register of Controlled Trials

1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 Randomized Controlled Trials/
4 Random allocation/
5 double-blind method/
6 single-blind method/
7 Random$.tw.
8 clinical trial.pt.
9 exp clinical trials/
10 (clin$ adj25 trial$).ti,ab,sh.
11 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab,sh.
12 Placebos/
13 placebo$.ti,ab,sh.
14 random$.ti,ab,sh.
15 Research design/
16 or/8-15
17 animal/ not (human/ and animal/)
18 7 or 16
Chinese herbal medicine for endometriosis (Review)

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33 endometriosis.mp. or ENDOMETRIOSIS/
34 32 and 33
35 17 and 34
36 from 35 keep 1

**EMBASE**
1 Controlled study/ or Randomized Controlled Trial/
2 Double blind procedure/
3 Single Blind Procedure/
4 Crossover procedure/
5 Drug comparison/
6 Placebo/
7 Random$.tw.
8 latin square.tw.
9 crossover.tw.
10 cross-over.tw.
11 placebo$.tw.
12 ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
13 (comparativ$ adj5 trial$).tw.
14 (clinical adj5 trial$).tw.
15 or/7-14
16 animal/ not (human/ and animal/)
17 15 not 16
18 alternative medicine/ or traditional medicine/ or chinese medicine/
19 Complementary Therapy$.ti,ab,hw,tn,mf.
20 Plant Extract/
21 Chinese Drug/
22 Chinese Herb/
23 Medicinal Plant/
24 Non Prescription Drug/
25 Herb/
26 phytodrug$.ti,ab,hw,tn,mf.
27 phytopharmaceutic$.ti,ab,hw,tn,mf.
28 (traditional adj medicine).ti,ab,hw,tn,mf.
29 alternative medicine.ti,ab,hw,tn,mf.
30 Complementary Therapy$.ti,ab,hw,tn,mf.
31 plant extract$.ti,ab,hw,tn,mf.
32 or/18-31
33 endometriosis.mp. or ENDOMETRIOSIS/
34 32 and 33
35 17 and 34
36 from 35 keep 1-8

**MEDLINE**
1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 Randomized Controlled Trials/
4 Random allocation/
5 double-blind method/
6 single-blind method/
7 or/1-6
8 clinical trial.pt.
9 exp clinical trials/
10 (clin$ adj25 trial$).ti,ab,sh.
11 (((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$))).ti,ab,sh.
Appendix 2. Commonly used Chinese herbs in the treatment of endometriosis.

Commonly used herbs in the treatment of endometriosis

Herbs to move Blood
- E Zhu (Curcuma Rhizoma)
- San Leng (Sparganii Rhizoma)
- Dang Gui (Weil) (Angelica sinensis)
- Chi Shao (Paeoniae Radix rubra)
- Tao Ren (Persicae Semen)
- Dan Shen (Salviae miltiorrhizae Radix)
- Yan Hu Suo (Corydalis Rhizoma)
- Chuan Xiong (Chuanxiong Rhizoma)
- Wu Ling Zhi (Trogopterorí Faeces)
- Hong Hua (Carthami Flos)
- Da Huang (Rhei Radix et Rhizoma)
- Mu Dan Pi (Moutan Cortex)
- Pu Huang (Pollen Typhae)
- Shui Zhi (Hirudo seu Whitmaniae)
- Yi Mu Cao (Leonuri Herba)
- Tu Bie Chong (Eupolyphaga/Steleophaga)
- Mo Yao (Myrrha)
- Ru Xiang (Olibanum)
- Xue Jie (Dragonis Sanguis)
- San Qi (Notoginseng Radix)
• Chuan Niu Xi (Cyathulae Radix)

**Herbs to move Qi**
• Xiang Fu (Cyperi Rhizoma)
• Wu Yao (Linderae Radix)
• Chai Hu (Bupleuri Radix)
• Chuan Lian Zi (Semen Nelumbinis Nuciferae)
• Zhi Ke (Aurantii Fructus)

**Herbs to nourish Blood**
• Dang Gui (Angelicae Radix sinensis)
• Bai Shao (Paeoniae Radix alba)
• Gou Qi Zi (Lycii Fructus)

**Herbs to nourish Qi**
• Huang Qi (Astragali Radix)
• Dang Shen (Codonopsis Radix)
• Bai Zhu (Atractylodes radix)

**Herbs to invigorate Yang**
• Du Zhong (Eucommiae Cortex)
• Ba Ji Tian (Morindae officialis Radix)
• Xu Duan (Dipsaci Radix)
• Yin Yang Huo (Herba Epimedi)
• Tu Si Zi (Cuscutae Semen)

**Herbs to dispel Cold**
• Gan Jiang (Zingiberis Rhizoma)
• Wu Zhu Yu (Evodiae Fructus)
• Rou Gui (Cinnamomi Cortex)
• Hui Xiang (Foeniculii Fructus)

**Herbs to resolve Phlegm and soften hardness**
• Zao Jiao Ci (Spina Gleditsiae Sinensis)
• Mu Li (Ostreae Concha)
• Xia Ku Cao (Prunellae Spica)
• Hai Zao (Herba Sargassii)
• Kun Bu (Eckloniae Thallus)

**Herbs to clear Fire Poison**
• Hong Teng (Sargentodoxae Caulis)
• Bai Jiang Cao (Patriniae Herba)

**WHAT’S NEW**

Last assessed as up-to-date: 31 October 2011.
### Date

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<th>Date</th>
<th>Event</th>
<th>Description</th>
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<td>19 March 2012</td>
<td>New citation required but conclusions have not changed</td>
<td>No new studies could be added to the review.</td>
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<td>19 March 2012</td>
<td>New search has been performed</td>
<td>An updated search of the same electronic databases has been conducted. No additional studies were able to be included in the review</td>
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### HISTORY

Review first published: Issue 3, 2009

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<td>7 April 2008</td>
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<tr>
<td>9 February 2007</td>
<td>New citation required and major changes</td>
<td>Substantive amendment</td>
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### CONTRIBUTIONS OF AUTHORS

AF adapted the original title, developed the protocol, co-authored the final review, and co-ordinated the project.
AF and JPL co-drafted the first versions of the protocol, and the final review.
AF and JPL conducted provisional Chinese and English language searches, and QL updated the searches and contacted authors to confirm trial eligibility for inclusion.
GL and PL reviewed and commented upon the initial drafts of the review.
SC and AF conducted the initial processes of trial selection and data extraction, reviewed and commented on by JPL. For the revised review LQ searched for and identified relevant studies. Any studies that may have been eligible for inclusion were discussed between LQ, JPL and AF.

### DECLARATIONS OF INTEREST

None known
SOURCES OF SUPPORT

Internal sources
- JP Liu and Q Li were supported by Beijing University of Chinese Medicine, China.

External sources
- Complementary Medicine Research Unit, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol it was stated that quasi-randomised trials would be included in the review. However these trials were excluded from the main review.

INDEX TERMS

Medical Subject Headings (MeSH)
Danazol [therapeutic use]; Drugs, Chinese Herbal [administration & dosage; "therapeutic use"; Dysmenorrhea [drug therapy]; Endometriosis [complications; "drug therapy"; Enema [methods]; Estrogen Antagonists [therapeutic use]; Gestrinone [therapeutic use]; Pelvic Pain ["drug therapy; etiology"; Progestins [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words
Female; Humans