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Chinese herbal medicine for endometriosis

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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.

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 the present): MEDLINE, EMBASE, AMED, CINAHL, NLH on the 30/04/09.
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 are 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 dysmenorrhea 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 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 either 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 dysmenorrhea 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 recurrence 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.
### 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 etiology 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 factors (Low 1993; Strauss 1992) 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 oestrogen 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 recently 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

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**SUMMARY OF FINDINGS FOR THE MAIN COMPARISON**

<table>
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<tr>
<th>Study</th>
<th>Risk of bias</th>
<th>Number of participants</th>
<th>Comparisons</th>
<th>RR (95% CI)</th>
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<tr>
<td>Wu SZ 2006a</td>
<td>B-moderate</td>
<td>100</td>
<td>CHM (oral + enema) versus gestri-none</td>
<td>RR 1.02 (95% CI 0.93 to 1.12)</td>
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<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>
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<tr>
<td></td>
<td></td>
<td></td>
<td>For ‘symptomatic relief’</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CHM oral+enema versus danazol</td>
<td>RR 5.63 (95% CI 1.47 to 21.54)</td>
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weight gain, and menopausal symptoms such as flushing and fatigue. Recent concerns 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-oestrogenic state than danazol with more severe menopausal side effects such as hot flushes, insomnia, reduced libido, and vaginal dryness (Prentice 2004). Low oestrogen levels can also cause serious osteoporosis and the long-term risks of add-back regimes using small amounts of progesterone and oestrogen have not been adequately assessed as yet.

Patients using progestin therapy reported a higher incidence of acne, fluid retention, bloating, and spotting. In addition progestins are known to unfavourably reduce the level of high-density lipoproteins in the blood, which could potentially increase the risk 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 recurrence 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 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 2004).

Why it is important to do this review

At present no 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 assess the short and long-term effectiveness of CHM in relieving the symptoms of endometriosis and in improving fertility in patients with endometriosis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing treatment using CHM with either an inactive placebo group or conventional biomedical treatment. RCTs comparing different CHM strategies and treatments have also been considered.

Types of participants

Women of reproductive age with a laparoscopically confirmed diagnosis of endometriosis.

Types of interventions

CHM versus placebo, conventional biomedical treatment, or CHM plus biomedical treatment versus biomedical treatment.
Types of outcome measures

Primary outcomes
Relief of endometriosis-related pain

Secondary outcomes
- Improvement in fertility rates
- Reduction in the size and extent of endometrial cysts
- Improvement in quality of life scores
- Improvement of endometriosis-related symptoms apart from pain (for example fatigue)
- Adverse effects resulting from CHM intervention
- Rates of reoccurrence

Search methods for identification of studies

Electronic searches
We searched the following on the 30/04/09:
1. The 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. The 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), Tiqiu Yao (plant extract), Buchong Yiya (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. AF and SC (in the UK) and JPL (in China) then independently reviewed the studies. We identified those for inclusion and rated them according to the quality criteria listed below. GL and PL acted in an advisory capacity during this process. Any differences of opinion were resolved through discussion.

Data collection and analysis
After discussion with the Cochrane Menstrual Disorders and Subfertility Group co-ordinators it was agreed that only trials with a laparoscopic confirmation of endometriosis would be included in the review. Furthermore, 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.

Trial characteristics
Trials were assessed to determine how successfully selection, performance, attrition, and detection biases were minimized.

To minimize selection bias
- Clear inclusion and exclusion criteria
- Appropriate data for characteristics of women included in the study including age, duration of illness
- Comparable treatment and control groups at entry
- A clear and acceptable method of randomisation
- Quality of allocation concealment (allocation concealment was scored as adequate (A), unclear (B), inadequate (C), or explicitly not used (D)).

To minimize performance bias
- Appropriate data on the types of Chinese herbs, placebo controls used, and methods of administration
- Details on the duration, timing, and location of the study
- Confirmation that the care programmes, apart from the trial options, were identical

To minimize 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 detection bias
- Were the outcome assessors blinded to the assignment status?
- Were the outcome measures used clearly defined and clearly and consistently reported?

Based on these criteria, we assigned studies to one of the following three categories:
A - all quality criteria met, low risk of bias;
B - one or more of the quality criteria only partly met, moderate risk of bias;
C - one or more criteria not met, high risk of bias.

Analysis
Only two trials (testing CHM against different conventional medical interventions) were eligible for this review so no meta-analysis or analysis of heterogeneity was required (Higgins 2003).
RESULTS

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

Results of the search
In total, 110 trials were identified from the search strategy described above. All of these trials took place in China and were reported in Chinese.

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, with one trial reported in three publications each describing different outcome measures (Wu SZ 2006b). The review authors were able to confirm adequate randomisation and 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 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.

Risk of bias in included studies
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.

- Adequate sequence generation?
- Allocation concealment?
- Blinding?
- Incomplete outcome data addressed?
- Free of selective reporting?
- Free of other bias?

![Graph showing methodological quality judgments](image)

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

- Wu SZ 2006a
- Wu SZ 2006b

![Summary chart showing quality judgments](image)
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.

**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. 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 from 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, 13, 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 dysmenorrhoea 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.

**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 standardized 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.

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 claimed to be a single blind trial 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 describe 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 these 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.

Implications for research

Despite the large number of clinical trials exploring the role of CHM in the treatment of endometriosis methodological shortcomings have led to the exclusion of all but two trials. There are a number of reasons for these exclusions including no laparoscopic confirmation 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 also incorporate quality of life outcome measures and qualitative research to provide a more detailed account of the effect of CHM intervention on the lives of women suffering from this disease.

AUTHORS’ CONCLUSIONS

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 generalise 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 postsurgical adjuvant in the treatment of endometriosis.

ACKNOWLEDGEMENTS

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Chinese herbal medicine for endometriosis (Review)

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Wu SZ 2006b [published data only]


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Chai H 1996 [published data only]

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Fan HX 2004 [published data only]

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He H 2004 [published data only]

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Hu 2005 [published data only]

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Huang 2000a [published data only]

Jia 2004 [published data only]

Kui JY 2001 [published data only]

Li 1999 [published data only]

Li 2003 [published data only]

Li 2004 [published data only]

Li 2006 [published data only]

Li 2007 [published data only]

Liao 2004 [published data only]

Lin 2006 [published data only]

Lin 2006a [published data only]

Liu 1994 [published data only]

Liu 1998 [published data only]

Liu 1998a [published data only]

Liu 1998b [published data only]

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Liu FY 2003 [published data only]

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Lu 2005 [published data only]

Lu 2007 [published data only]

Lu XP 1999 [published data only]

Luo JY 2001 [published data only]

Luo 2006 [published data only]

Pan XR 2003 [published data only]

Qi 2006 [published data only]

Qian 2000a [published data only]

Qian J 2000 [published data only]

Qiu L. 2005 [published data only]
Qiu YJ 2004 [published data only]

Ren YL 2005 [published data only]

Ren YL 2005 [published data only]

Shong 2005 [published data only]

Si 2006 [published data only]

Su CZ 2006 [published data only]

Sun YZ 2003 [published data only]

Wang 1996 [published data only]

Wang 1999 [published data only]

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Wang 2002 [published data only]

Wang 2002a [published data only]

Wang 2002b [published data only]

Wang 2004 [published data only]

Wang 2004a [published data only]

Wang 2005 [published data only]

Wang 2006a [published data only]

Wang 2006b [published data only]

Wang LX 2006 [published data only]

Wu 1999 [published data only]

Wu 2000a [published data only]

Wu 2003 [published data only]
Xiao 2004a (published data only)

Xuan JS 2005 (published data only)

Yan 2004 (published data only)

Yang 2006 (published data only)

Yang 2006a (published data only)

Yang 2006b (published data only)

Yang 2001 (published data only)

Yang Y (published data only)

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Zhao JL, Mu CL. Treatment of 75 cases of endometriosis related dysmenorrhoea using a combination of western and Chinese medicine [Zhong Xi Yi jie he zhi liao zhi gong nei

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Chinese herbal medicine for endometriosis (Review)

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Xu M, Si TY, Lao YR, Guo XF, Wen ZH, Lai SL. A literature review of clinical trials on Chinese medicine

**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 (Chi² test used for ‘overall improvement’)  
| Participants     | 100 cases of endometriosis complicated with 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:  
|                  | Nei Yi enema consisted of:  
|                  | 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  

### Risk of bias

<table>
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<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
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</table>

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*Chinese herbal medicine for endometriosis (Review)*

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Adequate sequence generation? Yes Randomisation achieved using random number sequence from table in statistical textbook

Allocation concealment? Yes Allocation concealment achieved by sorting numbers into envelopes

Blinding? Yes Described as patient and assessor blinded, confirmed with author to be patient blinded as in outpatient department so patients do not see each other

Incomplete outcome data addressed? Yes Two cases in treatment group and three cases in control group were lost during follow up. Adequate outcomes data presented

Free of selective reporting? Yes Identified outcomes adequately reported as compared with the description in methods

Free of other bias? Yes The funding resource was declared

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)

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: Dan Shen (Salviae multiflorae Radix), Xue Jie (Draconis Sanguis), San Leng (Sparganii Rhizoma), E Zhu (Curcumae Rhizoma), Tao Ren (Persicae Semen), San Qi (Notoginseng Radix), Dang Gui (Angelica sinensis), Gui Zhi (Cinnamomi Ramulus), Xiang Fu (Cyperi Rhizoma), Niu Xi (Achyranthis bidentate Radix)
Nei Yi enema consisted of: Dan Shen (Salviae multiflorae 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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<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
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<td>Yes</td>
<td>Randomisation for allocation of three groups was generated through random number table</td>
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<td>Yes</td>
<td>Allocation sequence was concealed through numbered, sealed, opaque envelopes</td>
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<td>Described as patient and outcome assessor blinded when contacted the authors; patients were treated separately in the outpatient department</td>
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<td>No patient was lost during treatment or follow up</td>
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<td>Identified outcomes adequately reported compared with the descriptions in the methods</td>
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<td>Free of other bias?</td>
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<td>Cai 1999</td>
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<td>Chai H 1996</td>
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<td>Chai LS 2004</td>
<td>Unequal group size with no account of randomisation process.</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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<tr>
<td>Chen 2006</td>
<td>Uses an experimental treatment (oral provera) as part of the active and control intervention</td>
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<tr>
<td>Chen 2006a</td>
<td>Combines CHM with therapeutic ultrasound.</td>
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<td>Chui YX</td>
<td>No clear data on diagnostic or outcomes criteria.</td>
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<td>Fan 2003</td>
<td>Combined TCM with experimental WM treatment (mifepristone).</td>
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<td>Fan HX 2004</td>
<td>Group allocation according to patient preference</td>
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<td>Fong 2004</td>
<td>Insufficient and unclear data to enable a reasonable assessment of the trial</td>
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<td>Control group used experimental WM treatment (tamoxifen)</td>
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<td>Fong DL 2006</td>
<td>Group allocation according to patient preference</td>
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<tr>
<td>Fu 2005</td>
<td>Acupuncture used together with CHM in active group.</td>
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<tr>
<td>Gao 2003</td>
<td>Unequal group size with no account of randomisation process.</td>
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<td>He JY 2005</td>
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<td>Kui JY 2001</td>
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<td>Li 2004</td>
<td>The trial did not use validated outcomes.</td>
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<td>Insufficient data on the primary outcome to enable a reasonable assessment</td>
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<td>Liao 2004</td>
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<td>Lin 2006</td>
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<td>Lin 2006a</td>
<td>Too many treatment variables-including experimental treatment mifespristone</td>
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<td>Liu 1994</td>
<td>Too many treatment variables-combined TCM plus hormonal treatment compared to a variety of hormonal control interventions</td>
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<td>Liu 1998</td>
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<td>Liu 1998b</td>
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<td>Use of acupuncture in the active treatment group.</td>
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<td>Did not consider pain as a primary outcome.</td>
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<td>Too many treatment variables. CHM combined with penicillin, metronidazole + oral contraceptive compared with gestrinone</td>
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<td>No validated outcomes measures. Control group used experimental treatment (tamoxifen)</td>
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<td>Too many treatment variables. Also use Tamoxifen with CHM as active treatment with unequal group size and no account of randomisation</td>
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<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>
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<td>Wu 2000a</td>
<td>Confounding Comparison of Laparoscopy + CHM with CHM and with Danazol. Too many treatment variables</td>
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<td>No control group—not a randomised controlled trial.</td>
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<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>
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<td>Yan 2004</td>
<td>Insufficient data about outcomes criteria and unequal group size with no account of randomisation process</td>
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<td>Yang 2006</td>
<td>Quasi randomised according to the time of patient presentation</td>
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<td>Uses experimental treatment (tamoxifen) as a control. Also unclear outcomes measures and no report on pain reduction</td>
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<td>Yang 2006b</td>
<td>Unequal group size with no account of randomisation process and insufficient data for evaluation</td>
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</tr>
<tr>
<td>Yang HY 2001</td>
<td>No laparoscopic confirmation</td>
<td></td>
</tr>
<tr>
<td>Yang Y</td>
<td>Included acupuncture in the active treatment group.</td>
<td></td>
</tr>
<tr>
<td>Ye LQ 2004</td>
<td>No laparoscopic confirmation</td>
<td></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>
<td></td>
</tr>
<tr>
<td>Yu 2003</td>
<td>Not a randomised controlled trial.</td>
<td></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>
<td></td>
</tr>
<tr>
<td>Zhang 2004</td>
<td>Unequal group size with no account of randomisation process.</td>
<td></td>
</tr>
<tr>
<td>Zhao 2002</td>
<td>The trial did not use validated outcomes measures.</td>
<td></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>
<td></td>
</tr>
<tr>
<td>Zhu 2001</td>
<td>Unequal group size with no account of randomisation process.</td>
<td></td>
</tr>
<tr>
<td>Zhu HY 2002</td>
<td>No laparoscopic confirmation</td>
<td></td>
</tr>
<tr>
<td>Zhu L 2000</td>
<td>No laparoscopic confirmation</td>
<td></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>
</tbody>
</table>
### 6.1 CHM Nei Yi pills vs Danazol

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.41 [0.79, 2.50]</td>
</tr>
</tbody>
</table>

### 6.2 CHM Nei Yi pills + CHM Nei Yi enema vs Danazol

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.70 [1.04, 2.78]</td>
</tr>
</tbody>
</table>

### Comparison 3. CHM versus CHM

#### Outcome or subgroup title
- **Symptomatic relief**
  - 1 Symptomatic relief
    - 1.1 CHM Nei Yi pills + CHM Nei Yi enema vs Nei Yi pills
      - 1 40 Risk Ratio (M-H, Fixed, 95% CI) 1.11 [0.65, 1.89]

- **Dysmenorrhea score**
  - 2 Dysmenorrhea score
    - 2.1 CHM Nei Yi pills + CHM Nei Yi enema vs Nei Yi pills
      - 1 40 Mean Difference (IV, Fixed, 95% CI) -1.89 [-3.89, 0.11]

- **Lumbosacral pain relief**
  - 3 Lumbosacral pain relief
    - 3.1 CHM Nei Yi pills + CHM Nei Yi enema vs Nei Yi pills
      - 1 40 Risk Ratio (M-H, Fixed, 95% CI) 0.95 [0.74, 1.23]

- **Rectal Irritation relief**
  - 4 Rectal Irritation relief
    - 4.1 CHM Nei Yi pills + CHM Nei Yi enema vs Nei Yi pills
      - 1 30 Risk Ratio (M-H, Fixed, 95% CI) 1.07 [0.79, 1.44]

- **Tenderness of vaginal nodules in posterior fornix**
  - 5 Tenderness of vaginal nodules in posterior fornix
    - 5.1 CHM Nei Yi pills + CHM Nei Yi enema vs Nei Yi pills
      - 1 27 Risk Ratio (M-H, Fixed, 95% CI) 0.96 [0.74, 1.25]

- **Adnexal masses disappearance or shrinkage**
  - 6 Adnexal masses disappearance or shrinkage
    - 6.1 CHM Nei Yi pills + CHM Nei Yi enema vs Nei Yi pills
      - 1 33 Risk Ratio (M-H, Fixed, 95% CI) 1.21 [0.85, 1.72]

### What’s New

Last assessed as up-to-date: 7 August 2008.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
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<tbody>
<tr>
<td>7 April 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
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**History**


Review first published: Issue 3, 2009

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>9 February 2007</td>
<td>New citation required and major changes</td>
<td>Substantive amendment</td>
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</table>

**Contributions of Authors**

AF adapted the original title, developed the protocol, and co-ordinated the project.

AF and JPL co-drafted the first versions of the protocol.

AF and JPL conducted provisional Chinese and English language searches.

JPL and PL reviewed and commented upon the initial drafts of the protocol.

SC and AF conducted the initial processes of trial selection and data extraction, reviewed and commented on by JPL.

**Declarations of Interest**

None known

**Sources of Support**

**Internal sources**

- No sources of support supplied

**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)
Drugs, Chinese Herbal [*therapeutic use]; Endometriosis [complications; *drug therapy]; Gestrinone [therapeutic use]; Pelvic Pain [drug therapy; etiology]; Progestins [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words
Female; Humans