

EBM Journal Club- Endometriosis and chinese medicine

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OUTLINE

- ▶ Background knowledge
- ▶ Clinical scenario
- ▶ Ask(PICO)
- ▶ Acquire
- ▶ Appraisal
- ▶ Apply
- ▶ Audit

Background Knowledge

About Endometriosis

Chocolate cyst Severe Dysmenorrhea Pelvic pain Dyspareunia Infertility

Treatment

Medical

NSAID

Symptomatic treatment

- Danazol
- Gestrinone
- GnRH-a
- COC
- Progestin

Recurrence in 6 months

Surgical

- Remove the endometrium tissue
- Nerve block
- Definite remove the ovary and uterus

Return of symptoms after 1 year

Clinical Scenario

醫師，我不想再吃西藥治療子宮內膜異位症了，如果改用中醫治療會不會比較好??

糟!!歪果仁的醫學我不太懂耶，快來EBM一下.....

Steps in EBM- 5As

- ▶ Ask 問
 - 提問:由個案的臨床資料提出可回答的臨床問題 (PICO)
- ▶ Acquire 查
 - 尋找最佳的實證文獻(各文獻資料庫，包括發表及未發表的資料)
- ▶ Appraisal 讀
 - 評估最佳實證醫學文獻的可信度、臨床重要性、以及可應用性
- ▶ Apply 用
 - 整合並應用於實際患者的治療決策(臨床應用)
- ▶ Audit 審
 - 溝通:以簡單病人可以聽懂的语言，告知各種處置之可能利益與風險(效果評估)

Step 1 – Ask

建立一個可回答的問題

PICO	
Problem 病人問題	Endometriosis induced dysmenorrhea and pelvic pain
Intervention 介入處置	Chinese Herbs
Comparison 對照處置	Conventional biomedical intervention
Outcome 臨床結果	Symptomatic relieve

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Step 2 – Acquire

- ▶ Search for the “BEST Evidence”
- ▶ Search strategies

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Search for the “best evidence”

- ▶ Background knowledge
- ▶ Secondary database
- ▶ Primary database
 - 原則：搜尋與病人問題相同或類似且證據等級較高的文獻，再謹慎評讀與評估此文章的證據在此問題的適用性。

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Level of evidence

The “5S” levels of organization of evidence from health care research—by R Brain Haynes (ACP Journal Club, 2006 Nov-Dec; 145:A8)

Systematic reviews (系統性回顧): Evidence based textbooks (evidence-based textbooks), Evidence based journal abstracts (evidence-based journal abstracts), Systematic reviews (系統性回顧), Original journal articles (original journal articles).
 Summaries (摘要): Evidence based textbooks (evidence-based textbooks), Evidence based journal abstracts (evidence-based journal abstracts), Systematic reviews (系統性回顧), Original journal articles (original journal articles).
 Synopses (摘要): Evidence based textbooks (evidence-based textbooks), Evidence based journal abstracts (evidence-based journal abstracts), Systematic reviews (系統性回顧), Original journal articles (original journal articles).
 Syntheses (綜覽): Evidence based textbooks (evidence-based textbooks), Evidence based journal abstracts (evidence-based journal abstracts), Systematic reviews (系統性回顧), Original journal articles (original journal articles).
 Studies (研究): Evidence based textbooks (evidence-based textbooks), Evidence based journal abstracts (evidence-based journal abstracts), Systematic reviews (系統性回顧), Original journal articles (original journal articles).

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Grade	UK Practice Guideline	WHO Guideline for Drug
A	This is good evidence to support the Recommendation	1a RR of RCT (with narrow confidence interval) 1b Individual RCT (with narrow confidence interval) 1c RCT or more studies
B	There is fair evidence to support the Recommendation	2a RR of cohort studies (with homogeneity) 2b Individual cohort study or low quality RCT (with follow-up) 2c Retrospective research - ecological studies 2d RR of case-control study 2e Individual case-control study
C	There is insufficient evidence for an opinion, but recommendation may be made on other grounds	Case series and poor quality cohort/case-control studies
D	There is fair evidence to exclude the Recommendation	Expert opinion without explicit critical appraisal, or based on best research
E	There is good evidence to exclude the recommendation	

917 - Randomized Control Trial (隨機試驗)
918 - Systematic Review

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UpToDate ONLINE

搜尋策略 / 過程

Key words : endometriosis and [Chinese herbal medicine or alternative complementary medicine]

Overview of the treatment of endometriosis
Acupuncture — A systematic review of treatment of pain associated with endometriosis with acupuncture found only one randomized trial that met inclusion criteria [62]. In that trial (n = 67), auricular acupuncture was significantly more effective than Chinese herbal medicine for treating dysmenorrhea in women with endometriosis [63]

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DynaMed
 4 4 4 Formally EBANIM

Key words : endometriosis and Chinese herbal medicine

RESULT: All(9) Fit(1)

Reference - Cochrane Database Syst Rev 2012, May 16(5):CD006568

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Ovid

Key words : [endometriosis and Chinese herbal medicine] and review

RESULT: All(5) Fit(0)

14

PubMed

Key words : [endometriosis and Chinese herbal medicine] and systemic review

RESULT: All(5) Fit(1)

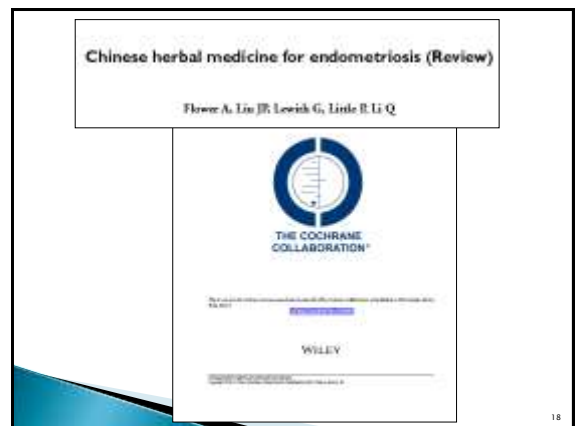
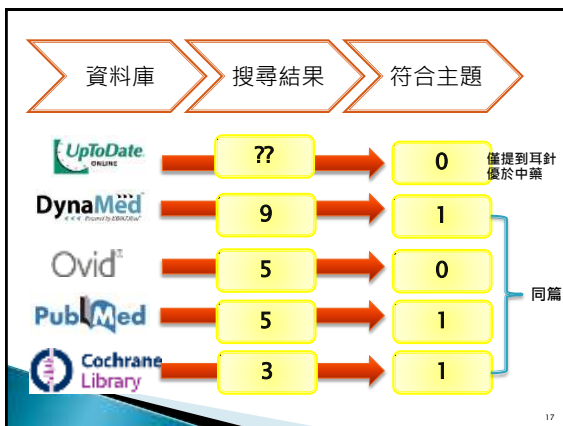
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Cochrane Library

Key words : endometriosis and Chinese herbal medicine

RESULT: All(3) Fit(1)

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Abstract

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

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Main results

- ▶ Two Chinese RCTs involving 158 women were included in this review. Both these trials described adequate methodology.
- ▶ 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).

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- ▶ 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).
- ▶ 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.

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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.**

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON (Explained)

Study	Risk of bias	Number of participants	Comparisons	RR (95% CI)
Yu QZ 2009	B-moderate	180	CHM oral + enema versus gestr-	RR 1.02 (95% CI 0.93 to 1.12)
Yu SZ 2009	B-moderate	58	CHM oral versus CHM oral + enema - for symptomatic relief CHM oral versus danazol RR 5.06 (95% CI 1.28 to 20.05) CHM oral + enema versus danazol RR 5.63 (95% CI 1.47 to 21.54)	

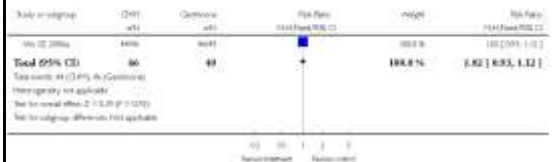
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Analysis 1.1. Comparison 1 CHM versus gestrinone, Outcome 1 Symptomatic relief.

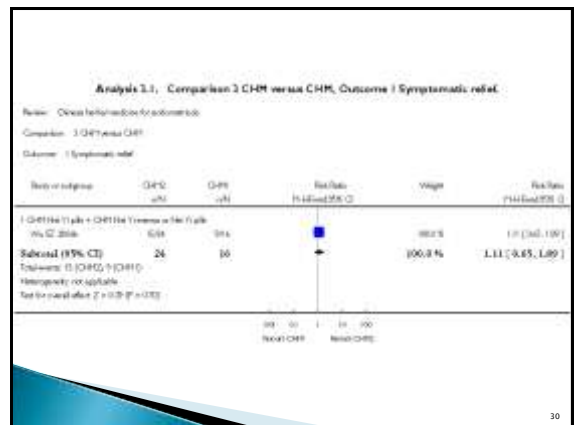
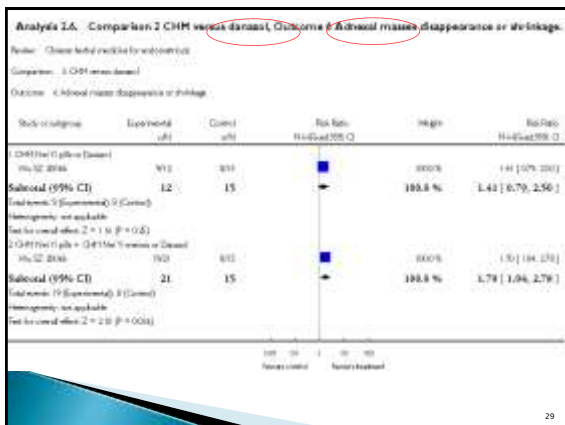
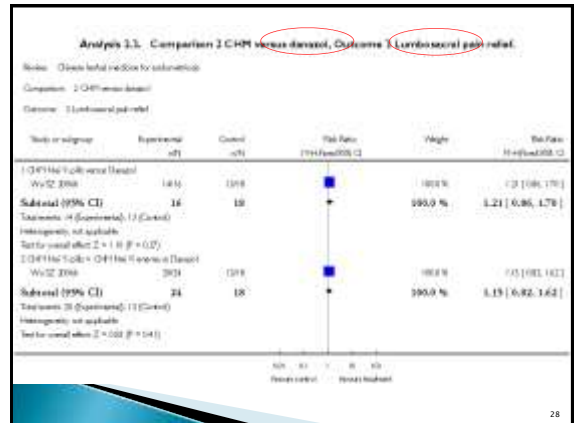
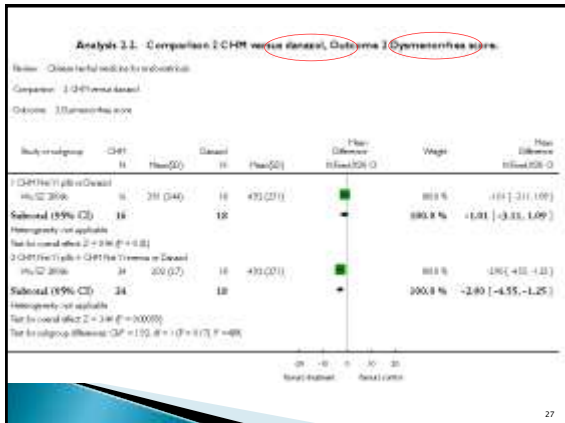
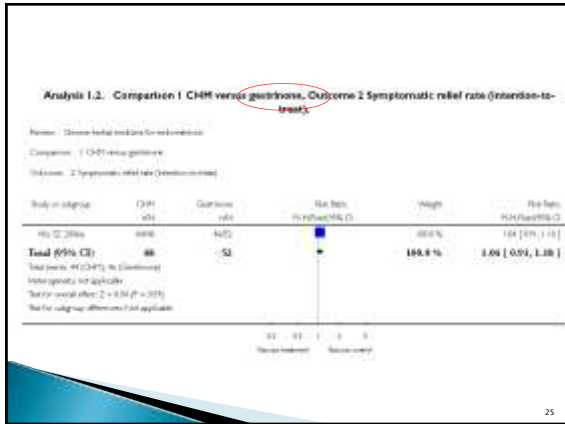
Review: Chinese herbal medicine for endometriosis

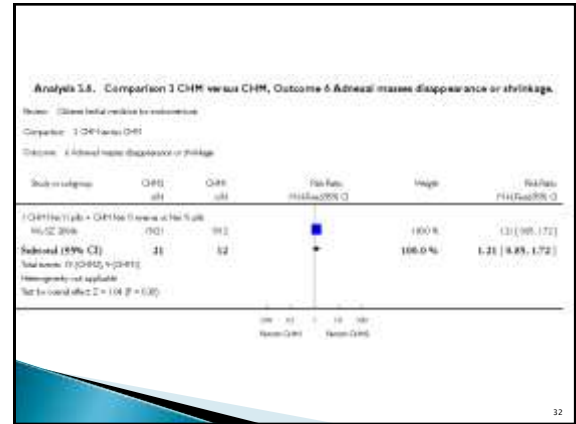
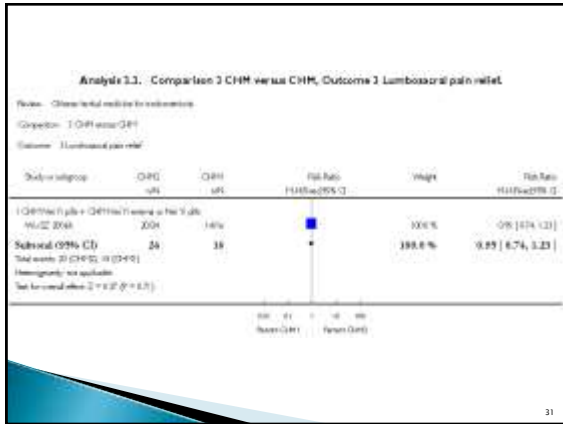
Comparison: 1 CHM versus gestrinone

Outcome: 1 Symptomatic relief




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Step 3: Appraisal



- Oxford CEBM Critical Appraisal Sheets
 - 此篇系統回顧是否提出明確定義的問題？
 - 是否此篇回顧的搜尋策略可能有遺漏可能合適的臨床試驗？
 - 1-研究收錄標準是否有明確的界定？
 - 2-關於研究族群、涉入治療、比較分組及結果評估是否適切？
 - 4.所收錄的研究是否有效力(valid)的研究 (randomization, blinding and completeness of follow-up) ？
 - 5.如果有meta-analysis，所收錄的研究是否有足夠的一致性以產生合併的資料？

1. 此篇系統回顧是否提出明確定義的問題？(PICO)

SYSTEMATIC REVIEW: Are the results of the review valid?

What is best?	Where do I find the information?
The main question being addressed should be clearly stated. The exposure, such as a therapy or diagnostic test, and the outcome(s) of interest will often be expressed in terms of a simple relationship.	The Title, Abstract or final paragraph of the introduction should clearly state the question. If you still cannot ascertain what the focused question is after reading these sections, search for another paper!

This paper: Yes No Unclear

Abstract

2. 是否此篇回顧的搜尋策略可能有遺漏可能合適的臨床試驗？

F - Is it unlikely that important, relevant studies were missed?

What is best?	Where do I find the information?
The starting point for comprehensive search for all relevant studies is the major bibliographic databases (e.g., Medline, Cochrane, EMBASE, etc.) but should also include a search of reference lists from relevant studies, and contact with experts, particularly to inquire about unpublished studies. The search should not be limited to English language only. The search strategy should include both MeSH terms and text words.	The Methods section should describe the search strategy, including the terms used, in some detail. The Results section will outline the number of titles and abstracts reviewed, the number of full-text studies retrieved, and the number of studies excluded together with the reasons for exclusion. This information may be presented in a figure or flow chart.

This paper: Yes No Unclear

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) Trial Search Co-ordinator:

Electronic searches

We searched the following on the 31/10/11:

- (1) Menstrual Disorders and Subfertility Group Trial 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;

MeSH terms

INDEX TERMS

Medical Subject Headings (MeSH)

MeSH check words

(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 Naïno* (endometriosis), *Chūwáng Yīyào* (traditional medicine), *Zhōng Yào* (Chinese medicine), *Cǎo Yào* (herbal medicine), *Tān Yào* (plant extract), *Bùchōng Yīyào* (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.

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3-1. 研究收錄標準是否有明確的界定?

A - Were the criteria used to select articles for inclusion appropriate?	
What is best? The inclusion or exclusion of studies in a systematic review should be clearly defined a priori. The eligibility criteria used should specify the subjects, interventions or exposures and outcomes of interest. In many cases the type of study design will also be a key component of the eligibility criteria.	Where do I find the information? The Methods section should describe in detail the inclusion and exclusion criteria. Normally, this will include the study design.
This paper: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/>	
Comment:	

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Inclusion and Exclusion

收錄族群

介入的治療

Criteria for considering studies for this review

Types of studies
Published and unpublished randomised controlled trials (RCTs) were eligible for inclusion. We included non-randomised studies for many trials with evidence of inadequate methods of random 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 therapy versus a different CHM therapy.

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3-2. 關於研究族群、涉入治療、比較分組及結果評估是否適切?

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Method	Two design, a pilot randomised controlled trial (RCT) and a single-blind, parallel, randomised controlled trial (RCT) (see Appendix 1 for details). The pilot RCT was conducted in 2009 and the main RCT was conducted in 2010. The pilot RCT was conducted in 2009 and the main RCT was conducted in 2010.
Participants	All cases of endometriosis confirmed by laparoscopy. Inclusion criteria: 1. Age 18-45 years. 2. Primary infertility. 3. Painful menstruation. 4. No previous surgery for endometriosis. Exclusion criteria: 1. Current pregnancy. 2. Current use of hormonal therapy. 3. Current use of oral contraceptives. 4. Current use of any other medical treatment for endometriosis. 5. Current use of any other medical treatment for infertility. 6. Current use of any other medical treatment for pain.
Interventions	Two parallel randomised controlled trials (RCTs) were conducted. The first RCT compared CHM (Sheng Luo Tang) with placebo. The second RCT compared CHM (Sheng Luo Tang) with conventional biomedical treatment (Gonadotropin-releasing hormone agonist). The CHM was administered daily for 12 weeks. The conventional biomedical treatment was administered daily for 12 weeks.
Outcomes	All clinical outcomes. 1. Symptom relief (defined as improvement of symptoms, patient-rated, compared to baseline) at 12 weeks. 2. Symptom relief (defined as improvement of symptoms, patient-rated, compared to baseline) at 24 weeks. 3. Symptom relief (defined as improvement of symptoms, patient-rated, compared to baseline) at 36 weeks. 4. Symptom relief (defined as improvement of symptoms, patient-rated, compared to baseline) at 48 weeks. 5. Symptom relief (defined as improvement of symptoms, patient-rated, compared to baseline) at 60 weeks. 6. Symptom relief (defined as improvement of symptoms, patient-rated, compared to baseline) at 72 weeks. 7. Symptom relief (defined as improvement of symptoms, patient-rated, compared to baseline) at 84 weeks. 8. Symptom relief (defined as improvement of symptoms, patient-rated, compared to baseline) at 96 weeks. 9. Symptom relief (defined as improvement of symptoms, patient-rated, compared to baseline) at 108 weeks. 10. Symptom relief (defined as improvement of symptoms, patient-rated, compared to baseline) at 120 weeks.

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Method	Two design, a pilot randomised controlled trial (RCT) and a single-blind, parallel, randomised controlled trial (RCT) (see Appendix 1 for details). The pilot RCT was conducted in 2009 and the main RCT was conducted in 2010.
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3-2.關於研究族群、涉入治療、比較分組及結果評估是否適切? **Unclear?**

- ▶ 列表說明所收錄的兩個RCT:
 - 研究族群: 參與人數 · 診斷標準
 - 涉入治療: 內異丸 · 內異塞劑 · danazol · gestrinone
且列出內異丸之中藥組成
- 比較分組 } 表中未呈現實驗組與控制組之結果比較 ·
- 結果評估 } 僅在內文中呈現 ·

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4.所收錄的研究是否是有效力(valid)的研究(randomization, blinding and completeness of follow-up)?

A - Were the included studies sufficiently valid for the type of question asked?

What is best?	Where do I find the information?
The article should describe how the quality of each study was assessed using predetermined quality criteria appropriate to the type of clinical question (e.g., randomization, blinding and completeness of follow-up).	The Methods section should describe the assessment of quality and the criteria used. The Results section should provide information on the quality of the individual studies.
This paper: Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Unclear <input type="checkbox"/>	
Comment:	

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- ▶ 2 RCT
- ▶ Single blind
- ▶ Follow up:
 - Wu SZ 2006a follow up from 1-24 months
 - Wu SZ 2006b no follow up data

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 extract. There was no evaluation of the success of blinding during the trial. 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 mechanism that could underpin the effectiveness of CHM. However, a detailed analysis of this work is beyond the remit of this review.

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5.如果有meta-analysis，所收錄的研究是否有足夠的一致性以產生合併的資料？

What were the results?

How are the results presented?

A systematic review provides a summary of the data from the results of a number of individual studies. If the results of the individual studies are similar, a statistical method (called meta-analysis) is used to combine the results from the individual studies and an overall summary estimate is calculated. The meta-analysis gives weighted values to each of the individual studies according to their size. The individual results of the studies need to be expressed in a standard way, such as relative risk, odds ratio or mean difference between the groups. Results are traditionally displayed in a figure, like the one below, called a forest plot.

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5.如果有meta-analysis，所收錄的研究是否有足夠的一致性以產生合併的資料？

NO!
只有兩篇RCT ·
未呈現Forest
plot資料 ·

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 explanation 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).

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Step 4: Apply & Step 5: Audit

- ▶ Step4: Integrating the **evidence** with our clinical **expertise** and patients' unique biology, values and circumstances (**expectation**). (3E)
- ▶ Step5: Evaluating our effectiveness and efficiency in executing steps 1-4 and seeking ways to improve them both for next time.

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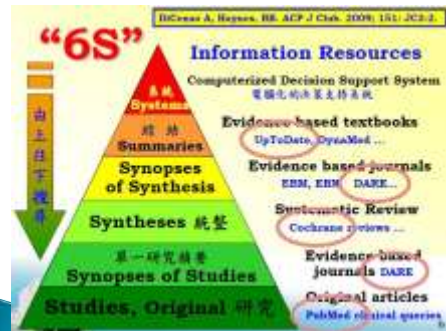
以簡單且病人可以聽懂的語言，告知其診療的決策

- 根據實證研究指出，口服中藥與塞劑的應用的確對於子宮內膜異位所造成的痛經有良好的效果，與口服西藥(以 danazol, gestriron 為例)相比，效果相似或更佳，且副作用較小。
- 對於中藥塞劑(瀉劑)的劑型，也許為將來可發展或研究的方向。
- 深受子宮內膜異位症所苦的患者，在無法承受西藥副作用的狀況下，的確可以鼓勵其接受中醫藥的治療，能達到減輕症狀/疾病治療的效果，且安全性高，副作用少，實為值得參考且推廣的治療模式。

Thank you for your listening

Acquire the Best Evidence: Finding the Best Evidence First

Hierarchy of Sources of Evidence Pyramid



Analysis 1.3. Comparison 1 CHM versus gestriron, Outcome 3 Pregnant rate (accumulated from 3-24 months of follow-up).

Review: Chinese herbal medicine for endometriosis

Comparison: 1 CHM versus gestriron

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

