

# Systematic Review of Chinese Medicine for Ovarian Endometriosis

**Eileen Lee, Yongqi Xie, Haiyong Chen and Wei Meng\***

School of Chinese Medicine, University of Hong Kong, Hong Kong

**\*Corresponding author:** Wei Meng, School of Chinese Medicine, The University of Hong Kong, Pokfulam, Hong Kong, Tel: +852 39170483, E-mail: bmeng@hku.hk

## Review Article

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## Abstract

**Background:** Ovarian endometriosis is a common disease found in women of childbearing age. Existing therapies in western medicine have limitations in various aspects including management of pain, prevention of recurrence and promotion of fertility. Numerous Chinese medicine preparations have been shown to possess therapeutic potential in relieving EMS symptoms and shrinking the OEMS without significant adverse effects, although the clinical efficacy needs to be further confirmed with large amounts of well-designed experiments.

**Objectives and Methods:** RCTs of Chinese medicine concerning ovarian endometriosis are included to work out this systematic review in order to provide scientific evidence for its efficacy and safety.

**Results:** 16 articles were selected out of 427 literatures for a systematic reviews and a meta-analysis was conducted. The studies suggest that the ovarian endometriosis patients' recurrence rate is lower and the pregnancy rate is higher in the Chinese medicine group, while the total effective rate, change in the size of endometrial cyst and CA125 level in both Chinese and Western medicine groups shows no statistical significance. Although the result favored the Chinese medicine group for lower dysmenorrhea rate and less adverse effects, the size of sample data and high heterogeneity between studies adversely affected the reliability of the results.

**Conclusion:** Chinese medicine has two advantages over Western medicine in treating ovarian endometriosis, which are the low recurrence rate and high pregnancy rate. However, due to the limited number of literatures available and variations in their experimental methods and outcome measures, the conclusive results remain elusive. Larger scales of randomized controlled trials and more scientific evidence are needed to prove the efficacy and safety of Chinese medicines for ovarian endometriosis.

**Keywords:** Ovarian endometriosis; Chocolate cyst; Traditional Chinese medicine; Randomized controlled trial; Systematic review

## Introduction

Ovarian endometriosis (OEM) is a hormone-dependent disease characterized by the unusual growth of endometrial tissue inside the ovaries. It behaves in malignant manner, for example, endometriosis can be distantly metastatic, invasive, and rapidly recurring. A French epidemiological study released in 2016 shows that, endometriosis patients account for 1.5% of 14,239,197 hospitalized women at childbearing age [1]. The increasing incidence rate of endometriosis, due to early menarche, late menopause and advanced maternal age, contribute to the burden of ill health in women [2]. According to The American Congress of Obstetricians and Gynecologists (ACOG), 54.9% endometriotic growth occurs at the ovary, the most common site of endometrial implantation [3]. Approximately 80% OEM are unilateral ovarian endometriosis, while around 50% of them involve both ovaries [3-5]. Although surgical approaches have been recommended as a definitive management of OEM, surgical treatment is an invasive procedure and causes tissue injury. Pharmacological therapies are effective in reducing the size of OEM and relieving symptoms. However, rapid recurrence and broad adverse side effects have largely limited the use of pharmacotherapy. A search for alternative treatment strategies is therefore needed. Numerous Chinese medicine preparations have been shown to possess therapeutic potential in relieving OEM symptoms and

shrinking the OEM size without significant adverse effects, although the clinical efficacy needs to be further confirmed. On the basis of empirical evidence and clinical practice, randomized controlled trials (RCTs) of Chinese medicine concerning ovarian endometriosis are located to conduct a systematic review for assessing its efficacy and safety.

## Materials and Methods

### Search Method

We searched for published RCTs of Chinese Medicine for ovarian endometriosis with the English keywords "Traditional Chinese medicine, Chinese medicine, Chinese herbal medicine, Herbal medicine, ovarian endometriosis, Chocolate cyst" and Chinese keywords "中醫，中藥，卵巢子宮內膜異位症，巧克力囊腫". Searching strategy used was presented in the figure below (Figure 1). The following databases were searched: MEDLINE (from 1950 to Jan 2016); PubMed (from 1927 to Jan 2016); Wan Fang Database (Chinese Ministry of Science and Technology) (from 1980 to Jan 2016); and China National Knowledge Infrastructure (CNKI) (from 1915 to Jan 2016). We also screened bibliographies of the selected articles and searched manually for any internet inaccessible articles. The language of the articles was limited to English and Chinese. Publications without full text were excluded.

A.	Searching strategy for RCTs in English	B.	Searching strategy for RCTs in Chinese
1.	Traditional Chinese medicine	1.	中醫
2.	Chinese medicine	2.	中藥
3.	Chinese herbal medicine	3.	方劑
4.	Herbal medicine	4.	湯劑
5.	Ovarian endometriosis	5.	卵巢子宮內膜異位症
6.	Chocolate cyst	6.	巧克力囊腫
7.	1 OR 2 OR 3 OR 4	7.	1 OR 2 OR 3 OR 4
8.	5 OR 6	8.	5 OR 6
9.	7 AND 8	9.	7 AND 8

Figure 1: Searching strategy for English and Chinese RCTs

## Systematic Review

### Inclusion Criteria

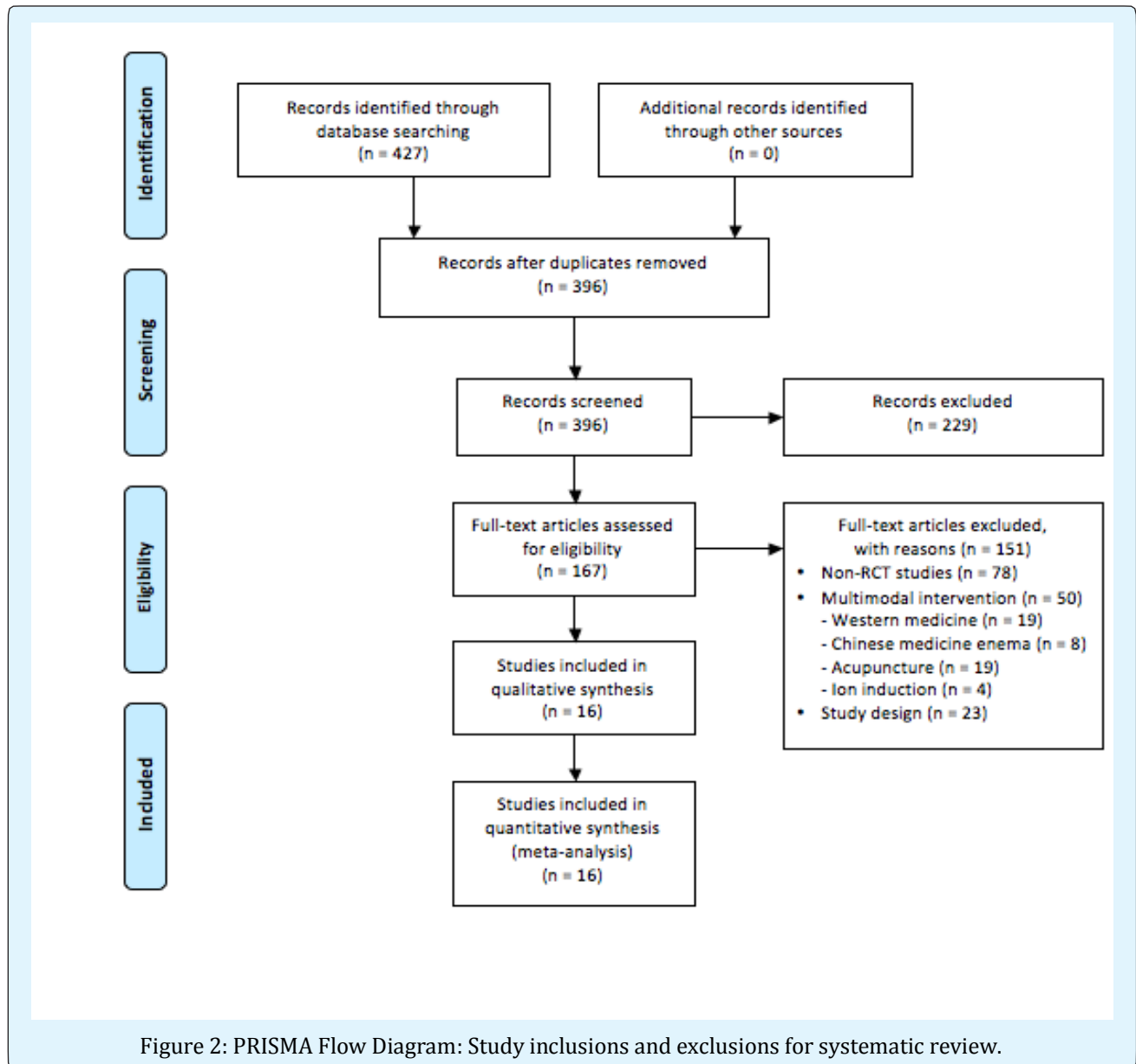
- **Types of Studies:** All RCTs reporting the applications of Chinese Medicine to OEM.
- **Participants:** Ovarian endometriosis patients diagnosed by laparoscopy, medical imaging examination or pathological examination.
- **Interventions:** All types of Chinese medicines of oral administration in either standard or combined formulas are accepted in the treatment group. All types of Western medicines are accepted in the control group.
- **Outcome Measures:** The effective rate, recurrence rate, pregnancy rate and also the safety of the intervention were studied.

### Exclusion Criteria

- Other Participants: Suspected OEM diagnosis without laparoscopy, medical imaging examination or pathological examination was excluded.
- Combined Therapies: If the intervention combined Chinese medicines with therapies other than surgical therapy, the study would be excluded.

- Other Type of Studies: Case reports, commentary studies, and review articles were excluded.

**Data Extraction and Quantitative Analysis:** 16 articles were selected out of 427 literatures and the exclusion criteria were presented in the PRISMA flow diagram below (Figure 2). Extraction forms were designed for data extraction from the selected publications quantitatively.



### Meta-analysis

**Data Synthesis:** We carried out the statistical analysis using RevMan5.3. Quantitative data was analyzed by standard mean differences (SMD), while categorical variables were analyzed with using odds ratio (OR) and relative risk (RR). If substantial statistical heterogeneity ( $P < 0.05$ ) were detected, random effects model (RE)

would be selected, otherwise, fixed model (FE) would be used for homogeneity ( $P > 0.05$ ). Results were presented in forest plot with its 95% confidence interval. Funnel plot would be used in presenting potential publication bias if necessary. Characteristics of the included studies and also their risk of bias were presented as follow (Tables 1 & 2).

Study	Case	Chinese Medicine	Western Medicine	Outcome Measure	Experiment #	Follow up #
Bai, et al. 2011 [6]	88	Yu Tong Shu Pills	Danazol	Effective rate, recurrence rate, dysmenorrhea rate, change in nodules tenderness, CA125 level	6	18
Cao, et al. 2008 [7]	60	E-leng capsule	Danazol	Recurrence rate、MMP-9 mRNA & TIMP-1 mRNA expression	6	9
Ding Shi 2012 [8]	56	Traditional Chinese Medicine	Namestran (Gestrinone)	Effective rate, pregnancy rate, adverse event rate	6	3
Ge Cao 2014 [9]	92	Compound EZhu powder	Mifepristone, Gestrinone	Effective rate, recurrence rate, pregnancy rate, adverse event rate	6	6
Huang, et al. 2008 [10]	50	E-leng capsule	Namestran (Gestrinone)	Dysmenorrhea rate, change in the diameter of endometrial cyst, CA125 level, PRL level, positive rate of serum EmAb, adverse event rate	4	0
Li 2012 [11]	94	Dan E Fu Kang Jian Plaster	Gestrinone	Effective rate, recurrence rate	6	0
Li, et al. 2011 [12]	61	Mu Da Decoction	Gestrinone	Pelvic pain rate, change in the diameter of endometrial cyst, CA125 level, adverse event rate	6	0
Liu, et al. 2015 [13]	80	Jian Pi Wen Shen Decoction	Mifepristone	Effective rate, adverse event rate	3	6
Luo, et al. 2016 [2]	50	Bu ShenHuoXue San Yu Decoction	Mifepristone	Effective rate, dysmenorrhea rate, score in TCM symptoms, change in the size of endometrial cyst, CA125 level	3	3
Shan 2011 [14]	82	WenShenHua Yu Decoction	Mifepristone	Effective rate, recurrence rate, pregnancy rate, adverse event rate	6	24
Wang Xiao 2013 [15]	86	Dan E Fu Kang Jian Plaster	Gestrinone	Effective rate, recurrence rate	6	0
Xia, et al. 2014 [16]	66	Zheng's Yi Wei Gui Yuan Decoction	Goserelin	Effective rate, recurrence rate, adverse event rate	6	12
Yan 2014 [17]	498	Hua Yu Decoction	Penicillin, Gentamicin, Norfloxacin, Spiramycin	Effective rate	1	3
Yang, et al. 2014 [18]	96	Traditional Chinese Medicine	Gestrinone	Dysmenorrhea rate, change in the diameter of endometrial cyst, adverse event rate	3	0
Zhou Song 2013 [19]	60	Bu ShenHuoXue Decoction	Leuprorelin	Effective rate, recurrence rate, pregnancy rate, adverse event rate	6	6
Zhu, Lei 2010 [20]	100	Dan E Fu Kang Jian Plaster	Gestrinone	Effective rate, recurrence rate, dysmenorrhea rate, lumbosacral bulge improvement rate, dyspareunia improvement rate	6	36

# Experiment and follow up duration measured in month(s).

Table 1: Characteristics of the included studies [2,6-19].

Author (Year)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bai et al 2011	?	?	?	?	+	+	?
Cao et al 2008	?	?	?	?	+	+	?
Ding & Shi 2012	?	?	?	?	+	+	?
Ce & Cao 2014	?	?	?	?	+	+	?
Huang et al 2008	?	?	?	?	+	+	?
Li 2012	?	?	?	?	+	+	?
Li et al 2011	?	?	?	?	+	+	?
Liu et al 2015	?	?	?	?	+	+	?
Luo et al 2016	?	?	?	?	+	+	?
Shan 2011	?	?	?	?	+	+	?
Wang & Xiao 2013	?	?	?	?	+	+	?
Xia et al 2014	?	?	?	?	+	+	?
Yan 2014	?	?	?	?	+	+	?
Yang et al 2014	?	?	?	?	+	+	?
Zhou & Song 2013	?	?	?	?	+	+	?
Zhu & Lei 2010	?	?	?	?	+	+	?

Table 2: Risk of bias of the included studies.

## Results and Discussion

16 clinical literatures were selected according to the inclusion and exclusion criteria, in which, 1619 cases were included. One of the selected clinical literatures included 3 groups, which can be seen as two randomized controlled trials. Hence, 17 randomized controlled trials were included in this study.

### Chinese Medicine for Ovarian Endometriosis

**Therapeutic Principles:** Chinese medicine treats the

human body as a whole system. Its therapeutic principle aims at resolving the causes of the disease and helps body in restoring internal dynamic balance, hence, relieving the symptoms. Amongst all the selected RCTs, “invigorating blood circulation” (78.57%) and “eliminating blood-stasis” (64.29%) were the most common therapeutic principle applied (Table 3). Less common ones included “resolving masses and swelling” (50.00%), “regulating the flow of vital energy/dispersing the depressed liver-energy” (50.00%) and “tonifying the kidney” (35.71%).

Therapeutic Principle	Frequency* (%)
Invigorates blood	11 (78.57%)
Disperses stasis	9 (64.29%)
Resolves accumulation, disperses accumulation	7 (50.00%)
Moves Qi, courses the liver	7 (50.00%)
Supplements the kidney	5 (35.71%)

\* % is the number of RCT using each therapeutic principle/ the number of included clinical trials × 100.

Table 3: Therapeutic principles application of Chinese medicines for ovarian endometriosis.

**Individual Chinese Medicines:** Amongst all the individual Chinese medicine studied for ovarian endometriosis (Table 4), Blue Turmeric Rhizome was the most frequently used individual Chinese medicine (62.5%). The top 10 most commonly used single Chinese medicines included Blue Turmeric Rhizome, Common Burreed Tuber, Yanhusuo Tuber, Red Paeoniae

Trichocarpace, Dan-shen Root, Licorice Root, Nutgrass Galingale Rhizome, Mongolian Milkvetch Root/Membranous Milkvetch Root, Chinese Angelica, and Chinese Thorawax Root in descending order. The frequently used herbs in the clinical trials were recorded and listed below.

Order	English name	Latin pharmaceutical name	Chinese name	Frequency* (%)	Daily dose (g) <sup>a</sup>	Therapeutic actions
1	Blue Turmeric Rhizome	Curcumae Phaeocaulis Rhizoma	莪朮	10 (62.5%)	10-15	Breaks blood, disperses accumulations, moves Qi, relieves pain.
2	Common Burreed Tuber	Sparganii Rhizoma	三棱	9 (56.25%)	10-15	Breaks blood, moves Qi, resolves accumulation, stops pain.
3	Yanhusuo Tuber	Corydalis Yanhusuo Rhizoma	延胡索	9 (56.25%)	5-10	Invigorates blood, disperses stasis, moves Qi, stops pain.
4	Red Paeoniae Trichocarpae	Paeoniae Rubra Radix	赤芍	9 (56.25%)	12-20	Clears heat, cools the blood, disperses stasis, and relieves pain.
5	Dan-shen Root	Salviae Miltiorrhizae Radix	丹参	7 (43.75%)	15-30	Invigorates the blood, regulates menstruation, dispels stasis, relieves pain, cools blood, relieves ulcer, clears the heart, eliminates vexation, nourishing the blood and calming mental state.
6	Liquorice Root	Glycyrrhizae Radix	甘草	7 (43.75%)	5-6	Supplements the spleen, boosts Qi, clears heat, resolves toxin, dispels phlegm, relieves cough, relaxes tension, relieves pain, and harmonizes the nature of other medicinal.
7	Nutgrass Galingale Rhizome	Cyperi Rhizoma	香附	6 (37.5%)	12-15	Moves Qi, resolves depression, regulates menstruation, and relieves pain.
8	Mongolian Milkvetch Root; Membranous Milkvetch Root	Astragali Mongolici Radix; Astragali Membranacei Radix	黄耆	5 (31.25%)	10-20	Supplements Qi, secures the exteriordefence, promotes urination, outthrusts toxin, expels pus, closes sore, and engenders flesh.
9	Chinese Angelica	Angelicae Sinensis Radix	当归	5 (31.25%)	10-15	Supplements the blood, invigorates the blood, regulates menstruation, relieves pain, moistens the intestines, and frees the stool.
10	Chinese Thorawax Root	Bupleuri Chinensis Radix	柴胡	5 (31.25%)	/ <sup>b</sup>	Harmonizes the interior and exterior, courses the liver, resolves depression, outthrust the exterior defense, discharge heat, upbears yang, and raises the sunken.

\* % is the number of RCT using each individual Chinese medicine/ the number of included clinical trials × 100.

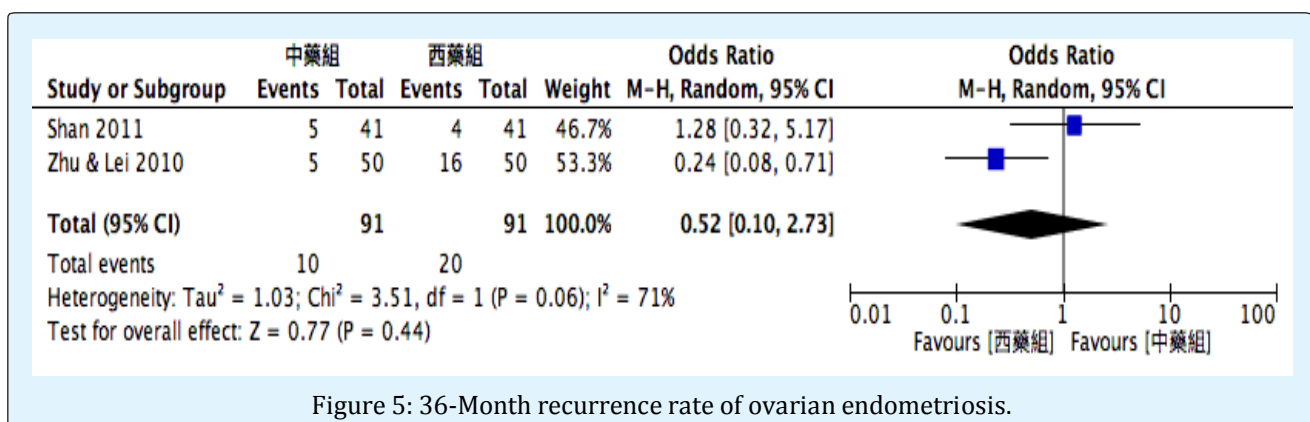
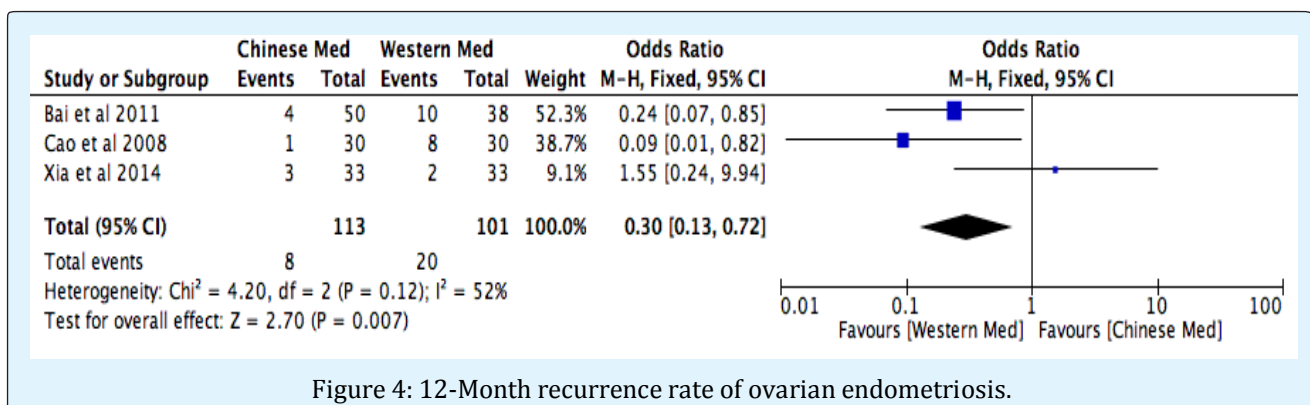
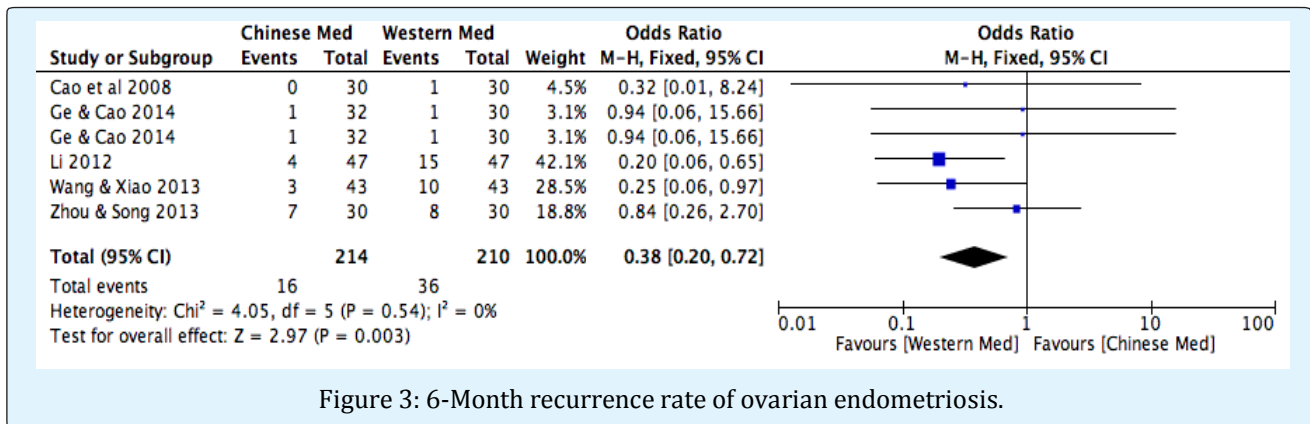
- Daily dose is the range of the reported daily dose in all included clinical trials.
- Not provided.

Table 4: Top 10 of most commonly used individual Chinese medicines for ovarian endometriosis.

## Effectiveness

The meta-analysis in limited randomized clinical trials suggested that the ovarian endometriosis patients recurrence rate is lower and the pregnancy rate is higher in the Chinese medicine group, while the total effective rate, change in the size of endometrial cyst and CA125 level in both Chinese and Western medicine groups shows no statistical significance. As shown in Figures 3 & 4, both the 6-month recurrence rate [FE: 0.38, 95% CI, 0.20-0.72,  $P=0.003$  ( $P<0.05$ )] and the 12-month

recurrence rate [FE: 0.30, 95% CI, 0.13-0.72,  $P=0.007$  ( $P<0.05$ )] of ovarian endometriosis in Chinese medicine group (Chinese Med) is lower than that in Western medicine group (Western Med). Although the 36-month recurrence rate in Chinese medicine group is also lower than that in Western medicine group [RE: 0.44, 95% CI, 0.10-2.73,  $P=0.44$ ] (Figure 5), the meta-analysis with only 2 randomized clinical trials provides limited support.



As shown in (Figure 6), the pregnancy rate in Chinese medicine group is higher than that in Western medicine group [FE: 2.32, 95% CI, 1.15-4.67, P=0.02 (P<0.05)]. Although the result favored Chinese medicines

for lower dysmenorrhea rate and less adverse effect, the lack of sample data and high heterogeneity adversely affected the reliability of the result.

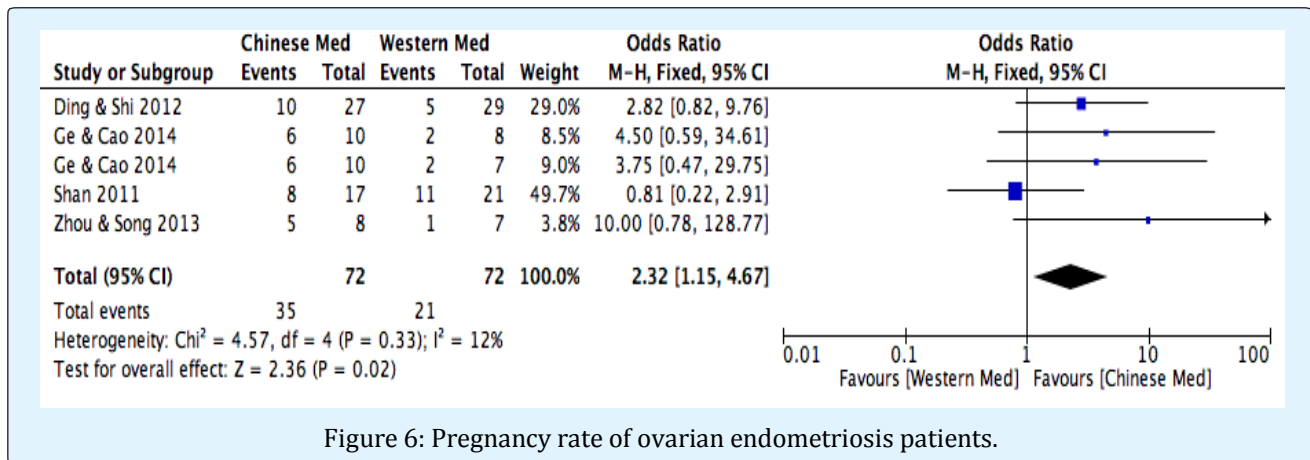


Figure 6: Pregnancy rate of ovarian endometriosis patients.

### Implications for further studies on the use of Chinese medicine in treating ovarian endometriosis

This study suggests that Chinese medicine is more effective than Western medicine in treating ovarian endometriosis: the recurrence rate is lower and pregnancy chances are higher, while the occurrence of dysmenorrhea and other associated symptoms are lower. However, the clinical efficacy of Chinese medicine for ovarian endometriosis needs to be further confirmed with large amounts of well-designed experiments. Moreover, it is difficult to carry out blinded trials between Chinese and Western Medicine since:

- Chinese Medicine is often boiled as a decoction drink in the clinical setting, which appearance and odor are difficult to create a Western Medicine look alike.
- Unlike Western medicine, Chinese medicine treats OEM by its own mechanism other than amenorrhea, leading to a variety of clinical symptom improvements which is difficult to measure in blinded trials. The methodology of Chinese medicine studies is therefore specially crafted, as it would be difficult to follow the double blinded trial model for international standards. An implication for future study will be the creation and standardization of a method for Chinese medicine clinical trial studies.

Future clinical Chinese Medicine studies should improve in the following:

- Adequate description of the randomization of studies and the allocation concealment, and blinding of the outcome to decrease the risk of bias;

- Provide data for both before and after changes in the clinical trials, according to international standards, and to clearly state each trial's inclusion and exclusion criteria;
- Description of the Chinese medicine prescription used, with a list of herbs and the net weight;
- Use an international standardized diagnostic tool for diagnostic and scoring system;
- Standardization of the reporting methods.

### Conclusion

In conclusion, Chinese medicine is more effective than Western medicine in treating ovarian endometriosis: the recurrence rate is lower and pregnancy chances are higher; while the effect of decreasing the size of endometriosis cyst is similar, while the chances of preventing reoccurrence of cyst and increasing the chances of pregnancy are higher. As pregnancy is the best method to curing endometriosis, the Chinese medicine treatment creates a positive cycle of enhancing the chances of pregnancy and curing the disease. There is medical and exploratory scientific research value in using Chinese medicine as a treatment method for ovarian endometriosis. There is need for future Chinese medicine clinical trials to be conducted based on an international standard, with bigger sample sizes, higher methodological quality, and be in accordance with Chinese medicine diagnostic and treatment theory. The future need to study and practice for the evaluation of Chinese medicine system, but also the direction of our efforts.



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