

# The Effectiveness of Traditional Chinese Medicine for Threatened Abortion: A Systematic Review and Meta-Analysis

Shun Yan HSU<sup>1#</sup>, Eileen LEE<sup>2,3</sup>, Rachel Hiu Yan CHAN<sup>2,3</sup>, Yan-Bo Zhang<sup>1,2,3</sup>, Lixing LAO<sup>1,2,3</sup>, Haiyong CHEN<sup>1,2,3\*</sup> and Wei MENG<sup>1,2,3\*</sup>

<sup>1</sup>School of Chinese Medicine, The University of Hong Kong

<sup>2</sup>Hong Kong Branch of Zhu's School of Gynecology of Chinese Medicine from Shanghai Workstation of Zhu Nansun, National Master of Chinese Medicine

<sup>3</sup>Hong Kong Branch of Yu Jin, Masters of Gynaecology of Integrative Medicine, Workstations for Training and Research

# First author

\*Corresponding author: Wei Meng and Haiyong CHEN, School of Chinese Medicine, The University of Hong Kong, Pokfulam, Hong Kong, Tel: +852 39170483; Email: bmeng@hku.hk

## Research Article

Volume 4 Issue 2

Received Date: May 03, 2019

Published Date: May 17, 2019

DOI: 10.23880/oajg-16000174

## Abstract

**Background:** Threatened abortion is a common complication during early pregnancy. Conventional managements for the miscarriage include bed rest, hormone therapy and muscle relaxants. Traditional Chinese medicine (TCM) is also the popular option for the women. Evidence to support the efficacy and safety of TCM in treating threatened abortion is still limited.

**Objective:** The study aimed to evaluate the safety and effectiveness of Chinese medicine in the treatment of threatened abortion compared with the hormone therapy through a systematic review and meta-analysis.

**Methods:** The randomized controlled trials (RCTs) were electronically retrieved in the database of China National Knowledge Infrastructure (CNKI), Wan Fang Database (Chinese Ministry of Science and Technology), VIP Data and PubMed between January 1 2008 and December 1 2018 with the pre-designed search strategy. The outcomes included the clinical effectiveness, the clotting time of vaginal bleeding, pain reduction in lower abdomen, and incidences of adverse events. The software RevMan 5.1 was employed for the meta-analysis.

**Results:** Twenty-three studies were included in the systematic review and meta-analysis, which enrolled 2014 pregnant women (1006 in the treatment group and 1008 in the control). The meta-analysis of clinical effectiveness showed that TCM significantly decreased rate of miscarriage compared with the conventional therapy. In the subgroup analysis of miscarriage rate in women, oral administration of TCM was more effective than either the injected or oral administration of conventional medications. Further analysis showed that oral TCM was more effective than the injection of progesterone only or combined with hCG, even the oral progesterone.

**Conclusions:** The study indicated that TCM was likely more effective than conventional therapy in treating threatened abortion with unclear adverse events. However, due to the low quality of included studies, larger scales of RCTs and more scientific evidence are needed to prove the efficacy and safety of TCM for threatened abortion.

**Keywords:** Threatened Abortion; Clinical Efficacy; Evidence-Based Medicine; Meta-Analysis; Traditional Chinese Medicine

## Introduction

Threatened abortion is a common complication during early pregnancy with an incidence of 15%-40%, 80% of which occur in early pregnancy [1]. Over the past few decades, rapid economic development and high stress level have led to increased age of marriage and pregnancy, which results in higher risk for threatened abortion [2]. Conventional management for the miscarriage includes bed rest, hormone therapy and muscle relaxants. Progesterone is commonest hormone therapy for the threatened abortion. A recent systematic review indicated the progesterone probably reduces the rate of spontaneous miscarriage while the congenital abnormalities were uncertain [3]. The uncertain effectiveness and concerns of side effects in some patients make them seek for the alternative therapies.

Traditional Chinese Medicine (TCM) has been widely used for the management of threatened miscarriage for thousands of years. The TCM therapy has showed the promising in treating threatened abortion according to clinical trials and animal studies [4-26]. However, systematic reviews on effectiveness and safety of TCM intervention in treating threatened abortion is still limited. In this systematic review, we aimed to evaluate the effectiveness and safety of TCM in treating threatened abortion by the systematic review and meta-analysis of randomized controlled trials.

## Materials and Methods

### Search Strategy

We searched for published RCTs of Chinese Medicine for threatened abortion with the keywords: (Chinese medicine OR herbal medicine) AND (Threatened abortion). The following databases were searched: China National Knowledge Infrastructure (CNKI), Wan Fang Database (Chinese Ministry of Science and Technology), VIP Data and PubMed between January 1, 2008, and December 1, 2018.

### Inclusion Criteria

- 1) Clear diagnosis of threatened abortion was required according to the definition in Gynecology of Traditional Chinese Medicine [27] or Gynecology [28] for both treatment group and control group: beta-human chorionic gonadotropin (beta-hCG) test positive, gestational sac on ultrasound, pregnancy-related bloody vaginal discharge or lower abdominal pain or lower back pain, without cervical contact bleeding, without cervical dilatation, fundal height matches gestational age, progesterone <20nmol/L.
- 2) Randomized controlled trials (RCTs), both single blinded or double blinded, were included.
- 3) Interventions. All types of oral TCM interventions were accepted in the treatment group. All types administration route of Western medicines were accepted in the control group.
- 4) Studies, both in Chinese and English, available between Jan. 1, 2008, and Dec. 1, 2018 were included.
- 5) Both treatment group and control group with  $\geq 20$  subjects were considered.

### Exclusion Criteria

- 1) Studies with treatment group using TCM combined with western medicine were excluded;
- 2) Studies with control group using TCM or TCM combined with western medicine were excluded;
- 3) Studies with normal pregnant women as control subjects were excluded;
- 4) Subjects diagnosed with ectopic pregnancy, molar pregnancy, uterine fibroids and dysfunctional uterine bleeding were excluded;
- 5) Subjects with pelvic lesions, genital tract malformations, female genital tract tumours such as uterine fibroids, and chromosome abnormalities were excluded;
- 6) Studies without control groups were excluded;
- 7) Non-RCTs were excluded;
- 8) Animal studies were excluded;
- 9) Duplicate publications or incomplete publications where valid data cannot be extracted were excluded.

## Outcome Measures

The clinical effectiveness was assessed by Clinical Research Guidelines for New Chinese Herbs [29] or Diagnostic Criteria and Therapeutic Effect of Internal Diseases and Syndromes in Traditional Chinese medicine [30], and was classified into either 4 grades (fully recovered, markedly improved, improved and failed) or 3 grades (fully recovered, improved and failed). Other outcomes included the clotting time of vaginal bleeding, pain reduction in lower abdomen, and incidences of adverse events.

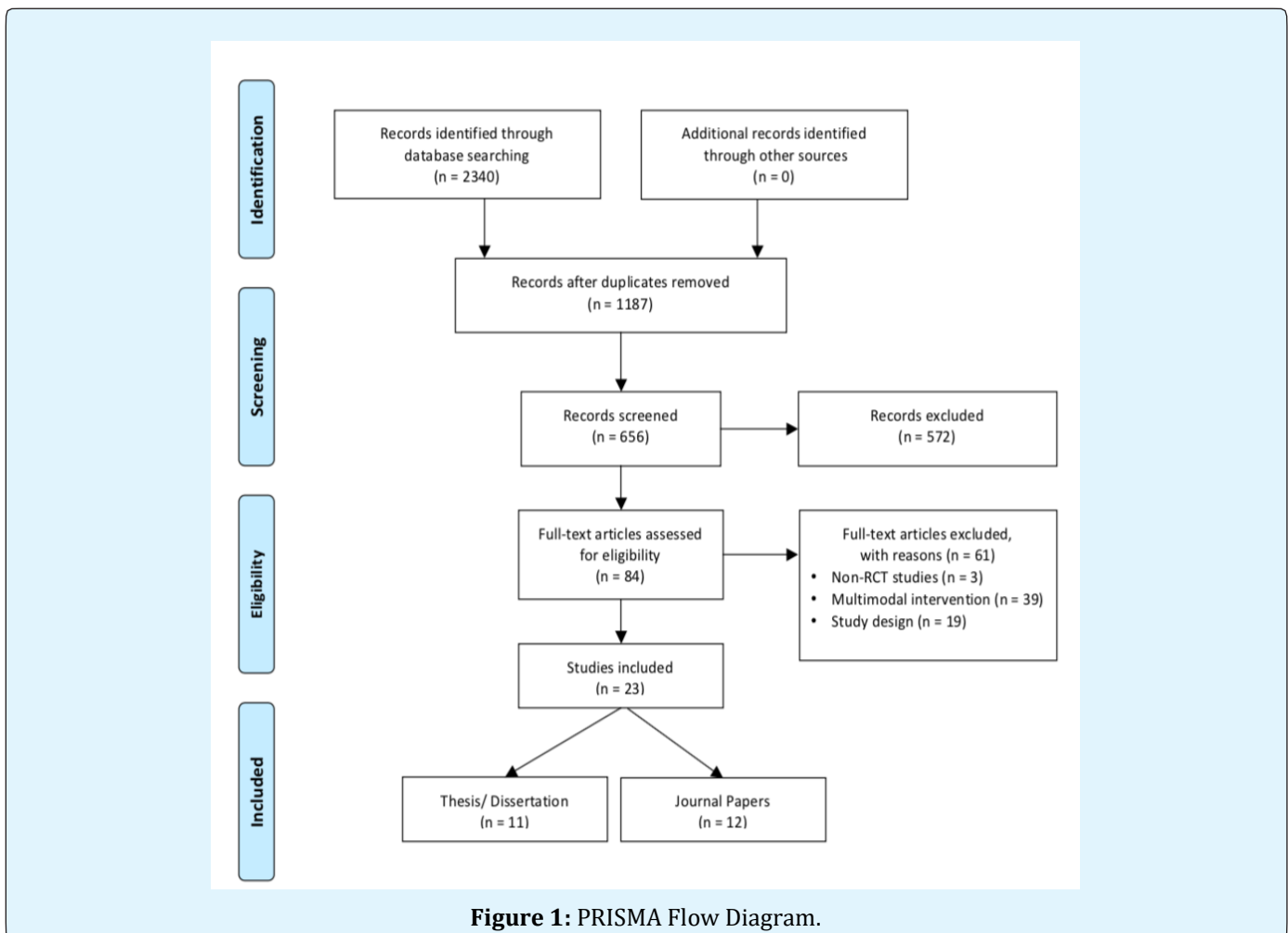
## Data Extraction and Quantitative Analysis

The data from the included studies was extracted into an Excel table, including study title, source, sample size, interventions, outcomes and adverse events. The software Rev Man 5.1 was employed for the meta-analysis. The Odds ratio was used for discontinuous data while mean difference (MD) was expressed for continuous data. The

fixed model was applied to the analysis if pooled studies had no statistical heterogeneity. Otherwise a random model was applied.

## Results

A total of 2340 subjects were retrieved through searching in the above database and pre-designed search strategy. The flow of the study selection was shown in Figure 1. Amongst all the studies, 2322 were published in Chinese and 18 were published in English. 1153 duplicate publications were screened out by using the Endnote software. 531 articles of apparently unrelated literature were discarded. After reading the abstracts and full-texts, 572 and 61 studies unmet the selection criteria were excluded respectively. Finally, a total of 23 eligible studies were included in this meta-analysis [4-26]. The characteristics of the included studies were presented in Table 1.



Study	Study type	Age (year)	Patient (number)			Interventions		Adverse event
			Total	TG(n)	CG (n)	TG	CG	
Huang [3]	Master's thesis	20-38	100	50	50	Oral, Yang Xue Gu Chong Decoction	Intramuscular (IM) injection, Progesterone	Nil
Jia [4]	Master's thesis	21-35	60	30	30	Oral, Bu Shen An Tai Decoction	Oral, Dydrogesterone Tablets	Nil
Wu [5]	Master's thesis	22-39	61	31	30	Oral, Bao Tai Yin Decoction	IM injection, Progesterone	Nil
Zhang [6]	Master's thesis	20-45	40	20	20	Oral, TCM	IM injection, Progesterone	Nil
Huang [7]	Master's thesis	26-30	60	30	30	Oral, An Zi He Ji Decoction	IM injection, Progesterone	Nil
Liu [8]	Journal paper	22-39	155	77	78	Oral, Bao Tai Decoction	Oral, Progesterone	Nil
Wang [9]	Master's thesis	21-39	80	40	40	Oral, Bao Tai Ling Capsule	IM injection, Progesterone	Nil
Wu [10]	Journal paper	20-39	60	30	30	Oral, Le Yun Ning Powder	Oral, Progesterone	Nil
Yang [11]	Master's thesis	23-36	53	28	25	Oral, Tai Er An Decoction	Oral, Aspirin	Nil
Zhao [12]	Master's thesis	23-41	60	30	30	Oral, Zhu Yun Ning Powder	IM injection, Progesterone; Oral, vitamin E	Nil
Xu [13]	Journal paper	21-36	144	68	76	Oral, Bao Tai Ling Pills	IM injection, Progesterone	Nil
Zhao [14]	Journal paper	20-45	142	72	70	Oral, Zi Yin He Ji Decoction	IM injection, Progesterone	Nil
Han [15]	Journal paper	21-40	100	50	50	Oral, Shou Tai Pill	IM injection, Progesterone	Nil
Fang [16]	Doctoral thesis	24-35	60	30	30	Oral, Zi Shen Yu Tai Pill	Oral, Dydrogesterone Tablets	Nil
Liu [17]	Master's thesis	23-39	60	30	30	Oral, An Ning Decoction	IM injection, Progesterone	Nil
Ni [18]	Journal paper	24-40	100	50	50	Oral, Ding Tong Zhi Xue An Tai Decoction	Oral, Dydrogesterone Tablets	Nil
Zeng [19]	Master's thesis	20-40	60	30	30	Oral, Shou Tai Pill	Oral, Dydrogesterone Tablets	4 cases of dizziness and nausea in CG
Li [20]	Journal paper	20-40	70	35	35	Oral, An Tai Fang Lou Decoction	IM injection, Progesterone; Oral, vitamin E	Nil
Liang [21]	Journal paper	23-40	120	60	60	Oral, Bu Shen Jian Pi Ning Xin Decoction	IM injection, Progesterone + hCG	Nil
Shen [22]	Journal paper	21-39	80	40	40	Oral, TCM	Oral, Dydrogesterone Tablets	Nil
Ding [23]	Journal paper	24-31	180	90	90	Oral, Fu Qin Decoction	IM injection, Progesterone + hCG	Nil
Song [24]	Journal paper	22-36	100	50	50	Oral, Yue Tai Decoction	IM injection, Progesterone	Nil
Yu [25]	Journal paper	20-42	69	35	34	Oral, An Tai Fang Lou Decoction	IM injection, Progesterone; Oral, vitamin E	Nil

**Table 1:** Characteristics of the included studies.

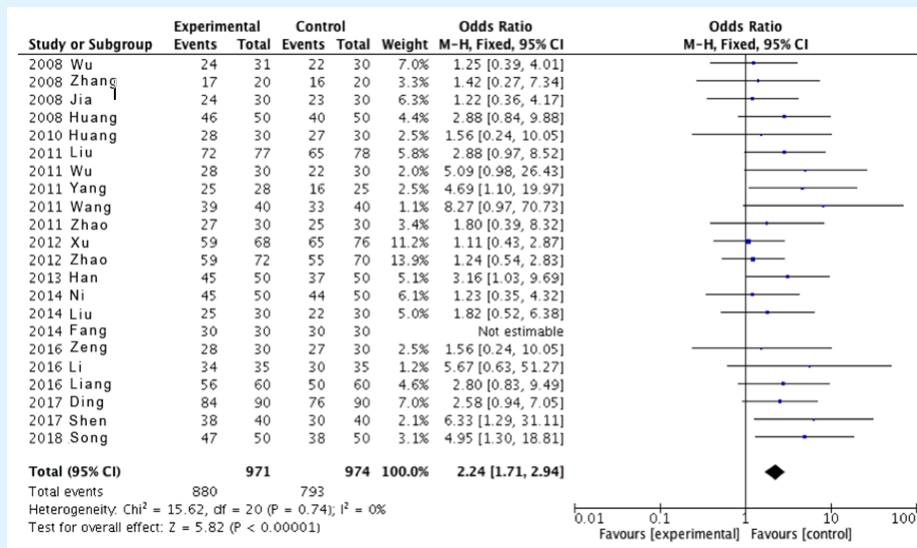
**Quality of Included Studies**

Among of 23 included studies, four articles used the random number table method for randomization [5,16-17,20]. 19 articles did not reported the randomization method [4,6-15,18-19,21-26]. No studies reported the details of blinding and allocation concealment. Two studies reported the dropout of subjects [12,20]. The 23 articles were evaluated by the Jadad score, 1 article scored 3, 4 articles scored 2 and 18 articles scored 1. Most of the articles were indicated as in the low quality.

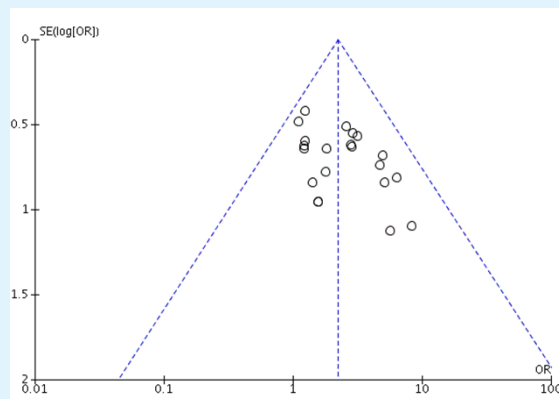
**Clinical Effectiveness**

Twenty-two of 23 included studies were pooled to analyze the total effectiveness of TCM treatment over the conventional therapy [4-25]. As shown in Figure 2A, TCM treatment significantly increased the total effectiveness compared with the conventional therapy (OR=2.24, CI=[1.71, 2.94], P<0.00001; heterogeneity, P=0.74). Studies in the funnel plot was asymmetrical indicating the low publication bias among these studies (Figure 2B).

**A. Forest plot**



**B. Funnel Plot**



**Figure 2:** Total effectiveness of TCM treatment over conventional therapy.

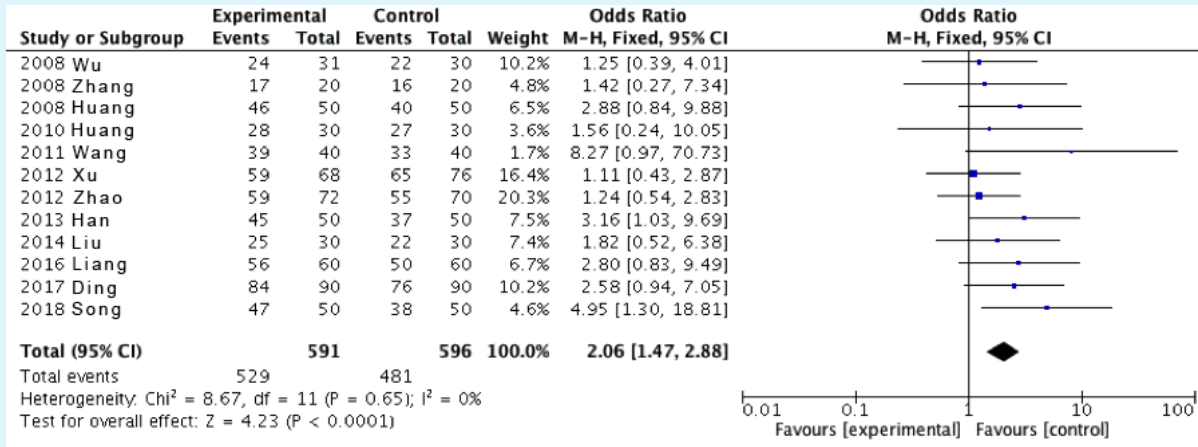
Twelve studies employed the intramuscular (IM) injection of conventional medications alone as the controls [4,6-8,10,14-16,18,22,24-25]. In the subgroup

analysis according to route of administration in control group, TCM therapy had significant higher total effectiveness compared to the IM injection of

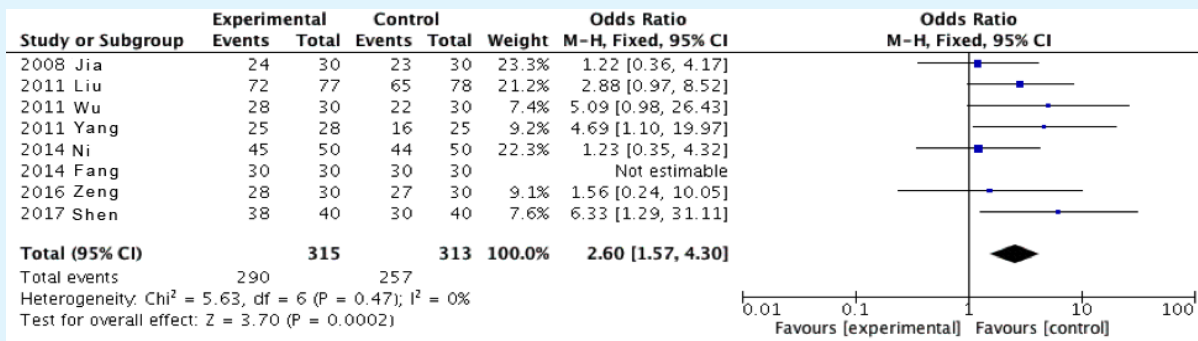
conventional medication alone (OR=2.06, CI=[1.47, 2.88],  $P < 0.0001$ ; heterogeneity,  $P=0.65$ ) as shown in Figure 3A. The control arm of eight studies received the oral administration of conventional medications [5,9,11,12,17,19,20,23]. As shown in Figure 3B, TCM

therapy had significant higher total effectiveness compared to the IM injection of conventional medication alone (OR=2.60, CI=[1.57, 4.30],  $P < 0.001$ ; heterogeneity,  $P=0.47$ ).

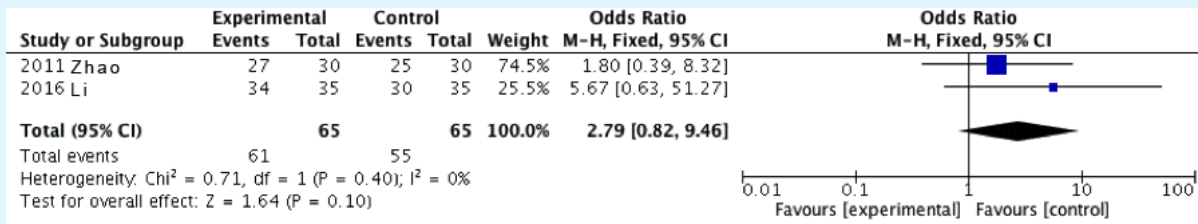
### A. TCM compared with IM injection of medications



### B. TCM compared with oral conventional medications



### C. TCM compared with IM combined with oral conventional medications



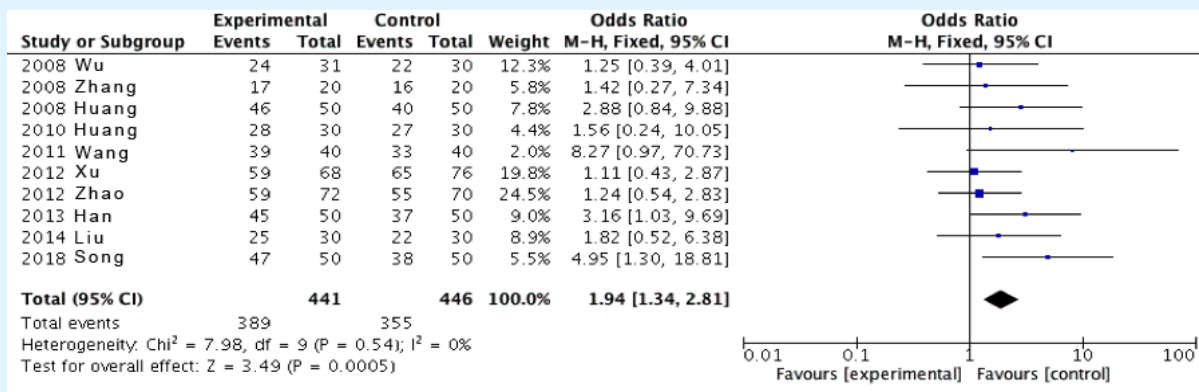
**Figure 3:** Total effectiveness in the subgroup analysis of the administration route of controls.

Two studies used the combine compared IM injection with oral medications in the control arm [13,21]. As shown in Figure 3C, the total effectiveness had no statistical difference between TCM only and the combined use of conventional medications (OR=2.79, CI= [0.82, 9.46],  $P > 0.05$ ; heterogeneity,  $P=0.40$ ).

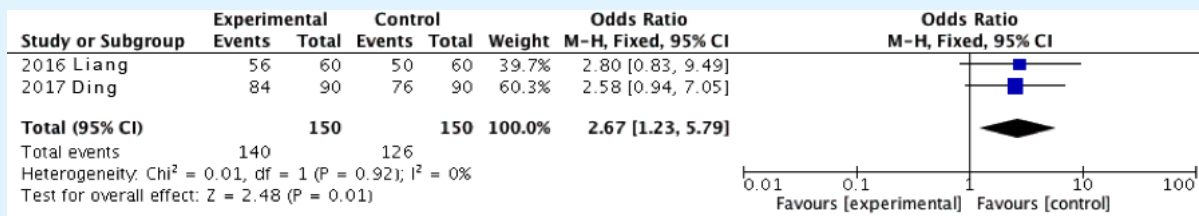
Progesterone, progesterone combined with HCG, and dydrogesterone are commonest medications for threatened abortion. Next, we performed the sub-group analysis according to the types of drug administered in control arm. Ten studies in control arm used the IM injection of progesterone [4,6-8,10,14-16,18,25]. As shown in Figure 4A, the total effectiveness in TCM treatment was higher than the IM injection of

progesterone (OR=1.94, CI= [1.34, 2.81],  $P < 0.001$ ; heterogeneity,  $P=0.54$ ). Similarly, TCM therapy had significant higher total effectiveness compared to the IM injection of progesterone combined with hCG (OR=2.67, CI= [1.23, 5.79],  $P=0.01$ ; heterogeneity,  $P=0.92$ ) in the pooled two studies [22,24] (Figure 4B). TCM treatment showed no statistical advantage over orally administrated dydrogesterone tablets (OR=1.89, CI=[0.96, 3.75],  $P=0.07$ ; heterogeneity,  $P=0.36$ ) in the subgroup analysis of five pooled studies [5,17,19-20,23] (Figure 4C). TCM therapy had significant higher total effectiveness compared to the IM injection of conventional medication alone (OR=3.45, CI= [1.40, 8.51],  $P < 0.01$ ; heterogeneity,  $P=0.77$ ) in two pooled studies [9,11] (Figure 4D).

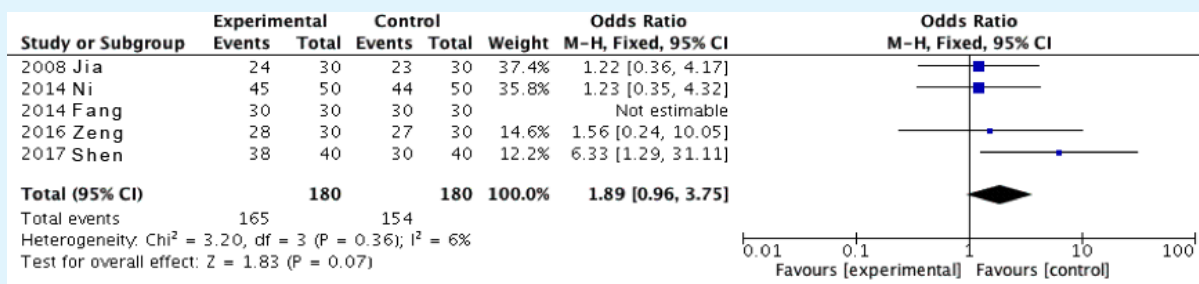
### A. TCM compared with IM injection of Progesterone



### B. TCM compared with IM injection of Progesterone and hCG



### C. TCM compared with oral dydrogesterone tablets



### D. TCM compared with oral progesteron

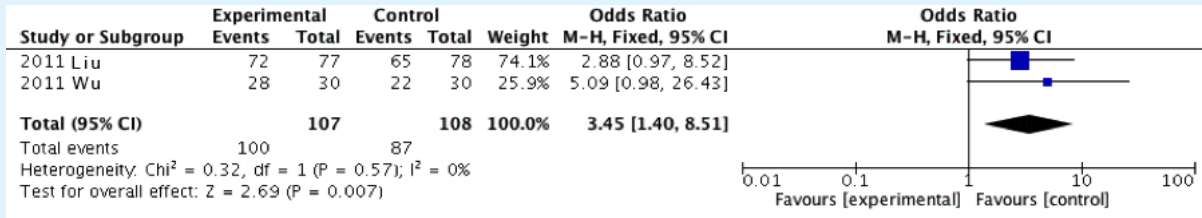


Figure 4: Total effectiveness in the subgroup analysis of medications.

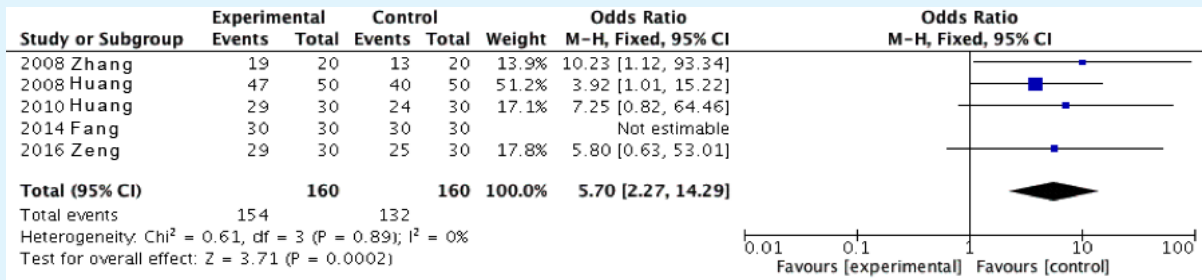
### Clinical Symptoms in TCM

Five of 23 included studies reported the reduction of TCM clinical symptoms in number of patients [4,7,8,17,20] while 3 studies reported the change of mean difference in TCM clinical symptoms [6,15,19]. The meta-analysis showed TCM therapy had significantly reduced the clinical symptoms reflected by the reduction of patient number or the change of symptom score compared with conventional therapy (OR=5.70, CI=[2.27, 14.29],  $P < 0.001$ ; MD = 5.33, CI=[4.12, 6.53],  $P < 0.001$ , respectively) as shown in Figure 5A&B.

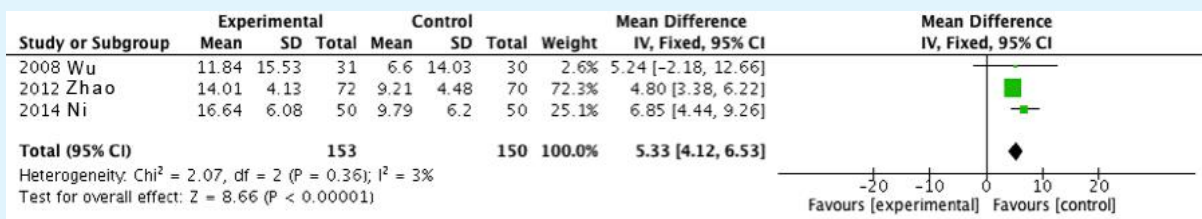
### Clotting Time for Pregnancy-Related Bloody Vaginal Discharge

Four of 23 selected articles reported the clotting time for pregnancy-related bloody vaginal discharge [5,6,19,23]. The pooled analysis showed TCM treatment reduced the clotting time for pregnancy-related bloody vaginal discharge (MD = -1.68, CI=[-2.17, -1.20],  $P < 0.001$ ; heterogeneity,  $P = 0.75$ ) in Figure 5C. Two studies reported pain reduction in the lower abdomen [5,23]. The meta-analysis showed that patients in TCM therapy had low pain intensity compared with the conventional therapy (MD = -1.44, CI=[-2.40, -0.48],  $P < 0.01$ ; heterogeneity,  $P = 0.1$ ) in Figure 5D.

### A. Number of patients with clinical symptom reduction

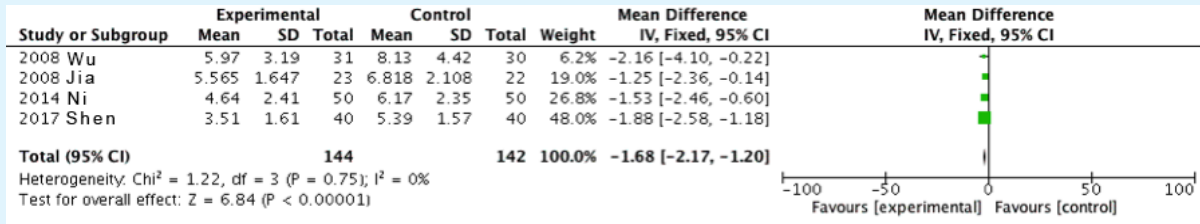


### B. Change of scores in clinical symptoms

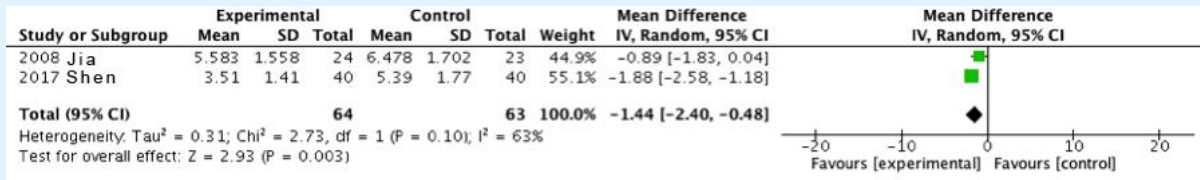




**C. Clotting time of pregnancy-related bloody vaginal discharge**



**D. Abdominal pain reduction**



**Figure 5:** Secondary outcomes in TCM and conventional therapy.

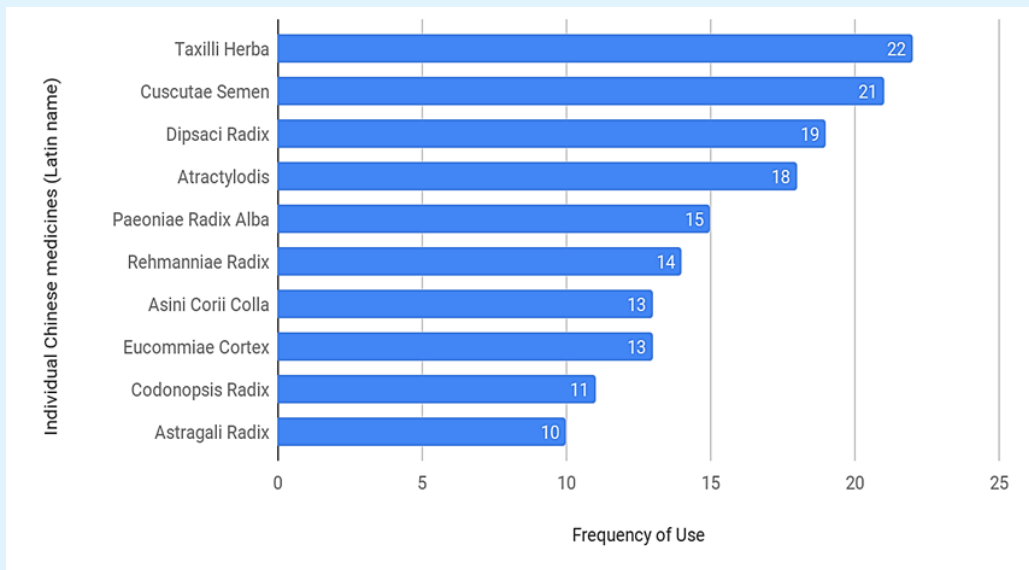
**Adverse Events**

Only one study reported adverse events happened in conventional therapy arm. The safety of TCM remains unclear.

**Frequency of Individual Chinese Medicines**

Fifty-three herbal medicines were identified among 23 studies. The top 10 most commonly used individual

Chinese medicines included *Taxilli Herba* (Sangjisheng), *Cuscutae Semen* (Tusizi), *Dipsaci Radix* (Xuduan), *Atractylodis Macrocephalae Rhizoma* (Baizhu), *Paeoniae Radix Alba* (Baishao), *Rehmanniae Radix* (Dihuang), *Asini Corii Colla* (Ejiao), *Eucommiae Cortex* (Duzhong), *Codonopsis Radix* (Dangshen) and *Astragali Radix* (Huangqi) (Figure 6).



**Figure 6:** Frequency of individual herbal medicines.

## Discussion

Through the meta-analysis, our study gathered articles that compared effectiveness of TCM with conventional therapy in the treatment of threatened abortion in the past 10 years. We found that TCM therapy had significant total effectiveness compared with conventional therapies. The subgroup analysis indicated TCM therapy achieved higher total effectiveness in the single use of either IM injection or oral administration. However, no significant difference was found in TCM therapy and the combination of IM injection and oral administration. It indicated the combined conventional therapy may result in the maximal effect in clinical practice while TCM therapy had higher or similar effects on the threatened abortion. Subgroup analysis further indicated TCM therapy on total effectiveness was superior to progesterone or progesterone combined with hCG, but had no difference to oral dydrogesterone tablets.

Secondary outcome analysis is consistent with the primary findings. TCM therapy improved the number of patients with clinical symptom reduction and the score of clinical symptoms compared with conventional therapy. Patients with oral TCM had shorter vaginal bleeding and less pain compared with conventional treatment. The frequency of individual Chinese medicine analysis indicated the frequently used herbs are the components of a classic TCM formula, Shou Tai Wan listed in Gynecology of Traditional Chinese Medicine [27] which commonly used to treat threatened abortion for kidney deficiency syndrome. It probably indicated the kidney deficiency in TCM syndrome differentiation is the major type of TCM syndrome in patients with threatened abortion. However, scientific evidence is needed for strengthening this hypothesis. *Asini Corii Colla* and *Astragali Radix* promote the blood cell differentiation and traditionally used for stopping bleeding [31,32]. *Paeoniae Radix Alba* has anti-inflammatory and immunomodulatory effect, and attenuates pain [33-35]. However, the mechanism of TCM for the threatened abortion needs to be further studied.

The safety of Chinese medicine for treating threatened abortion in our study is unclear because only one reported the adverse events. Most of studies did not report the events. It is consistent with the previous publication which indicated no difference in TCM and conventional therapy [36]. The limitation of the study is that the included studies are in low quality, which leads to high risk of bias. Most of studies do not report the details of randomization and allocation concealment. As the effectiveness studies, it quite difficult to blind the

intervention. But the blinding of outcome assessors could be implemented so as to minimize the assessment bias. Though these effectiveness studies reflected the “real-world” of TCM practice, rigorously designed randomized controlled trials are needed to examine roles of TCM on threatened abortion.

In conclusion, TCM therapy likely increases the total effectiveness, shortens the bleeding duration and reduces lower abdominal pain. The findings need to be further studied with rigorous randomized controlled trials due to low quality of evidence.

## Acknowledgement

This systematic review included 23 studies. Although there are some imperfections in the research, we still thank each author.

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