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INTEGRATED TRADITIONAL CHINESE AND WESTERN MEDICINE FOR MENOPAUSAL SYNDROME: META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Abstract

Background: To critically assess the evidence of integrated Chinese and western medicine for treating Menopausal syndrome (MPS).

Methods and Materials: A search across the Chinese Biomedical Medicine (CBM), Chinese National Knowledge Infrastructure (CNKI), VIP database (VIP), Wangfang database (Wanfang), PubMed and the Cochrane Library databases was conducted (up to October 31st, 2013) in commonly used integrated Chinese and western medicine therapies for menopausal syndrome. A number of Randomized Controlled Trials (RCTs) evaluating the therapeutic efficacy of integrated Chinese and western medicine in patients with PPS were included. The quality of the included studies was evaluated and a meta-analysis was performed using the RevMan5.0 software.

Results: Twelve RCTs with 1155 patients were evaluated in this review. The results of meta-analysis showed that the therapy of using integrated Chinese and western medicine was significantly superior to that of western medicine alone towards improving the efficacy, relieving the clinical symptoms and decreasing follicle-stimulating hormone (FSH） levels ($P<0.05$), even though the effects of two treatments were the same in regulating the levels of luteinizing hormone (LH) and estradiol (E_2).

Conclusion: Compared to a regular treatment with western medicine alone, the therapeutic approach that utilizes integration of Chinese with western medicine can effectively improve the clinical efficacy and serum hormone levels in patients with menopausal syndrome. However, the evidence was not very strong due to the poor quality of the included studies.

Key words: Integrated Traditional Chinese and Western Medicine, Menopausal Syndrome, Meta-analysis

Introduction

Menopausal syndrome (MPS), also known as perimenopausal syndrome (PPS), is an autonomic nervous system dysfunction associated with neuropsychological syndromes, which results from the declining of ovarian function and the estrogen levels during the pre-or postmenopausal phases (Yu et al., 2012). MPS mostly occurs in women around 45–55 years of age. According to the reports, about 90% women who suffered from menopause may present one or more symptoms (Zhou et al., 2003). It does not only affect the female physical and mental health, but also their work, family life and interpersonal relationships.

A lot of groups reported that the average age of women with natural menopause is between 49 to 51 years of age. The median age of menopause is about 50-52 years in the developed countries, 47 years in Asia, 47 years in developing countries, and 47.5- 49.5 years in China.

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These pieces of data indicate that there is a significant difference in the menopausal age depending on race and cultural background. The climacteric symptoms in western women are common and the incidence rate reaches up to 80%. However, this incidence rate is different from that of their Asian counterparts. For instance, in Thailand, the incidence rate of hot flashes or sweating, which incidentally is lower in rural than urban communities, is 20%-58%. About 65% of women in Japan and 85% in Malaysia believe that menopause does not affect their health and life. Moreover, in Indonesia, approximately 95% of women think that they still keep physically fit in the perimenopausal phase. According to some epidemiological statistics in China, the present data demonstrate that the number of women who suffered from menopause is about 130 million. 100 million out of them were presented with menopausal syndromes (Lu, et al., 2001).

Considerable studies of related menopausal diseases to date are mainly embodied in the treatment and prevention. Vasomotor, mental and urogenital symptoms (UGS) are the main commonly accompanying symptoms, and also the primary reasons for seeking treatment. In the 1960s, western medicine believed that menopause is a disease that occurs due to reduced estrogen levels. As a result, many countries and regions around the world quickly adopted estrogen therapy for the treatment of postmenopausal women. Both the advantages and disadvantages of hormone replacement therapy (HRT) therapies are always conducted by the clinical researchers. Specifically, in the last 10 years, large sample sizes of RCTs were performed to obtain better clinical evidence, and make a more scientific and objective evaluation.

The Writing Group for the Women's Health Initiative Investigation (2002) illustrated that, compared with placebo, the occurrences of heart disease, stroke, and breast cancer with pulmonary embolism are somewhat increased by using HRT (Writing Group for the Women's Health Initiative Investigation, 2002). Taking into account the limitations of HRT, alternative therapies were adopted, such as traditional Chinese medicine (TCM) therapy, dietary modifications, exercise and psychological training. The RCTs suggested that some herb medicines have an estrogen-like effect, no toxicity, no side effect and non-carcinogenic risk. Therefore, by using an individual herb medicine or compound prescriptions to treat vasomotor symptoms, depression, and insomnia in women with menopausal syndrome, the long-term use of this therapy seems beneficial (Kass-Annese., 2000).

Currently, the effects of the available treatments for MPS are not very good. In order to discover better approaches, Chinese scholars carried out a large number of randomized controlled clinical studies associated with this disease. We have yet to see the Meta-analysis of the various randomized controlled trials using the integration of Chinese and western medicine for the treatment of MPS. Therefore, it has been necessary to offer a review of the available randomized controlled trials, in order to provide reasonable strategies for clinical treatments.

Methods

The supporting PRISMA checklist is available as supporting information; see Checklist Figure1.

Search Strategies and Study Selection

Literature research was conducted in the National Knowledge Infrastructure (1999-2013), VIP Database for Chinese Technical Periodicals (1989-2013), PubMed (1950-2013), Chinese Bio-Medical Literature Database (1990-2013), and the Cochrane library (Issue 10 of 12, 2013). Search ended at the end of October 2013. We used the search terms "Menopausal syndrome", "Perimenopausal syndrome", "Integrated Chinese and Western Medicine" and "TCM combined with Western medicine". Various combinations of the terms were used, depending on the database searched. The bibliographies of the included trials were searched for additional references.

Two authors (Liu and Kou) extracted the data from the included trials independently. The extracted data included authors, year of publication, study size, details of methodological information, drug name and outcomes (for example, the total effective rate). Disagreements were resolved by discussion and reached consensus through a third party (Chen and Hu, 2006).

Inclusion Criteria

Included were all the parallel randomized controlled trials (RCTs) comparing the treatment approach of integrated Chinese and western

medicine with that of western medicine alone in patients with menopausal syndrome, between the ages of 40 to 55. The included RCTs had to report the diagnostic criteria clearly. There were no restrictions on population characteristics, language and publication type. Outcome measures included the total effective rate, the levels of serum hormones i.e. FSH, LH, E_2, Kupperman score， as well as the scale for TCM syndrome and symptom differentiation (TCM-SSD) scores and so forth. The criteria "recovery, obviously effective, effective, or ineffective" was also included in the outcome measurement. All the included literature reported two evaluation indexes at the least. Duplicated publications reporting the same groups of participants were excluded.

Trial Quality Assessment

Two authors (Liu and Kou) evaluated the quality of the included trials. The quality of included trials was evaluated and scored according to Jadad evaluation standards (Jadad et al., 1996) to address the following four criteria: Randomization (appropriate: 2 points, unclear: 1point, inappropriate: 0 point), Concealment of allocation (appropriate: 2 points, unclear: 1point, inappropriate: 0 point), Double blinding (double blinding and description: 2 points, double blinding and description was unclear: 1point, No blind or no description: 0 point), Withdraws and dropouts (Description: 1point, no description: 0 point). The scores ranged from 1 to 7 points, of1-3scores belonged to poor quality studies of 4-7 scores classified into high quality studies.

Data Analysis

The statistical package (RevMan 5.0) provided by the Cochrane Collaboration was used for data analyses. Dichotomous data were presented as risk ratio (RR) and continuous outcomes as Standard Mean Difference (SMD), both with 95% confidence interval (CI).Meta-analysis was performed if the intervention, control, and outcome were the same or similar. The statistical heterogeneity was presented as significant when I square (I^2) is over 50% or P<0.1.Random effect model was used for the meta-analysis if there was significant heterogeneity (I^2>50%) and fixed effect model was used when the heterogeneity was not significant (I^2<50%) (Zhai et al. 2001).

Results

Description of Included Studies

The flow chart depicts the whole search process and study selection (Figure 1). After searching the six databases, 507 citations were screened. The vast majority of them were excluded due to obvious ineligibility that included irrelevant titles and abstracts (some pieces of literature were accessed from more than one database) after reading the titles and abstracts. The full text of 273 papers was retrieved, while 62 papers were excluded because of experiments reporting, theory discussion, traditional review, other diseases and case reports. An additional 261 articles were excluded because of non-RCTs, duplicated publication, incomplete data and unqualified control. Finally, 12 RCTs (Xia et al., 2008; Deng et al., 2005; Cao et al., 2007; Xing et al., 2001; Yuan, 2006; Yan, 2002; Shi et al., 2008; Liu et al., 2012; Wan et al., 2013; Li, 2012; Zhang et al., 2008; Yang, 2012) were included and summarized in Table 1.

All the RCTs were conducted in China and published in Chinese. None of the included RCTs was published in English. A total of 1155 participants with menopausal syndrome were involved, with an average number of 96 participants per trial, and a range of 18 to 88 (Table 1). Five trials (Xing et al., 2001; Yuan, 2006; Yan, 2002; Wan et al., 2013; Li, 2012; Zhang et al.) provided detailed information about the patient's syndrome differentiation. The reported outcome measures included the total effective rate, the levels of serum hormone, Kupperman score, the scale for TCM syndrome and symptom differentiation (TCM-SSD), endometrial thickness, adverse reaction and bone mineral density.

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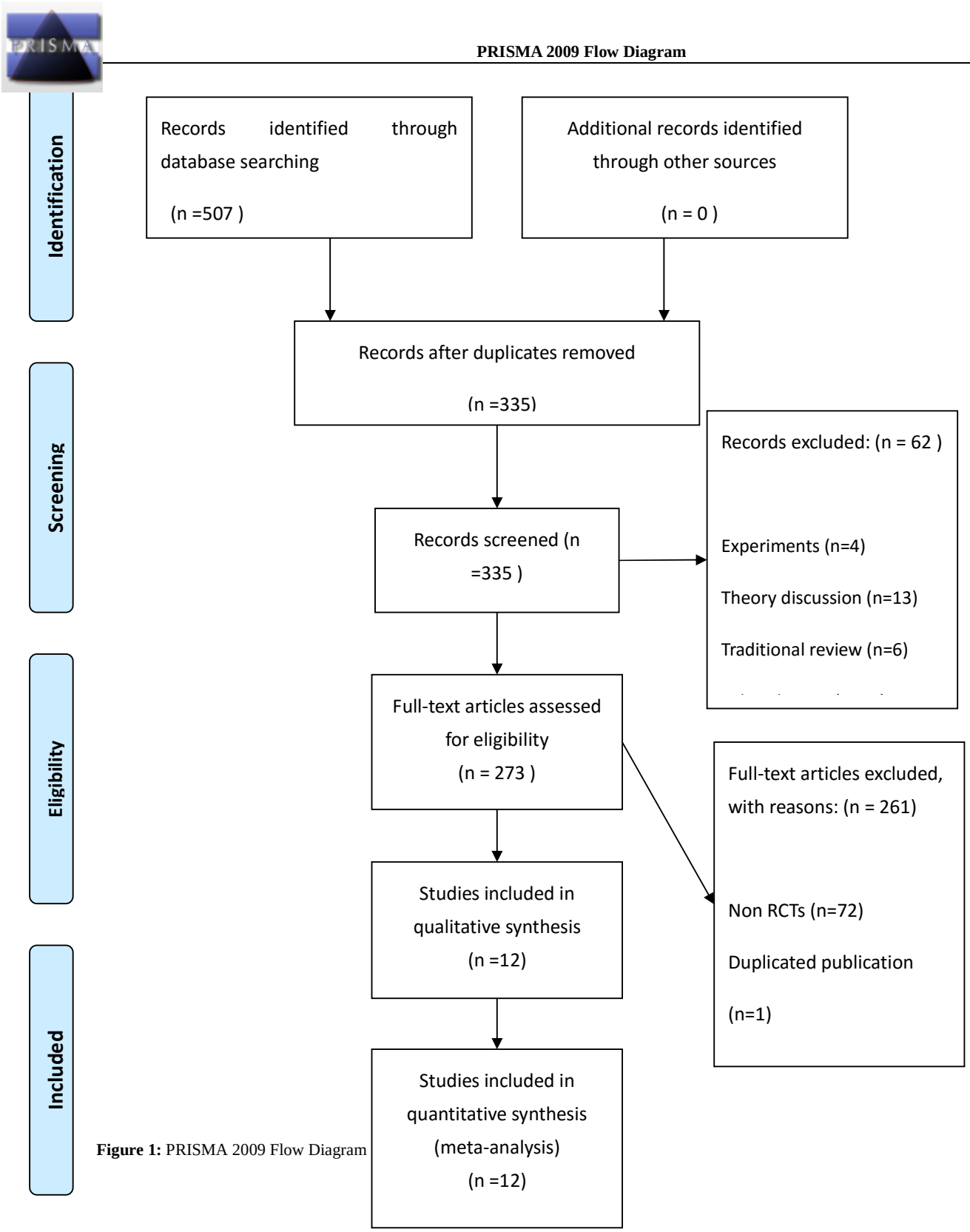

Figure 1: PRISMA 2009 Flow Diagram

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Table 1: The basic features of included randomized controlled trials

Study ID	Time (d)	N (E/C)	Chinese Herbs	Western Medicine	Outcome Measures
Xia YD et al., 2008	90	20/18	Bushenshugan dcoction	Nilestriol Tables	Clinical comprehensive effective, Kupperman score, The levels of FSH, LH, and E_2
Cao et al., 2007	360	80/80	Liuwei dihuang pills, Xinshenning tablets, Xiaoyao pills	Conjugated Estrogens Tablets, Medroxyprogesterone17-acetate	Clinical comprehensive effective, The levels of E_2, Endometrium thickness, TCM syndrome and symptom differentiation scores
Xing et al., 2001	60	45/45	Chinese herbs dcoction	Oryzanol, Vitamin E, Vitamin B6, Diazepam, Cod liver oil, Calcium tablet	Clinical comprehensive effective, The levels of FSH, LH, and E_2
Yan et al., 2002	90	30/30	Liuwei dihuang pills, Jiarong tablets	Medroxyprogesterone acetate complex capsules	Clinical comprehensive effective, The levels of FSH and E_2
Shi et al., 2008	84	40/40	Xiaoyao pills	Tibolone tablets	Clinical comprehensive effective, The levels of E_2, Adverse effect.
Liu et al., 2012	90	88/81	Liuwei dihuang pills, Xiaoyao pills	Oryzanol, Vitamin E, VitaminnB6, Calcium tablet, Estazolam, Conjugated Estrogens Tablets,	Clinical comprehensive effective, Kupperman score
Wan et al., 2013	840	40/40	Liuwei dihuang dcoction	Medroxyprogesterone17-acetate Hormone, Medroxyprogesterone17-acetate	Clinical comprehensive effective, The levels of E_2, FSH, LH, P, AKP, TC and TG, Adverse effect.
Zhang et al., 2008	90	61/60	Bazhen dcoction	Nilestriol Tables	The levels of E_2 and FSH, Clinical comprehensive effective, Adverse effect.
Yang et al., 2012	64	30/31	Xiaoyao pills	Nilestriol Tables	Clinical comprehensive effective, The levels of E_2 and FSH, Adverse effect.
Li et al., 2012	90	30/30	Chinese herbs dcoction	Nilestriol Tables	Kupperman score, Clinical comprehensive effective
Deng et al., 2005	78	40/40	Xiaoyao pills	Conjugated Estrogens Tablets	Kupperman score, The levels of FSH and E_2, Endometrium thickness, TCM syndrome and symptom differentiation scores
Yuan et al., 2006	90	88/68	Duifu bawei decoction, xiaoyao powder	Nilestriol Tables, Oryzanol, Vitamin E	Clinical comprehensive effective, Bone density, The levels of E_2

Methodological Quality

According to the predefined quality assessment criteria, the majority of the included trials assessed were of generally poor methodological

quality. One (Liu et al., 2012) out of a total of 12 RCTs was evaluated as high quality, while the remaining 11 RCTs were evaluated as being of poor quality. The randomized allocation of participants was mentioned in all trials; however, only one trial stated the drawing method for sequence generation, and the rest provided insufficient information for judging whether or not were conducted properly. Allocation concealment was just mentioned in one RCT (Liu et al., 2012). Double-blind was not mentioned in any of the trials. Single blind was mentioned using as drawing lots (Yuan, 2006; Liu et al., 2012) without providing further information as to who was blinded. Only one trial reported drop-out or withdraw (Liu H et al., 2012); however, the trial did not intend to analyze the cause. Both follow-up and drop-out were only mentioned in one RCT (Liu H et al., 2012). See Checklist Table 2.

Table 2: Quality assessment of included randomized controlled trials

Study ID	Sequence generation	Allocation concealment	Blinding	Attrition and dropout	Withdraw and retreat	score
Xia et al. (2008)	Unclear	Unclear	Unclear	No	No	1
Cao et al. (2007)	Unclear	Unclear	Unclear	No	No	1
Xing et al. (2001)	Unclear	Unclear	Unclear	No	No	1
Yan et al. (2002)	Unclear	Unclear	Unclear	No	No	1
Shi et al. (2008)	Unclear	Unclear	Unclear	No	No	1
Liu et al.(2012)	drawing	Yes	Single blind	Yes	Yes	6
Wan et al.(2013)	Unclear	Unclear	Unclear	No	No	1
Zhang et al.(2008)	Unclear	Unclear	Unclear	No	No	1
Yang et al.(2012)	Unclear	Unclear	Unclear	No	No	1
Li et al.(2012)	Unclear	Unclear	Unclear	No	No	1
Deng et al.(2005)	Unclear	Unclear	Unclear	No	No	1
Yuan et al.(2006)	Unclear	Unclear	Single blind	No	No	3

Effect Estimates

The General Effective Rate

The total effective rate was deemed as the combination of “cure” and “significant effect” with “effective rate”. These different kinds of measurements were put together to assess the general effectiveness. Eleven out of twelve RCT (Xia et al., 2008; Cao et al., 2007; Yang, 2012) reported the general effectiveness of menopausal syndrome by using the two approaches: integrated Chinese and western medicine, and western medicine alone. Meta-analysis results showed a significant difference in the general effective rate between the two treatments [RR=1.51, 95%CI (1.10，1.20), Z=6.57, P=0.01] (Figure 2). Overall, the clinical efficiency of integrated Chinese and western medicine was better than western medicine alone in the treatment of menopausal syndrome.

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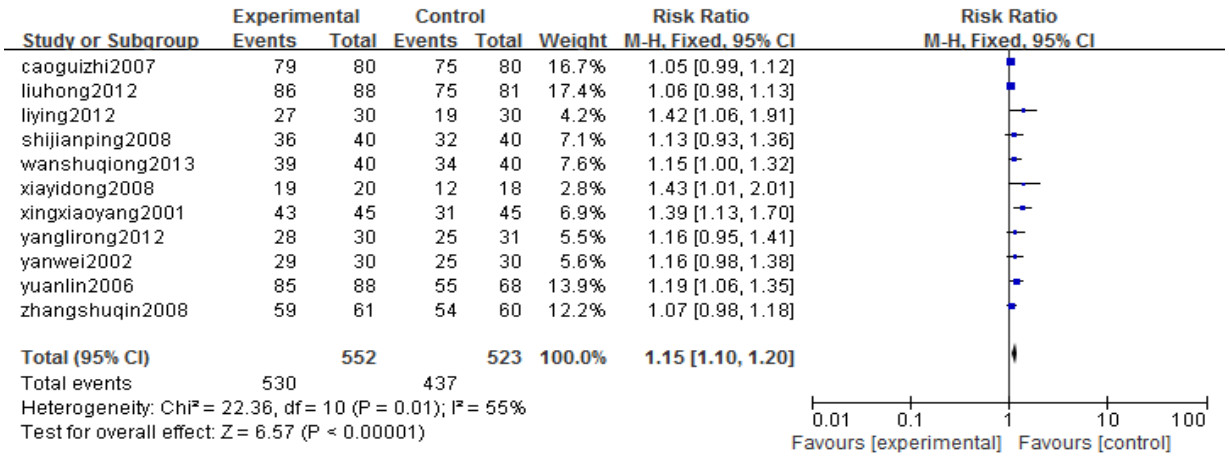

Figure 2: The forest plot of the general effective rate

The Levels of Serum Hormone

FSH

A total of eight trials (Xia YD et al., 2008; Deng YJ et al., 2005; Cao GZ et al., 2007; Xing XY et al., 2001; Yan W, 2002; Wan SQ et al., 2013; Zhang SQ et al., 2008; Yang LR, 2012) undertook a comparison of the therapeutic effects on FSH levels in patients with Menopausal Syndrome using integrated Chinese and western medicine and western medicine alone. Meta-analysis of the results showed a significant difference in regulating (serum) FSH levels between the two treatments [SMD=-0.59, 95%CI (-1.06, -0.11), Z=2.44, P=0.01] (Figure 3). More specifically, the therapeutic efficacy of integrated Chinese and western medicine was superior to that of western medicine alone in decreasing FSH levels.

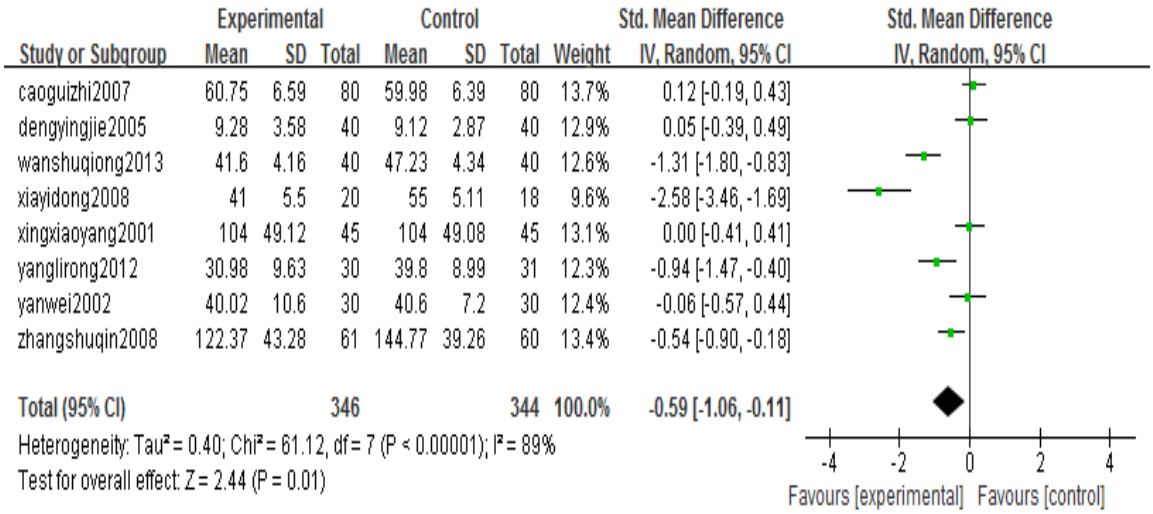

Figure 3: The forest plot of FSH levels

LH

Six trials (Xia et al., 2008; Cao et al., 2007; Xing et al., 2001; Yan, 2002; Wan et al., 2013; Zhang et al., 2008) reported the LH levels in all,

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and provided data for evaluation. The results of the meta-analysis showed there were no significant differences in regulating LH levels between the integrated Chinese and western medicine group and the western medicine alone group [SMD=-0.75, 95%CI (-1.51, -0.02), Z=1.92, P=0.06] (Figure 4), which indicated that the efficacy of the two approaches in reducing LH levels are the same.

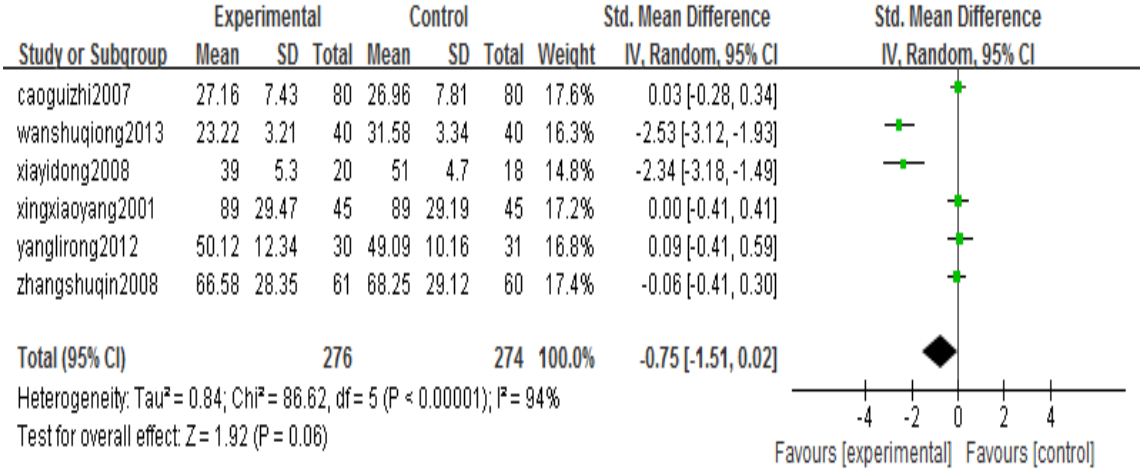

Figure 4: The forest plot of LH levels

E_2

10 out of 12 RCTs (Xia et al., 2008; Deng et al., 2005; Cao et al., 2007; Xing et al., 2001; Yuan, 2006; Yan, 2002; Shi et al., 2008; Zhang et al., 2008; Yang, 2012) conducted a comparison of the therapeutic effects of E_2 levels between integrated Chinese and western medicine and western medicine alone. Meta-analysis results indicated that there were no significant differences between two treatments in regulating the E_2 levels. [SMD=-0.43, 95%CI (-0.01, 0.88), Z=1.90, P=0.06] (Figure 5). Although there were no significant differences in elevating E_2 levels between two treatments, the trends appearing in the management using the integrated Chinese and western medicine was undeniably better than the western medicine alone.

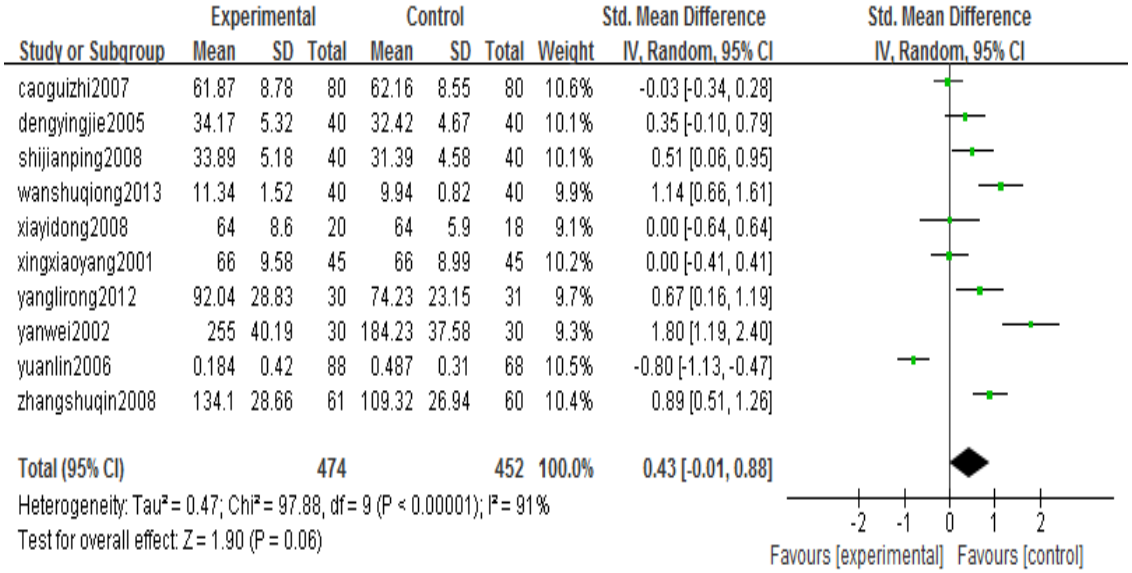

Figure 5: The forest plot of E_2 levels

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Kupperman Score of Menopausal Symptoms

A total of three trials (Xia et al., 2008; Liu et al., 2012; Li, 2012) conducted a comparison of the Kupperman score for menopausal symptoms after treating patients with integrated traditional Chinese and western medicine or western medicine alone. Meta-analysis showed that, among the two, there was a significant difference in the Kupperman score [SMD=-1.43, 95%CI (-2.66, -0.20) Z=2.28, P=0.02] (Figure 6). The diamond on the left side of the invalid line points out that the treatment of integrated Chinese and western medicine was better than western medicine alone in ameliorating menopausal symptoms.

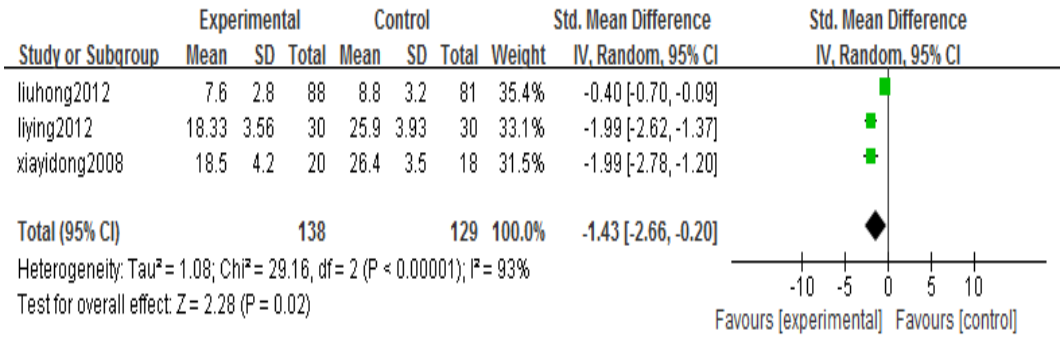

Figure 6: The forest plot of Kupperman score

Publication Bias

While comparing the integrated Chinese and western medicine versus western medicine alone, a funnel plot analysis revealed a serious asymmetry in the general effective rate among the 11 trials (Figure 7).

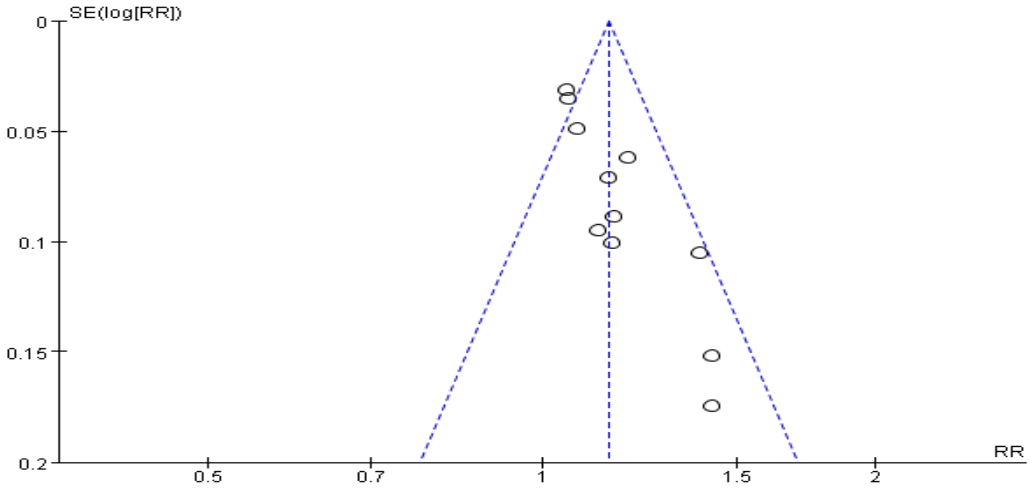

Figure 7: The funnel plot

TCM Syndrome and Symptom Differentiation Scores

A total of two trials (Deng et al., 2005; Cao et al., 2007) reported TCM syndrome and symptom differentiation scores. However, the score items, score standards, and intervention measures in each was different, therefore, the results cannot be analyzed by Meta-analysis, but only

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evaluated for descriptive analysis (Table 3).

Table 3: TCM syndrome and symptom differentiation scores

Study ID	Index	Intervention	Control	P Value	clinical significance
Y. J. Deng 2005[6]	Hectic fever and night sweat, wakefulness, mood swings, depressed, headache, bone and joint pain, palpitation, vertigo, abnormal sensation, Libido drops, urinary symptoms, tired	Conjugated estrogens tablets and Xiaoyao pills	Conjugated Estrogens Tablets	P<0.01	Experiment group was better than control group
G. Z. Cao 2007[7]	Hectic fever, abnormal sensation, wakefulness, anxiety and irritability, depressed and suspicious, vertigo, weak, headache, vaginal dryness, urinary tract infection	Conjugated estrogens tablets, Medroxyprogesterone17-acetate, Liuwei dihuang pill, Xinshenning tablets and Xiaoyao pills	Conjugated Estrogens Tablets and Medroxyprogesterone17-acetate	P<0.05	Experiment group was better than control group

Discussion

At present, the pathogenesis of MPS is not yet fully understood. Modern medicine believes that the etiology of MPS is the excessive reduction of estrogen levels resulting from hypovarianism. The reduced levels of female hormone evidently led to the function disorder of the hypothalamic pituitary adrenal axis (HPA) or the hypothalamic pituitary ovarian axis, further resulting in the imbalance of neurotransmitters, hormones, and cytokines. Therefore, neuroendocrine-immune has a close relationship with MPS (Yan et al., 2003). However, we believe that the etiology and pathogenesis of hypovarianism in TCM is mainly due to kidney imbalance. The Yellow Emperor's classic states: Su Wen · Shang Gu Tian Zhen Lun recorded: "when the female is seven years old, her kidney qi increases, she starts losing her baby teeth and hair grows longer; at forty-nine years old, the function of ren meridian is weak and the function of tai chong meridian gradually exhausts. The kidney-essence promoting reproductive function depletes and menstruation stops. This indicates that the function and energy of the human body heavily declines, and [eventually] becomes unable to produce offspring". Therefore, these records demonstrate that after women suffer from menopausal syndrome, their kidney-essence which promotes the reproductive function, declines. The function of the ren and the chong meridians gradually wears down, both the essence and blood become deficient, and the kidney develops yin and essence deficiency. Subsequently, it fails to warm other organs and various other clinical symptoms gradually appear.

Currently, the treatment of MPS in western medicine mainly involves hormone replacement therapy (HRT). HRT can not only adjust the menstrual cycle disorder during the menopausal transition, but also can alleviate and eliminate the menopausal symptoms (Duan, 2003). However, long-term blind application of HRT may increase the risk of endometrial cancer, breast cancer, stroke and pulmonary embolism (Zhang et al., 2003). Many studies demonstrated that the therapy of integrated Chinese and western medicine is beneficial to MPS, and can dramatically improve the therapeutic rates of MPS in comparison to the hormone replacement and other western approaches. Although there was no significant difference in regulating the levels of FSH, LH and E_2 in comparison to hormone therapy, the integrated Chinese and western medicine approach have advantages in elevating the E_2 levels (Nie et al., 2004). As mentioned above, doctors prefer choosing the integrated Chinese and western medicine therapy to treat MPS, and in fact the available research has shown that the integrated medicine approach has an excellent effect in treating MPS. This is because this therapy is not only able to alleviate MPS, but also reduce the side effects of hormone replacement, such as the distending pain of breast and the endometrial thickening. Furthermore, it can enhance the therapeutic security to a

greater extent (Chen et al., 2003).

The results of this review show that the therapeutic effect of integrated Chinese and western medicine is superior to that of western medicine alone, in relieving the symptoms, decreasing the FSH levels and improving clinical efficiency. While, there was no significant difference between the two therapeutic methods in regulating the levels of LH and E_2 in patients, the clinical efficiency of integrated Chinese and western medicine was undeniably better than the western medicine alone. Due to the limitations regarding the included literature for this evaluation, we cannot draw firm conclusions about the efficacy of the treatment of MPS with integrated Chinese and western medicine.

The obtained literature for RCTs in treating MPS with integrated Chinese and western medicine was published only in Chinese, while the methodology of the clinical trials described was of generally poor quality. The methods for randomization and allocation concealment in these trails were mainly described inadequately or incompletely. Most randomized studies failed to follow any standard. For example, only 2 out of the included 12 trials mentioned using single blind method, but without providing sufficient information. Although the TCM therapy is difficult to be blind, the researchers should correctly apply randomization, and make a detailed record of withdrawal, dropout and long-term follow-up. In addition, since these factors are closely related to the effect of the examined therapies, they may result in no statistical difference and selective bias. In summary, we need high-quality clinical trials to evaluate the curative effect of integrated Chinese and western medicine in patients with MPS, even though abundant clinical experiences, especially case reports, have been repeatedly published for decades (Chen et al., 2001; Chen et al., 2006). Therefore, a perfect, multi-centered and larger sample size of trials is required for providing better evidence-based medicine (EBM) confirmation.

Conflict of Interest: The authors declare that there is no conflict of interest.

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