Original article

Chinese Herbal Medicine for premature ovarian failure: A systematic review and meta-analysis

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Abstract

Introduction: Premature ovarian failure (POF), loss of normal ovarian function before the age of 40 commonly results in infertility. This systematic review/meta-analysis evaluates the effectiveness of Chinese herbal treatments on POF.

Methods: Systematic searches of six electronic databases were conducted for articles published through June 2013. All randomized controlled trials which compared Chinese Herbal Medicine (CHM) as solitary treatment vs. hormone replacement therapy (HRT) for POF were included. Measurement of treatment effect was done through pooled odds ratio (OR) of effective cases in the two groups, and weighted mean difference (WMD) of hormonal levels (E_2, FSH, LH) after treatment.

Results: This meta-analysis includes 10 randomized controlled trials (RCTs) involving 888 patients in comparing CHM with HRT for the treatment of POF. The pooled data showed an improvement in symptoms in the CHM group compared to that of the HRT group (OR = 2.50, 95% CI: 1.49–4.18, $P < 0.001$). FSH levels were significantly lower in patients treated with CHM compared to that of patients treated with HRT (≥ 6 M: WMD = −8.34, 95% CI: −11.96, $P < 0.001$, −4.71; <6 M: WMD = −5.23, 95% CI: −8.68, −1.78, $P = 0.003$). There was no significant difference ($P > 0.05$) observed in E_2 and LH levels when CHM and HRT were compared.

Conclusions: CHM may relieve symptoms of POF partly through decreasing serum FSH levels, this may provide guidance for future studies.
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Keywords: Premature ovarian failure; Chinese Herbal Medicine; Hormone replacement therapy

Introduction

Premature ovarian failure (POF) is the loss of ovarian function which is characterized by amenorrhea, hypoestrogenism, and elevated serum gonadotropin levels in women younger than the age of 40. The estimated incidence of POF is 1:10000 women by age 20; 1:1000 women by age 30; and 1:100 women by age 40 [1,2]. This condition occurs in 10–28% of women with primary amenorrhea and 4–18% with of women with secondary amenorrhea [3]. Women with POF experience menopausal symptoms such as hot flashes, vaginal dryness, dyspareunia, insomnia,

vaginitis, and mood swings [4]. In many cases, patients suffer from infertility due to the absence of follicles and failure to respond to stimulation of hormones [5].

A definitive diagnostic criterion for POF has not been established [6]. In clinical practice, a diagnosis is usually based on amenorrhea for 3–6 months, elevated serum follicle-stimulating hormone (FSH) levels (usually above 40 IU/L) detected on at least two separate occasions several months apart, and low estrogen levels [7]. Other causes of amenorrhea such as pregnancy, polycystic ovarian syndrome, and thyroid dysfunction need to be excluded. Although specific standardized guidelines for the management of POF are absent, hormone replacement therapy (HRT) with estrogen or progesterone is widely considered as appropriate medical options [6]. However the use of HRT has been associated with increased risks of breast cancer, heart attacks and strokes [8].

For thousands of years, Chinese Herbal Medicine (CHM) has been used to treat many diseases. The philosophy of Chinese

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Medicine in terms of biology, pathophysiology and pharmacology takes an entirely different approach. When compared to Western Medicine, the diagnostic and therapeutic modalities rely on experience and social customs. For this reason, many treatments still do not have a concise mechanism of action and clear side effect profile. Currently, CHM are mainly used to decrease the risk and treat common pathologies i.e. hypertension, hypercholesterolemia, diabetes mellitus, obesity, cancer, depression, prevention of miscarriages and even POF. People mainly use CHM either because they experience fewer side effects and/or they have had no effect from Western Medicine treatments. The outlook that CHM takes on POF is a unique one. Animal experiments have demonstrated the efficacy of Chinese herbs to inhibit the production of anti-ovarian antibodies (AoAb) and to further protect the ovaries from autoimmune destruction [9]. Studies have been done to reveal CHM's influence on the serum level of hormones and its involvement with the hypothalamic–pituitary–ovarian (HPO) axis [10,11]. For example, several case reports suggest that CHM may alleviate symptoms, reduce elevations in FSH, promote estrogen production, and regulate levels of luteinizing hormone (LH) [12,13]. CHM is also effective in the management of the infertility caused by POF [14]. However, evidence in terms of larger sample sizes and multi-center, randomized controlled trials (RCTs) are lacking. In addition, when comparing the outcomes of CHM and HRT in terms of treatment profile (effective cases) and overall efficacy (hormone levels) the results are controversial. We herein provide a systematic review and meta-analysis of the available literature to compare the outcomes of CHM and HRT in POF treatment. We measure the effectiveness of treatment based on primary outcome (relief of symptoms of POF) and secondary outcome (serum hormone levels).

Materials and methods

Eligibility criteria

All RCTs comparing the efficacy of Chinese herbs with HRT in the treatment of POF were included. The diagnostic criteria for POF included women who were age 40 and below who presented with amenorrhea for more than four months with perimenopausal symptoms, such as chills and pain of the waist and the knees, vaginal dryness, and sexual hypoactivity. These symptoms along with ancillary laboratory findings such as FSH levels greater than 40 IU/L, and estrogen (E_2) less than 110 mol/L were enough to diagnose patients with POF. Other diseases such as insensitive ovarian syndrome and gonadal dysgenesis were excluded. Baseline characteristics, such as age and course, in the patients of the two groups were required to be comparable. The therapeutic intervention was any CHM with the function of tonifying the kidney, including decoction, pill, granule and recipe. The outcome measures included primary and secondary measurements. Our primary measurement was the effective cases which comprised of relief of symptoms of POF including the recurrence of menstruation, improvement of chills and pain (the waist and knees), alleviation of vaginal dryness, and increased libido. Our secondary measurement was

hormone levels of E_2, FSH and LH after treatment in both CHM groups and HRT groups. The number of events, participants in each group, mean and standard deviation for hormone levels were clearly defined. Case reports, reviews, animal experiments, non-randomized controlled trials, and studies failing to mention Chinese herbs or using CHM plus other treatments compared with solitary treatment with HRT were excluded.

Search methods for identification of studies

We searched the Cochrane Menstrual Disorders and Subfertility Group trials register (June 2013), MEDLINE (1966 – June 2013), EMBASE (1974 – June 2013), China National Knowledge Infrastructure (CNKI, 1982 – June 2013), Wanfang Data (1982 – June 2013) and the Chinese Scientific and Technical Journals database (VIP, 1989 – June 2013). No restrictions of language or publication type were placed in any of the searches.

The following free text terms were searched: Traditional Chinese Medicine, Chinese Herbal Medicine, Herbal Drugs, Plant Extracts, Decoction, Tang. Medical subject headings were also searched, which included the terms: Recipe and premature ovarian failure, primary ovarian insufficiency, premature menopause, premature ovarian dysfunction, amenorrhea, and menstruation disturbance.

Selection of studies

A total of 379 citations were obtained from electronic search engines. After screening the titles and abstracts, 319 articles that did not fit the eligibility criteria were excluded. Further exclusion of studies was taken after review of the selected studies. Studies with incomplete data of all hormonal levels (E_2, FSH, LH) and unclear number of valid cases, or that did not meet our requirements of group stratification were excluded. At last, 10 published RCTs were selected for meta-analysis after strict exclusion and inclusion criteria were implemented [12,16–24]. This methodology of exclusion and inclusion criteria is depicted by Fig. 1.

Assessments bias risk

Two independent reviewers assessed the risk of bias with the criteria in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [15]. Sequence generation, allocation concealment, blinding, incomplete data assessment, selective outcome reporting and other potential sources of bias were assessed. Any disagreements between reviewers were resolved by discussion and arbitration by a third reviewer (FQ).

Data extraction and management

Data were carefully extracted from all eligible articles independently by two reviewers (YW and YTW). Relevant data that was collected included the year of publication, country of study, study design, patient characteristics, sample size, and outcome measurements. Treatment effect was measured through the pooled odds ratio (OR) for significant efficiency and differences