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Review Article

Comparative effectiveness of acupuncture and HRT interventions for premature ovarian failure: a bayesian meta-analysis

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Abstract: Premature ovarian failure (POF) is the loss of normal function of the ovaries before age 40. While hormone replacement therapy (HRT) significantly improves the effective rate of patients with POF, it may also raises a woman's risk of heart disease and breast cancer. Acupuncture is a form of alternative medicine and has been sanctioned by many countries. Acupuncture is usually safe and has definite effect without side effects on the treatment of patients with POF, so long as it is administered by experienced physicians. This Bayesian meta-analysis of randomized trials was designed to synthesize the evidence of the comparative effectiveness of Acupuncture and HRT interventions used for patients with POF. Seven electronic literature databases, including Cochrane Library, PubMed, EMBASE, China National Knowledge Infrastructure (CNKI), Chongqing VIP, Wanfang DATA and the Chinese Biomedicine (CBM) databases, were searched for relevant randomized controlled trials until September 20, 2016. Only RCTs that compared acupuncture to HRT alone for women POF were selected. Study selection and data extraction were carried out by two reviewers independently. Study quality was assessed with the Cochrane Collaboration risk of bias tool. Results were pooled by a hierarchical Bayesian random-effects model with parameters used non-informative prior distributions. The primary outcomes examined were follicle-stimulating hormone (FSH), estradiol (E2), luteinizing hormone (LH) and effective rate after treatment in both Acupuncture groups and HRT groups. The 2-level hierarchical Bayesian random effect models were developed to estimate posterior means and 95% credible intervals (CrI) for mean difference (MD) of hormonal levels (FSH, E2, LH) and pooled odds ratio (OR) of effective cases. Eight studies involving 735 patients (368 with acupuncture treatment, 367 with HRT treatment) with POF were included in the meta-analysis. The posterior means and 95% CrI for pooled OR (5.587, [3.095, -9.196]) showed between-group difference and a higher effective rate of patients with acupuncture than with HRT interventions. Compared to HRT treatment, included studies in this review showed that acupuncture therapy was effective in reducing the levels of FSH (MD=-7.691, 95% CrI: -11.87 to -3.91) and increasing the levels of E2 (MD=26.670, 95% CrI: 3.004 to 49.85), whereas acupuncture therapy had no effect on reducing the levels of LH (-3.164, 95% CrI: -6.815 to 1.292). In addition, there was no evidence of significant publication bias. The results of sensitivity analyses showed that pooled OR and MD estimates were influenced by no single study. In conclusion, this Bayesian meta-analysis provides evidence that acupuncture therapy is superior to HRT in some areas of comparisons, including effective rate, reduced the level of FSH and increased the E2 level. However, there is no evidence that acupuncture therapy has effect on reducing the levels of LH compared to HRT treatment. High quality and well-designed studies are needed to enhance the credibility of the results about the effectiveness of acupuncture in patients with POI.

Keywords: Premature ovarian failure, acupuncture therapy, hormone replacement therapy, bayesian meta-analysis

Introduction

Premature ovarian failure (POF) is characterized by hypoestrogenism, elevated serum follicle-stimulating hormone (FSH, usually above 40 IU/L) and luteinizing hormone (LH) levels in women under 40 years old [1, 2]. The etiology of POF is very complex and patients with POF might experience menopause, infertility and other systemic results (such as osteoporosis) [3]. The estimated incidence of POF is 0.01% of women under 20 years old, 0.1% of women

under 30 years old and 1% of women below 40 years old, which influenced nearly 1% of women in period reproduction [4, 5]. Generally, hormone replacement therapy (HRT) (including estrogen and progesterone) is considered as the appropriate therapeutic method and plays an irreplaceable role against POF [6]. However, previous studies found that HRT had been related to increased risks of strokes, breast cancer and coronary heart disease [7-9]. Further, the influence of HRT adverse events on older women was usually greater than younger women. Acupuncture is a form of alternative medicine and a main component of traditional Chinese medicine and has been used as medical means since antiquity in China [10]. At present, Acupuncture has been sanctioned by many countries and become commonplace in the US, Australia, and Europe. Acupuncture has been used to treat many diseases. Some studies suggested that acupuncture was effective for gastrointestinal dysfunction [11], gastrointestinal disorders [12] and POF [13]. As long as acupuncture was administered by experienced physicians, it was generally safe and had definite effect without side effects. There have been concerns about the effectiveness of acupuncture on POF, but the important efficacy variables may become apparent only in larger sample. Therefore, we searched the literatures in which POF patients had been treated with acupuncture and compared to patients treated with HRT alone and performed a Bayesian meta-analysis to evaluate the effect of acupuncture in patients with POF. Non-informative prior distributions were used for all parameters, so that the pooled estimates were determined by the included study data.

Materials and methods

Eligibility criteria

Studies were selected according to the following criterion: Study designs: Randomized controlled trials (RCTs) without restrictions for publication language which compared the efficacy of Acupuncture with HRT in the treatment of Premature Ovarian Failure were eligible for inclusion in the Meta-Analysis. Case-control design, letters, reviews, cross-over trials or case reports were excluded.

Populations: All women with Premature Ovarian Failure (POF) were eligible for inclusion. Premature Ovarian Failure (POF) is defined as primary or secondary amenorrhea associated with high levels of follicle stimulating hormone (>40 IU/L) on two occasions at intervals of 1 month, and estrogen (E2) less than 73.2 mol/L in women less than 40 years of age [22].

Interventions and comparisons: We included all the studies in which patients had been treated with Acupuncture and compared to patients treated with HRT alone. Studies investigating the combined effects of acupuncture plus other interventions were excluded. In addition, we also excluded trials in which patients of control group were not just given HRT.

Outcomes: Our outcomes were hormone levels (FSH, LH, E2) and effective rate after treatment in both Acupuncture groups and HRT groups. We included the studies in which the mean and standard deviation for hormone levels, the total number of Subjects and the effective number of Subjects in each group were clearly present.

Search strategy

The Cochrane Library, PubMed, EMBASE, China National Knowledge Infrastructure (CNKI), Chongqing VIP, Wanfang DATA, and the Chinese Biomedicine (CBM) databases were searched to identify published studies. We also identified all relevant articles found on PubMed by using the 'related articles' feature. These databases were searched until September 20, 2016, without restrictions for starting date of search or publication language. Search terms, combined with an RCT filter, were "premature ovarian failure", "premature ovary dysfunction", "premature ovary insufficiency", "estrogen therapy", "Acupuncture", "Acupressure", "Electroacupuncture", "hormone replacement therapy", and "combined estrogen and progestogen therapy".

Study selection and data extraction

The titles and abstracts of all relevant studies were screened by the first author (###) to exclude the studies that failed to meet the purposes of this Bayesian meta-analyses. Two reviewers (### and ###) independently extracted data on study characteristics including author, year of publication, sample size of participants, methods, acupoints, outcomes measures and duration of follow-up. The differenc-

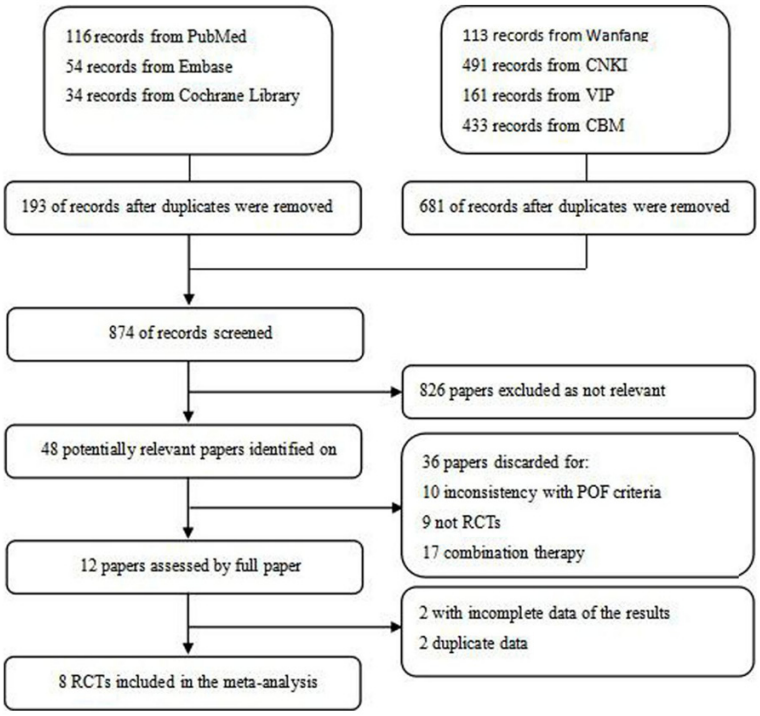

Figure 1. Flow diagram of articles selection process for Bayesian meta-analysis.

es between the extracted datasets were resolved by discussion with the third reviewer (###) when necessary.

Quality assessment

Risk of bias was assessed independently by two reviewers (### and ###) using the Cochrane Collaboration risk of bias tool [23], and all disagreements were resolved by discussion and arbitration by a third reviewer (###). The Cochrane Collaboration risk of bias tool consists of six domains: selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of assessors), attrition bias (incomplete outcome data), reporting bias (selective reporting of outcomes), and other source of bias.

Statistical methods

Statistical analyses were performed with R statistical software (version 3.31). Statistical heterogeneity was tested using the Chi-squared test and I^2 statistic. The I^2 statistic values of 25%, 50%, and 75% correspond to low, moderate, and high levels of heterogeneity, respectively [24]. In the absence of heterogeneity the Bayesian fixed effects model was adopted for combining the data (I^2<50%, P>0.05). The Bayesian random effects model was performed if there was significant heterogeneity (I^2>50%, P<0.05). The Bayesian fixed effects model and Hierarchical Bayesian random effects model were implemented with the OpenBUGS software (version 3.2.3) by running it from within the R statistical software using the "R2OpenBUGS" package.

The results were pooled and expressed as the posterior mean of the overall odds ratio (OR) with 95% credible interval (CrI) for dichotomous data and mean difference (MD) with 95% CrI for continuous data. The 95% CrI was obtained by calculating the 2.5th and 97.5th percentiles of the posterior distributions. If 1(0) was included in the 95% CrIs of OR (MD), there was significant difference between experimental group and control group. All posterior parameters were calculated by Markov chain Monte Carlo methods (MCMC). In order to the pooled estimates were determined by the included studies, non-informative prior distributions were used for all parameters, and the details of the statistical model were shown in **Supplementary Appendix**. We initiated three chains with disparate initial values, and each chain was run for 10000 iterations with a burn-in of 1000 iterations. Convergence was assessed through Trace plot and Gelman-Rubin statistic. We let the chain run until the MC error was less than 5% of the posterior SD. Potential publication bias was investigated by Begg's rank correlation test, with P<0.05 indicating statistical significance [25]. In the end, sensitivity analysis was done to examine the effect of a single study on the overall meta-analysis estimate.

Results

Search results and baseline characteristics

The literature search results identified 1402 articles, of which we excluded 874 as they were

Table 1. Summary of characteristics of clinical studies included in the Bayesian meta-analysis

Author	Year	Design	Diagnostic criteria of POF	Sample size	Experimental group	Acupuncture points	Control group	Outcomes measures	Measurement time (month)
Luo JJ [14]	2015	RCT	Age ≤40, Amenorrhea ≥4 months, FSH>40 U/L (two checks, interval time ≥1 month), E2<73.2 pmol/L	60	Electroacupuncture	Taixi, Qihai, Guanyuan, Uterus, Zhongji, Uterus, Zusanli, Sanyinjiao	HRT	ER, FSH, E2	3 months
Fu M [15]	2015	RCT	Age ≤40, Amenorrhea ≥4 months, FSH>40 U/L (two checks, interval time ≥1 month), E2<73.2 pmol/L	96	Acupuncture	Xuepishu, Ganshu, Guan yuan, Xuehai, Mingmen, Shenshu, Taixi, Uterus, Sanyinjiao	HRT	ER, FSH, E2, LH	6 months
Luo YY [16]	2014	RCT	Age ≤40, Amenorrhea ≥4 months, FSH>40 U/L (two checks, interval time ≥1 month), E2<73.2 pmol/L	48	Acupuncture	Guan yuan, Mingmen, Shenshu, Uterus, Sanyinjiao, Uterus, Xuehai, Taixi, Ganshu, Pishu	HRT	ER, FSH, E2, LH	6 months
Li L [17]	2014	RCT	Age ≤40, Menoxenia, Amenorrhea, FSH>40 ug/L	60	Acupuncture	Guan yuan, Zhongji, Uterus, Shenshu, Shenmen, Baihui, Taichong, Neiguan	HRT	ER, FSH, E2, LH	6 months
Yang XH [18]	2008	RCT	Age ≤40, Amenorrhea ≥4 months, FSH>40 U/L, E2<73.2 pmol/L	60	Acupuncture	Guan yuan, Guilai, Uterus, Zhongji, Sanyinjiao, Zusanli, Xuehai, Taichong, Taixi	HRT	ER, FSH, E2, LH	6 months
Liu LJ [19]	2008	RCT	Age ≤40, Amenorrhea ≥4 months, FSH>40 U/L (two checks, interval time ≥1 month), E2<73.2 pmol/L	132	Acupoint catgut implantation	Ganshu, Pishu, Shenshu, Qimen, zhangmen, Jingmen	HRT	ER, FSH, E2	6 months
Sha GE [20]	1998	RCT	Age ≤40, Menoxenia, Amenorrhea, FSH>40 ug/L	126	Acupuncture	Guan yuan, Zhongji, Dahe, Uterus, Shenshu	HRT	ER, FSH, E2, LH	6 months
Ma RH [21]	1997	RCT	Age ≤40, Amenorrhea, no clear criteria on FSH and E2	97	Acupuncture	Guan yuan, Zhongji, Dahe, Uterus, Shenshu	HRT	ER, FSH, E2, LH	6 months

Notes: FSH (Follicle-stimulating hormone), LH (Luteinizing hormone), E2 (Estradiol), ER (effective rate).

Table 2. Risk of bias of clinical studies included in the Bayesian meta-analysis

Author	Year	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting of outcomes	Other source of bias
Luo JJ	2015	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Fu M	2015	Unclear risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Luo YY	2014	Unclear risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Li L	2014	Unclear risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Yang XH	2008	Unclear risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Liu LJ	2008	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Sha GE	1998	Unclear risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Ma RH	1997	Unclear risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias

Table 3. Bayesian Meta-Analysis output and statistics for each target

Target	The number of included articles	Mean (95% CrI)	I^2	DIC	Rhat	Begg's test (P)
Effective rate (OR)	8	5.587 (3.095, 9.196)	0.0%	14.6	1.004	0.386
FSH (MD)	8	-7.691 (-11.870, -3.910)	39.0%	51.4	1.004	0.536
E2 (MD)	8	26.668 (3.004, 49.840)	94.1%	54.1	1.001	0.386
LH (MD)	6	-3.164 (-6.815, 1.291)	61.0%	36.9	1.002	0.707

reviews, duplicated reports, animal studies, without suitable controls, etc. The 874 trials were excluded for the detailed reasons shown in **Figure 1**. Eight RCTs met our inclusion criteria and were remained for further analysis [14-21]. The characteristics of the studies included in the Bayesian meta-analysis were summarized in **Table 1**. Eight RCTs studies had been conducted in China between 1997 and 2015. The total of 368 participants with premature ovarian failure were treated with Acupuncture and 367 participants were treated with HRT. Further, some details characteristics of the studies included were presented in the **Table 1**.

Quality assessment

The risk of bias assessed for included studies were presented in **Table 2**. The risk of bias was low for the random sequence generation process for two included studies (Luo JJ, 2015 and Liu LJ, 2008). Because the other six studies [15-18, 20, 21] didn't describe the specific randomization strategies, we assigned an unclear risk of bias. All included studies [14-21] didn't provide details of the method of allocation concealment and report any information on blinding of outcome assessors. All of the included trials were classified as having low risk of bias for incomplete outcome data, selective reporting of outcomes and other source of bias.

Effects of interventions

As shown in **Table 3**, the heterogeneity (I^2) varied from 0% to 94.1%. We accounted for such heterogeneity by using Bayesian random effects model in our analysis. We also calculated the deviance information criterion (DIC) [26] and DIC values were lower for all Bayesian random effects model for each outcome measure. Trace plots for chains using different starting values for the estimated parameter. All convergence plots indicated that the algorithm has reached convergence since trace plots did not present irregularities and ergodic means had been stabilized (**Figure 2**). In addition, Rhat is the potential scale reduction factor. The result also illustrated that convergence had been reached, with all Rhat values closed to 1.0 (**Table 3**).

A total of 8 studies [14-21] including 735 patients reported effective rate after treatment in both Acupuncture groups and HRT groups. We observed that the overall pooled data suggested a higher effective rate of premature ovarian failure patients with acupuncture than with HRT interventions (odds ratio 5.587, 95% credible interval: 3.095-9.196). Eight of the RCTS [14-21] evaluated the FSH and E2 between treatment and control groups. We found that there were significant differences in FSH and E2 between acupuncture group and

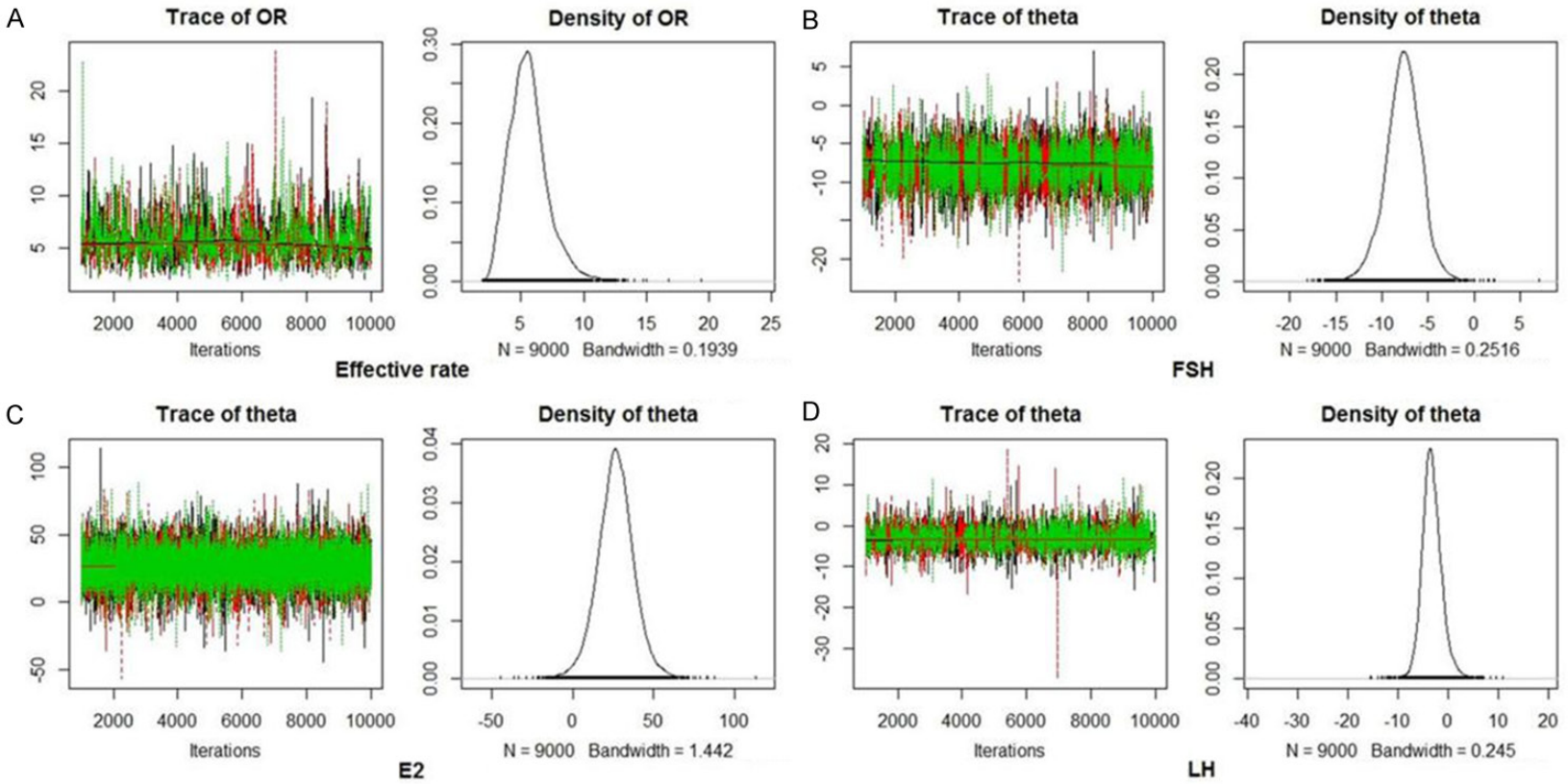

Figure 2. Trace plots and density plots of posterior distribution of OR and theta.

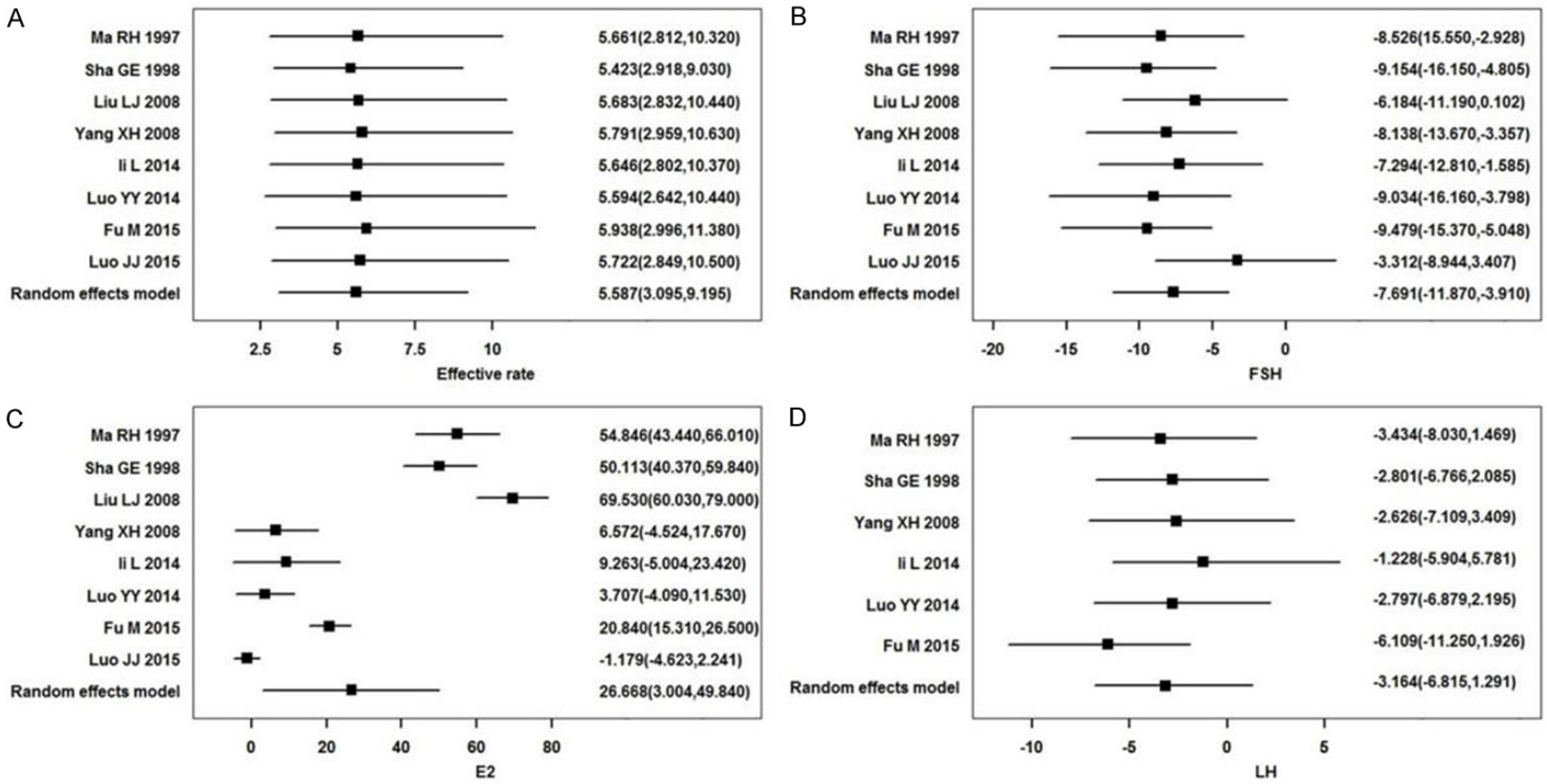

Figure 3. Forest plots showing OR and MD of eligible studies comparing acupuncture with HRT alone in a Bayesian random effect model.

HRT group, and the pooled posterior mean differences (MD) were -7.691 (95% CrI: -11.87 to -3.91) and 26.67 (95% CrI: 3.004 to 49.85), respectively. Six studies [15-18, 20-21] involving 487 patients were included in the Bayesian meta-analysis to evaluate the LH levels after treatment. The posterior MD for LH levels was -3.164 (95% CrI: -6.815 to 1.292) and the difference between the two treatment groups was not statistically significant. The single article estimates with their credibility intervals were showed through forest plots as seen in **Figure 3**.

Publication bias and sensitivity analyses

Publication bias was analyzed by Begg's test. The results showed that there were no significant publication biases (P>0.05), as shown in **Table 3**. Finally, sensitivity analyses of effective rate, FSH, E2 and LH levels were conducted by sequentially omitting one study at each turn. The results suggested that the pooled OR and MD estimates were affected by no single study. Therefore, we confirmed that the results were statistically robust.

Discussion

The objective of our Bayesian meta-analysis was to observe the curative effect of acupuncture to POF. The main findings of the current Bayesian meta-analysis provided evidence that acupuncture intervention could significantly increase the effective rate in POF women. Specifically, the effective rate of POF women who received acupuncture intervention is higher (odds ratio: 5.587, 95% CrI: 3.095-9.196) than in their counterparts who received HRT intervention alone. For example, Jo J et al. [13] also reported that the effective rate in acupuncture group was higher than that of the control group. Moreover, These Bayesian meta-analysis findings support that acupuncture intervention reduce FSH levels (MD=-7.691, 95% CrI: -11.870 to -3.910) and increase E2 levels (MD=26.670, 95% CrI: 3.004 to 49.85). These findings are similar with the general meta analysis [13] which revealed no statistically significant differences on FSH levels (SMD=-9.260, 95% CI: -13.11 to -5.41) and E2 levels (SMD=31.510, 95% CI: 6.060 to 56.950) between the patients in acupuncture intervention groups and those in control groups. It was worth noting that Jo J et al. included studies which adopted no treatment, or other treatments for control group, and also included studies which adopted other treatments for experimental group and control group in the same manner. In the current Bayesian meta analysis, six of the RCT [15-18, 20, 21] evaluated the LH levels but no statistically significant decrease in LH levels was found for acupuncture treatment. Yang, XH et al. [18] found no significantly reduction of LH levels with acupuncture as compared to the HRT approach. However, the different results were found in the research by Luo YY et al. [16].

The strengths of our Bayesian meta-analysis are as follows. First, we only included the studies in which patients had been treated with Acupuncture and compared to patients treated with HRT alone. In addition, studies investigating the combined effects of acupuncture plus other interventions were excluded. These made it more precise when we compared the effective of Acupuncture and HRT interventions for POF.

Second, we searched multiple databases to identify published studies, including Cochrane Library, PubMed, EMBASE, China National Knowledge Infrastructure (CNKI), Chongqing VIP, and so on. Further, these databases were searched without restrictions for starting date of search and publication language. Third, the 2-level hierarchical Bayesian random effect model was selected to perform meta-analysis could handle the heterogeneity of the included studies, and yet provided more precise estimates by borrowing strength using information from all included studies even when few studies were available. The Bayesian hierarchical model conclusions needs to be supported by a 'significant result' using the credibility interval of the posterior parameter, it is superior to the traditional meta-analyses [27, 28].

However, although only RCTs were included in the Bayesian current meta-analysis, there were several limitations that might influence on the results. First of all, the randomization strategies were inadequate in 6 of 8 included studies [15-18, 20, 21], which could led to bias of selection. And as in Ma RH et al., the diagnostic criteria for POF hadn't been described in detail. Because sample sizes of some studies [14, 16] were small, which might be a source of heterogeneity. Next, all studies included in this

Bayesian meta-analysis were all single-center RCTs studies done in China, even though we didn't apply language restrictions to our literature search. The Bayesian meta-analysis results were based on published data only, not unpublished data. Third, of the eight studies included in this review, only two [14, 15] reported information about age, and therefore the subgroup analysis based on age wasn't implemented.

Finally, the 2-level hierarchical Bayesian random effect models were constructed and based on non-informative prior distributions for all parameters, sometimes the normality assumption for the parameters' posterior distribution might not be reasonable but this problem and the alternative approaches had not been done systematically. In this study, we also didn't try out a community of priors and examine the sensitivity of the results to the choice of the prior. In spite of the limitations listed earlier, the general conclusion was that this Bayesian meta-analysis supported the patients who were given acupuncture therapy had better effects than who were HRT interventions.

Furthermore, the acupuncture safety is an important problem concerned by patients all the time. It is a popular belief that it is generally safe as long as acupuncture is administered by experienced physicians and the side effects of acupuncture therapy are less when compared to hormone therapy.

To conclude, this is the first Bayesian meta-analysis to synthesize evidence on the comparative effectiveness of acupuncture and HRT interventions for POF. This research has revealed that acupuncture therapy is even superior to HRT in some areas of comparisons, for instance, effective rate, reduced the level of FSH and increased the E2 level, yet HRT plays an irreplaceable role in the treatment of premature ovarian failure. In addition, high quality and well-designed studies with larger samples articles are required to enhance the credibility of the results about the effectiveness of acupuncture in patients with POI.

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Disclosure of conflict of interest

None.

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Supplementary appendix

1. The Bayesian random-effects model for binary data

```
model <- function() {
  for(i in 1:n) {
      d[i]<-log(rt[i]/(nt[i]-rt[i]))-log(rc[i]/(nc[i]-rc[i]))
      sigmasquare[i]<-1/rt[i]+1/(nt[i]-rt[i])+1/rc[i]+1/(nc[i]-rc[i])
      d[i]~dnorm(delta[i],precision[i])
      precision[i]<-1/sigmasquare[i]
      delta[i]~dnorm(theta,precision.tau)
  }
  precision.tau~dgamma(0.001,0.001)
  sigma2<-1/precision.tau
  theta~dnorm(0.0,1.0E-6)
  OR<-exp(theta)
}

inits <- function()
{
  list(theta= rnorm(1,0,1),precision.tau= runif(1, 0, 1))
}
```

2. The Bayesian random-effects model for Continuous data

```
model <- function() {
  for(i in 1:r)
  {
     d[i]<-x1[i]-x2[i]
     v[i]<-s1[i]*s1[i]/n1[i]+s2[i]*s2[i]/n2[i]
     t[i]<-1/v[i]
     d[i]~dnorm(delta[i],t[i])
     delta[i]~dnorm(theta,inv.tau)
  }
  theta~dnorm(0.0,1.0E-6)
  inv.tau~dgamma(0.001,0.001)
  tau2<-1/inv.tau
  tau<-sqrt(tau2)
}

inits <- function()
{
  list(theta=rnorm(1,0,1),inv.tau=runif(1, 0, 1))
}
```