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The effects of acupuncture on polycystic ovary syndrome:**A systematic review and meta-analysis**

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Running title: acupuncture for PCOS

Abstract

Introduction: To assess the clinical effectiveness of acupuncture in treating polycystic ovarian syndrome (PCOS).

Methods: A systematic review and meta-analysis was conducted of RCTs that compared either acupuncture with no/sham (placebo) acupuncture or a certain therapy with acupuncture added in the treatment of PCOS. Measures of treatment effectiveness were the pooled odds ratios (OR) for women with PCOS having acupuncture compared with women in the control group for the recovery of menstrual cycles, standardized mean difference (SMD) for body mass index (BMI), fasting insulin (FINS), fasting plasma glucose (FPG), luteinizing hormone (LH), follicle stimulating hormone (FSH), and the ratio of LH/FSH.

Results: A total of nine RCTs (531 women) met criteria for inclusion into the systematic review. Using the random effects model, pooling of the effect estimates from all RCTs showed recovery of menstrual cycles (OR = 0.20, 95% CI: 0.09 to 0.41, $P < 0.01$), BMI (SMD = -0.63, 95% CI: -1.04 to -0.21, $P=0.04$), and LH (SMD = -0.39, 95% CI: -0.65

to -0.12 , $P < 0.01$) which favored the acupuncture group. No significant differences were observed for FINS, FPG, FSH and the ratio of LH/FSH between acupuncture and control groups ($P > 0.05$).

Conclusions: Acupuncture appears to significantly improve the recovery of the menstrual cycles and decrease the levels of BMI and LH in women with PCOS. However, the findings should be interpreted with caution due to the limited methodological quality of included RCTs.

Keywords: Acupuncture; Polycystic ovary syndrome (PCOS); Meta-analysis.

Introduction

Polycystic ovary syndrome (PCOS) is recognized as one of the most common endocrine and metabolic disorders in women, which has a prevalence of 6 to 15% in unselected reproductive-aged women [1, 2]. The PCOS patients often need pharmacological treatment over a long period of time [3, 4]. Although oral contraceptives are the most common therapy to effectively alleviate hirsutism and acne of patients with PCOS, they can adversely affect glucose tolerance, coagulability and fertility [5].

Acupuncture, through stimulating specific points on the body, has been used to treat gynecological disorders for thousands of years [6]. Acupuncture is sometimes chosen by women with PCOS as an alternative to pharmacotherapy, with some choosing to use it as an adjunct while undergoing infertility treatment [7]. We herein provide a systematic review and meta-analysis of the available literature to assess the effectiveness of acupuncture in the treatment of PCOS.

Methods

Eligibility criteria

Randomized controlled trials (RCTs) comparing either acupuncture with no/sham (placebo) acupuncture or a certain therapy with acupuncture added in the treatment of PCOS were included. “Acupuncture” was defined as traditional needling, auricular acupuncture, electro-acupuncture (EA), auricular acupressure, or warm needling acupuncture. PCOS was diagnosed according to the European Society for Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM) sponsored PCOS Consensus Workshop criteria (the Rotterdam criteria) [8]. For inclusion, at least one of the following outcomes had to be available for extraction: recovery of menstrual cycles, body mass index (BMI), fasting insulin (FINS), fasting plasma glucose (FPG), luteinizing hormone (LH), follicle stimulating hormone (FSH), the ratio of LH/FSH and testosterone (T). The numbers of events, participants in each group, mean and standard deviation (SD) for continuous data had to be clearly defined. Case reports, reviews, animal experiments, non-randomized controlled trials and studies comparing the combination of acupuncture and another therapy with a third therapy were excluded.

Search strategy

A systematic literature search was performed using the following databases: MEDLINE, EMBASE, SCISEARCH, the Cochrane Menstrual Disorders and Subfertility Group trials register, China Academic Journal Electronic full text Database in China National Knowledge Infrastructure, Wanfang Database, Index to Chinese Periodical Literature, and the International Standard Randomized Controlled Trial Number (ISRCTN) Register and

meta-register for randomized controlled trials (mRCT). All the databases were searched from their inception to May 2015. The reference lists of the relevant primary and review articles were examined to identify cited articles that were not captured by electronic searches. No restrictions of language or publication type were placed on the searches.

The following keywords were searched: “polycystic ovary syndrome” or “polycystic ovary” or “ovary polycystic disease” or “PCOS” or “polycystic ovary morphology” or “oligo-amenorrhea” or “oligoamenorrhea” or “oligoanovulatory” or “oligohypomenorrhea” or “amenorrhea” or “amenorrhoea” or “hirsutism” AND “acupoint” or “acupressure” or “acupressure-acupuncture therapy” or “acupuncture” or “electro-acupuncture” or “electroacupuncture” or “moxibustion” or “Tui Na” or “ traditional medicine” or “traditional Chinese medicine” or “traditional Chinese medicine combined with western medicine”. All search terms were back translated into Chinese terms in order to conduct the searches in Chinese databases.

Study selection

Two reviewers independently scrutinized titles and abstracts from the electronic searches (F. Q. and Y.W.), and full manuscripts of all citations that were likely to meet the predefined inclusion criteria were obtained. The final inclusion or exclusion decisions were made on examination of the full manuscripts. In cases of duplicate publication, the most recent and complete versions were selected. Any disagreements about inclusion were resolved by discussion or arbitration by a third reviewer (X.H.).

Quality assessment and data extraction

Two independent reviewers (F.Q. and Y.W.) assessed the risk of bias with the criteria in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0

(<http://community.cochrane.org/handbook>). Any disagreements between the reviewers were resolved by discussion and arbitration by a third reviewer (X.H.).

Two reviewers (F. Q. and Y.W.) extracted data from all eligible articles independently. Data that was collected included the year of publication, study design, patient characteristics, sample size and relevant outcome measurements. The safety of using acupuncture and other therapies was also assessed by exploring the description of side effects in the included RCTs.

Statistical analysis

The results were pooled and expressed as odds ratio (OR) or standard mean difference (SMD) with 95% confidence interval (CI). Heterogeneity of treatment effects was evaluated graphically using a forest plot and a chi-square test. A value greater than 50% was considered as substantial heterogeneity. In the meta-analysis, a random effects model was used for the encountered heterogeneity of the trials' characteristics and populations studied. A sensitivity analysis was conducted to examine the effect of excluding each study. The statistical analysis was performed with STATA 12.0 software (StataCorp, College Station, USA).

Results

Main study characteristics

A total number of 173 citations were obtained from the electronic searches and examination of the reference lists of primary and review articles, of which, 75 were selected for retrieval (as shown in Figure 1). We followed the protocol of "Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)" in the flow diagram. The process of literature identification and selection is given in the flowchart

(Figure 1). Of the 75 full manuscripts examined, nine trials including a total of 531 women met inclusion criteria. All nine RCTs were included in the meta-analysis. The quality evaluation and summary of the characteristics of the included trials are identified in Table 1 and Table 2 respectively.

Measurement of risk of bias

The risk of bias was measured for each of the nine studies included. Although all the trials mentioned randomization, only five studies described their specific randomization strategies [9-14].

Two of the included RCTs had a high risk of selection bias as the sequence was generated by the registration order [9, 12]. Seven trials had a high risk of performance bias as the sham acupuncture was not used as a control in the trials [9, 12, 14-19]. The reporting bias was unclear in eight RCTs because we were unable to obtain access to the protocol and verify their primary/secondary outcome measurements [9-12, 14-19]. The summary of the assessment of risk of bias was shown as Supplemental Table 1.

Recovery of menstrual cycles

For the recovery of menstrual cycles, data were available for 5 of the 9 included trials (N = 247) [9, 12-14, 18]. Using the random effects model, no significant statistical heterogeneity between the studies was found ($I^2 = 0.0\%$, $P = 0.93$). Pooling of the effect estimates from all of the five trials showed significant efficacy ($P < 0.01$) of acupuncture in improving the recovery of menstrual cycles of women with PCOS (OR = 0.20, 95% CI: 0.09 to 0.41, Figure 2A). The sensitivity analysis showed that the significance of the pooled OR derived from the 5 RCTs was not excessively influenced by any single study.

Body Mass Index (BMI)

For BMI, data were available from 3 of the 9 included trials (N = 155) [13, 15, 19]. Using the random effects model, the statistical heterogeneity between the studies was not significant ($I^2 = 29.5\%$, $P = 0.24$). The pooled SMD of BMI showed significant effectiveness ($P = 0.04$) of acupuncture in reducing BMI of the women with PCOS (SMD = -0.63 , 95% CI: -1.04 to -0.21 , Figure 2B). The sensitivity analysis of BMI found that one RCT [15] affected the pooled SMD. When the study was removed, the pooled SMD was not significant (SMD = -0.66 , 95% CI: -1.47 to 0.14).

Fasting Insulin (FINS) and Fasting Plasma Glucose (FPG)

For FINS and FPG, the data were available from the same three trials as BMI (N = 155) [13, 15, 19]. Using the random effects model, no significant statistical heterogeneity for FINS and FPG was found ($I^2 = 0.0\%$ and 0.0% , $P = 0.83$ and 0.61 , respectively). Pooling of the results from all three trials showed no significant difference on FINS and FPG between the acupuncture and the control groups (SMD = 0.11 , 95% CI: -0.21 to 0.43 ; SMD = 0.02 , 95% CI: -0.30 to 0.34 , respectively, Figure 2C and D). The pooled SMD derived from the 3 RCTs was not excessively influenced by any single study.

Hormone levels

For the hormone levels, the data of LH and FSH were available from five trials (N = 302) [10, 11, 13-17]. Using the random effects model, no significant statistical heterogeneity for LH and FSH was found ($I^2 = 20.9\%$ and 20.7% , $P = 0.28$ and 0.28 , respectively). Pooling of the results from all five trials showed significant efficacy ($P = 0.02$) of acupuncture in regulating serum LH levels of the women with PCOS (SMD = -0.39 , 95% CI: -0.65 to -0.12 , Figure 3A), however, there was no significant difference for serum

FSH levels between acupuncture and the control groups (SMD = -0.11, 95% CI: -0.37 to 0.15, Figure 3B). Data of the ratio of LH/FSH were available from 5 of the 9 included trials (N = 282) [10, 11, 13, 14, 16, 17, 19]. Using the random effects model, no significant statistical heterogeneity was found ($I^2 = 0.0\%$, $P=0.74$). Pooling of the results from all five trials showed no significant difference in the ratio of LH/FSH between the acupuncture and control groups (SMD = -0.20, 95% CI: -0.43 to 0.04 Figure 3C). Sensitivity analysis showed that the pooled SMDs of LH, FSH and LH/FSH were not excessively influenced by any single trial.

As hyperandrogenism is an important feature of PCOS, testosterone should be included in the meta-analysis. Testosterone was measured in five of the included RCTs [13-17, 19], however, four of them failed to clarify whether it was total testosterone or free testosterone [14-17, 19]. Moreover, the unit of testosterone was not mentioned in one of them [19] and in the other four trials, the units of testosterone were different. As such, it was determined that testosterone is not an appropriate outcome measurement for the present meta-analysis. However, four of these five studies showed acupuncture could significantly decrease the serum level of testosterone in PCOS women [14-17, 19].

The safety of acupuncture in treating PCOS

Unfortunately, none of these nine included RCTs assessed the adverse effects of acupuncture or other therapies during the research period.

Discussion

Summary of evidence

Based on the findings from the present systematic review and meta-analysis, acupuncture appeared to significantly improve the recovery of menstrual cycles and lower BMI and

LH levels in women with PCOS; however, there was no evidence to suggest that acupuncture could improve the levels of FINS, FPG, FSH or the ratio of LH/FSH of the PCOS patients.

For clinical trials, a detailed description of study design is critical to evaluate the evidence. In seven of the included studies, the methods of allocation concealment and blinding were not mentioned [9, 12, 14-19], which may lead to selection and performance biases. The randomization strategies were inadequate in six of the nine studies [9, 12, 15-19], which could also lead to selection bias. In addition, the maximum sample size was no larger than 100, and the minimum was only 15. Given the low methodological quality of these studies, conclusions about the clinical effectiveness of acupuncture for treating PCOS should be interpreted with caution.

In the present meta-analysis, seven single-center trials were conducted in China [9, 12, 14-19]. Chinese patients have a preference for acupuncture as a treatment, which may enhance the placebo effect on them. It is also more likely that acupuncture research conducted in Asian countries have positive outcomes [20].

Recall bias may also exist, as all the included trials failed to provide detailed information of patients who were loss to follow-up. Moreover, some high-quality RCTs are not included in the present meta-analysis due to unavailable data[21, 22].

The results of the bias assessment in the present meta-analysis, the majority of included trials were determined to have “unclear” or “high” risks of bias in the domains of allocation concealment, blinding and random sequence generation. These methodological domains should be assured in future RCTs. In addition, multi-center trials with larger samples should also be taken into consideration.

In the process of reviewing articles, we found that most Chinese studies only evaluated the recovery of menstrual cycles and measured the hormone levels, while other studies had more outcome measurements. As PCOS is a multisystem disease with various clinical symptoms, more outcomes, such as Ferriman-Gallwey score, insulin sensitivity, and blood lipids, should also be measured. The quality of life among patients with PCOS has also received more attention in recent years and many scales, such as the Montgomery Åsberg Depression Rating Scale (MADRS-S), Brief Scale for Anxiety (BSA-S), Swedish Short-Form 36 (SF-36), and PCOS Questionnaire (PCOSQ) scores have been used to evaluate this [23]. These patient-centered outcome measures should also be used to evaluate the effect of acupuncture on PCOS, in conjunction with conventional measures.

During the process of data extraction, we found that continuous data in some high-quality studies were not shown as mean and SD; and various units of some indicators were used in different trials. These problems limited the number of included studies and influenced the statistical power in the current meta-analysis. Therefore, the integrity of data need to be ensured in further studies.

In our review, only two RCTs [10, 11, 13] adhered to STRICTA, a series of guidelines to provide authors a way to structure their reports of acupuncture interventions with a minimum set of items using a checklist. According to the STRICTA, acupuncture rationale, details of needling, treatment regimen, other components of treatment, practitioner background, and the control or comparator interventions should all be reported in the methods section [24].

Another limitation in this review was that all trials comparing acupuncture and other

interventions were included in the meta-analysis, irrespective of the design of control group. This was due to the variety of PCOS treatment and an inadequate number available in same comparison. However, the heterogeneity is acceptable in the meta-analysis, as all the I^2 is less than 30%.

For any clinical intervention, the safety of patients should be monitored critically and reported as part of the trial procedures. None of the trials identified in this review provided information on records of adverse effects during the research period. Future RCTs should incorporate reporting of adverse effects with detailed information of receiving acupuncture and any treatment related events.

Conclusion

From our meta-analysis, acupuncture appears to significantly improve the recovery of menstrual cycles and lower BMI and LH levels in women with PCOS. However, given the limited methodological quality of included RCTs, these findings should be interpreted with caution.

Conflicts of interest

No competing financial interests exist.

Acknowledgements

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Figure Legends

Figure 1. The process of study selection for the systematic review with meta-analysis of the effects of acupuncture on polycystic ovary syndrome.

Citations from electronic searches and from examination of reference lists of primary and review articles: $n = 173$

excluded after screening titles and/or abstracts: $n = 98$

Full manuscripts retrieved for detailed evaluation: $n = 75$

Articles excluded with reasons: 66
Reviews/commentaries = 27
Prospective case-controlled studies = 7
Other observational design = 7
Inappropriate study design = 13
PCOS-related data not collected = 12

The controlled trials with usable information for meta-analysis ($n=9$)

Figure 2. Meta-analysis of the studies evaluating the effects of acupuncture on the recovery of menstrual cycles (A), body mass index (B), fasting insulin (C) and plasma glucose (D) of the women with polycystic ovary syndrome.

OR, odds ratio; SMD, standardized mean difference; CI, confidence interval.

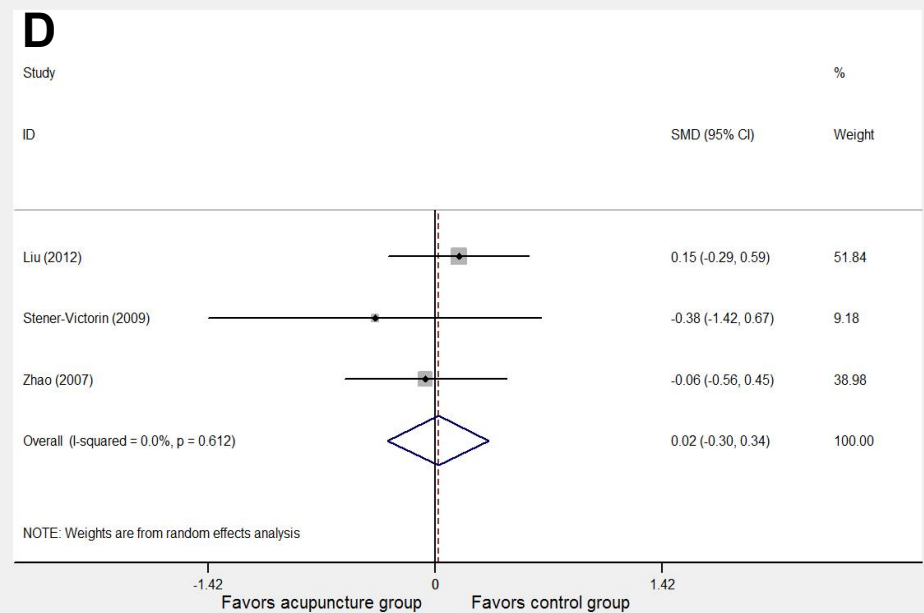
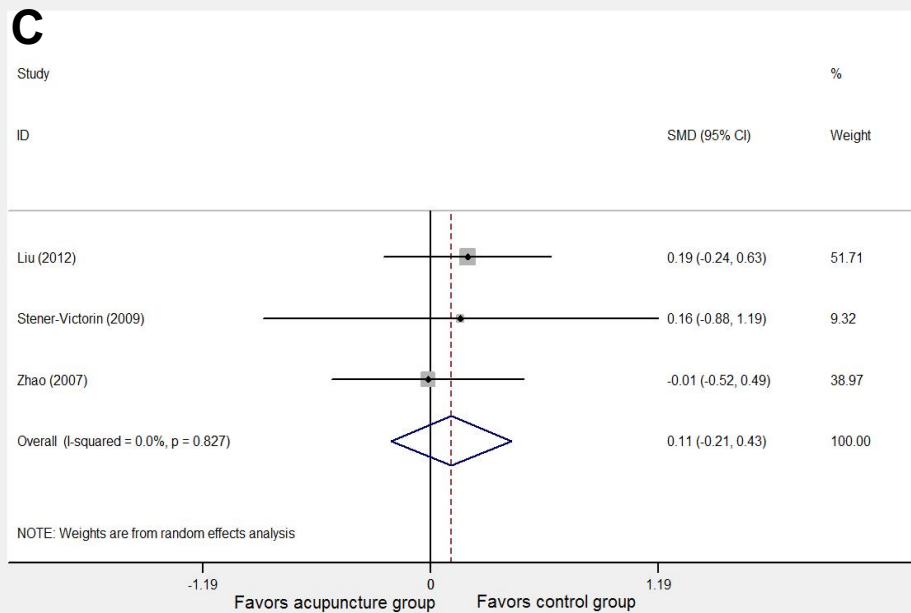
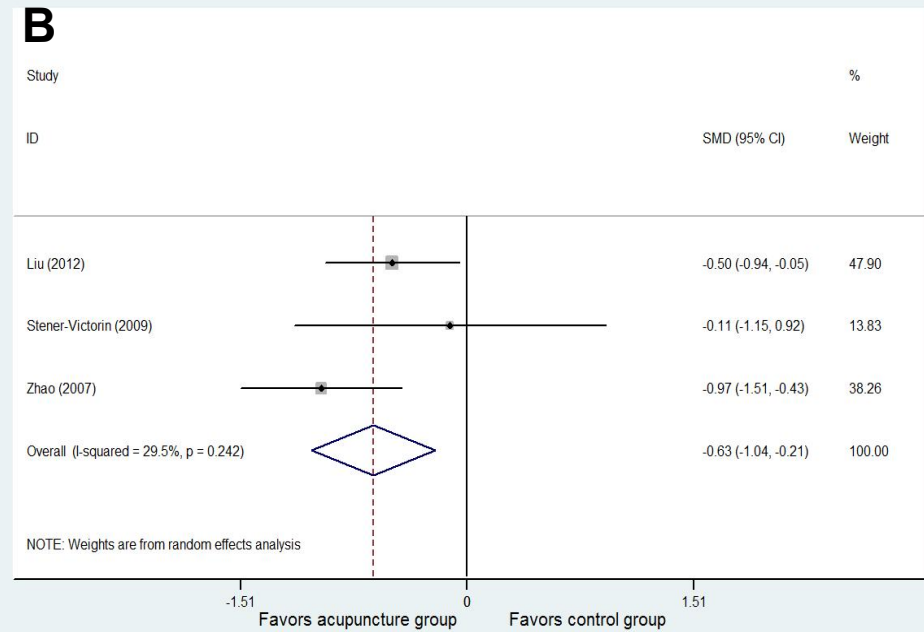
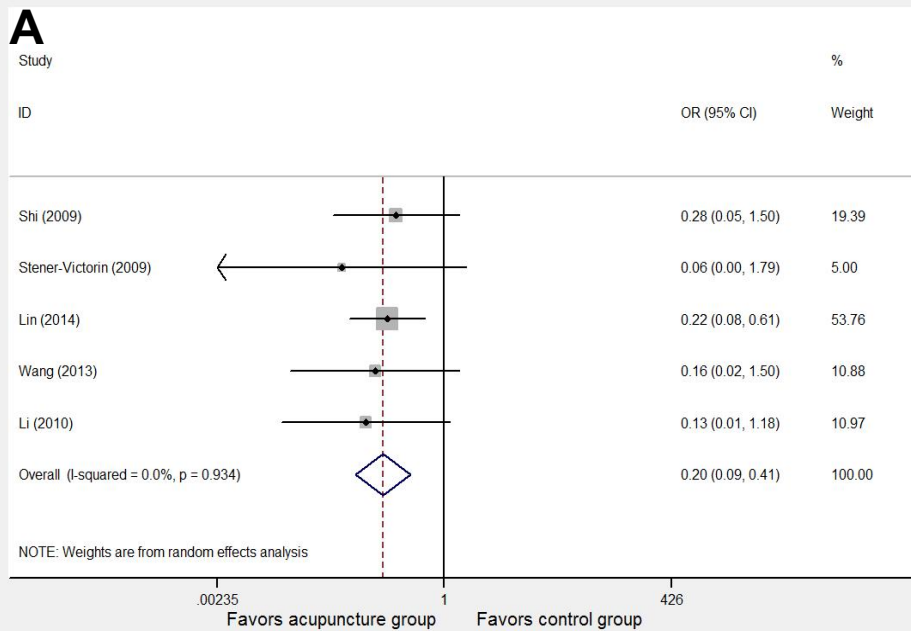


Figure 3. Meta-analysis of the studies evaluating the effects of acupuncture on the serum luteinizing hormone (A), follicle stimulating hormone (B) and the ratio of the serum luteinizing hormone levels to serum follicle stimulating hormone levels (C) of the women with polycystic ovary syndrome.

SMD, standardized mean difference; CI, confidence interval.

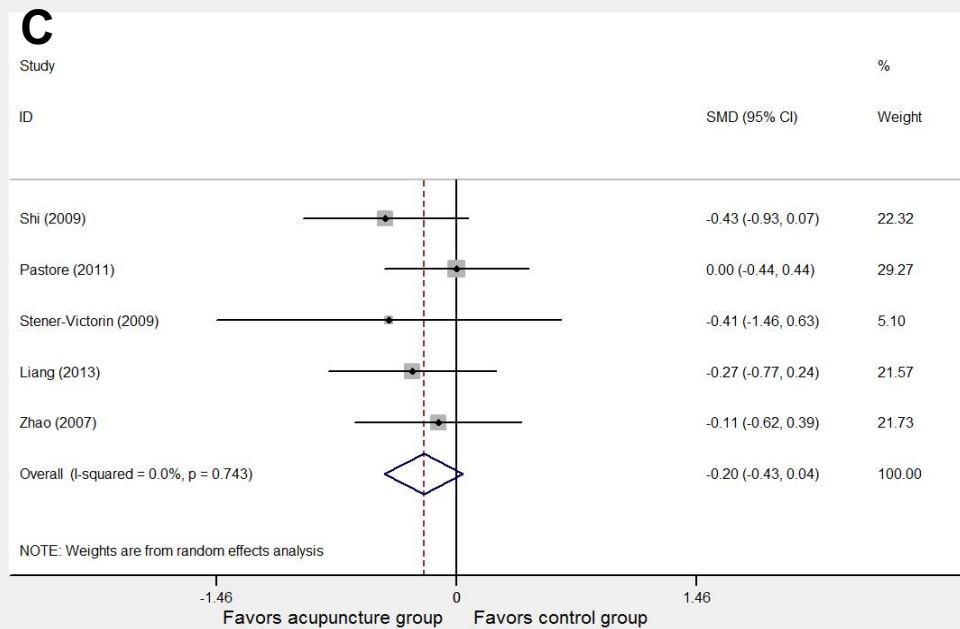
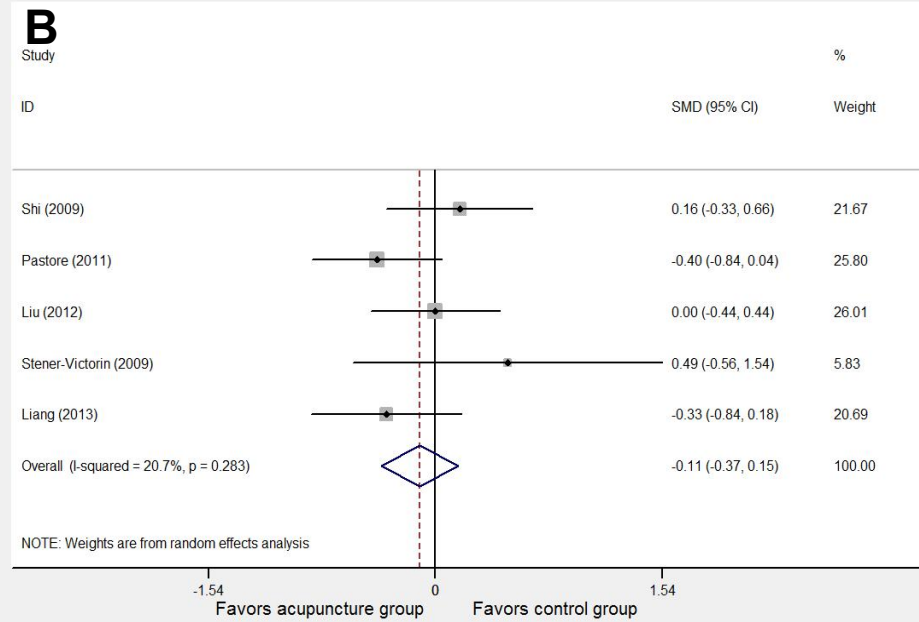
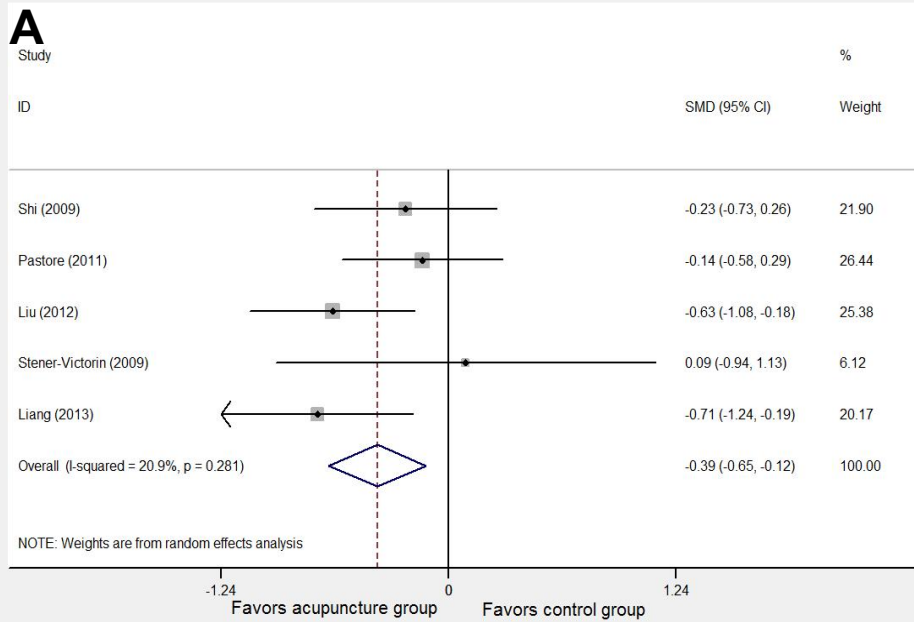


Table 1. Quality evaluation of the studies

Study	Description of information of ethical approval	Randomization Method	Single-/Multi-centre	Concealment of allocation	Placebo Intervention	Blinding	Comparability at baseline	Sample size calculation	Acupuncture practitioner	Description of adverse effects	Follow-up	Adherence to STRICTA
Shi et al. [14]	Yes	A random number table	Single	ND	No	No	Yes	ND	ND	No	No	No
Stener-Victorin et al. [13]	Yes	Computerized randomization	Single	Adequate	No	Yes	Yes	ND	Acupuncturist	No	No	Yes
Pastore et al.; Franasiak et al. [10, 11]	Yes	A random number generator program.	Single	Adequate	Yes	Yes	Yes	Yes	Acupuncturist	No	Yes	Yes
Liu et al. [15]	No	ND	Single	ND	No	No	ND	ND	ND	No	No	No
Liang et al. [16, 17]	Yes	ND	Single	ND	No	No	Yes	ND	ND	No	No	No
Lin et al. [18]	No	ND	Single	ND	No	No	Yes	ND	ND	No	No	No
Zhao et al. [19]	No	ND	Single	ND	No	No	ND	ND	ND	No	No	No
Wang et al. [9]	No	Sequence of recruitment	Single	ND	No	No	Yes	ND	ND	No	No	No
Li et al. [12]	No	Sequence of recruitment	Single	ND	No	No	Yes	ND	ND	No	No	No

Note: STRICTA: stands for the standards for reporting interventions in clinical trials of acupuncture; ND: not described

Table 2. Summary of the studies

Study	Participants	Country	Intervention	Control	Outcomes
Shi et al. [14]	63 women with PCOS	China	Acupuncture+ CMH	CMH	MF, FSH, LH, T
Stener-Victorin et al. [13]	15 women with PCOS without known endocrine or neoplastic causes of hyperandrogenemia	Sweden	Low-frequency EA	No intervention	Muscle sympathetic nerve activity, MF, Anthropometrics, hemodynamics, hormones, insulin sensitivity, blood lipids
Pastore et al.; Franasiak et al. [10, 11]	84 women with PCOS aged 18-43 years without hormonal intervention 60 days before enrollment.	U.S.A.	EA	Sham acupuncture with the validated Park sham device	LH, FSH, OR, longitudinal AMH
Liu et al. [15]	80 women with PCOS	China	Acupuncture+ ECAT	ECAT	FSH, LH, T, E2, PRL, BMI, FINS, FPG
Liang et al. [16, 17]	60 infertile women with PCOS	China	Acupuncture+ Gn	Gn	Mature follicle, FSH, LH, T, PRL, P, E2
Lin et al. [18]	84 women with PCOS	China	Acupuncture+ ECAT	ECAT	MF, ovarian volume, sex hormone levels
Zhao et al. [19]	60 obese women with PCOS without hormonal intervention 90 days before enrollment.	China	Acupuncture+ Metformin	Metformin	BMI, WHR, MF, LH/FSH, T, FINS, FPG, HOMA-IR, TC, HDL-C, LDL-C
Wang et al. [9]	40 women with PCOS without hormonal intervention 180 days before enrollment.	China	Acupuncture+ CMH	CMH	MF, CPR, BBT
Li et al. [12]	45 women with PCOS	China	Acupuncture+ CMH	CMH	MF(+), BBT, ovulation, hormones

Note: PCOS: polycystic ovary syndrome; CMH: Chinese medicinal herbs; MF: menstrual frequency; FSH: follicle stimulating hormone; LH: luteinizing hormone; T: testosterone; EA: electro-acupuncture; OR: ovulation rate; AMH: anti-müllerian hormone; ECAT: ethinylestradiol and cyproterone acetate tablets; E2: estradiol; PRL: prolactin; BMI: body mass index; FINS: fasting insulin; FPG: fasting plasma glucose; Gn: gonadotropin; P: progesterone; WHR: waist-hip ratio; HOMA-IR: homeostasis model assessment for insulin resistance; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CPR: clinical pregnancy rate; BBT: basal body temperature.