Effectiveness of acupuncture in polycystic ovary syndrome
A systematic review and meta-analysis of randomized controlled trials
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Abstract
Objective: To evaluate the effectiveness of acupuncture in reproductive-age females with polycystic ovary syndrome (PCOS).

Methods: We searched the PubMed, Web of Science, Embase, Cochrane, China National Knowledge Infrastructure (CNKI), Wanfang Data, and Chongqing VIP databases for the relevant literature. The meta-analysis was performed with a random-effects model with RevMan 5.3. The primary outcomes of interest included the rate of live birth, pregnancy and ovulation, and the secondary outcomes included the recovery of menstrual period and hormone levels. Results were expressed as the relative risk (RR) for the discrete data and the mean difference (MD) for the continuous outcomes with a 95% confidence interval (CI).

Results: Twenty-two studies with 2315 participants were included in this systematic review and meta-analysis. A pooled analysis showed a recovery of the menstrual period (5 trials; 364 participants; SMD, 0.52; 95% CI [−0.89, −0.14]; I² = 67%; P = 0.0007; low certainty) in the acupuncture group. Furthermore, there were significant decreases in the luteinizing hormone (LH) (13 trials; 917 participants; MD, −0.92; 95% CI [−1.43, −0.41]; I² = 60%; P = 0.0004; very low certainty) and testosterone (13 trials; 923 participants; SMD, −0.46; 95% CI [−0.73, −0.20]; I² = 75%; P = 0.0006; very low certainty) in the acupuncture group. No significant differences were observed in the rates of live birth, pregnancy, and ovulation, and no significant differences were observed in the LH/follicle-stimulating hormone (FSH) ratio.

Conclusions: There was insufficient evidence to support that acupuncture could promote live birth, pregnancy, and ovulation. However, acupuncture could promote the recovery of menstrual cycles as well as downregulate the levels of LH and testosterone in patients with PCOS.

Study registration: PROSPERO CRD42019128574.

Abbreviations: CC = clomiphene citrate, CI = confidence interval, CNKI = China National Knowledge Infrastructure, FSH = follicle-stimulating hormone, GnRH = gonadotropin-releasing hormone, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, HCG = human chorionic gonadotropin, ICSI = intracytoplasmic sperm injection, IVF = in-vitro fertilization, LE = letrozole, LH = luteinizing hormone, LUFS = luteinized unruptured follicle syndrome, MD = mean difference, OCPs = oral contraceptive pills, PCOS = polycystic ovary syndrome, Revman = Review Manager software, RR = relative risk, SMD = standardized mean difference.

Keywords: acupuncture, LH, menstrual frequency, ovulation, polycystic ovary syndrome, testosterone
1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine and metabolic disorder among reproductive-age women. The worldwide prevalence of PCOS ranges from 6% to 21%, while it ranges from 5.6% to 11.2% in China.[1] Excessive androgen with clinical or biochemical manifestations, oligo-ovulation or anovulation, and polycystic ovaries on ultrasound are the main features of PCOS. Up to 90% of the women with anovulation infertility have PCOS.[2] An increased gonadotropin-releasing hormone (GnRH) pulse frequency has been observed in patients with PCOS. This neuroendocrine abnormality causes the hypersecretion of luteinizing hormone (LH) as compared to the follicle-stimulating hormone (FSH), thereby increasing the circulating LH/FSH ratio.[3] High LH levels can disturb normal follicular growth and may lead to the premature luteinization of granulosa cells, thereby impairing normal follicular development. Moreover, the excessive stimulation of LH enhances androgen hypersecretion in theca cells, further disturbing the follicular maturation.[3] Thus, the reduction of LH and androgens is essential for the treatment of infertility due to PCOS. Oral contraceptive pills (OCPs) have been widely used as first-line therapies for the treatment of anti-androgens and for decreasing LH in patients with PCOS, particularly women who are not seeking fertility. For fertility treatment, letrozole (LE) is the first line of pharmacological therapy for PCOS to restore ovulation.[4] Clomiphene citrate (CC) could also be used to induce ovulation. Metformin also improves fertility outcomes when combined with other medications such as CC.[5] Gonadotrophins are often used as second-line pharmacological agents after the failure of the first-line oral ovulation induction therapy.[4] However, these treatments have some drawbacks, such as a considerable time commitment before pregnancy and increase the risk of multifetal pregnancies. Therefore, new therapies are urgently needed to improve reproductive outcomes.

Over the years, acupuncture has become increasingly popular worldwide for its convenience and low incidence of adverse effects.[5] This non-invasive technique has been widely applied for pain relief and for the treatment of neurological disorders, digestive disorders, and other diseases.[6] Several studies have reported that acupuncture may have a positive impact on ovulation and fertility.[3] However, the design of these studies is considerably different, and it is difficult to obtain conclusive results. Recently, Lim and his colleagues[9] performed a systematic review to investigate the overall effects of acupuncture this July, yet the quality of the evidence is low and only focused on the clinical symptoms, such as live birth, pregnancy, ovulation, and menstrual period. Hence, we think that it is necessary to conduct a new systematic review and meta-analysis to look into the effect of acupuncture on PCOS women of childbearing age, not only from the perspectives of live birth, ovulation rate, pregnancy rate, and menstrual period but also by using the related hormone profiles, which include LH levels, LH/FSH ratio, and testosterone levels. Thus, we hope to provide more accurate evidence-based estimates for the application of acupuncture in cases of PCOS.

2. Methods and materials

We followed the PRISMA reporting guidelines[10] to design and report this systematic review and meta-analysis. This study addresses women with PCOS (P) and compares acupuncture therapy (I) with sham-acupuncture or non-acupuncture treatment (C), and infertility-related outcomes and hormone changes (O). The protocol was registered in PROSPERO Centre for Reviews and Dissemination (CRD42019128574).

2.1. Strategy

Studies were searched in the Pubmed, Web of Science, Embase, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure (CNKI), Wanfang Data, and Chongqing VIP databases without any language restriction from inception to March 2019. The search strategies used a combination of the terms “polycystic ovary syndrome,” “PCOS,” “acupuncture,” and “electroacupuncture.” The detailed search strategies are provided in the supplemental material (Appendix 1, http://links.lww.com/MD/E301).

2.2. Selection criteria and study selection

PCOS was diagnosed according to the Rotterdam criteria. We studied the effects of acupuncture on fertilization-related outcomes. The control groups included sham-acupuncture, CC, LE, metformin, Dainese-35, Chinese medicine, and no treatment. Studies on the combined effects of acupuncture and the other treatments were not included in this study. Only published RCTs were included in this meta-analysis. More detailed selection criteria are given in the appendix (Appendix 2, http://links.lww.com/MD/E301). The results of the studies were screened according to the eligibility criteria. The primary selection was performed on the basis of the title and the abstract by 2 independent reviewers. Any disagreement was resolved by the third reviewer. All of the selected studies were processed for further review.

2.3. Outcomes of interests

Based on the recommendations from the International PCOS Network,[11] live birth, and pregnancy are proper indexes for women seeking fertility, while ovulation is a preferable index for women seeking symptom control. Therefore, we used the live birth rate, ovulation rate, and pregnancy rate as the primary outcomes of interests. The secondary outcomes included the menstrual frequency, LH/FSH ratio, and LH and testosterone levels. Live birth was defined as the delivery of a live-born infant (more than 20 weeks’ gestation). Pregnancy was confirmed by ultrasonography or the elevated human chorionic gonadotropin (HCG) level, while ovulation was confirmed by ultrasonography or elevated serum progesterone level. The level of hormones (LH, FSH, and testosterone) was detected during the menstrual period or withdraw bleeding period.

2.4. Data extraction

Data were extracted from full-text articles by using a pre-designed form, in which the characteristics of the participants, interventions, comparisons, and the main outcomes were included. Two independent reviewers judged the study eligibility and assessed the study quality. Discrepancies were discussed, and decisions were made by consensus.

2.5. Assessment of risk of bias

The risk of bias of the studies was evaluated following the guidance provided in the Cochrane Handbook for Systematic
Reviews of Interventions.\textsuperscript{11} All of the studies were critically evaluated by 2 independent reviewers. Any disagreements were resolved via discussion. More detailed assessments are provided in the appendix (Appendix 3, http://links.lww.com/MD/E301).

2.6. Statistical analysis
A meta-analysis was performed by using the Review Manager software (Revman), version 5.3, with the random-effects model. The relative risk (RR) was used for the discrete data. The mean difference (MD) was used for the continuous data if the included studies used the same measurement scales; otherwise, the standardized mean difference (SMD) was used. All of the outcomes were calculated with 95\% confidence intervals (CIs). A subgroup analysis was conducted on the basis of the type of control. The FSH and LH levels showed as IU/L, multiple unit used in testosterone levels, including ng/dl, μg/l, nmol/l and ng/ml. The ovulation outcome was reported as times per cycle. The menstrual frequency was reported as days or months per cycle. We evaluated the heterogeneity between studies by using Cochran’s Q statistic with the associated $P$ value. The degree of heterogeneity was quantified by measuring $I^2$. $I^2 < 50\%$ and $P > .1$ indicated that all of the studies were homogeneous; $I^2 > 75\%$ suggested the heterogeneity was high; $I^2$ between 50\% and 75\% suggested the heterogeneity was moderate.\textsuperscript{12} We explored the source of heterogeneity by conducting a subgroup analysis or a sensitivity analysis. The statistical significance was set as $P < .05$.

2.7. Quality of evidence
The quality of evidence of the outcomes was evaluated according to GRADE (Grading of Recommendations Assessment, Development, and Evaluation).\textsuperscript{13}

3. Results
3.1. Study selection
A flow chart of the study selection is shown in Figure 1. In all, 927 records were retrieved in the initial search, and 630 records remained after the removal of duplicates. Furthermore,
491 records were excluded after screening titles or abstracts. The remaining 139 papers were selected for the full-text review. Finally, 22 studies were included in this systematic review and meta-analysis.

3.2. Characteristics of included studies

The characteristics of the included studies are presented in Table 1. Of these 22 studies, 19 trials were performed in China. Among the 19 trials, 17 were published in Chinese and the other 2 in English. Two studies originated from Sweden and 1 from the USA. Seven papers were master’s theses and 1 was a doctorate thesis and the other 14 studies were peer-review papers. The sample size ranged from 28 to 926 with a total of 2315 participants. The duration of therapy varied from 8 weeks to 6 months. The baseline characteristics among the groups were compared in all of the studies.

3.3. Validity of included studies

As shown in Figure S1, the risk of bias was evaluated in all of the studies. The risk of bias in most of the studies was either unclear or high. This was mainly attributed to the lack of performing or mention of blinding in the process of randomization and allocation. A summary of evidence is provided in the GRADE Certainty of evidence profiles (Table S1).

3.4. Outcomes

We reported the outcomes according to the type of control group: acupuncture vs sham-acupuncture, acupuncture vs non-treatment, acupuncture vs medication, acupuncture vs Chinese medicine, acupuncture with medication vs medication, and acupuncture with Chinese medicine vs Chinese medicine.

3.5. Acupuncture vs sham-acupuncture

There were 5 studies with a total of 1182 participants in this group (Fig. 2). Among these 5 studies, 1 study reported the live birth rate and the testosterone level, 2 studies reported the ovulation rate, LH level, and LH/FSH ratio, and 3 studies reported the pregnancy rate. Only Kong reported the testosterone level and showed a significant between the groups (MD = −12.15, 95% CI [−21.69, −2.61], P = .01, Fig. 2F). The differences were insignificant in the other outcomes (Fig. 2A-E).

3.6. Acupuncture vs non-treatment

There was only 1 study with 40 participants in this group, and it focused on the menstrual frequency. The analysis showed an improvement in the menstrual frequency of the acupuncture group (MD = −4.70; 95% CI [−21.69, −2.61]; P < .00001; Fig. 3).

3.7. Acupuncture vs medication

There were 8 studies with a total of 591 participants in this group. No study reported the live birth rate. Only 1 study reported the ovulation and pregnancy rates. Three studies reported the menstrual frequency, 7 studies reported the LH levels, and 5 studies reported the LH/FSH ratio. All of the studies reported the testosterone levels. The pooled analysis showed an improvement in the menstrual frequency in the acupuncture plus medication group (MD = −0.28; 95% CI [−0.53, −0.02]; I² = 0%; P = .03; Fig. 4C). There was a significant decrease in the circulating LH in the acupuncture group (MD = −0.85; 95% CI [−1.59, −0.10]; I² = 64%; P = .03; Fig. 4D). We also conducted a subgroup analysis based on the type of control. The pooled analysis comparing acupuncture with CC showed a decrease in LH levels (MD = −2.03; 95% CI [−2.86, −1.25]; I² = 0%; P = .00001; Fig. 4D). The subgroup analysis also showed a downregulation of testosterone (SMD = −0.32; 95% CI [−0.60, −0.04]; I² = 10%; P = .03; Fig. 4F). No significant difference was observed in the other outcomes (Fig. 4A-4B, 4E).

3.8. Acupuncture with medication vs medication

Seven studies with 436 participants were included in this group. No study reported the live birth rate. Three studies reported the ovulation rate and the LH/FSH ratio. Two studies reported the pregnancy rate. One study reported the menstrual frequency, and 4 studies reported the LH and testosterone levels. The ovulation rate was presented with times per cycle, what is, the value is higher, the ovulation occurrence more. The pooled results showed that acupuncture combined with medication improved the ovulation compared to medication alone (RR = 1.19; 95% CI [1.07, 1.32]; I² = 22%; P = .001; Fig. 5A). The pooled results showed a significant downregulation in LH levels in the acupuncture plus medication group (MD = −1.13; 95% CI [−2.13, −0.12]; I² = 77%; P = .03; Fig. 5D). The subgroup analysis also revealed that acupuncture combined with Chinese medicine improved the LH results compared to Chinese medicine alone (RR = −1.49; 95% CI [−2.61, −0.38]; I² = 65%; P = .008; Fig. 5D). An decrease in testosterone was found (SMD = −0.87; 95% CI [−1.26, −0.49]; I² = 61%; P = .00001; Fig. 5F). However, the heterogeneity was high and could not be solved after we conducted the subgroup analysis based on the type of control. Moreover, there was an improvement in the menstrual frequency in the acupuncture with Chinese medicine group compared with the Chinese medicine alone group (MD = −3.60; 95% CI [−16.69, −0.51]; P = .02; Fig. 5C). No significant results were observed in the other outcomes (Fig. 5B and E).

3.9. Overall analysis

We also conducted an overall analysis of all of the outcomes. The differences were significant in the ovulation rate (RR = 1.11; 95% CI [1.00, 1.24]; I² = 65%; P = .05; Fig. S2A, http://links.lww.com/MED/324) (GRADE Certainty of evidence: very low), menstrual frequency (SMD, −0.52; 95% CI [−0.89, −0.14]; I² = 67%; P = .007; Fig. S2B, http://links.lww.com/MED/324) (GRADE Certainty of evidence: low), LH levels (MD, −0.92; 95% CI [−1.43, −0.41]; I² = 60%; P = .0004; Fig. S2C, http://links.lww. com/MED/324) (GRADE Certainty of evidence: very low), and testosterone levels (SMD, −0.46; 95% CI [−0.73, −0.20]; I² = 75%; P = .0006; Fig. S2D, http://links.lww.com/MED/324) (GRADE Certainty of evidence: very low). No significant results were observed in the other outcomes.

4. Discussion

4.1. Summary of main findings

This review aimed to summarize and evaluate the effect of acupuncture therapy on the live birth rate, ovulation rate,
Table 1
Characteristics of the included studies.

| Author, year | Province/country | Acup | Ctrl | Acup | Ctrl | acupuncture type | comparison | acu-session | main outcomes |
|-------------|-----------------|------|------|------|------|-----------------|------------|-------------|---------------|
| Jedel, 2011 | Sweden          | 21   | 19   | 29.7±4.3 | 30.2±4.7 | EA               | physical exercise | 1/week for 2 weeks, 1/week for 6 weeks, and 1/2 weeks for 8 weeks, for a total of 14 treatments over 16 weeks. | T, LH, FSH, LH/FSH ratio, menstrual frequency. |
| Johansson, 2013 | Sweden         | 16   | 12   | 28.4±3.1 | 27.9±3.2 | MA + EA          | attention control | 2/week for 10–13 weeks | T, LH, FSH, LH/FSH ratio, ovulation rate, menstrual frequency, LH, FSH, LH/FSH ratio |
| Pastore, 2011 | USA            | 38   | 43   | 28.0±6.3 | 26.5±5.8 | EA               | sham-acup | 2/week for the first 4 weeks followed by 1/week for an additional 4 weeks | LH, FSH, LH/FSH ratio |
| Kong, 2015   | China          | 29   | 26   | 28.14±3.78 | 27.88±3.42 | MA + EA          | sham acup | 2–3/week for a total of 32 times | FSH, LH, LH/FSH ratio, T, lipid profiles, FINS, LH, LH/FSH ratio, T, pregnancy rate |
| Hu, 2016     | China          | 38   | 38   | 28.05±3.84 | 27.34±3.49 | EA               | sham acup | 1/2–3 day, at least 2/week, 32 times at maximum | menstrual, BBT, ovulation |
| Du, 2011     | China          | 30   | 30   | 28.63±3.30 | 28.33±2.95 | aA               | CC         | 1/day for first 3 days, then every other day, 30 days for a course, 3 courses in total | menstrual cycle, ovulation rate, pregnancy rate, LH, LH/FSH ratio |
| Zhuo, 2016   | China          | 50   | 50   | 29±5     | 28±5     | MA               | CC         | 1/2–3 days, when D > 18 mm, change into every day for 3 menstrual cycles | LH, LH/FSH ratio, pregnancy rate, FSH, LH, LH/FSH ratio, T, ovulation |
| Fang, 2016   | China          | 30   | 30   | 29.97±4.44 | 29.37±4.50 | EA               | CC         | 1/day for 3 consecutive days, then 1/2 days for 3 times for each menstrual cycle, 3 cycles in total | menstrual frequency, FSH, LH, LH/FSH ratio, FINS |
| Zheng, 2013  | China          | 43   | 43   | 26.5±3.0  | 2.9±4.9   | aA               | meflofin    | 2/week for 6 months, 30 min each time | LH, FSH, LH/FSH ratio, T, FINS |
| Yao, 2018    | China          | 48   | 48   | 27.5±4.8  | 26.7±4.5  | MA + EA          | Meflofin    | 3/week, for 6 months. | LH, FSH, LH/FSH ratio, FSH, LH, LH/FSH ratio, T, BMI |
| Jin, 2014    | China          | 33   | 33   | 29.4     | 27.5     | EA               | Diane-35   | 3/week, for 3 months, 40 times in total | LH, FSH, LH/FSH ratio, T, ovulation |
| Jin, 2016    | China          | 35   | 33   | 28.61±1.72 | 27.9±3.76 | MA + EA          | Diane-35   | 3/week, for 3 months. | LH, FSH, LH/FSH ratio, T, ovulation |
| Yang, 2017   | China          | 29   | 29   | 27±5     | 27±3     | EA               | Diane-35   | 3/week, for 3 months. | LH, FSH, LH/FSH ratio, T, ovulation |
| Gu, 2014     | China          | 43   | 29   | 29±7     | 27±3     | EA               | EA         | 1/2 days for 3 menstrual cycles, 3 days in total | LH, FSH, LH/FSH ratio, T, ovulation |
| Wu, 2017     | Multiple center, China | 458 | 458 | 30±4 | 29±5 | EA + CC | CC | 2/week from D3, 32 times in total | LH, FSH, LH/FSH ratio, T, ovulation |
| Yu, 2018     | China          | 38   | 37   | 30±4     | 29±5     | EA + CC          | CC         | 2/week from D3, 32 times at maximum | LH, FSH, LH/FSH ratio, T, ovulation |
| Ma, 2016     | China          | 29±30 | 28   | 23±2±2.4±3 | 25±4   | MA + CC/MA       | CC         | 3/week, for 3 months. | LH, FSH, LH/FSH ratio, T, ovulation |
| Huang, 2018  | China          | 33   | 32   | 26.97±2.80 | 25.50±3.00 | EA + CC        | CC         | 1/2 days (3 times/week) from D5, 36 times in total | LH, FSH, LH/FSH ratio, T, ovulation |
| Yao, 2017    | China          | 19   | 19   | 24.1±1.72 | 26.0±4.1  | EA + Chinese medicine | Chinese medicine | 1/2 days from D5, for 3 menstrual cycles | LH, FSH, LH/FSH ratio, T, ovulation |
| Zhao, 2018   | China          | 32   | 33   | 27.94±3.52 | 27.18±4.25 | MA + Chinese medicine | Chinese medicine | 2–3/week for 3 menstrual cycles | LH, FSH, LH/FSH ratio, T, ovulation |
| Pang, 2018   | China          | 27   | 29   | 28.9±4.9  | 28.4±4.7  | MA + Chinese medicine | Chinese medicine | 1–2/week for 3 months | LH, FSH, LH/FSH ratio, T, ovulation |
| Yin, 2018    | China          | 40   | 40   | 26±3     | 26±4     | EA + Chinese medicine | Chinese medicine | 1/2 days for 3 or 6 months | LH, FSH, LH/FSH ratio, T, ovulation |

‡ Gu 2014 and Wu 2017 had 2 acupuncture arms and 2 sham-acupuncture arms with or without CC or placebo CC respectively, we combined 2 acupuncture arms and 2 sham-acupuncture together. 
§ Ma 2016 had 3 arms, acupuncture with CC, acupuncture alone and CC alone and we compared CC alone with the other 2 arms respectively.
¶ Yao 2017: 2 Hz electro-acupuncture with CM and CM group were included.
= Inter = intervention, Acup = acupuncture, Ctrl = control, EA = electro-acupuncture, D = day, d = diameter, T = testosterone, LH = luteinizing hormone, FSH = follicle stimulating hormone, CM = Chinese medicine, MA = manual acupuncture, FINS = fasting insulin, aA = abdominal acupuncture, CC = clomiphene citrate, LE = letrozole, BBT = basal body temperature, BMI = body mass index, E2 = estradiol, AMH = anti-müllerian hormone.
pregnancy rate, menstrual cycles, and hormonal changes in PCOS women. Overall, we found that acupuncture had no significant effect on the live birth rate, ovulation rate, pregnancy rate, and LH/FSH ratio. Instead, acupuncture was closely associated with the downregulation of LH and testosterone levels as well as the recovery of menstrual periods. Because of the high risk of bias in most studies, our confidence in these findings was limited. The sensitivity analysis showed that the pooled results were not excessively impacted by any single trial (Table S2, http://links.lww.com/MD/E325).

4.2. Applicability of current evidence

The included studies poorly addressed live birth. Only 1 study reported the live birth rate. In this study, the researchers compared acupuncture with sham-acupuncture and found no
Figure 4. Forest plots of meta-analysis outcomes between acupuncture and medication. (A) ovulation; (B) pregnancy; (C) menstrual frequency; (D) LH levels; (E) LH/FSH ratio; (F) testosterone. LH, luteinizing hormone; FSH, follicle-stimulating hormone; CC, clomiphene; met, metformin; Std, standardized; CI = confidence interval. Test for heterogeneity, Chi-Squared statistic with its degrees of freedom (d.f.) and $P$ value; $I^2$, inconsistency among results; test for overall effect, Z statistic with $P$ value.
Figure 5. Forest plots of meta-analysis outcomes between acupuncture with medication and medication alone. (A) ovulation; (B) pregnancy; (C) menstrual frequency; (D) LH levels; (E) LH/FSH ratio; (F) testosterone. LH = luteinizing hormone, FSH = follicle-stimulating hormone, CC = clomiphene, met = metformin; CM = Chinese medication, Std = standardized, CI = confidence interval. Test for heterogeneity, Cha-Squared statistic with its degrees of freedom (d.f.) and P value; I², inconsistency among results; test for overall effect, Z statistic with P value.
significant changes. The results of the ovulation rate, pregnancy rate, and menstrual period were reported in a few studies. We found that acupuncture significantly improved menstrual recovery, yet the differences in the ovulation and pregnancy rates were insignificant.

Caution should be exercised when interpreting these findings. First, the definition of ovulation or pregnancy was not the same across the studies. In some studies, ovulation was defined as elevated progesterone. Luteinized unruptured follicle syndrome (LUFS), a syndrome featured with unruptured follicles and no release of the oocyte, exhibits the normal production of progesterone and the duration of the luteal phase of the cycle. Therefore, only the use of elevated progesterone as an indicator of ovulation may cause a bias in the assessment of the ovulation rate, the more reliable way should be through the ultrasound. A similar situation was observed in the pregnancy evaluation. One study defined pregnancy on the basis of the elevated HCG, which may include biochemical pregnancy or ectopic gestation and is misleading. To avoid the bias caused by definitions, consistent and well-defined measures of the outcomes should be applied in future trials.

Acupuncture seemed to have an impact on menstrual cycles. However, the heterogeneity was high. Two possible resources could contribute to the high heterogeneity. One is the variety of control groups, such as exercise, CC, diane-35, and Chinese medicine. The other is acupuncture itself. Among these studies, different acupuncture strategies with different acupuncture sessions, acupoints, and expertise were used. Both Pastore and Kong compared acupuncture and sham-acupuncture but with different acupuncture sessions. Pastores group performed acupuncture twice a week for the first 4 weeks and then switched to once a week for another 4 weeks, while Kongs group performed acupuncture 2 to 3 times a week for a total of 32 times. Other factors such as the acupoint and acupunctural expertise also influenced the outcomes. Moreover, we found that acupuncture could affect the LH and testosterone levels despite the high heterogeneity of the study. The neuroendocrine mechanism of acupuncture has been widely studied in reproductive medicine. Studies have shown that acupuncture can reduce cortisol concentrations and regulate the generation and secretion of β-endorphin, thereby affecting the release of GnRH in the hypothalamus and the secretion of pituitary gonadotropin, eventually influencing the menstrual cycles and decreasing ovarian androgen in women with PCOS. With respect to the hormone profiles, the heterogeneity of the study was high and the PCOS phenotype might be the cause, as different clinical and endocrine features were observed in different phenotypes.

4.3. Strengths and limitations of this study

Although several systematic reviews and meta-analyses have been published on this topic, there are no consistent results. Ma showed an improvement in the ovulation rate, but Jo and Lim reported opposite results. Jo showed an increase in the pregnancy rate, but Lim found no significant change. This might be attributed to the differences in search strategies (including research and data extraction). Moreover, there were some limitations in previous studies. Ma only focused on the testosterone level and the ovulation rate. Qu evaluated the menstrual cycles and hormonal changes. Lim only studied the menstrual cycle, ovulation rate, and pregnancy rate; Jo obtained more results but lacked the latest research. As we targeted both PCOS women seeking fertility and symptom control, we conducted this meta-analysis by including more recent research and more comprehensive results in an attempt to assess the efficacy of acupuncture on PCOS.

Our study also has some limitations. Above all, we used the GRADE method to assess the certainty of evidence. However, because of the methodological limitations of the included studies, the quality of most of the evidence ranged from low to very low. Of the 22 studies, only 7 studies described allocation concealment, while 4 studies described the blinding strategy. The absence of proper blinding and allocation might have led to a selection and performance bias. Only a few studies used a double-blind or single-blind design because of the difficulty of establishing an applicable control in acupuncture research. Moreover, 19 trials were conducted in China, where many patients are more inclined to undergo acupuncture. The placebo effect of acupuncture might have been strengthened and have led to a performance bias in these studies. Meanwhile, in the included trials, the sample size of most of the trials ranged from 30 to 100, except for 1 trial wherein the sample size was greater than 500. This study heavily weighted the analysis, and this might have caused a bias. Moreover, 7 studies which are Master’s and doctorate theses were included in our analysis, considering the potential bias from these low-quality studies, we also conduct sensitivity analysis by omitting these studies, the results were same after the excluding, indicating the robustness of our results. However, due to the limitation, caution should be exercised while interpreting these results.

4.4. Implications for practice and research

Considering the benefits of acupuncture as demonstrated in this study, acupuncture may be an alternative or a good adjunctive therapy for PCOS, particularly for patients with menstrual disorders who do not require pregnancy. For PCOS patients who require pregnancy, acupuncture can also be used as a pretreatment to regulate the menstrual cycles and normalize LH levels before the in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatment.

According to our systematic review and meta-analysis, acupuncture has no effect on the live birth rate, ovulation rate, and pregnancy rate but can decrease the LH and testosterone levels and promote the recovery of menstrual cycles in patients with PCOS. Still, clinical trials with a larger scale and better design are needed to clarify the effects of acupuncture on PCOS.

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Author contributions

J.L. W conceived the systematic review; J.L. W and D. C. performed literature searches, study selection, data extraction, risk of bias assessment, meta-analysis and wrote the initial draft; all of the authors critically revised the manuscript.

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