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Wen Pan

Shanghai University of Traditional Chinese Medicine

Feng-xing Li

Shanghai University of Traditional Chinese Medicine

Qiao Wang

Shanghai University of Traditional Chinese Medicine

Xiu-qi Yin

Shanghai University of Traditional Chinese Medicine School of Nursing

Zou-qin Huang

Shanghai Pudong New Area Hospital of Traditional Chinese Medicine

Yu-ming Yan

Shanghai University of Traditional Chinese Medicine

Ling Zhao (✉ zl2@shutcm.edu.cn)

Shanghai University of Traditional Chinese Medicine <https://orcid.org/0000-0002-4017-8167>

Xue-yong Shen

Shanghai University of Traditional Chinese Medicine

Research

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A Randomized Sham-controlled Trial of Manual Acupuncture for Infertile Women with Polycystic Ovary Syndrome

Wen Pan^{1#}, Feng-xing Li^{1#}, Qiao Wang¹, Xiu-qi Yin², Zou-qin Huang³, Yu-ming Yan¹, Ling Zhao^{1*}, Xue-yong Shen^{1,2 *}

1. Acupuncture-moxibustion & Tuina School, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China

2. Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China

3. Shanghai Pudong New District Hospital of Traditional Chinese Medicine, Shanghai 201203, China

[#] These authors contributed equally to this study and should be considered as co-first authors

* Corresponding authors: Ling Zhao: zl2@shutcm.edu.cn, Xue-yong Shen:

sxy1@shutcm.edu.cn

Abstract

Background: To evaluate the effectiveness of acupuncture combined with herbal medicine among the infertile female with polycystic ovary syndrome (PCOS).

Method: A randomized, sham-controlled trial was conducted. A total of 86 women who were diagnosed as PCOS infertility for more than 1 year were randomly assigned to receive manual acupuncture (MA) or sham acupuncture (SA) twice per week for three menstrual cycles. Both groups received herbal medicine treatment. The evaluations were conducted at baseline, each menstruation, after three menstrual cycles and 24 weeks follow-up, including pregnancy rate, ovulation rate, sex hormones level, PCOS symptoms and Traditional Chinese Medicine (TCM) syndrome scores.

Results: Among 86 randomized patients, 79 (91.86%) completed the trial. The pregnancy rate in the MA group was significantly higher than the SA group (46.34% vs 18.42%; $P=0.008$). The ovulation rate of the MA group was higher than the SA group (58.14% vs 45.74%; $P=0.046$). The improvement rate of PCOS score and testosterone level showed a statistical difference between the two groups ($P<0.05$), others were no significant difference between the two groups. PCOS score and TCM symptom score of the two groups were both decreased after treatment ($P<0.001$). Sex hormones level including E2, T, P, LH and LH/FSH were significantly lower after intervention in the MA group (P values were <0.05) compared with baseline, while only the progesterone level was reduced in the SA group ($P=0.008$).

Conclusion: Manual acupuncture combined with herbal medicine may be clinically useful for infertile women with PCOS in improving pregnancy and ovulation rate.

Trial Registration: Chinese Clinical Trial Registry, [ChiCTR1800014997](https://www.clinicaltrials.gov/ct2/show/study?term=ChiCTR1800014997).

Keywords

Polycystic Ovary Syndrome; Manual Acupuncture; Chinese Herbal Medicine; Infertility

1. Background

Polycystic ovary syndrome (PCOS) is a complex polygenic disease and is one of the most common endocrinological and reproductive disorders,[1, 2] threatening 10% of women of child-bearing age.[3] It is characterized by biochemical hyperandrogenism, chronic

anovulation and the presence of polycystic ovaries,[4] which cause more than 75% of an ovulatory infertility.[5] PCOS syndromes including obesity, impaired glucose tolerance, excessive body hair, acne, menstrual cycle disturbances, infertility and imbalance of hormones.[6] PCOS is complicated by depression, anxiety, et al, and posing a health hazard to women of childbearing age.[7, 8]

Clomiphene citrate (CC) has been used as the first-line treatment for an ovulatory infertility in women with PCOS, metformin and letrozole are also widely prescribed.[9, 10] Cumulative ovulation rates of CC are as high as 90%, with pregnancy rate is 50~70%.[11] But up to 40% of women who received treatment with clomiphene show little clinical improvement,[12] a relatively high multiple-pregnancy rate (3~8%), and side effects such as mood changes, hot flushes,[13] dizziness, nausea, gastrointestinal symptoms, and symptoms associated with ovarian enlargement and ovulation,[14] even birth defects.[15] Acupuncture and TCM methods have a long history of using for gynecological diseases and fertility issues such as those associated with PCOS.[16, 17] However, available evidence is limited. The present study was aimed to estimate the efficacy of acupuncture combined with herbal medicine on ovulation rate, pregnancy rate and related hormones level in infertile women with PCOS.

2. Materials and methods

2.1. Study design

This investigation was a randomized, sham-controlled study. It was conducted

between March 2018 and December 2019, in the outpatient clinics in Shuguang Hospital in Shanghai, China. The protocol was published and is available in the Supplement.[18] This study was registered on 27 February 2018 in the Chinese Clinical Trial Registry ([ChiCTR1800014997](https://www.chictr.org.cn/showproj.aspx?proj=25583)). <https://www.chictr.org.cn/showproj.aspx?proj=25583>.

2.2. Patients

Eligible women were aged 20 to 40 years, and met the diagnosis criteria for both infertility and PCOS defined by the Rotterdam criteria proposed in 2003.[4] Besides, the husband was required to have normal semen examination results.

Women with any of the following conditions were excluded: hyperprolactinemia, adrenal or ovarian tumors, thyroid disease, Cushing syndrome, and other heart and kidney diseases; oral contraceptives and hormone drugs during the first month and other type of infertility; history of receiving acupuncture/moxibustion treatment within 2 months; use of other drugs that could affect the reproductive function or metabolism; Participation in another clinical study in the past two months.

2.3. Randomization and blinding

A total of 86 eligible participants were recruited and were randomly assigned at a 1:1 ratio to receive MA or SA treatment. Randomization sequence was generated using Excel by Dr. Cheng. Allocation concealment was ensured in an envelope. The envelopes were sealed, and the assignment records weren't disclosed until the end of the study. Ms. Wang enrolled participants, and Ms. Pan assigned participants to interventions. Patients were

blinded after assignment to interventions. Acupuncturists could not be blinded to the treatment assignments given the nature of the interventions. Communication among participants was discouraged and avoided as they were treated in separate room. Therefore, in this trial, participants, outcome assessors, data collectors, and statisticians were blinded to the treatment allocation.

2.4. Interventions

Both groups received real herbal medicine treatment twice a day as a basic treatment. During the menstrual period, patients were orally administered the *Taohong Siwu* decoction. Non-menstrual period treatment, were based on pattern differentiation: for spleen-kidney yang deficiency, applied *Bushen Tiaojing* decoction and liver-kidney deficiency were given *Guishao Dihuang* decoction.

Two acupuncturists with a clinical experience of more than three years were responsible for the manipulation of MA and SA after training. Sterile, disposable acupuncture needles (0.25×40mm), blunt-tip needles (0.25×25mm, Wuxi Jiajian Medical Instrument Co. Ltd, China) and simple adhesive pads (for fixation) were used. Participants received three menstrual cycles of acupuncture treatment (twice per week) and Chinese herbal medicine (twice a day). They received acupuncture on-obligatory points, including RN4, bilateral EX-CA1, ST29, ST36 and SP6. The other points were chosen according to syndrome differentiation and the menstrual cycle. The potential acupoints include RN6, RN12, DU20, and bilateral ST25, KI3, KI6, LR3, SP10, PC6.

Each patient was selected no more than 13 points. The use of additional acupoints other than the prescribed ones was not allowed. The semistandard prescriptions is based on the textbook “*Acupuncture and Moxibustion*” and previous clinical experience.[19] If the participant has evidence of pregnancy, she will no longer receive treatment.

During acupuncture treatment, adhesive pads were pasted on acupoints after sterilization. The acupoints were needled through the pad and 10-30mm into the skin (depend on location). were manipulated with even twirling, lifting, and thrusting to achieve the “*DeQi*” sensation (a sensation of soreness, numbness, distention, or radiating that indicates effective needling) or needling sensation once every 10 minutes for 30 minutes.[20] The treatment procedure in the SA group was identical in the MA group except not achieve *DeQi* sensation. [18]

2.5. Outcome measures

Participants were assessed at baseline, each menstruation, after three menstrual cycles of treatment, and 24 weeks follow-up after the completion of the treatment. The primary outcome was the pregnancy rate during the trial. Patient reported pregnancy or HCG positive in blood or urine, which was confirmed by B-ultrasound. The secondary outcomes included the ovulation rate observed through Basal body temperature (BBT) or B ultrasound every menstrual cycle; change from baseline in PCOS and TCM syndrome score (scoring was additive which higher values indicating increased severity); and change from baseline of the serum sex hormones level included estradiol (E₂),

testosterone (T), progesterone (P), luteinizing hormone (LH), follicle stimulating hormone (FSH). In addition, insulin resistance index ($\text{HOMA-IR} = \text{fasting blood glucose} \times \text{fasting insulin} / 22.5$) was assessed at baseline and after treatment of three menstrual cycles. 24 weeks after the completion of the treatment, follow up performed through the telephone to ask if the participants were pregnant. Acupuncture-associated adverse events were recorded and reported to the study coordinators at each treatment session.

2.6. Ethical considerations

The ethics committee has been approved by Institutional Review Board of Shuguang hospital affiliated with Shanghai University of TCM (22 Dec 2017, Approval Number: 2017-569-52-01). All participants have signed written informed consent after the trial procedures were fully explained and they also consented to the publication of clinical results. The protocol was approved by the institutional ethics review board of Shuguang Hospital and was performed in accordance with the Declaration of Helsinki.

2.7. Sample size calculation

We designed the trial to determine whether there was a difference between the MA group and the SA group in terms of the pregnancy rate. According to the other studies,[21, 22] we hypothesized that the pregnancy rate would be 76% in the MA group and 40% in SA group. Assuming a two-side alpha of 0.05, power of 90%, and a 20% drop-out rate, a sample size of 36 would be needed for each group to detect a between-group difference. We expanded the sample size to 86 cases (43 cases per group) to increase the reliability of

the study.

2.8. Statistical analysis

We performed a statistical analysis based on the intention-to-treat population, which includes participants who had a least 1 treatment and 1 primary outcome measure (n=79). Missing data were completed by the last observed value. Continuous data were presented with mean and standard deviation ($\bar{x} \pm s$) if they were normally distributed or with median (interquartile range, IQR) if they were abnormally distributed. Categorical variables were expressed as numbers and percentages. Chi-square tests were used to compare categorical variables, and 2 sample t-test or Wilcoxon rank sum test for continuous data, as appropriate. The variance analysis will be performed on the difference between the two groups and within the group. All reported *P* values were two-sided and used a significance level of 0.05. All statistical analyses were performed using SPSS statistical software (version 21.0, International Business Machines Corporation, China).

3. Results

3.1. Participants and baseline characteristics

A total of 178 participants were invited to participate in the study, of whom 92 were excluded, and 86 were eligible and randomly assigned to the MA group or the SA group. 2 dropped out in MA group (1 case changed her job and 1 case had time inconvenience). 5 dropped out in SA group (2 cases had job changeds, 2 cases had time inconvenience and 1

case unwilling to follow up). Seventy-nine participants (91.86%) completed the study (Figure 1).

Baseline characteristics were similar between the groups (Table 1). No significant difference was found between the two groups in age, duration of illness, BMI, PCOS score, TCM score and serum sex hormones level. Patient characteristics were well balanced by randomized.

3.2. Primary outcome

During treatment, out of 79 patients were included in the statistical analysis, a total of 15 participants were successfully conceived, including 10 in the MA group and 5 in the SA group (Table 2). The pregnancy rate was 24.39% (10/41) in patients who received manual acupuncture combined with herbal medicine and 13.16% (5/38) in the sham acupuncture combined with herbal medicine group.

During the 6-month follow-up period, a further 11 patients reported pregnancy. There were 9 participants in the MA group with a pregnancy rate of 29.03% (9/31) and 2 in the sham acupuncture group with a pregnancy rate of 6.06% (2/33) ($P=0.015$). Thus, the pregnancy rate in the MA group was 46.34% (19/41) throughout the trial, significantly better than the 18.42% (7/38) in the SA group ($P=0.008$).

3.3. Secondary outcomes

During the treatment period, the ovulation rate was 58.14% in the MA group, which

was significantly better than 45.74% in the SA group ($P=0.046$, Table 3). At the end of three menstrual cycles treatment, patients randomized to MA group had statistically significant differences in PCOS score and testosterone levels compared to the SA group, with greater improvements observed in the MA (Table 4).

After completion of treatment, compared the baseline, patients in MA group had statistically significant improvement in PCOS score, TCM score, estrogen (E_2), testosterone (T), progesterone (P), luteinizing hormone (LH) level and the ratio of luteinizing hormone to follicle stimulating hormone, but no significant improvement in follicle stimulating hormone (FSH) level or insulin resistance index (HOMA-IR). Details are listed in Table 4. Patients of SA group showed statistically significant improvement in PCOS score, TCM score and progesterone level compared with baseline, while no significant changes were found in other hormone levels ($P>0.05$). There were no significant adverse reactions in the two groups during the treatment period.

4. Discussion

This randomized sham-controlled trial found that manual acupuncture combined with herbal medicine was superior to sham acupuncture combined with herbal medicine for improving the pregnancy rate, ovulation rate and quality of life among infertile women with PCOS and that manual acupuncture provided some additional benefit over sham acupuncture. These findings support acupuncture combined with herbal medicine as an infertility treatment in patients with PCOS.

Pregnancy is the ultimate evaluation indicator of infertility treatment. We found manual acupuncture combined with Chinese herbal medicine (MA group) for three menstrual cycles period showed significant efficacy in improving pregnancy rate and ovulation rate compared with SA group, and have a better long-term effect. Our findings are similar to previous reports.[23-25] In a systematic review reported a promising effect that *Bushen Huoxue* herbal medicine had advantages on increasing pregnancy rate, while the quality of evidence was relatively low.[26] Complementary and alternative medicine therapies, including TCM and acupuncture is increasingly widely used.[27] In this trial, we selected the acupuncture points according to literatures. [28-30]

According to the theory of TCM, syndrome differentiation and treatment is an important therapeutic principle. Treatment according to the phase of the menstrual cycle is also common in gynecological diseases. Patients received acupuncture treatment from the third day of menstruation to the third day of ovulation may took full advantages of acupuncture, promoted the development and discharge of follicles, and avoided the risk of acupuncture treatment during pregnancy.

Evidence from systematic reviews suggested that true acupuncture may improve ovulation and menstruation rates compared with no acupuncture.[31, 32] Effectiveness of acupuncture for PCOS is inconclusive due to insufficient overall evidence.[33] A randomized controlled trial demonstrated that acupuncture failed to treat the women with PCOS,[34] which was attracted wide attention and controversy.[35, 36] Acupuncture is a complex intervention associated with therapeutic gains.[37] Different treatment efficacy

may be related to the treatment regimen, selection of acupoints, manipulation, treatment duration, frequency and qualification of the acupuncturist.[38] We considered these factors in the design of the trial. The compliance of the participants in the trial was high (91.86%), maybe since these patients had a strong desire to get pregnant. No serious side effects were observed during the trial.

Peripheral blood examination showed that the manual acupuncture group could significantly reduce E2, T, P, LH levels and LH/FSH ratio in infertility patients with PCOS. However, only a statistically significant decrease in P level was observed in the SA group. Acupuncture may improve the hyperandrogenic state in PCOS patients, leading to improve ovulation and pregnancy rates. Studies have shown that acupuncture can reduce the LH/FSH ratio, decrease T, LH, and BMI levels, improve ovarian function, and can improve the local microcirculation and uterine wall environment in patients with polycystic ovary syndrome, which is conducive to implantation of fertile eggs, similar to Diane-35.[39, 40] Research has demonstrated that oral contraceptives can effectively reduce LH/FSH ratio and androgen levels, improve symptoms and restore ovulation to some extent, and reduce endometrial hyperplasia.[41]

Infertile PCOS patients show a tendency of the insulin resistance index improvement after acupuncture with no significant difference compare with the sham group. Both groups have similar effect in improving TCM symptoms may be due to the role of Chinese herbal decoction. While the improvement of clinical symptoms of manual acupuncture combined with herbal medicine is significantly better than that of the sham

group. Thus provided evidence of acupuncture in the treatment of infertile PCOS patients.

The limitations of this study are its small sample size, and missing of an assessment of the blinding effectiveness and record of how many patients in the MA and SA groups reported achieving *deqi*. This trial was conducted in a single clinical trial center, and the imputation method for missing data that we used, the last observation carried forward method, may result in bias.

5. Conclusion

Manual acupuncture of three menstrual cycles combined with herbal medicine increased pregnancy rate and ovulation rate compared with sham acupuncture combined with herbal medicine among infertile women with PCOS. A larger sample of clinical trial is warranted to understand the long-term efficacy and the mechanism of action of acupuncture intervention.

Abbreviations

PCOS: Polycystic ovary syndrome; IR: Insulin resistance; MA: manual acupuncture; SA: Sham acupuncture; TCM: Traditional Chinese Medicine; CC: Clomiphene citrate; OHSS: Ovarian Hyper-stimulation Syndrome; RCTs: Randomized controlled trials; IRI: Insulin Resistance Index; HOMA-IR: insulin resistance index; E₂: estradiol; T: testosterone; P: progesterone; LH: luteinizing hormone; FSH: follicle stimulating hormone.

Declarations

Ethics approval and consent to participate

The ethics committee has been approved by the Institutional Review Board of Shuguang hospital affiliated with Shanghai University of TCM (22 Dec 2017, Approval Number: 2017-569-52-01). All participants have signed written informed consent.

Availability of data and materials

All the data used to support the findings of this study are available from the corresponding authors upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LZ and XYS: Conceived the idea and designed the trial. WP and QW: Participated in the planning of the project, analyses and interpretation of the results and wrote the manuscript. ZQH: Obtained funding and participated in the planning of the project. FXL and YMY: Participated both in statistical analyses. XQY: Provided the administrative, technical, or material support. All authors read and approved the final manuscript.

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Consent to publish

We declare that the Publisher has the Author's permission to publish the relevant contribution.

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Table 1. Baseline and clinical characteristics of the study population

Characteristic	MA group (n=41)	SA group (n=38)	<i>p</i>
Age, year [†]	30.8±3.5	29.7±3.2	0.918
Duration of illness, month [†]	23.5±12.2	22.0±8.5	0.34
BMI [†]	18.8±2.3	17.9±2.1	0.611
PCOS Scores [†]	3.6±1.6	3.7±1.9	0.371
TCM Scores [†]	4.9±2.4	4.7±2.3	0.954
Serum sex hormones level [‡]			
E ₂ , pmol/L	125.0(103.5,169.5)	163.3(104.5,201.5)	0.285
T, nmol/L	1.6(1.2,2.0)	1.4(1.0,2.1)	0.283
P, nmol/L	0.8(0.5,1.0)	0.9(0.6,1.4)	0.325
FSH, IU/L	5.4(4.3,6.0)	5.0 (4.3,6.1)	0.765
LH, IU/L	6.1(3.1,9.6)	4.2 (2.5,7.0)	0.116

Abbreviations: MA group, manual acupuncture group; SA group, sham acupuncture group;

BMI, body mass index, is the weight in kilograms divided by the square of the height in

meters; PCOS, polycystic ovary syndrome; TCM, traditional Chinese medicine; E₂,

estradiol; T, total testosterone; P, progesterone; FSH, follicle-stimulating hormone; LH,

luteinising hormone;

[†], Mean (SD);

[‡], Median (IQR).

Table 2. Comparison of pregnancy rates between the two groups During the Entire

Study	N (%)			
Groups	N	After treatment	During follow-up	Total
MA group	41	10(24.39)	9(29.03)	19(46.34)
SA group	38	5(13.16)	2(6.06)	7(18.42)
<i>p</i>	-	0.203	0.015	0.008

Abbreviations: MA group, manual acupuncture group; SA group, sham acupuncture group;

Table 3. Comparison of ovulation rate between the two groups (number of times)

Groups	Ovulation	No ovulation	Ovulation rate	<i>p</i>
MA group	75	54	58.14%	0.046
SA group	59	70	45.74%	

Abbreviations: MA group, manual acupuncture group; SA group, sham acupuncture group;

Table 4. Comparison of other secondary outcomes before and after treatment in the two groups ($\bar{x} \pm s$) / [$M(Q25, Q75)$]

Items	Groups	N	Baseline	After treatment	<i>p</i> value (intra-group)	Index value reduction change ^b (%)	<i>p</i> value (between groups)
PCOS Score	MA group	31	3.71±1.75	2(0,3)	<0.001	60 (33.33,100)	0.003
	SA group	33	3.64±1.85	2(1.5,3)	<0.001	33.33(0,100)	
TCM Score	MA group	31	5.0±2.61	2(1,3)	<0.001	60(50,71.43)	0.317
	SA group	33	4.67±2.33	2(1,3)	<0.001	60(46.43,66.67)	
E ₂ (pmol/L)	MA group	31	131(107,167)	119.33±52.31	0.009	18.29(-2.9,42.8)	0.131
	SA group	33	161.48(90.5,203)	132(77.5,187.5)	0.513	-6.9(-18.44,34.48)	
T(nmol/L)	MA group	31	1.59(1.32,2.03)	1.15(0.95,1.57)	<0.001	23.77±22.99	0.037
	SA group	33	1.15(0.95,2.08)	1.14(0.87,1.68)	0.131	2.13(-14.58,35.29)	
P(nmol/L)	MA group	31	0.8(0.5,1.0)	0.6(0.4,0.79)	0.023	20(0,40)	0.824
	SA group	33	0.8(0.59,1.33)	0.6(0.4,0.9)	0.008	14.26±50.344	
FSH(IU/L)	MA group	31	5.26±1.08	5.08±1.26	0.368	1.80±21.42	0.92
	SA group	33	5.04(4.27,6.23)	5.02(4.19,5.81)	0.561	1.98(-16.66,16.61)	
LH(IU/L)	MA group	31	6.89±4.01	3.94(2.48,6.58)	0.043	13.99(-13.7,55.33)	0.108
	SA group	33	4.17(2.50,6.83)	4(2.59,6.84)	0.888	0(-69,35.4)	
LH/FSH	MA group	31	1.35±0.75	0.82(0.55,1.3)	0.038	20.88(-17.02,39.78)	0.149
	SA group	33	0.84(0.56,1.34)	0.83(0.62,1.30)	0.728	-0.17(-47.18,33.42)	
HOMA-IR	MA group	31	2.06(1.32,2.56)	1.7(1.18,2.7)	0.753	-2.62±40.53	0.736
	SA group	33	1.69(1.15,2.71)	1.86(1.22,3)	0.845	0(0,8.15)	

^b Index value reduction change = (After treatment–Baseline)/ Baseline x100%.

Abbreviations: MA group, manual acupuncture group; SA group, sham acupuncture group; PCOS, Polycystic Ovary Syndrome; TCM,

Traditional Chinese Medicine; E₂, estradiol; T, total testosterone; P, progesterone; FSH, follicle-stimulating hormone; LH, luteinising hormone;

HOMA-IR=fasting blood glucose × fasting insulin/22.5.