How does acupuncture affect insulin sensitivity in women with polycystic ovary syndrome and insulin resistance? Study protocol of a prospective pilot study

Yanhua Zheng,1,2 Elisabet Stener-Victorin,3 Ernest H Y Ng,4 Juan Li,1,5 Xiaoke Wu,6 Hongxia Ma1,5

ABSTRACT

Introduction: Hyperinsulinaemia and insulin resistance (IR) are key features of polycystic ovary syndrome (PCOS) and metabolic syndrome. The effect of 5 weeks of acupuncture treatment has been investigated in a completed prospective pilot trial (Clinicaltrials.gov: NCT01457209), and acupuncture with electrical stimulation applied to insulin-resistant rats with dihydrotestosterone-induced PCOS was shown to improve insulin sensitivity. Therefore, we now aim to conduct a prospective pilot study to evaluate whether using the same acupuncture treatment protocol given over a longer period of time (6 months) than in the previous pilot trial will improve insulin sensitivity in women with PCOS and IR. Our hypothesis is that acupuncture with combined manual and low-frequency electrical stimulation of the needles will improve insulin sensitivity in women with PCOS and IR.

Methods/analysis: This is a prospective pilot trial. A total of 112 women with PCOS and IR will be recruited and categorised according to their body mass index (BMI) as normal weight (BMI=18.5–23 kg/m²) or as overweight/obese (BMI>23 kg/m²). Acupuncture will be applied three times per week for 6 months at 30 min per treatment. The primary outcome will be the change in insulin sensitivity before and after 6 months of acupuncture treatment, as measured by an oral glucose tolerance test.

Ethics/dissemination: Ethical approval of this study has been granted from the ethics committee of the First Affiliated Hospital of Guangzhou Medical University (No. 2013039). Written and informed consent will be obtained from each patient before any study procedure is performed, according to good clinical practice. The results of this trial will be disseminated in a peer-reviewed journal and presented at international congresses.

Trial registration numbers: NCT02026323 and ChiCTR-OCH-13003921.

BACKGROUND

Features of polycystic ovary syndrome (PCOS) include ovulatory dysfunction, clinical and biochemical signs of hyperandrogenism, and the presence of polycystic ovaries on pelvic scanning.1 2 PCOS is the most common endocrine and metabolic disorder in reproductive-age women,2 and is found in 5.6% of Chinese women aged 19–45 years, as shown in a recent community-based study.1 The main metabolic phenotype is hyperinsulinaemia and insulin resistance (IR), which is observed in about 50–70% of all women with PCOS.3 4 Importantly, IR can be present in lean and in obese women with PCOS,5 6 and especially in those with hyperandrogenism and ovulatory dysfunction.7 8

PCOS causes significant menstrual and fertility issues, but over the past few decades its additional metabolic and cardiovascular risks have become apparent. Women with PCOS display IR and reduced insulin responsiveness9 10 and have at least a threefold increased risk of developing type 2 diabetes mellitus.10 IR in women with PCOS has been attributed to postbinding defects in adipocytes and skeletal muscle insulin signalling.9 11 Furthermore, compensatory hyperinsulinaemia fuels ovarian androgen production by stimulating androgen production and secretion by theca cells, and by reducing sex hormone-binding globulin (SHBG) levels, which increases free androgens and further exacerbates PCOS symptoms.12 Thus, there is a strong association between hyperinsulinaemia and hyperandrogenaemia.

Overweight/obesity is a common feature of PCOS.13 A Korean study showed that 61% of women with PCOS were lean, 10.3% were overweight and 28.4% were obese.14 Obesity aggravates most of the metabolic...
dysfunctions in women with PCOS. Women with comorbid PCOS and depression have been found to have higher body mass index (BMI) and IR compared with women with PCOS without depression, and this increase in BMI negatively affects quality of life.

Despite the high prevalence of IR, impaired glucose tolerance and/or type 2 diabetes mellitus in women with PCOS, there is no consensus on the best long-term management of these conditions. Pharmacological treatments, including metformin, are symptom oriented and usually effective but have unpleasant gastrointestinal side effects. Therefore, it is important to evaluate other non-pharmacological treatment strategies because most women with PCOS require long-term treatment.

Acupuncture, which is one of the main treatment modalities of traditional Chinese medicine, is increasingly being used in the area of reproductive endocrinology and infertility in many different parts of the world. Interestingly, increasing the treatment frequency and the number of treatments leads to higher ovulation frequency, indicating the importance of the correct treatment dose. In a secondary analysis of the trial by Jedel et al., low-frequency electroacupuncture (EA) decreased high plasminogen activator inhibitor 1 (PAI-1) activity without affecting insulin sensitivity, as measured by the euglycaemic hyperinsulinaemic clamp. Clearly, the intensity, frequency and duration of low-frequency EA treatment in that study were too low to affect insulin sensitivity. Support for this assumption comes from our experimental studies in the dihydrotestosterone (DHT)-induced PCOS rat model, in which we demonstrated that low-frequency EA improves whole-body insulin sensitivity in a dose-dependent manner.

EA induces systemic as well as local effects involving intracellular insulin signalling pathways in skeletal muscle and adipose tissue. Furthermore, EA has been shown to reduce plasma glucose levels by promoting insulin production and to improve insulin sensitivity by inducing secretion of endogenous β-endorphin in different rodent models of diabetes mellitus. The potential role of acupuncture in the treatment of women with PCOS and IR has not yet been determined, and this is an important area to investigate because most women with PCOS require long-term treatment. There is one completed prospective pilot trial investigating the effect of 5 weeks of acupuncture treatment with combined manual and low-frequency electrical stimulation of the needles (Clinicaltrials.gov: NCT01457209). Therefore, the aim of this pilot study is to investigate the clinical effectiveness of acupuncture on insulin sensitivity in women with PCOS and IR when acupuncture is given over a longer period of time (6 months) than in the previous pilot trial using the same treatment protocol. Our hypothesis is that acupuncture with combined manual and low-frequency electrical stimulation of the needles will improve insulin sensitivity in women with PCOS and IR.

MATERIALS AND METHODS

Study design

This is a single-centre prospective pilot study, and participants will be enrolled from the First Affiliated Hospital of Guangzhou Medical University. The trial has been registered at ClinicalTrial.gov (NCT02026323) and with the Chinese Clinical Trials Registry (ChiCTR-OCH-13003921).

Participants

Participants will be recruited if they fulfil all of the inclusion criteria and do not meet any of the exclusion criteria.

Inclusion criteria

1. Age between 18 and 40 years.
2. BMI ≥18.5 kg/m².
3. Presence of PCOS as defined by the Rotterdam criteria and including at least two of the following three features:
   - Oligomenorrhoea or amenorrhoea: Oligomenorrhoea is defined as an intermenstrual interval >35 days or <8 menstrual bleedings in the past year. Amenorrhoea is defined as complete cessation of menstrual cycles for 6 months or more when a patient has previously had regular cycles and for 12 months or more when the patient has had irregular cycles.
   - Clinical or biochemical hyperandrogenism: Biochemical hyperandrogenaemia is defined as a total serum testosterone concentration above 60 ng/dL and clinical hyperandrogenism is defined as a Ferriman-Gallwey (FG) score ≥5, in mainland China.
   - Polycystic ovary morphology: This is defined as ≥12 antral follicles (2–9 mm in diameter) or an ovarian volume >10 mL on transvaginal scanning.
4. Presence of IR as defined by the homeostatic model assessment (HOMA-IR: (fasting insulin (μU/mL)×fasting glucose (mmol/L))/22.5). A value ≥2.14 will be considered to be indicative of IR.
5. No desire to bear children and having used barrier methods of contraception for 1 year.
6. Willingness to sign the consent form.

Exclusion criteria

1. Having other endocrine disorders such as hyperprolactinaemia (defined as two prolactin levels measured at least 1 week apart of 25 ng/mL or greater or as determined by local normative values), non-classic congenital adrenal hyperplasia (17-hydroxypregesterone <3 nmol/L), or androgen-secreting tumours.
2. Follicle-stimulating hormone (FSH) levels >15 mIU/mL. A normal level within the last year is adequate for entry.
3. Uncorrected thyroid disease defined as thyroid-stimulating hormone (TSH) <0.2 mIU/mL or TSH >5.5 mIU/mL. A normal level within the last year is adequate for entry.

4. Patients with type I diabetes mellitus or type I and type II who are receiving antidiabetic medications such as insulin, thiazolidinediones, acarbose, sulfonylureas, or other medications that are likely to confound the effects of the study. Patients currently receiving metformin for a diagnosis of type I or type II diabetes or for PCOS are also specifically excluded.

5. Suspected Cushing’s syndrome.

6. Use of hormones or other medications in the past 3 months, including Chinese herbal prescriptions, which might affect the outcome.

7. Pregnancy within the past 6 weeks.

8. Postabortion or post partum within the past 6 weeks.

9. Breast feeding within the past 6 months.

10. Receiving acupuncture treatment related to PCOS within the past 2 months.

11. Having undergone a bariatric surgery procedure within the past 12 months or being in a period of acute weight loss.

12. Having known congenital adrenal hyperplasia.

13. Lack of written consent to participate in the study. Eligible participants will be recruited and categorised according to their BMI as normal weight (BMI=18.5–23 kg/m²) or overweight/obese (BMI≥23 kg/m²).

Interventions

The acupuncture protocol is based on Western medical theories, and the study protocol follows the CONSORT31 and STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)32 recommendations with detailed descriptions of the treatment, including the number of needles used, depth of needle insertion, how needles will be stimulated (manual or electrical), frequency of sessions and length of the treatment period. Acupuncture will be given according to a fixed protocol by traditional Chinese medicine practitioners educated in theoretical and practical acupuncture. The protocol is based on experimental studies elucidating the effect of acupuncture in rodent models of diabetes mellitus and PCOS20–22 and in women with PCOS.23

Acupuncture protocol

Acupuncture will be given three times per week over 6 months for a total of 80 sessions. Disposable, sterilised needles for single use made of stainless steel (0.20×30 mm and 0.20×40/50 mm; Hwoto, Suzhou Medical Appliance Factory, Suzhou, China) will be inserted to a depth of 15–35 mm in segmental acupuncture points located in the abdominal and leg muscles, with innervations corresponding to the ovaries and pancreas that have been shown to improve insulin sensitivity in rodents. Two sets of acupuncture points will be alternated for every other treatment session. The two acupuncture protocols follow the STRICTA recommendations and are presented in table 1. The rationale for using the traditional nomenclature of acupuncture points is that they are well described in the literature, and acupuncturists trained according to medical acupuncture theories or trained in classic traditional Chinese medicine theories all know the locations of such points and how the needles should be inserted. Thus, using the acupuncture name/number makes it easier for all practitioners to know where the needles were placed. All needles will be stimulated manually by rotation until needle sensation is evoked, which is indicative of activation of a-delta and c-fibres when the needles are inserted. Needles placed in the abdominal muscles and leg muscles will be attached to an electrical stimulator (Export Abteilung, Schwa-Medico GmbH, Germany) and electrically stimulated at 2 Hz for 30 min during each treatment session. Needles not connected to the electrical stimulator will be stimulated manually four times during each 30 min treatment session (table 1).

Study procedures

This pilot study has two phases. The first phase is the 6 months of acupuncture treatment, and the second phase is 6 months of follow-up (figure 1). Each specific visit and measurement is summarised in table 2.

The women in the study will be screened for IR. Those with a HOMA-IR ((fasting insulin (μU/mL)×fasting glucose (mmol/L))/22.5) ≥2.14 will be included and divided into the normal weight (BMI=18.5–23 kg/m²) group and the overweight/obese (BMI≥23 kg/m²) group. After inclusion and baseline measurements, acupuncture treatment will start and last for 6 months followed by 6 months of follow-up.

Outcome measurements

Primary outcome

The primary outcome will be the changes in HOMA-IR between baseline and after 6 months of acupuncture treatment, and between baseline and the 6-month follow-up. The oral glucose tolerance test (OGTT) with 75 g glucose will be performed in all participants after an overnight fast. Blood samples will be obtained to measure plasma glucose and serum insulin at 0, 60 and 120 min during the OGTT.

Secondary outcomes

1. HOMA-B: Islet β-cell function will be evaluated by the formula (20×fasting insulin (mU/mL)/(fasting plasma glucose (mmol/L) −3.5))34 and by the C peptide index (CPI), which is measured as (fasting C peptide (nmol/L)/fasting plasma glucose (mmol/L)×100).35

2. The insulin response to glucose will be assessed by calculating the area under the curve during the OGTT for glucose (AUCglu) and insulin (AUCins) using the trapezoidal rule.36

3. Menstrual bleeding patterns will be evaluated.

4. Body composition will be determined as weight, height, waist-to-hip circumference and BMI.

5. Metabolic measures will include glycated haemoglobin, C peptide, adiponectin, fasting cholesterol, fasting triglycerides (TG), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB) and blood pressure.
<table>
<thead>
<tr>
<th>Acupuncture point</th>
<th>Stimulation</th>
<th>Localisation</th>
<th>Muscle</th>
<th>Muscle innervation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Set 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhongji, CV3</td>
<td>EA</td>
<td>4 cun caudal to the umbilicus</td>
<td>Fibrous tissue, linea alba</td>
<td>L1</td>
</tr>
<tr>
<td>Zhongwan, CV12</td>
<td>EA</td>
<td>On the midline, 4 cun superior to the umbilicus</td>
<td>Fibrous tissue, linea alba</td>
<td>Th7–8</td>
</tr>
<tr>
<td>Guili; ST29</td>
<td>EA</td>
<td>1 cun caudal to the pubic bone and 2 cun lateral of the midline</td>
<td>M. rectus abdominis</td>
<td>Th6–12</td>
</tr>
<tr>
<td>Bilateral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liangqi, ST34</td>
<td>EA</td>
<td>2 cun above the superior lateral border of the patella on the line connecting</td>
<td>M. quadriceps femoris</td>
<td>femoral nerve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>the anterior superior iliac spine found with the knee flexed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yinshi; ST33</td>
<td>EA</td>
<td>3 cun above the superior lateral border of the patella on the line connecting</td>
<td>M. quadriceps femoris</td>
<td>femoral nerve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>the anterior superior iliac spine found with the knee flexed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanyinjiao; SP6</td>
<td>DeQi four</td>
<td>3 cun proximal to the medial malleolus</td>
<td>Mm. flexor digitorum longus, tibialis posterior</td>
<td>L4–5, S1–2</td>
</tr>
<tr>
<td>Zusanli; ST36</td>
<td>DeQi four</td>
<td>On the anterior lateral side of the leg, 3 cun below Dubi (ST35), one finger</td>
<td>Musculi tibialis anterior</td>
<td>L4–5, S1</td>
</tr>
<tr>
<td></td>
<td>times</td>
<td>width (middle finger) from the anterior crest of the tibia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hegu; LI4</td>
<td>DeQi four</td>
<td>On the highest point at m. interosseus dorsalis</td>
<td>Mm. interosseus dorsalis I, lumbricals II, adductor pollicis</td>
<td>C8, Th1</td>
</tr>
<tr>
<td></td>
<td>times</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Set 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daju; ST27</td>
<td>EA</td>
<td>3 cun caudal to the pubic bone and 2 cun lateral to the midline</td>
<td>M. rectus abdominis</td>
<td>Th6–12</td>
</tr>
<tr>
<td>Qhaif; CV6</td>
<td>EA</td>
<td>1.5 cun caudal to the umbilicus</td>
<td>Fibrous tissue, linea alba</td>
<td>Th11</td>
</tr>
<tr>
<td>Xiawan; CV10</td>
<td>EA</td>
<td>2 cun caudal to the umbilicus</td>
<td>Fibrous tissue, linea alba</td>
<td>Th8</td>
</tr>
<tr>
<td>Extra meridian point</td>
<td>EA</td>
<td>6 cun above the patella in line with SP10</td>
<td>M. quadriceps femoris</td>
<td>L2–4</td>
</tr>
<tr>
<td>Xuehai, SP10</td>
<td>EA</td>
<td>With the knee flexed, on the medial side of the thigh 2 cun above the superior</td>
<td>M. quadriceps femoris</td>
<td>L2–4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>medial corner of the patella on the prominence of the medial head of the</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>quadiceps muscle of the thigh</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanyinjiao; SP6</td>
<td>DeQi four</td>
<td>3 cun proximal to the medial malleolus</td>
<td>Mm. flexor digitorum longus, tibialis posterior</td>
<td>L4–5, S1–2</td>
</tr>
<tr>
<td>Taichong; LR3</td>
<td>DeQi four</td>
<td>Between metatarsal I &amp; II, just distal to the caput</td>
<td>M. interosseus dorsalis I</td>
<td>S2–3</td>
</tr>
<tr>
<td>Neiguan; PC6</td>
<td>DeQi four</td>
<td>2 cun proximal to the processus styloideus radii, between the tendons of the</td>
<td>M. flexor digitorum superficialis</td>
<td>C8, Th1</td>
</tr>
<tr>
<td></td>
<td>times</td>
<td>palmaris longus and the flexor carpi radialis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The two sets will be alternated for every other treatment.

C, cervical vertebra; CV, conception vessel; EA, electroacupuncture; L, lumbar vertebra; LI, large intestine; LR, liver; M, musculus; PC, pericardium; S, sacral vertebra; SP, spleen; ST, stomach; Th, thoracic vertebra.
6. Endocrine measures will include hirsutism as assessed by FG score, the presence of acne, and serum concentrations of testosterone, SHBG, FSH, luteinising hormone and dehydroepiandrosterone sulfate (DHEAS).

7. Questionnaires will include the short form-36 (SF36), the PCOS questionnaire (PCOSQ), generic and diagnosis-specific health-related quality of life questionnaires, and the Chinese Quality of Life (ChQOL) questionnaire. Symptoms of anxiety and depression will be assessed by the Zung Self-Rating Anxiety Scale (Zung SAS), and the Zung Self-Rating Depression Scale (Zung SDS). In addition, the International Physical Activity Questionnaire (IPAQ) written in Chinese will be used to measure the frequency and duration of moderate physical activity every week.

8. Adverse events will be recorded.

Data entry and quality control of data
Case report forms will be developed for data entry, and quality control of the data will be handled at two different levels. The investigators will be required to ensure the accuracy of the data as the first level of control, and the second level will include data monitoring and validation that will be carried out on a regular basis throughout the study.

Sample size calculations and statistical analysis
Our previous study on treating obese women with PCOS with abdominal acupuncture showed that the HOMA-IR was significantly reduced after treatment (3.9±1.4) compared with baseline measurements (2.5±1.7). A HOMA-IR ≥ 2.14 was considered to be abnormal. If we assume a more moderate 20% reduction in HOMA-IR, that is, a reduction by 0.78, we will have to recruit 40 overweight or obese participants and 40 normal-weight participants. With an estimated 40% drop out rate, we plan to recruit 56 normal weight and 56 overweight/obese women with PCOS.

One sample of the Kolmogorov-Smirnov test will be used to test the normal distribution of continuous variables.

Table 2 Overview of study visits, including screening, baseline measurements, after-treatment measurements and follow-up measurements

<table>
<thead>
<tr>
<th>Screening and baseline visit</th>
<th>Month</th>
<th>Follow-up 6th month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st</td>
<td>2nd</td>
</tr>
<tr>
<td>Body composition (weight, height, waist circumference, hip circumference)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Menstrual cycle diary</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Fasting blood samples for Apoa1, ApoB, TC, TG, C peptide, HbA1c</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Fasting blood samples for FSH, LH, SHBG, T, E2, P, DHEAS</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Transvaginal ultrasound</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Questionnaire</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>FG/acne</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>OGTT</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Months indicate when each specific measurement takes place.
Apoa1, apolipoprotein A1; ApoB, apolipoprotein B; DHEAS, dehydroepiandrosterone sulfate; E2, estradiol; FG, Ferriman-Gallwey score; FSH, follicle-stimulating hormone; HbA1c, glycated haemoglobin; LH, luteinising hormone; OGTT, oral glucose tolerance test; SHBG, sex hormone-binding globulin; T, total testosterone; TC, total cholesterol; TG, triglyceride.
variables. Continuous variables will be shown as means ±SDs if they are normally distributed or as medians with IQRs if they are not normally distributed. Statistical comparisons will be carried out according to the intention to treat by Student t test, Mann-Whitney U-test, and Wilcoxon signed-ranks test for continuous variables and by χ² tests for categorical variables where appropriate. All statistical analyses of the data will be performed using the SPSS program V.21.0 (SPSS Inc, Chicago, Illinois, USA), and a p value <0.05 will be considered statistically significant.

Safety and ethical considerations

Acupuncture is a safe procedure, and few side effects have been reported. The major risks of acupuncture are local skin irritation, discomfort and vasovagal reactions during the procedure. The women who agree to participate in the study will sign a consent form.

DISCUSSION

Acupuncture has been used in the treatment of women with PCOS, but the effect of acupuncture on IR in women with PCOS is still unknown. This prospective pilot study has been designed, therefore, to evaluate whether acupuncture improves insulin sensitivity in women with PCOS and IR. The research seeks to add to the clinical evidence base and to allow conclusions to be made on the role of acupuncture in the treatment of PCOS.

A limitation of the present study is that it is a single-centre study without comparison groups, and it can be argued that it lacks scientific rigour because of this. To increase the validity of the study, we will have experts controlling the quality of study procedure through regular site visits. The experts will monitor the recruitment of study participants, the measurement and treatment procedures, and the data analysis. We plan to conduct a randomised controlled trial at a later date using standard care as a control.

This pilot study was conceived and designed in 2013, and the first participant was recruited on 18 February 2014. As of 18 December 2014, out of 368 women approached, 176 did not fulfil selection criteria, 85 declined participation and 107 consented to participate in the study. In total, 99 women were screened and 83 were recruited.

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Contributors YZ, ES-V and EHYN contributed equally to this work. ES-V, EHYN and HM conceived and designed the study. YZ, EHYN and ES-V drafted and critically revised the manuscript for important intellectual content. HM sought funding and ethical approval. All the authors contributed to the further writing of the manuscript and approved the final manuscript.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval This study was approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University (No. 2013039).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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