Japanese Journal of Gastroenterology and Hepatology

Protocol Paper

ISSN: 2435-1210 | Volume 10

Effects of Acupuncture on Body Mass Index in Overweight/Obese Women with Polycystic Ovary Syndrome: Study Protocol for a Randomized Controlled Trial

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Trial registration: Clinical Trials.gov NCT04193371. Registered on 6 November 2019.

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Received: 16 Aug 2023
Accepted: 09 Oct 2023
Published: 17 Oct 2023
J Short Name: JJGH

Citation:

Di L, Li R. Effects of Acupuncture on Body Mass Index in Overweight/Obese Women with Polycystic Ovary Syndrome: Study Protocol for a Randomized Controlled Trial. J Gastro Hepato. 2023; V10(3): 1-10

Keywords:

Acupuncture; Polycystic ovary syndrome (PCOS); Overweight, Obesity

Abbreviations:

AMH: antimüllerian hormone; BMI: body mass index; CONSORT: Consolidated Standards of Reporting Trials; CV: conception vessel; E2: estrogen; EQ-5D: EuroQol health index scale; FSH: follicle stimulating hormone; FAI: free androgen index; GCP: Good Clinical Practice; HbA1c: glycated hemoglobin; IR: insulin resistance; LI: large intestinal; LR: liver; LH: luteinizing hormone; OGTT: oral glucose tolerance Test; PCOS: polycystic ovary syndrome; P: progestin; PRL: prolactin; PCOSQ: polycystic ovary syndrome questionnaire; PC: pericardium; RCT: randomised controlled trial; ST: stomach; SP: Spleen; SOPs: Standard Operating Procedures; SHBG: sex hormone binding globulin; SDS: Zung symptom depressions score; SAS: Zung symptom anxiety score; SPIRIT: Recommendations for Interventional Trials Statement; STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture; SF-36: short form-36; TCM: traditional Chinese medicine; T: testosterone; T2: androstenedione; TSH: thyroid stimulating hormone; T3: triiodothyronine; T4: free thyroxine

1. Abstract

1.1. Background: Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among reproductive-aged women, characterized by endocrine, metabolic and psychological features. Weight management is recommended as a first-line treatment for PCOS. Acupuncture is assumed to be an effective and safe treatment for reducing weight. However, evidence supporting its efficacy in PCOS is lacking. We aimed to investigate whether lifestyle management with active or control acupuncture treatment could reduce body mass index (BMI), as well as associated endocrine, metabolic and psychological symptoms in overweight/obese women with PCOS.

1.2. Methods/design: The present study is a prospective, two-arm, blinded (assessors and participants), randomized, sham-controlled trial. 212 participants will be recruited and randomized into two groups: active acupuncture plus lifestyle management; and sham acupuncture combined with lifestyle management. The lifestyle inter-

vention is applied through web-based (including the websites, apps, and wearable devices) health coaching. Clinical outcomes will be evaluated at baseline, 16 weeks after treatment, and 16 weeks follow-up after treatment termination. The primary outcome measure is body mass index (BMI) before and after treatment. The secondary outcomes include anthropometric, serum reproductive, metabolic, and neuroendocrine profiles, lifestyle, and quality of life. Adverse events will be assessed at every visit.

1.3. Discussion: The present study is expected to investigate the effectiveness of acupuncture on the BMI of overweight/obese PCOS women compared with sham acupuncture. We hypothesize that active acupuncture with lifestyle intervention is superior to control acupuncture with lifestyle management. The result of this trial will contribute to advancing evidence in acupuncture treatment for weight control of PCOS women and demonstrate improved metabolic, reproductive function, and psychological health of PCOS women.

2. Introduction

Polycystic ovary syndrome (PCOS), the most common endocrine, metabolic and psychological disorder affecting 4%–20% of women of reproductive age worldwide [1, 2], is characterized by a variety of clinical features such as anovulation, hyperandrogenism, obesity, polycystic ovaries on ultrasonography, anovulatory infertility, insulin resistance (IR), cardiovascular disease and a higher risk of psychological complications [3]. PCOS women have a 3 to 7-fold increased risk of higher rate of weight gain and a higher prevalence of overweight [4], obesity and central obesity compared to age-matched controls, which worsen features of PCOS. Weight loss, in turn, improves most symptoms related to PCOS [5]. Lifestyle (diet, physical activity and behaviour) intervention and weight management are recommended as first line treatment for PCOS [6], according to international evidence-based guidelines, especially before the initiation of infertility treatment for higher ovulation rates [7].

Available evidence supports behavioural, pharmacologic, surgical, and device interventions for obesity treatment [8, 9]. However, it is important to note that the effectiveness of these practices is frequently unsatisfactory but accompanied by many side effects. Even though a few anti-obesity drugs have been approved by the FDA, their clinical application is limited because of the modest efficacy (approximately 3% BMI reduction over 12 months) and adverse effects such as oily spotting and flatus with discharge, headache, dizziness and nausea or negative mood changes caused by body weight regaining after cessation of therapy [10, 11]. Thus, complementary and alternative therapies are pursued to overcome these limitations [12].

Acupuncture, one of the most ancient medical therapies and as a crucial segment of traditional Chinese medicine (TCM), has been increasingly recognized as an alternative therapy in weight loss with fewer adverse effects [13-15]. Existing evidence-based reviews have demonstrated that in non-PCOS population, acupuncture may achieve weight loss by regulating appetite and energy expenditure [16]. Further, acupuncture alleviates anxiety symptoms and improves quality of life in people with obesity, possibly through controlling food intake and regulating energy homeostasis [17].

In the PCOS population, a couple of studies indicate that acupuncture improves reproductive and metabolic function of PCOS women [18]. However, its efficacy on weight management of PCOS is lacking, and the factors associated with success in weight loss interventions are not known in PCOS. Therefore, we aim to compare the effect of active and sham acupuncture with usual care (lifestyle management which conducted by Doctor-Regulation–Based web and mobile health intervention targeting an active lifestyle with a wearable device (Patent ZL 2015 10500978.9, ZL201520614862.3) for weight control [19, 20], with BMI (body mass index) as the main outcome, along with improvement of reproductive and metabolic dysfunction in overweight/obese women with PCOS. Results from the present study hopefully aid the involvement of acupuncture in PCOS healthcare considering its low cost and few side effects.

3. Methods

3.1. Objectives

The primary aim of the 32-week randomized controlled study is to investigate the efficacy and safety of acupuncture plus lifestyle management on BMI of overweight/obesity PCOS women in comparison with sham acupuncture and lifestyle modification. Secondary objectives include the body composition, ovarian functions including sex hormones, frequency of the menstrual cycle and ovulation, circulating sex steroids, changes in insulin resistance evaluated by the oral glucose tolerance test (OGTT) and glycated hemoglobin (HbA1c). Other metabolic indicators are lipid profile, ghrelin and so on. Health-related quality of life and symptoms of anxiety and depression, side effects are also evaluated. Potential mechanisms of acupuncture are assessed from metabolomics.

3.2. Study Design

The present study is a prospective two-arm randomised sham-controlled design with a 32-week study duration based on previous studies. The interventions to be tested are 1) Active acupuncture (3 times/week for a total of 48 sessions over 16 weeks) + lifestyle management; 2) Sham acupuncture (3 times/week during 16 weeks) + lifestyle management. Participants will be enrolled at at Peking University Third Hospital, Beijing China. The flow chart of the trial is shown in Figure 1 and 2. The design of this study is compliant with the Consolidated Standards of Reporting Trials (CONSORT) guidelines [21] and with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement 2013 [22] (Table 1). The study protocol has been approved by the Regional Ethical Review Board of Peking University Third Hospital, China. Approval Number: PKU3-IRB-M2019021 and registered in ClinicalTrials.gov (NCT04193371).

	Enrolment	Baseline (0)	Months 1	2	3	4	Follow-up after 4 months of treatment	Follow-up 16 weeks after last treatment
Enrolment	√							
Eligible screen	√							
Informed consent	√							
Allocation		√						
Interventions								
Active acupuncture + lifestyle management			√	√	√	√		
Sham acupuncture + lifestyle management			√	√	√	√		
Anthropometry								
Body composition (weight, height, waist circumference, hip circumference), FG/acne, blood pressure		√					√	√
Menstrual cycle diary		√	√	√	√	√	√	√
Transvaginal or transrectal ultrasound			√				√	√
Metabolic measures								
OGTT and Ins. Fasting blood samples for FGLU, FINS, HbA1c, Lipids (TC, TG, HDL, LDL) and inflammatory markers			√				√	√
Endocrine measures								
Fasting blood samples for LH, FSH, E2, P, PRL, T, T2, FAI, SHBG, AMH, TSH, T3, T4 and Neuroendocrine hormone			√				√	√
Questionnaires								
SF-36, EQ-5D, PCOSQ, SAS, SDS			√				√	√
Blinding assessment							√	

Figure 1: The recommended SPIRIT figure with overview of this study protocol.

[antimüllerian hormone (AMH); dopamine (DA); Estrogen (E2); EuroQol health index scale (EQ-5D); Ferriman–Gallwey score (FG); follicle stimulating hormone (FSH); Free Androgen Index (FAI); glycated haemoglobin (HbA1c), high density lipoprotein (HDL); low density lipoprotein (LDL); luteinizing hormone (LH); Progestin (P); Prolactin (PRL); polycystic ovary syndrome questionnaire (PCOSQ); sex hormone binding globulin (SHBG); short form-36 (SF36); thyroid stimulating hormone (TSH); triiodothyronine (T3); thyroxine (T4); total cholesterol (TC); triglycerides (TG); testosterone(T); androstenedione (T2); Zung Self-Rating Anxiety Scale (Zung SAS); Zung Self-Rating Depression Scale (Zung SDS)].

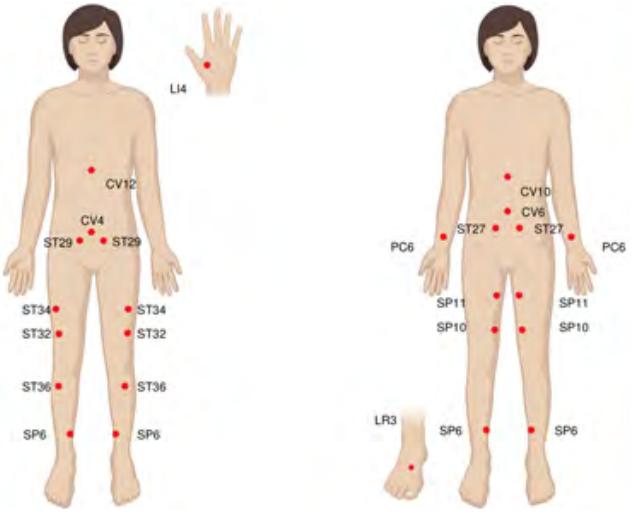

Figure 2: The location of the chosen acupoints on women in treatment group.

2.3. Study Setting

The study is being conducted in Peking University Third Hospital, Beijing, China. The overall study duration per patient is 32 weeks.

2.4. Participants and Recruitment

Eligible participants will be identified by their clinician and fulfil the following criteria:

2.4.1. Inclusion criteria

1) Age 20 to 40 years;

2) BMI ≥ 24 and <40;

3) PCOS diagnosis according to Rotterdam criteria 2003 [23] with at least two of the following three symptoms: (1) infrequent ovulation or anovulation; (2) hyperandrogenism or clinical manifestations of high blood androgen; (3) ultrasound findings of polycystic ovaries in 1 or 2 ovaries, or ≥12 follicles measuring 2 to 9 mm in diameter, and/or ovarian volume ≥10 mL;

4) No immediate fertility wishes and willingness to use barrier contraceptive methods for 32 weeks;

5) Willingness to sign the consent form;

3.4.2. Exclusion Criteria

1) Exclusion of other endocrine disorders such as androgen secreting tumors, suspected Cushing's syndrome and non-classic congenital adrenal hyperplasia, thyroid dysfunction and hyperprolactinemia;

2) Type I diabetes or not well controlled type II diabetes;

3) Pharmacological or acupuncture treatment within past 3 months;

4) Pregnancy or breastfeeding in the last 6 months;

5) Daily smoking and alcoholic intake;

6) Mental problems;

The participants will be recruited from outpatients of two departments, obstetrics and gynaecology and endocrinology and metabolism, via hospital poster, WeChat (a free popular social application in China) and advertisements in public transportation by two study physicians.

3.5. Randomization and Allocation

PCOS women fulfilling the inclusion criteria will be randomized to one of two groups as:

1. Active acupuncture (3 times/week during 16 weeks) + lifestyle management

2. Sham acupuncture (3 times/week during 16 weeks) + lifestyle management

Acupuncture intervention will be conducted for 30 minutes three times per week over 16 consecutive weeks, with a maximum of 48 acupuncture treatments sessions during 16 weeks and then follow up 16 weeks. In this study, the subjects who meet the inclusion and exclusion criteria will be randomly grouped by the method of mixed zone group randomization, with block sizes 4 and 6 via a computer-generated randomization list (prepared by SAS 9.4, SAS Institute Inc., Cary, NC, USA). Randomization scheme will be performed at the Peking University Third Hospital good clinical practice (GCP) centre through three different steps: sequence generation, allocation concealment, and implementation. Once the participant has provided written informed consent, she will be randomly assigned to one of two groups in a 1:1 ratio: body acupuncture and lifestyle intervention or sham acupuncture with lifestyle modification. Randomization is performed by the coordinating study staff using the computer-generated randomized list and the computer reveals only one result at a time. The results of the randomization are provided via telephone to the acupuncturist, and all women who enter the study will be given a unique study number, and only the acupuncturist know the differences from true and sham acupuncture treatment. If the study physicians ensure the patient is eligible for participation, they will contact the coordinating study staff. The staff will generate the allocation and communicate the result to the acupuncturist via telephone and WeChat. Then, the acupuncturist will communicate the result of the randomization to the patient, and all participants will be told accolated to the treatment group due to the study design, and only the acupuncturist know the differences from true and sham acupuncture treatment.

3.6. Blinding

The investigators and statistician will be blinded to treatment allocation, so that independent assessments and statistical analysis can be carried out. The subjects in the control group also be blinded due to the sham-acupuncture trial design only the acupuncturists will not be blinded throughout the study.

3.7. Interventions

3.7.1. Active Acupuncture: The rationale of acupuncture protocols is based on traditional Chinese and Western medical theories., and the study protocol follows the CONSORT [21] and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [24] recommendations. The rationale of the acupuncture protocol is based on literature and our previous study on acupuncture treatment of PCOS. The acupuncture protocol is fixed following the previous RCT in women with PCOS including ClinicalTrials.gov, NCT01457209 [24], ClinicalTrials.gov, NCT01573858 [25] and ClinicalTrials.gov, NCT02647827 [26]. Two sets of 14 acupuncture points are selected and will be alternated every other treatment for use. The first set consists of points located in the abdomen: conception vessel (CV)4, CV12 and stomach (ST)29; points around the keen includes: ST32, ST34 ST36 and spleen (SP)6 bilaterally, as well as large intestinal (LI) 4 located in hand bilaterally. The second set also consists of abdominal points: ST 27 bilaterally, CV6 connected to CV10; leg points: SP10 and SP11; SP 6 and liver (LR) 3 bilaterally, hand points: pericardium (PC) 6 bilaterally. The details of acupoints and their functions are listed in Table 1 and Figure. 3.

Disposable, single-use, sterilized acupuncture needles (sterilized CE marked needles, 0.25 x 30 mm and 0.30 x 40/50 mm, Huatuo, Suzhou Medical Co Ltd, China) will be inserted at a depth of 15–40 mm into the points, and all points will be stimulated manually by rotating the needle to evoke needle sensation (de qi) immediately after inserted. CV4 and 12, ST29 bilateral, ST32 and ST34 bilateral of first set, while CV6 and CV10, ST27 bilateral, SP11 and SP10 bilateral of second set will be connected to an electrical stimulator (HANS-200, Nanjing, China). The stimulation frequency will be set at 2 Hz (0.3 ms pulse length), and the intensity will vary from 0.1 mA to a maximum of 2.0 mA until the needle handle begins to slightly tremble without pain or discomfort. Needles not connected to the electrical stimulator will be manually stimulated to evoke needle sensation every 10 min, in total four times.

Acupuncture treatment will be given by registered Chinese medicine doctors with more than 3 years of clinical experience. The acupuncturist can choose 2-3 additional acupoints beyond this main acupuncture prescription according to their TCM diagnoses and experiences.

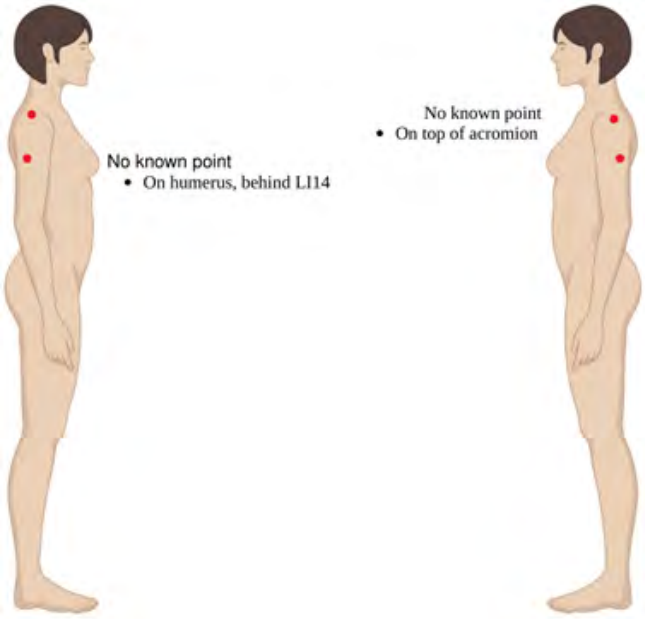

Figure 3: The location of the unknown points on women in control group.

Table 1: Acupuncture protocol.

Point	Stimulation	Localization	Muscle	Muscle innervation
Set 1				
Guan Yuan (CV4)	EA	3 cun caudal to the umbilicus	Fibrous tissue, linea alba	L1
Zhongwan (CV12)	EA	On the midline, 4 cun superior to the umbilicus	Fibrous tissue, linea alba	Th7–8
Guilai (Bilateral, ST29)	EA	1 cun cranial to the pubic bone and 2 cun lateral of the midline	M. rectus abdominis	Th6–12
Futu (Bilateral, ST34)	EA	2 cun above the superior lateral border of the patella on the line connecting the anterior superior iliac spine found	M. quadriceps femoris	femoral nerve
Liangqiu (Bilateral, ST32)	EA	6 cun above the superior lateral border of the patella on the line connecting the anterior superior iliac spine found	M. quadriceps femoris	femoral nerve
Sanyinjiao (Bilateral, SP6)	DeQi, four times	3 cun proximal to the medial malleolus	Mm. flexor digitorum longus, tibialis posterior	L4–5, S1–2
Zusanli (Bilateral, ST36)	DeQi, four times	On the anterior lateral side of the leg, 3 cun below Dubi (ST35), one finger width (middle finger) from the anterior crest of the tibia	Musculi tibialis anterior	L4–5, S1
Hegu (Bilateral, LI4)	DeQi, four times	On the highest point at m. interosseus dorsalis	Mm. interosseus dorsalis I, lumbricalis II, adductor pollicis	C8, Th1
Set 2				
Qihai (CV6)	EA	1.5 cun caudal to the umbilicus	Fibrous tissue, linea alba	Th11
Xiawan (CV10)	EA	2 cun cranial to the umbilicus	Fibrous tissue, linea alba	Th8
Daju (Bilateral, ST27)	EA	3 cun cranial to the pubic bone and 2 cun lateral to the midline	M. rectus abdominis	Th6–12

JiMen (Bilateral, SP11)	EA	6 cun above the patella in line with SP10	M. quadriceps femoris	L2–L4
Xuehai (Bilateral, SP10)	EA	On the medial side of the thigh 2 cun above the superior medial corner of the patella on the prominence of the medial head of the quadriceps muscle of the thigh	M. quadriceps femoris	L2–L4
Sanyinjiao (Bilateral, SP6)	DeQi four times	3 cun proximal to the medial malleolus	Mm. flexor digitorum longus, tibialis posterior	L4–5, S1-2
Taichong (Bilateral, LR3)	DeQi four times	Between metatarsal I & II, just distal to the caput	M. Interosseus dorsalis I	S2–3
Neiguan (Bilateral, PC6)	DeQi four times	2 cun proximal to the processus styloideus radii, between the tendons of the palmaris longus and the flexor carpi radialis	M. flexor digitorum superficialis	C8, Th1

C: cervical vertebra; CV: conception vessel; L: lumbar vertebra; LI: large intestine; LR: liver; PC: pericardium; S: sacral vertebra; SP: spleen; ST: stomach; Th: thoracic vertebra.

3.7.2. Sham acupuncture: In the control group, disposable, single-use, sterilized needles made of stainless steel, 0.20 × 20 mm (Huatuo, Suzhou Medical Co Ltd, China) needles are inserted superficially to a depth of <5 mm, with one needle in either shoulder and upper arm at non-acupuncture and non-meridian points with no stimulation [25]. Placement of needles is unlikely to affect ovulation or IR in women with PCOS. Meanwhile, electrodes will be attached to the needles and the stimulator was turned on zero intensity (no electrical stimulation) to mimic active acupuncture (Table 2 and Figure. 3).

Table 2: Sham acupuncture protocol

Point	Stimulation	Localization	Skin innervation
No known point	Sham acupuncture	On humerus, behind LI14	C5-6, n. cutaneous brachii lateralis
No known point	Sham acupuncture	On top of acromion	C3-4, n. supraclavicularis

3.7.3. Lifestyle intervention: All participants will receive lifestyle advice starting from the baseline visit. The lifestyle intervention is assisted by a patent PCOS lifestyle management system (National invention patent, ZL 2015 10500978.9, ZL201520614862.3) [19], which combine the website, app and wearable device, via the Doctor-Regulation–Based web and mobile health intervention targeting an active lifestyle with a wearable device [20]. A face-to-face nutritional consultation will be subsequently arranged for each patient to tailor an individualized lifestyle treatment. Meanwhile, individualized nutrition and activity advice will be provided to each patient in terms of their weight-loss goals and food diaries each week following WHO recommendations. All participants will receive a step-counter and upload a lifestyle App for daily use, a recipe for exercise and diet each day, and a physical exercise diary for daily reporting of exercise and diet: number of steps, type of activity, intensity and time (minutes). Daily nutrient intake will feed back to the researcher immediately. We set strict exercise and diet rules. For example, step counts accumulated with a frequency of 100–150 steps/min are considered as "effective steps" and recorded using a prescription pedometer, and the duration of each continuous exercise should last a minimum of 10 min.

3.8. Outcome Measurement

3.8.1. Primary Outcome: The primary outcome is the change of BMI from baseline to the end of treatment (16th week). Body weight (kg) and body height (cm) are recorded to the nearest 0.1 kg and 0.1 cm, respectively. BMI is calculated as body weight (kg) divided by squared body height (m^2). The formula for BMI is as follows:

$BMI = mass\ (kg)/(height(m))^2$.

The BMI reduction will be assessed by a blinded investigator from the Sports Institute of the Hospital.

3.8.2 Secondary Outcomes: Secondary outcome measures include other anthropometric measures, endocrine and metabolic outcomes, psychological, quality of life, side-effects and adverse events:

Anthropometric measures

Weight, height and waist circumference are measured using standard methods. All women will be examined with a body composition analyzer (Tanita Corporation, model MC-180, Japan) to measure total body fat, visceral fat mass and ratio, lean mass and basal metabolic rate etc. Hirsute assessment by Ferriman-Gallway (FG), acne standard acne lesion counts, and pelvic examination will also be conducted.

Metabolic measures:

Glucose tolerance and insulin sensitivity are assessed by the OGTT and Ins with 75 g glucose, as well as the HOMA-IR [fasting insulin (μU/mL) × fasting glucose (mmol/L)] / 22.5), HOMA-β /islet β-cell function 20 × fasting insulin (mU/mL) / (fasting plasma glucose (mmol/L) − 3.5) [27]. Further, fasting blood samples will be obtained to measure glycated haemoglobin (HbA1c), inflammatory markers, lipids (total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein (LDL)), lip metabonomic and bile acid are detected with the methods of metabonomic [19, 26].

Endocrine measures:

Menstrual frequency:

Menstrual cyclicity will be calculated from menstrual diaries over 32 weeks.

Ovarian morphology:

Total antral follicle count, ovarian volume in three dimensions, uterine size and endometrial thickness (mm) will be checked by transvaginal or transrectal ultrasound. The size of the largest ovarian follicle/cyst and size of each follicle with a mean diameter greater than 10 mm, and total antral follicle count (small follicles with mean diameter <10 mm) of each ovary will be obtained through B-ultrasound to assess PCOS yes/no [6].

Hormonal profile:

Blood samples will be drawn for analyses of sex steroids (luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone(T), androstenedione (T2), Progestin (P), estrogen (E2), prolactin (PRL)), Neuroendocrine hormone, as well as sex hormone binding globulin (SHBG), Free Androgen Index (FAI), antimüllerian hormone (AMH), thyroid stimulating hormone (TSH), triiodothyronine (T3) and free thyroxine (T4).

Quality of life:

The quality of life will be evaluated by short form-36 (SF36) [28], EuroQol health index scale (EQ-5D) [29] and polycystic ovary syndrome questionnaire (PCOSQ) [30, 31].

Psychological measures:

Negative emotion will assess the by the Zung symptom depressions score (SDS) and Zung symptom anxiety score (SAS) be used [32, 33]. Depression symptoms of potential clinical relevance is for Zung SDS ≥ 0.5 (Depressive index), Anxiety symptoms of potential clinical relevance is for Zung SAS ≥50 (Standard total score).

3.9. Sample size

An independent statistician will monitor the study design from the beginning of the study and take responsibility for calculating the sample size and all data. Samples size calculation derives from our pilot study demonstrating to detect that group sample sizes of 170 patients (85 in group 1; 85 in group 2) would provide 80% power assessed by body mass index to reject the null hypothesis of equal means when the mean difference is 2.59 (5.63-3.04) with standard deviations of 5.8 for group 1 and 6.18 for group 2 at a two-sided alpha of 0.05. Given an anticipated dropout rate of 20%, total sample size required is 212 (106 in group 1; 106 in group 2).

3.10. Data collection and management

All researchers including the acupuncturists, outcome assessors, data collectors, data managers, data entry personnel and statisticians will receive special training regarding the standard procedure and data management. Each person's Case Record Form (CRF) is marked by a unique code.

The patients will receive a separate list of the study set-up and protocol deviations, and the importance of completion of the follow-up will be stressed. The patients have been informed of the value of completing the study course. All patients are reminded throughout the study to fill out the daily exercise and diet data required by the lifestyle intervention system, questionnaires every 16 weeks during study visits, The patients receive reminding phone calls if they miss an acupuncture treatment or a questionnaire has not been returned in time. Throughout the follow-up period, the researchers will check responses and, if necessary, contact patients for completion of their follow-up. If a patient drops out of treatment, it will be documented on a special study discontinuation form.

3.11. Statistical Analysis

The statistical analyses will be performed by qualified statisticians and biostatisticians. Both per protocol (PP) and intention-to-treat (ITT) analysis will be used to determine the robustness of the evidence. Observation carried forward (LOCF) analysis will be applied for ITT.

The primary outcome is the change of BMI after 16th week treatment. To determine differences between the 2 groups, independent sample t-test or Mann Whitney U-test for quantitative data and the chi-square test for qualitative data will be performed to test homogeneity of the baseline characteristics between the two groups. Continuous variables will be presented as means ± standard deviations if they are normally distributed or as medians with interquartile ranges if they are not normally distributed. Different treatment groups will be compared according to the changes from baseline to after-treatment condition and from baseline to follow-up. And the group comparison will be carried out by ANOVA followed by Dunnet post-hoc test or Kruskal-Wallis followed by Mann Whitney U-test when analyzing continuous variables and by $\chi 2$ tests when analyzing categorical variables. The frequency and percentage of classified data were calculated by Pearson chi-square test or Fisher exact Chi-square test. A mixed model approach will also be used if necessary. All statistical analyses of the data will be performed using the SPSS program version 25.0 (IBMInc., New York, USA) or higher, and a P-value < 0.05 will be considered statistically significant.

4. Discussion

Obesity is a global health problem with profound clinical, social,

and economic consequences [34]. The prevalence of severe obesity increases at least 4-fold since 1985, causing increased risks for developing type 2 diabetes, cardiovascular disease, sub-fecundity and infertility, emotional and social complications, which requires lifelong treatment [35]. PCOS is one of the leading causes of infertility, characterized by reproductive, metabolic and psychological features [3]. Women with PCOS appears to have a higher prevalence of overweight, obesity and greater longitudinal weight gain, which worsens the clinical and biochemical presentation of the syndrome, contributing to IR, hyperandrogenism, reproductive disorders, diabetes and cardiovascular disease [4, 5]. Weight management is recommended as initial first line treatment in international evidence-based guidelines in PCOS, but is difficult to achieve in many patients [8, 9].

Current literature evidence indicates that PCOS women are dissatisfied with conventional medical treatments [36] and often disclose poor adherence to lifestyle behaviour [7]. Acupuncture is a low-risk, non-pharmacological Chinese medical treatment that has been shown to be efficacious for weight loss in non-PCOS population [37]. However, it is unclear if women with PCOS could achieve similar benefits.

Although previous studies have shown that acupuncture is effective and safe in improving glucose metabolism and insulin sensitivity in patients with PCOS [38, 39], there is a paucity of evidence from rigorous RCTs for acupuncture on weight loss in the same population. Importantly, there is a need for Comparative Effectiveness Research (CER) to strengthen the evidence base for clinical and policy decision-making.

Our pilot study indicates high levels of acceptance of acupuncture as a possible adjunct to lifestyle interventions for weight loss [19]. Acupuncture may bring about weight loss by regulating appetite and energy expenditure [15-17]. Therefore, we design the current prospective randomized controlled trial to investigate the efficacy, safety and acceptability of acupuncture as a novel adjunctive intervention, with usual care (lifestyle management) for weight loss in PCOS, as well as the ovulation, hyperandrogenism, insulin sensitivity and related biomarkers that are clinically relevant in PCOS.

It will be the first study on the Chinese population and will gain evidence for utilizing acupuncture in overweight and obese women with PCOS. For better remote management and administration of the patients, the current study applies web- and mobile-based medical care techniques which are developed by our group [19]. This system adopts evidence-based medicine rationale to provide individualized exercise and diet advices for different PCOS subpopulations. This represents an innovation in the delivery of lifestyle intervention, allowing the device to be used at home, reducing the need for frequent clinic visits, to a certain extent, it prevented the loss [20].

The current study also aims to uncover new knowledge in the pathophysiology of PCOS and develop additional treatment strategy for weight control in women with PCOS and related conditions. Study findings will provide deeper insight into revealing the effect of acupuncture, compared with usual care (lifestyle management) for weight control, in overweight and obese women with PCOS. Otherwise, there are some limitations of the proposed research, as the sample size is not very large and it is a single-centre trial, limited to women in Beijing. However, the trial is proposed to be a pilot study for a later large-scaled clinical trial, and the results from the present study have the potential to be immediately implemented into the healthcare system since it has previously been shown to be cost-effective with few negative side effects.

5. Trial Status

This trial began in November 2019 after IRB approval. Trial completion is expected by the end of August, 2024. The progress has been affected by the epidemic COVID-19, and the recruitment is currently ongoing.

6. Acknowledgements

We express gratitude towards Ming Yi and Lin Zeng for the preparation of the study documents and the monitoring of the data, the patient advisors as Ping Song and Ying Xiao who help us for participants' enrolment and follow-up.

7. Authors' contributions

DL, RL and JQ are supervisor of the study; HLZ, ZJH, DL and RL all contributed to the design and development of the study protocol; WW and JQ conceptualized and coordinated the study; WW and HLW are responsible for patient recruitment and data collection; LS is responsible for the generation of random numbers; HLZ, ZJH, XYX, YY and YTZ provided scientific advice regarding the development of the intervention, and HLZ, ZJH, XYX and YTZ acquired the patient data, performed the treatments; HZ gave guidance to statistical methodology and prepared the data analysis; HLZ contributed to the writing of the manuscript, and all authors read and approve the final manuscript.

8. Funding Statement

The work is supported by the Special Grant for Capital Health Research and Development (Grant No. 2022-2-4098), National Natural Science Foundation of China (Grant No. 82174151), Peking University Third Hospital "Key Young Talents" Training Program (Grant No. BYSYFY2021032), CAMS Innovation Fund for Medical Sciences (2019-I2M-5-001 and Beijing leading scholar program of learning TCM and the project funds of Beijing institute of integrated traditional Chinese and western medicine. The funders have had no role in study design, and will not have any role in data collection and analysis, decision to publish, or preparation of the manuscripts.

9. Data Availability Statement

The datasets used and/or analysed in the current study are available from the corresponding author upon reasonable request

10. Ethics approval and consent to participate

The study conducted in accordance with the Declaration of Helsinki

and has been approved by the Regional Ethical Review Board of Peking University Third Hospital, China. Committee approval number: PKU3-IRB-M2019021. All eligible patients will be informed of the details of the study and the benefits and risk. Meanwhile, participants will be clearly told about the equal chance of allocation to one of the two groups, each participant will be given written and oral information and asked for her signed informed consent to be randomized and followed-up by research staff.

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