

Comparative Effectiveness of Aerobic Exercise Versus Yi Jin Jing On Reproductive Health In Young Overweight/Obese Women With Polycystic Ovary Syndrome: Study Protocol For A Randomized Controlled Trial.

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Study protocol

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Abstract

Background: Polycystic ovary syndrome (PCOS) is the most common heterogeneous endocrine disease among women of childbearing age, affecting women throughout life on their reproductive, metabolic and cardiovascular health, as well as psychological health. Aerobic exercise is an important solution used to manage PCOS, due to its multiple benefits. Yi Jin Jing is an important component of traditional Chinese exercise (TCE), based on the root of traditional Chinese medicine theory (TCM), which focuses on keeping the body as a whole in a harmonious state. However, to date there is no literature on the benign effects of Yi Jin Jing on PCOS. The primary purpose of this protocol is to assess the effectiveness of aerobic exercise versus Yi Jin Jing, on the management of PCOS-related reproductive health in young overweight/obese women.

Methods: The study will conduct a three-armed parallel-group of a randomized controlled trial, recruiting 90 women diagnosed with PCOS, ages between 18 and 35 years, with a body mass index (BMI) ≥ 23 kg/m². Women will be randomly assigned to either control group (combined oral contraceptives) or one of the intervention groups (Yi Jin Jing group or aerobic exercise group) with an allocation rate of 1:1:1. The intervention will be conducted within a 12-week period. The primary outcomes would be anti-Mullerian hormone (AMH) level and menstrual frequency; the secondary outcomes would be biochemical profiles, ovarian volume, antral follicle count, BMI and homeostasis model assessment of insulin resistance (HOMA-IR). Outcome measures would be collected during baseline and end of treatment. Reporting of the study will follow the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.

Discussion: This proposed study will be the first randomized clinical trial to evaluate the comparative effectiveness of aerobic exercise versus Yi Jin Jing on the management of PCOS-related reproductive symptoms in young overweight/obese women. The results will provide a new evidence-based management strategy for young women with PCOS.

Trial registration: Chinese Clinical Trail Registry, ID: ChiCTR1900022385. Registered on 9 April 2019, <http://www.chictr.org.cn/listbycreator.aspx>.

Background

Polycystic ovary syndrome (PCOS) is the foremost endocrinopathy which affects 6–10% of the reproductive stages in women [1]. PCOS is characterized by androgen excess, ovarian dysfunction and polycystic ovarian morphology [2] and is further aggravated by hyperinsulinemia [3], thus causing a number of reproductive and metabolic dysfunctions. The main clinical features include anovulation, menstrual irregularity, infertility, acne and metabolic disorders [2, 4, 5], affecting diagnosed limiting women lifespan [6], and reducing health related quality of life. Presenting signs and symptoms are heterogeneous and could change with aging, reproductive function disorders are the primary disturbances in younger women with PCOS [7–9]. About 60% PCOS women are overweight or obese [10],

and excess weight could significantly worsen reproductive features for PCOS [11], as well as weakening the effectiveness of fertility treatment and increasing the risk of pregnancy complications [12]. In 2005, the annual cost on reproductive-aged PCOS women in the United States was up to \$4.36 billion, of which 46.2% were used to treat reproductive health problems [13], resulting in a tremendous economic burden to families and the society as a whole. Thus, improving reproductive health is crucial for young overweight/obese women with PCOS.

Lifestyle modification (diet and exercise) is recommended as the first-line management for PCOS to achieve effective weight management and to optimize hormonal profiles, ultimately improve quality of life [14, 15]. In relation to diet, exercise has equal and sustainable effect in maintenance of weight loss, improvement of menstrual status and ovulation in overweight/obese women with PCOS [16]. While dietary program is at the expense of muscle mass [16], exercise could reduce more fat mass, retain lean muscle mass and improve body composition [17, 18], suggesting the optimal role exercise plays in lifestyle management for PCOS. Al-Eisa et al. [19] found that 12-weeks aerobic training can significantly improve reproductive function by decreasing body mass index (BMI), anti-Mullerian hormone (AMH) and antral follicle count in PCOS group, while increasing follicle stimulating hormone (FSH) and estradiol (E_2). Aerobic exercise could significantly reduce the number of follicles developments between 2–9mm and improve ovarian morphology [20]. Aerobic exercise could improve quality of life of women with PCOS [21]. An updated meta-analysis consisting of 18 studies, with total of 1978 participants showed that exercise intervention may improve pregnancy rates in women with reproductive health problems [22]. However, another recent meta-analysis including 14 studies which evaluated a total of 617 women with PCOS, pointed out that the impact of exercise interventions on reproductive function remains ambiguous, without sufficient evidence to quantify the effect of exercise on reproductive health outcomes of affected women [23]. The conflicting evidence suggest the need for further studies on the effect of exercise intervention on reproductive function of women with PCOS.

According to traditional Chinese medicine (TCM) theory, kidney deficiency is viewed as the root problem in PCOS [24], kidney dominates the function of “kidney-Tian Gui-Chong Ren-uterus axis” [24]. The dysfunction of hypothalamic-pituitary-ovary (HPO) axis plays a role on pathogenesis of PCOS, resulting in increased gonadotrophin releasing hormone and luteinizing hormone (LH), then impacting ovarian androgen synthesis and folliculogenesis [2]. The “kidney-Tian Gui-Chong Ren-uterus” axis of TCM is similar to HPO axis in modern medicine [25]. Where the function of the kidney resembles that of the hypothalamus [24], the function of Tian Gui resembles that of the sex hormone [26], and the function of Chong meridian and Ren meridian resemble that of the pituitary gonadotropin [24]. Thus the kidney deficiency could lead to disturbance of Tian Gui [27], and disharmony of Chong and Ren meridians [26].

Furthermore, overweight/obese PCOS women are closely related to phlegm-dampness constitution [28, 29], phlegm-dampness could block meridians, causes Qi stagnation and blood stasis, aggerating a number of reproductive dysfunctions.

Yi Jin Jing, which dates back to ancient China, consists of soft and stretching body movements, breath control and meditation [30]. Practicing Yi Jin Jing could achieve harmonious integration of body and mind, by attaining a relaxed and deep focused state. Yi Jin Jing, as an important part of traditional Chinese exercise (TCE), has a theoretical root on TCM, having a dual nature of exercise and medical treatment [31]. Yi Jin Jing training emphasis on waist movement, thus could strengthen the kidney through waist movement exercises, and the waist is termed as “the house of kidney” from the TCM theory [31]. Yi Jin Jing could also stimulate the Chong and Ren meridians through flexion and extension movements, balancing of the Yin and Yang, and harmonizing Qi [31, 32] to attain the holism and benign effects .

Hong et al.[33] discovered that Yi Jin Jing may balance level of estrogen and progesterone, reduce the level of prostaglandins PGF_{2a} and improve primary dysmenorrhea symptoms, while Chen et al.[34] found that 3-month of Yi Jin Jing training could improve sex hormones levels of FSH, LH and testosterone (T), reduce the proportion of E₂/T in elderly men, hinting the benign role of Yi Jin Jing on reproductive health. Yi Jin Jing could reduce BMI, fat mass and improve lean muscle [35], helping to improve phlegm-dampness constitution. In conclusion, Yi Jin Jing could be used to manage PCOS related symptom by addressing both manifestation (phlegm-dampness) and root cause (kidney deficiency). To our knowledge no studies investigating the effect of Yi Jin Jing in women with PCOS have been conducted. Therefore, we intend to see the effect of Yi Jin Jing in PCOS and comparative effectiveness of aerobic exercise versus Yi Jin Jing on the reproductive health in young overweight/obese women with PCOS, proving evidence-based solution for feasibility and executing a new convenient mean for managing PCOS.

Methods /design

Objectives

The main objective of this study is to find out the effect of Yi Jin Jing in PCOS and to evaluate the comparative effectiveness of aerobic exercise versus Yi Jin Jing on reproductive health in young overweight/obese women with PCOS.

Study design

The study is designed as a controlled randomized, three-arm parallel group trial. Reporting of the study will follow the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (Additional file 1). A total number of 90 diagnosed PCOS patients will be recruited from Yue yang Integrated Chinese and Western Medicine Hospital; Affiliated to Shanghai University of Traditional Chinese Medicine. Patients will be recruited from the gynecologist ward through fliers, posters and gynecologist recommendations. Patients will be randomly assigned to two intervention and control group with an allocation ratio of 1:1:1. The intervention groups will undergo either Yi Jin Jing or aerobic exercise training for 12 consecutive weeks and the control group with no training intervention but take oral contraceptives (OCPs). Post-test measurements will be conducted based on the primary and secondary outcomes in comparison to the baseline measures.

Study setting

All the medical tests will be conducted in the Yue yang Integrated Chinese and Western Medicine Hospital; Affiliated to Shanghai University of Traditional Chinese Medicine. The aerobic exercise and the Yi Jin Jing intervention will be conducted at Shanghai University of Sport.

Inclusion criteria

- (1). Women aged between 18 and 35 years [36, 37];
- (2). Diagnosed with PCOS using the Rotterdam criteria, that at least two of the following are present: oligo-ovulation or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries as defined by ultrasonography, that is presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter, and/or increased ovarian volume (> 10 mL) [38];
- (3). BMI \geq 23 kg/m².

Exclusion criteria

- (1). Known disorders that mimic the PCOS, such as congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome [38];
- (2). Cardiovascular diseases, thrombotic diseases;
- (3). Acute or chronic hepatitis or nephritis;
- (4). Taking medications known to affect reproductive function within the past 3 months;
- (5). Any pulmonary or musculoskeletal diseases that could be impaired by exercise;
- (6). Participating or having regular exercise training during the past 3 months;

Interventions

Aerobic exercise intervention

Aerobic exercise intervention will be conducted on stationary bikes, for 50 mins with an intensity level of 65%-75% maximum heart rate, 3 times a week (one exercise session for every two days), accumulating to 150 mins every week [14, 39, 40]. The sessions will include 5-min warm-up and cool down protocols before and after exercise. Aerobic exercise will be conducted at Shanghai University of Sports under the supervision of an accredited physical trainer.

Yi Jin Jing intervention

Yi Jin Jing group will conduct the Yi Jin Jing practice 30 mins, 5 times a week [34], the sessions will include 5-min warm-up and cool down protocols before and after Yi Jin Jing practice. Practice will be

conducted at Shanghai University of Sport with the guidance of an experienced Yi Jin Jing instructor who has been teaching Yi Jin Jing for 5 years.

Control group

Control group will take OCPs. OCPs are the first-line pharmacologic therapy for patients with polycystic ovary syndrome who are not trying to conceive [41, 42]. Diane-35, a kind of OCPs containing 2-mg cyproterone acetate and 35- μ g ethinyl estradiol, is the first choice for the management of PCOS patients not seeking fertility in China [43]. The control group will take Diane-35 once daily at the same time from the 5th day of menstruation or withdrawal bleeding for a period of 21 days and for 3 menstrual cycles.

The study flow chart is shown in Fig. 1.

Harms

The study will have its own physical trainers and specialized practitioners to ensure proper measures are taken in cases of adverse events. Monitoring of adverse events for the aerobic exercise and Yi Jin Jing during the trial, will include acute pain, heart rate, adverse events occurring is estimated to be low. Side effects of taking Diane-35 including headaches, nausea, weight gain, breast tenderness, and loss of libido will be monitored. Serious adverse reactions will be reported to the ethical committee and other reactions that are thought to be causally associated with the intervention will be managed and recorded in the study.

Adherence and compliance

Prior to allocation, all participants will undergo a face-to-face education program with a doctor. All patients are assigned to smart phone app support. These steps are taken to ensure adherence. Control group patients will be asked to send monthly self-monitored information regarding their medication usage and any side effect via their phones for 3 months. Adherence and compliance will be determined from supervised exercise session attendance. Data from participants with less than 75% adherence will be included in the intention to treat analysis.

Adherence and compliance

Prior and post to intervention, the following will be measured. Transvaginal ultrasound scan will be performed during the early follicular phase (cycle days 3–5) to document ovary morphology, including antral follicle count and ovarian volume. Fasting blood will be taken for 2–5 days during spontaneous menstrual cycle to check biochemical profiles, including AMH, LH, FSH, T, E₂, sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), fasting insulin (FINS), fasting blood glucose (FBG) level. Free androgen index (FAI = $T \times 100 / \text{SHBG}$) and homeostasis model assessment of insulin resistance (HOMA-IR = $\text{FINS} \times \text{FBG} / 22.5$) will be calculated. All participants will receive a menstrual diary to record menstrual bleedings. Anthropometric indicators include weight, height and BMI will be measured.

Outcome measurements

The primary outcomes are serum AMH level and menstrual frequency. AMH could be noticed as a suitable hormonal marker of the ovarian follicular count [44] and as a diagnostic marker for ovarian hyperandrogenism [45]. AMH is the best marker of the ovarian function [46]. Therefore, we choose AMH as one of primary outcomes. Another primary outcome is menstrual frequency. Participants will record their menstrual bleedings during 12 weeks. Menstrual frequency which will be calculated by dividing the number of menstrual bleedings by 3 (ordinal variables: "0", "1/3", "2/3", "1").

Secondary outcomes include:

- (1). biochemical profile including FSH, LH, T, E₂, SHBG, DHEA-S, FAI;
- (2). antral follicle count and ovarian volume;
- (3). BMI;
- (4). HOMA-IR.

Participant timeline

Participant timeline is described in Fig. 2.

Sample size

AMH is the target effect, according to a similar research by Moran [47], where the mean AMH level before intervention was 59.1pmol/L, standard deviation was 20.5pmol/L, AMH declined by 13.2pmol/L in response to exercise. We require 25 participants per group to achieve a power of 80%, two-sided $\alpha = 0.05$. With an approximate attrition rate of 20%, we will recruit 90 participants in total with 30 participants per group.

Recruitment

Enough patients will be recruited through posters, word of mouth, and recommendations from gynecologists.

Recruitment

Prior to provision of written informed consent, eligible participants will be randomly assigned into the control group or the intervention group (aerobic exercise group or Yi Jin Jing group) with an allocation rate of 1:1:1. The randomization procedure will be conducted by an independent statistician using a computerized program. The allocation sequence will be stored in a sealed envelope and will not be announced until the baseline measurements have been completed.

Blinding

Due to the characteristic of exercise intervention, all participants and the aerobic exercise supervisor and Yi Jin Jing instructor will not be blinded. But the staff who undertake outcome measuring and statistician who undertake data processing will be blinded to group allocation.

Data collection and management

Study-related information, such as participant's identity, the data collected relating to the study and medical records, will remain confidential. Case report forms (CRFs) will be completed on paper forms. With regard to self-reported measures, participants will monitor their menstrual cycles using a menstrual diary.

Data monitoring

The data will be recorded in the CRFs. The CRFs will be filled out truly and accurately. Confidentiality of participants will be protected and guaranteed by storing the hard copies of the data collection forms in locked cabinets in the principal investigator's office. Access to electronic clinical report forms stored in the excel spreadsheets data file will be password-encrypted, and restricted to the principal investigators. The blinded analyst will be provided with a de-identified dataset to preserve confidentiality.

Statistical methods

The intention-to-treat principle will be used in the statistical analysis. Continuous variables will be presented by mean \pm standard deviation. We will use the Kolmogorov-Smirnov test to see the normality and Levene test to see homogeneity of variance. Data transformations, such as logarithmic transformation or arcsine square root transformation will be applied in cases of a non-normal distribution. Analysis of variance (ANOVA) will be used for comparing the differences between groups, and Bonferroni test will be applied if the difference is found to be significant. Paired t-test will be used for comparing the differences within groups. Differences between groups of the categorical data (menstrual frequency) will be compared by Kruskal-Wallis test, and Nemenyi test will be applied if the difference is found to be significant. A two-sided *P* value less than 0.05 will be considered significant.

Discussion

Existing pharmaceutical agents such as OCPs have been associated with side effects and are not appropriate for PCOS women with infertility, OCPs may potentially have an adverse cardiovascular risk, elevated inflammatory markers, decreased insulin sensitivity [48]. Non-pharmacological interventions, such as aerobic exercise and Yi Jin Jing have limited side effects and are widely applicable. Yi Jin Jing is a pleasant mind-body exercise, which is similar to other TCEs, such as Tai Chi, which has mild intensity [49]. We are intended to find out whether Yi Jin Jing could have equal or even superior effect on reproductive health for younger women with PCOS when compared to aerobic exercise. We hypothesis that, Yi Jin Jing and aerobic exercise could decrease AMH level and improve menstrual pattern as well as other secondary outcomes compared to control group, thus improve reproductive health of young

overweight/obese women with PCOS. Obesity, insulin resistance, and metabolic disturbances are predominant in older women with PCOS, the early management of younger PCOS women might reduce their risk of insulin resistance and metabolic disturbances later in life [7]. As a result, Yi Jin Jing may offer an easy and inexpensive alternative management for younger women with PCOS, to further avoid long-term complications.

Trial Status

The recruitment phase has begun in July 2019 and is expected to be finished in October 2021.

Abbreviations

PCOS: polycystic ovary syndrome; BMI: body mass index; AMH: anti-Mullerian hormone; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; FSH: follicle stimulating hormone; E2: estrogen; TCE: traditional Chinese exercise; TCM: traditional Chinese medicine; FINS: fasting insulin level; FBG: fasting blood glucose; FAI: Free androgen index; SHBG: Sex hormone binding globulin; T: testosterone; DHEA-S: dehydroepiandrosterone sulfate; ANOVA: Analysis of variance.

Declarations

Ethics approval and consent to participate

The study protocol has been approved by the Institutional Review Board at the Shanghai University of Sport (reference number:102772019RT047). The patients will be informed both in writing and verbally about the purpose and details of the study and all patients enrolled will provide written consent.

Consent for publication

Not applicable.

Availability of data and materials

The authors will have access to the datasets, the datasets are not publicly available. Data will be available from the authors on reasonable request.

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Author's contributions

XYL and YC are equal contributors responsible for study design, overseeing study implementation, providing methodological support to coordinators. JZ and AK drafted the manuscript and participating in recruitment, organizing the intervention materials, and intervention sessions.

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Competing interests

The authors declare that they have no competing interests.

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Figures

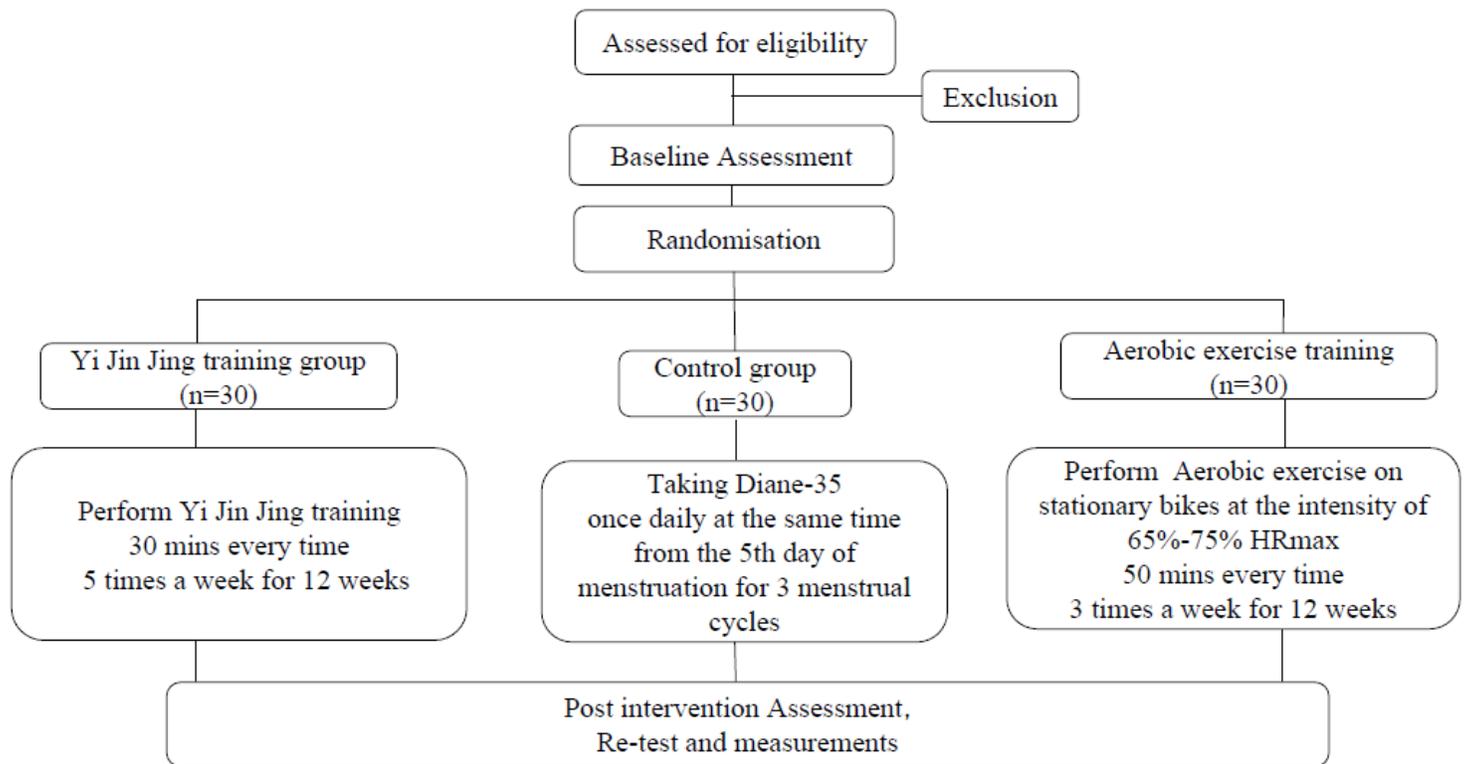


Figure 1

Study flow chart

STUDY PERIOD						
	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT**	0	0	wk 1-4	wk 5-8	wk 9-12	t _x
ENROLMENT:						
Eligibility screen	X					
Education program	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
Yi Jin Jing exercise group			←-----→			
Aerobic exercise group			←-----→			
Control group			←-----→			
ASSESSMENTS:						
Anthropometric indicators		X				X
Transvaginal ultrasound scan		X				X
Biochemical profiles		X				X
Menstrual bleedings			X	X	X	
Adherence, drop out, adverse events			X	X	X	X

Figure 2

Participant timeline

Supplementary Files

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