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Acupuncture and Clomiphene Citrate for Anovulatory Infertility in Polycystic Ovary Syndrome: Study Design of a Randomized Controlled Trial

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Abstract

Acupuncture is an alternative therapy to induce ovulation in women with polycystic ovary syndrome (PCOS)but there is no study reporting the live birth rate following ovulation induction by acupuncture or its potential as an adjuvant treatment to clomiphene citrate (CC). We assess the efficacy of acupuncture with or without CCin achieving live births among 1000 infertile PCOS women in China. This article reports the methodology of an ongoing multi-center randomized controlled trial. The randomization scheme is coordinated through the central mechanism and stratified by the participating site. Participantswill be randomized into one of the four treatment arms: A) true acupuncture and CC, B) control acupuncture and CC, C) true acupuncture and placebo CC, and D) control acupuncture and placebo CC. Acupuncture will be administered twice a week for up to 16 weeks, starting on day 3 after a spontaneous period or a withdrawal bleeding. Either CC or placebo CC 50 mg will be given dailyfrom day 3 to day 7 of the cycle and the dose will be increased in subsequent cycles for non-respondents up to 150 mg/day. To ensure the quality and integrity of the trial we have developed a unique multinational team of investigators and Data and Safety Monitoring Board. Up to the end of April 2013, 326 subjects were recruited. In conclusion, the success of this trial will allow us to evaluate the potential benefit of acupuncture beyond the first line medicine for infertility treatment in PCOS women in an unbiased manner.The trial has been registered at clinicaltrials.gov (NCT01573858) as well as the Chinese clinical trial registration site (http://www.chictr.org/cn/; ChiCTR-TRC-12002081), prior to the start of randomization.

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. It is characterized by ovulatory dysfunction, hyperandrogenism and polycystic ovaries (PCO) and affects 5-10% of premenopausal women [1]. Cloimphene citrate (CC) is considered as the first line treatment to induce ovulation in women with PCOS. Side effects of CC are related to its combined estrogenic and antiestrogenic properties, which include hot flushes, breast discomfort, abdominal distension, nausea, vomiting, nervousness, sleeplessness, headache, mood swings, dizziness, hair loss, and disturbed vision[2]. Approximately 7% of pregnancies resulting from CC-induced ovulation are twin pregnancies and 0.5% are triplet pregnancies [3].

New or adjuvant treatments that are readily accessible, affordable, and safe are needed. Findings from previous clinical and experimental studies indicate that acupuncture may induce ovulation and improve pregnancy in women with PCOS. The objective of the present trial is to test the following three hypotheses in anovulatory women with PCOS: 1) true acupuncture and CC is more likely to result in live birth than control acupuncture and CC, 2) control acupuncture and CC is more likely to result in live birth than true acupuncture and placebo CC, 3) true acupuncture and placebo is more likely to result in live birth than control acupuncture and placebo CC.

2. Materials and methods

2.1 Study population

Women with PCOS who attempt to get pregnant are eligible if they fulfill the following criteria.

Inclusion criteria are:

1. Age of women between 20-40 years.
2. Chronic oligomenorrhea or amenorrhea
3. Hyperandrogenism or polycystic ovaries on ultrasound.
4. Further, at least one patent tube and normal uterine cavity
5. Sperm analysis is normal.
6. Agree to have regular intercourse, i.e., 2-3 times per week.

Exclusion criteria are:

1. Exclusion of other endocrine disorders
2. Use of hormonal or other medication including Chinese Herbal prescriptions in the past 3 months.
3. Pregnancy within the past 6 weeks.
4. Within 6 weeks post-abortion or postpartum.
5. Breastfeeding within the last 6 months.
6. Not willing to give written consent to the study.
7. Additional exclusion criteria
   a) Patients on oral contraceptives, depot progestins,or hormonal implants (including Implanon).
   b) Patients with liver disease defined as AST or ALT > 2 times normal or total bilirubin>2.5 mg/dL.Patients with renal disease defined as BUN > 30 mg/dL or serum creatinine> 1.4 mg/dL.
   c) Patients with hemoglobin < 10 g/dL.
   d) Patientswith a history of deep venous thrombosis, pulmonary embolus, or cerebrovascularaccident.
   e) Patients with known heart disease that is likely to be exacerbated by pregnancy.
   f) Patients with a history of, or suspected cervical carcinoma, endometrial carcinoma, or breast carcinoma.
   g) Patients with a current history of alcohol abuse. Alcohol abuse is defined as > 14 drinks/week or binge drinking.
   h) Patients enrolled into other investigative studies that require medications, prescribe the study medications, limit intercourse, or otherwise prevent compliance with the protocol.

i) Patients who anticipate taking longer than a one month break during the protocol should not be enrolled.

j) Patients taking other medications known to affect reproductive function or metabolism.

k) Patients with a suspected adrenal or ovarian tumor secreting androgens.

l) Couples with previous sterilization procedures (vasectomy, tubal ligation) which have been reversed.

m) Subjects who have undergone a bariatric surgery procedure in the recent past (<12 months) and are in a period of acute weight loss or have been advised against pregnancy by their bariatric surgeon.

n) Patients with untreated poorly controlled hypertension defined as a systolic blood pressure 160 mm Hg or a diastolic100 mm Hg

o) Patients with known congenital adrenal hyperplasia.

2.2 Study design

Participants are randomized to receive either an initial oral dose of 50 mg of CC or placebo CC from day 3 to day 7 of the cycle and acupuncture treatments. In order to maintain the double-blinding for the medication, CC and placebo CC were packaged in identically appearing numbered study kits which were then directly shipped to each clinical site. All participants receive acupuncture treatment twice a week and each treatment session can be separated by an interval of 2-4 days, with a maximum of 32 treatment sessions during 16 weeks. Each treatment session lasts for 30 minutes. Acupuncture treatment will start on day 3 after a spontaneous period or a withdrawal bleeding following progestin, when starting with CC/placebo tablet.Participants will be contacted by phone if they miss the appointment as scheduled. If they miss appointments in the early part of the cycle, more appointments will be arranged in the later part to compensate the missing part. Missed appointments will be clearly documented in the record for analysis later. If the participants miss 6-8 acupuncture treatments (3-4 weeks), she should be scheduled not to take study medications and have this treatment cycle “rested” until she can get acupuncture.

2.3 Study specific visits and procedures

Each specific visit and measurement is summarized in Table 1.

3. Ethical Consideration

Ethics approval has been sought from Ethics Committee at First Affiliated Hospital in Heilongjiang University of Chinese Medicine on behalf of the State Administration of Traditional Chinese Medicine (2010HZYLL-010) and from each participating site. Approval will be applied again after each amendment of protocol. All authors have no conflicts of interest to declare that would affect the conduct of this trial.

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Table 1: Overview of the study visits

	Screening Visit	Baseline Visit	Week 1		Week 2		Week N+ 1		Week 16		End of Treatment Visit
Visit #	1	2	3	4	5	6	N	N+1	33	34	35
Sign Consent	×										
History	×										×
Urine pregnancy test	×		×	×	×	×	×	×	×	×	
Physical examination	×										×
Transvaginal ultrasound	×										×
Semen Analysis	×										
Hysterosalpingo-gram	×										
SafetyEligibilityLads	×										×
Fasting PhlebotomyFor Study Parameters		×									×
Depression, anxiety and quality of life questionnaires	×										×
Credibility check questionnaire			×		×						×
Progesterone assay	×			×		×		×		×	×
HCG assay	×			×		×		×		×	×
Acupuncture treatments (twice weekly)			×	×	×	×	×	×	×	×	
Assess adverseevents and concomitant meds				×		×		×		x	×