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Homoeopathy in polycystic ovarian syndrome: A randomized placebo-controlled pilot study

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) is an emerging health problem in young females characterized by ovarian dysfunction and hyperandrogenism. Existing information indicates a positive role of homoeopathy but more rigorous studies are desirable. This protocol has been developed to undertake a pilot study to evaluate the efficacy of homoeopathic intervention using established diagnostic criteria.

Methods/Design: It will be a multi-centric, randomized, placebo controlled pilot study with a 6-month intervention and follow up period. Minimum 60 cases fulfilling the eligibility criteria will be enrolled and randomized to receive either the homoeopathic intervention or the identical placebo. Both the arms follow lifestyle modification for weight reduction. Primary endpoint will be the establishment of regular menstrual cycle along with improvement in either ultrasonology or hirsutism/acne. Secondary endpoints will be to compare the changes in total and individual domain scores of PCOS questionnaire at monthly interval and the changes in ultrasound of polycystic ovaries. For the primary outcome and each of the secondary outcomes, both per protocol and modified intention to treat analysis will be done.

Discussion: This pilot study has been planned considering the varied presentation of PCOS as per international diagnostic criteria and accordingly the composite endpoints have been kept for evaluation. The outcome of this pilot study will help in planning a definite study.

Trial registration: CTRI/2013/09/003983 [Registered on: 16/09/2013].

Keywords: Anovulation, Homoeopathy, Hyperandrogenism, Insulin resistance, Oligomenorrhoea, Polycystic ovarian syndrome, Polycystic ovary syndrome questionnaire

BACKGROUND

Polycystic ovarian syndrome (PCOS) is a complex metabolic, endocrine and reproductive disorder affecting approximately 5-10% of the female population in developed countries. The developing countries like China and India, undergoing rapid nutritional transitions due to westernised diets and lifestyle also indicate similar prevalence (9.13%).[1,2] Its clinical characteristics include hyperandrogenism, chronic anovulation, insulin resistance and infertility. While reproductive features are prominent, it has potential for major metabolic consequences including obesity, type 2 diabetes and cardiovascular disease.[3] It remains a syndrome and, as such, no single diagnostic criterion (such as hyperandrogenism

or PCO) is sufficient for diagnosis. It also remains a diagnosis of exclusion. Known disorders such as late-onset congenital adrenal hyperplasia that mimic the PCOS phenotype should be excluded.[4]

Although there are more than 5,000 scientific publications, majority relates to pathophysiology and treatment of PCOS but assessment of psychological impact has largely been ignored. Only recently has the complexity of the symptomatology of PCOS begun to be investigated in a comprehensive manner to address the psychosocial implications. It has been concluded that depression and anxiety are common in patients with PCOS as compared with healthy women. Depression in PCOS is often associated with obesity and metabolic abnormalities.[5,6] The depression and anxiety did not show a significant change in PCOS after treatment with oral contraceptive pills.[7] Homoeopathic prescription being holistic might help in these aspects, hence, polycystic ovary syndrome questionnaire (PCOSQ), which evaluates emotional aspects along with body hair, weight, infertility and menstrual problems for the assessment of quality of life is being used in the study.[8]

Lifestyle modification is the first line of treatment and it is known that even 5-10% weight loss has led to significant clinical benefits improving psychological outcomes, reproductive and metabolic features.[9,10] In conventional medical system, metformin, oral contraceptives, anti-androgens, clomiphene citrate and thiazolidinediones are used for the management of different presentations of PCOS. Metformin is commonly used either alone or in combination with other medicines for the treatment of most of the clinical manifestations of PCOS.[11] In a study, metformin reduced hyperinsulinaemia and hyperandrogenaemia, independently of changes in body weight. In a large number of subjects these changes were associated with striking, sustained improvements in menstrual abnormalities and resumption of ovulation[12] but it causes gastrointestinal intolerance (nausea, abdominal pain and/or diarrhoea) in 30% of patients. It is contraindicated in liver disease and certain other clinical conditions. Other medicines also have their side effects.[11]

There are few reports indicating the usefulness of homoeopathic treatment. Sanchez *et al*.,[13] and Gupta *et al*.,[14] reported symptomatic as well as ultrasonological improvement but more studies are required with proper rigor. Council has developed this protocol for a pilot study. The primary objective of the study shall be to determine the feasibility of the study to evaluate the efficacy of homoeopathic intervention in PCOS in establishing the menstrual regularity with either ultrasonological improvement of PCO or improvement in hirsutism/acne and the secondary objective shall be to assess the changes in ultrasound reports of polycystic ovaries and to assess the changes in the total and individual domain scores of PCOSQ.

METHODS/DESIGN

Study Design

The study shall be multi-centric, randomized, placebo controlled with 6-month intervention and follow up period.

Eligibility Criteria

The inclusion criteria for the study are: (1) female aged 18-36 years (2) oligomenorrhoea (intermenstrual period of more than 35 days for 3 consecutive cycles)/ amenorrhoea for more than 3 months (2 years after menarche) (3) ultrasound findings of polycystic ovaries [The PCO should have at least one of the following: either 12 or more follicles measuring 2 ± 9 mm in diameter or increased ovarian volume (>10 cm^3). If there is evidence of a dominant follicle (>10 mm) or a corpus luteum, the scan should be repeated during the next cycle. Only one ovary fitting this definition or a single occurrence of one of the above criteria is sufficient to define the PCO.[15] (4) clinical evidence of hirsuitism (Ferriman score 8 and above)[16] and/ or acne (acne global severity scale score 1 and above)[17]; (5) Body Mass Index (BMI) 23 and above (6) participants willing to adopt healthy diet and to take regular exercise (at least 30 minutes of exercise for at least 5 days a week) (7) written informed consent from the patient.

The exclusion criteria includes: (1) diabetes mellitus, Cushing's disease, hyper-prolactinemia; (2) untreated hypo or hyperthyroidism (3) adrenal hyperplasia and adrenal tumour (4) ovarian tumour (5) hyperthecosis (6) significant renal impairment (7) history of intake of drugs aldactone/ metformin or history of oral contraceptive pills (OCP) use or intake of drugs known to interfere with carbohydrate metabolism 4 weeks prior to

enrolment (8) pregnancy, breast feeding (9) cases with any systemic disease.

The patients presenting with PCOS will be screened for eligibility and will undergo pelvic ultrasound, complete blood count with erythrocyte sedimentation rate, fasting glucose, thyroid function test, serum prolactin, basal morning 17α-hydroxyprogesterone (17OHP), complete urine examination and urine pregnancy test in case of married women with amenorrhoea prior to enrolment.

Types of Intervention

Patients fulfilling the eligibility criteria will be enrolled and randomized as per computer generated randomization chart[18] to receive either the homoeopathic intervention or the identical placebo as illustrated in Figure 1. Medicine shall be given in Q, 6C, 30C, 200C or 1M potency as per the prescribing totality. Mother tincture shall only be prescribed in persistent amenorrhoea. The medicine will be repeated depending on the potency and complaints of the patient in accordance with the principles of homoeopathy.[19] All the participants will be asked to follow healthy diet and to take up regular exercise (at least 30 minutes of exercise at least 5 days a week).

Criteria for Baseline Assessment and Follow Up

All the enrolled subjects will undergo complete case taking along with clinical examination, baseline investigations for sex hormone binding globin, Luteinizing Hormone/Follicle Stimulating Hormone (LH/FSH) ratio, total Testosterone, Dehydroepiandrosterone sulphate (DHEAS), serum insulin, glucose insulin ratio, triglycerides and High-Density Lipoprotein (HDL)-cholesterol at baseline and shall fill PCOSQ.

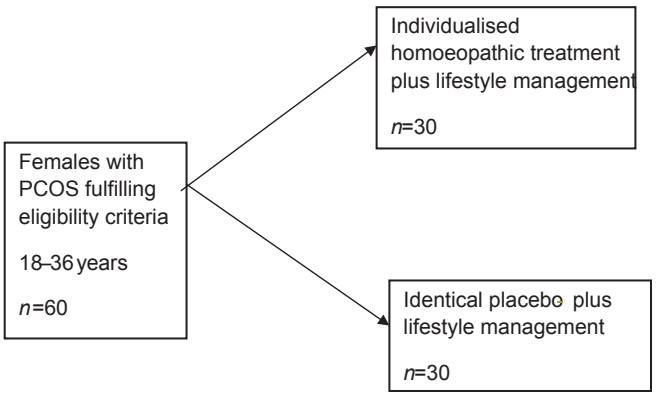

Figure 1: Flow chart of the study groups

Patient will be assessed at monthly intervals (or earlier as per the need) for 6 months. Symptomatic assessment and clinical examination will be done every month and PCOSQ will be filled. Any inter-current complaint arising during the treatment period is to be managed as per the acute totality in both the groups. Prescription will be changed and selection of the medicine will be based on the characteristic symptoms including exciting cause, mental and physical generals and qualified particular symptoms modified as a consequence of acute disease. Previously prescribed medicine/placebo is to be discontinued as per the need of the case till acute phase is over. Record of any such event is to be maintained in follow up sheet for acute phase. If the case does not respond to the homoeopathic intervention, patient shall be referred accordingly for the conventional treatment. The patient will be encouraged to revert back after the acute phase gets over. Such cases will be followed up as per the protocol subsequently.

At completion of the study, symptomatic assessment, clinical examination and pelvic ultrasound will be done. All patients will fill PCOSQ. Only those investigations will be repeated at 6 months, which were out of range at baseline.

Study Endpoints

Primary study endpoint is the establishment of regular menstrual cycle along with either ultra sonological improvement of PCO or improvement in hirsutism/acne. Secondary study endpoints are to compare the changes in total and individual domain scores of PCOSQ (consists of five domains, each relating to a common symptom of PCOS; emotions, body hair, weight, infertility and menstrual problems. Each question on the PCOSQ is associated with a 7-point scale in which 7 represents optimal function and 1 the poorest function) in verum and placebo groups at monthly interval for 6 months and to compare the changes in ultrasound reports of polycystic ovaries at entry and 6 months in verum and placebo groups.

Randomization

Separate sets of random numbers have been generated for the two study sites (each site is strata) using stratified randomization method.

Allocation

The patients fulfilling the eligibility criteria shall be enrolled and randomized as per computer

generated randomization chart to receive either the homoeopathic intervention or the identical placebo.

Blinding

The patients will remain blinded to the identity of the treatment group.

Sample Size Calculation

In the initial stage of the study, 30 cases of PCOS in verum and 30 cases in placebo group shall be enrolled. After the analysis of the data, the sample size shall be revisited and according to the outcome of this study, further study shall be continued or discontinued.

Study Duration

The duration of the study will be 2 years (1 year for enrolment, 6 months for follow up and 6 months for data compilation).

Data Collection

Each case will be followed up for 6 months to assess the outcome results of the treatment. Study data will be collected at baseline, every follow up (monthly or early if required) and at final/termination visit. The patients will be evaluated for symptomatic, clinical assessment, laboratory parameters and adverse events, if any, as per the study protocol.

Statistical Analysis

Data obtained during the study would be verified and analyzed using Statistical Package for Social Sciences (SPSS) version 20. Chi square test shall be applied for checking the improvement in menstrual cycle and acne. Pre and post analysis (paired *t* test) shall be applied for checking the changes in hirsutism, ultrasound assessment of ovaries and laboratory investigations. Repeated measure analysis of variance (ANOVA) and pre and post analysis (paired *t* test) shall be applied for checking the difference in the total score and individual domain score of PCOSQ. Hereditary factor, socio-economic status, stress, etc., would be considered as potential confounders in PCOS.

For the primary outcome and each of the secondary outcomes, both per protocol and modified intention to treat (mITT) analysis will be done. mITT analysis will be done on the patients completing a minimum of three scheduled follow up visits.

Regulatory and Ethical Approval

The study protocol is in accordance with the latest revision of the Helsinki declaration[20] on human experimentation and Good Clinical Practices India.[21] Although, medicines proposed to be used during the study are known homoeopathic pharmacopoeal preparations, yet necessary clearance of the Ethical Committee and Scientific Advisory Committee has been obtained before undertaking the study.

DISCUSSION

As the PCOS is a multi-faceted problem with reproductive, endocrine and metabolic dysfunction; therefore, the study has been planned keeping in view the multi-factorial evaluation of the intervention. Accordingly, to establish the diagnosis of PCOS, the criteria laid down by 2003 Consensus Statement on PCOS[4] and 2006 Androgen Excess Society have been followed.[22] It is reported that Lifestyle modification should be the first line of treatment and is effective in reducing the signs and symptoms of PCOS,[13] therefore, the study has been designed as placebo controlled trial with both the arms following Lifestyle modification so that the effect of Lifestyle modification and homoeopathy can be evaluated.

As the investigations are only suggestive and not fully confirmatory, therefore, the outcome will be assessed on composite endpoints, namely, menstrual regularity, ultrasonological improvement of PCO[15] and hyperandrogenism (hirsutism and/or acne as per Ferriman–Gallwey scoring system[16] and/or acne global severity scale[17]). PCOSQ, a validated questionnaire, will be used for evaluation of quality of life in cases of PCOS.[8]

Conventional treatment varies as per the symptoms and also has some side effects. Studies in homoeopathy[14,15] have indicated a positive role but these studies primarily evaluated menstrual irregularity and PCO through ultrasonography. Hyperandrogenism and effect of Lifestyle modification was not evaluated and statistical rigor was also lacking. Due consideration has been given to all these aspects while drafting this protocol.

High quality protocols facilitate proper conduct, reporting and external review of clinical trials. This study protocol is in accordance with the SPIRIT 2013[23] and covers all the domains of model validity of homoeopathic trials (MVHT).[24] The protocol shall generate data that can be reported as per CONSORT guidelines for reporting randomised trials

with parallel groups[25] and the Reporting data on Homoeopathic Treatments (RedHot) supplement to CONSORT.[26] The overall risk of bias appears to be minimal as only one domain (allocation concealment) out of six has high risk of bias.[27] The study is not double-blind due to nature of disease, which may require multiple prescriptions in different potencies depending on the presentation, and moreover the outcome measures are not likely to be influenced by lack of blinding. The outcome of this pilot study will help in planning a definite study subsequently.

Trial Status

Participant recruitment has been initiated in February 2014.

CONTRIBUTIONS

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पृष्ठभूमि: बहुपुटिक डिम्बग्रन्थि सिन्ड्रोम (पीसीओएस) युवतियों में एक उभरती हुई स्वास्थ्य समस्या है जोकि डिम्बग्रन्थि शिथिलता व उच्च एन्ड्रोजेन द्वारा चित्रित की जाती है। मौजूदा सूचना इस समस्या में होम्योपैथी की सकारात्मक भूमिका की ओर संकेत करती है, लेकिन और अधिक कठोर अध्ययनों की आवश्यकता है। यह प्रोटोकोल स्थापित नैदानिक मानदण्डों का प्रयोग कर होम्योपैथिक हस्तक्षेप की प्रभाविता का आकलन करने के लिये एक पायलट अध्ययन शुरू करने के लिये विकसित किया गया है।

विधि: यह छः माह के हस्तक्षेप व अनुसरण काल के साथ बहुकेन्दिक, यादृच्छिक, प्लासिबो नियन्त्रित पायलट अध्ययन होगा। पात्रता के मापदण्डों को पूरा करने वाले कम से कम 60 मामलों को नामांकित किया जायेगा और उनको या तो होम्योपैथिक हस्तक्षेप या प्लासिबो के लिये यादृच्छित किया जायेगा। दोनो ही शाखायें जीवन शैली संशोधन को भार कम करने के लिये अनुसरण करेंगी। प्रथम अन्तबिन्दु या तो अल्ट्रासोनोलोजी या मुँहासे में सुधार के साथ नियमित मासिक धर्म स्थापित करना होगा। द्वितीय अन्तबिन्दु पीसीओएस प्रश्न पत्र के कुल व व्यक्तिगत अनुक्षेत्र स्कोर में परिवर्तनों का मासिक अन्तराल व बहुपुटिक डिम्बग्रन्थियों में अल्ट्रासाउण्ड परिवर्तन में तुलना करना होगा। प्रथम परिणाम व प्रत्येक द्वितीयक परिणामों के लिये, प्रोटोकॉल के अनुसार और विश्लेषण की विवेचना के लिये संशोधित गहनता दोनो ही किया जायेगा।

चर्चा: इस पायलट अध्ययन की योजना पीसीओएस के सघन अन्तबिन्दु व अर्न्तराष्ट्रीय नैदानिक मापदण्डों के अनुसार विविध प्रस्तुति पर विचार करने के बाद आकलन के लिये बनाई गयी है। इस अध्ययन के परिणाम एक निश्चित अध्ययन की योजना बनाने में सहायता करेगें।