International Journal of Clinical Trials
Panda SR et al. Int J Clin Trials. 2022 Aug;9(3):217-220
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259

DOI: https://dx.doi.org/10.18203/2349-3259.ijct20221874

Protocol

Trial design and protocol of randomized controlled trial comparing the efficacy of combined letrozole and clomiphene versus only letrozole as a method of ovulation induction in women with polycystic ovarian syndrome (CCLOP trial)

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Received: 19 March 2022
Revised: 14 April 2022
Accepted: 15 April 2022

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ABSTRACT

Background: Both clomiphene (CC) and letrozole are commonly used oral ovulation induction agents, with different mechanism of action. Apart from letrozole or CC, options for ovulation induction in polycystic ovarian syndrome (PCOS) patients are limited and thus leaving the use of gonadotropin injections as the only option of ovulation induction in these patients. The objective of this study is to evaluate the efficacy of combined therapy of letrozole and CC compared to the use of letrozole alone to achieve ovulation in infertile women with PCOS.
Methods: This will be a single-centre, double arm, triple-blind randomized controlled trial. The study was conducted after taking approval from institutional ethics committee and was prospectively registered with the clinical trials registry- India. Women were randomly assigned to receive a combination of 2.5 mg letrozole and placebo daily or a combination of 2.5 mg letrozole and 50 mg CC daily on cycle days 3–7 for one treatment cycle.
Conclusions: If combination of clomiphene and letrozole is proved to be more efficacious than letrozole alone, there will be several breaks through advantages in the management of infertility. The novel method of ovulation induction with combined letrozole and clomiphene will bring down overall cost of infertility treatment.
Trial registration: The study is prospectively registered with the clinical trials registry- India CTRI/2020/09/028012.

Keywords: Clomiphene, Letrozole, Polycystic ovarian syndrome, Ovulation induction

INTRODUCTION

Clomiphene citrate (CC) is a commonly prescribed pharmacologic agent used to induce ovulation in women with polycystic ovarian syndrome (PCOS) because of its antiestrogenic property. It acts by inhibiting the negative feedback of estrogen resulting in increased secretion of gonadotropin hormones which induces ovarian follicular growth. CC also has an antiestrogenic effect on endometrial development and cervical mucus production, which has been suggested to contribute to a relatively low pregnancy rate despite a high ovulation rate.[1,2] Letrozole is another commonly used oral ovulation induction agent, with a different mechanism of action. It works as a highly selective aromatase inhibitor, preventing androgen-to-estrogen conversion. One proposed mechanism of action is via suppressed estrogen production resulting in decreased negative feedback on the hypothalamus and increased secretion of follicle stimulating hormone (FSH). An additional proposed mechanism of improved ovulatory

rates with the use of letrozole is via increased follicular sensitivity to FSH resulting from temporarily increased intraovarian androgens.[3] Other than letrozole or CC for ovulation induction, there are few treatment options available to PCOS patients except proceeding to gonadotropin injections or in vitro fertilization, both of which are associated with increased cost and risks, especially of ovarian hyperstimulation. As letrozole and CC have different mechanisms of action, we postulated that the combination of these medications may result in an improved ovulatory rate over letrozole alone.

Objective

The primary objective was to evaluate the efficacy of combined therapy of letrozole and CC compared to the use of letrozole alone in terms of ovulation rate in infertile women with PCOS. Secondary objectives were to characterise the side-effects profile and to evaluate the ultrasonographic cycle characteristics on this treatment regimen.

METHODS

Study design

This is a single-centre, double arm, triple-blind randomized controlled trial. The study will be conducted at All India Institute of Medical Sciences, Mangalagiri, India after taking approval from the institutional ethics committee (IEC/AIIMS/MG/2020/32). The study is prospectively registered with the clinical trials registry-India CTRI/2020/09/028012. The study will be reported following the consolidated standards of reporting trials (CONSORT) guidelines (Figure 1).[4]

Participants and setting

The study will be conducted over a period of 1 year at a tertiary care teaching institute in India after obtaining informed written consent from the participants. Eligible participants will be women aged 20-35 years with anovulatory infertility due to PCOS diagnosed by Rotterdam's criteria which entails any two of the following finding: ovulatory dysfunction, clinical or biochemical features of androgen excess, and polycystic ovarian morphology on ultrasound.[5] The threshold for defining polycystic ovarian morphology was ≥12 follicles of 10 ml. The participants, the consultant who performed transvaginal ultrasound (TVS) for outcome assessment and the data analyst were blinded to treatment allocation.

Intervention

Randomization will be done during the first 3 days of spontaneous menses or while taking medroxyprogesterone (10 mg twice for 5 days) to induce withdrawal bleed. Women will be randomly assigned to receive a combination of 2.5 mg letrozole and placebo daily or a combination of 2.5 mg letrozole and 50 mg CC daily on cycle days 3–7 for one treatment cycle. A baseline scan will be done on day 2 or 3 of the menstrual cycle. The growth of follicles will be monitored by performing TVS on day 11 of the cycle and the scan will be repeated afterwards depending on the follicular growth. All the scans will be performed by a single consultant using a transvaginal probe (frequency of 3-10 MHz) of the diagnostic ultrasound system (Ecube i7, Alpinion medical systems). Injection human chorionic gonadotropin 5,000 unit will be given after at least one follicle reached a size of 18 mm diameter. Timed intercourse will be advised 24 hours to 36 hours after human chorionic gonadotropin (hCG) injection. Ovulation will be confirmed by TVS 48 hours later with or without serum progesterone estimation. Those who conceived after treatment will be followed up at our hospital and their pregnancy outcomes will be tracked with regular follow up visits. All the clinical decisions will be taken with the mutual agreement of two consultants.

Inclusion criteria

Infertile patients attending outpatient department (OPD) will be included in our study if the following inclusion criteria were fulfilled: the age of the patient between 20 years to 35 years; diagnosed as PCOS according to Rotterdam criteria; a documented normal hysterosalpingogram or laparoscopy; no recorded history of pelvic surgery and/or pelvic inflammatory disease; male partners having a normal semen analysis, according to the 2010 World Health Organization criteria, within the preceding 6 months and; no history of treatment with exogenous gonadotropin and not on treatment with metformin.

Exclusion criteria

The exclusion criteria were- endocrine factors other than anovulatory PCOS like hyperprolactinemia, hypothalamic amenorrhea, premature ovarian failure and ovarian tumour or clinical suspicion of other etiologies that mimic PCOS warranting additional evaluation; uncorrected thyroid disease; uncontrolled type 1 or 2 diabetes mellitus or hypertension; allergy or contraindications to letrozole or CC; and other associated factors of infertility like a malefactor, uterine factor and endometriosis.

Outcome measures

The primary outcome measure will be documentation of ovulation, confirmed by TVS 48 hours later with or without serum progesterone estimation.

The secondary outcomes include: size and number of developing follicles and endometrial thickness noted in TVS on the day of hCG injection; conception with the treatment cycle: a positive serum or urinary test of hCG; clinical pregnancy: an intrauterine pregnancy with fetal heart motion determined by ultrasonography; multiple pregnancies; pregnancy loss, including biochemical

miscarriage or ectopic pregnancy; and adverse events related to the medications: adverse events are defined as any side effects that the subject recorded on her daily calendar log during the study cycle, serious adverse events (SAEs) are defined as events that were fatal or immediately life-threatening or required inpatient hospitalization; and live birth rate.

Sample size calculation

Thirty-three subjects per group will be required to obtain 80% statistical power to demonstrate a clinically meaningful 34% absolute difference in ovulation rate between treatment groups, assuming a 43% ovulation rate for letrozole a two-sided significance level of 0.05 using open Epi software version 3.01. The sample size will be increased to 40 per arm to allow for a dropout rate of 20%. We selected a benchmark of 34% difference between groups based on a previous study that compared combined letrozole and clomiphene with letrozole alone for ovulation induction.[6]

Randomization

Randomization will be done in a ratio of 1:1. We will use the block randomization technique with a block size of 8 for patient recruitment. The random allocation will be done using computer-generated random numbers for each block and stored in a sealed non-transparent cover. The study drug and placebo will be coded as A and B. A nursing officer will be assigned to distribute the drugs based on the participant's allocation. The allocation scheme will not be disclosed to the patients, investigators, and data analyst. The study drug and placebo will be matched for color, shape, and size (Table 1).

Table 1: Comparison of physical characteristics of drugs and placebo.

Characteristics	Clomiphene	Placebo
Shape	Round	Round
Colour	White	White
Size (cm)	1×1	1×1
State	Solid	Solid

Statistical analysis

All the analysis will be performed by using statistical package for social sciences (SPSS) software (version 21.0). Analysis will be based upon intention to treat (ITT) as well as per-protocol (PP). ITT analysis included all participants who will be randomized, irrespective of whether or not they will receive the study drug. Per protocol analysis will include only those participants who will complete the study after randomization. Lost to follow-up participants will be assumed neither to have ovulated nor to have conceived in the ITT analysis. For categorical variables, either chi-square or Fisher exact test will be used at a two-sided significance level of 0.05 for testing differences between the two treatment groups. For continuous variables, the mean±standard deviation (SD) in each group will be reported. Student t-test will be used to analyze normally distributed data and in the case of skewed data, the median and interquartile range will be reported and Mann-Whitney U tests will be applied. A subgroup analysis will be performed to assess ultrasound characteristics among those who ovulated.

DISCUSSION

Recently letrozole and CC are compared in various studies for infertile PCOS women.[7-11] A systematic review found higher pregnancy and live birth rates with letrozole compared to CC.[12] However, as the included studies were having high risk of bias, the evidence generated was not of optimum quality.

Gonadotropin injections like human menopausal gonadotropins (hMG), urinary or recombinant FSH, have been used as an advanced step of ovulation induction in cases of CC or letrozole failure or resistance.[13,14] However, the high cost of gonadotropins and the risk of ovarian hyperstimulation (OHSS) especially in women with PCOS makes their use cumbersome.

The only randomised controlled trial that compared similar treatment groups as ours was performed by Mejia et al.[6] They found a higher ovulation rate in the combined letrozole and CC group compared to the letrozole alone group. However, in their study, they did not exclude patients who were on treatment with metformin which could have an additive effect on ovulation induction and thus has the potential to confound the result. Also, the study was not blinded to participants and the investigator.

CONCLUSION

If combination of clomiphene and letrozole is proved to be more efficacious than letrozole alone, there will be several breaks through advantages in the management of infertility. The novel method of ovulation induction with combined letrozole and clomiphene will bring down overall cost of infertility treatment. At the same time this method of ovulation induction has less chance of complications like risks of ovarian hyperstimulation or multiple pregnancy. Hence, we will have a better cost-effective alternative for method of ovulation induction before proceeding to ovulation induction by gonadotropins.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Panda SR, Sharmila V, Kalidos VK, Hota S. Trial design and protocol of randomized controlled trial comparing the efficacy of combined letrozole and clomiphene versus only letrozole as a method of ovulation induction in women with polycystic ovarian syndrome (CCLOP trial). Int J Clin Trials 2022;9(3):217-20.