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Clomiphene Citrate versus Letrozole in the treatment of anovulatory infertility: A randomized controlled trial.

Gihan MC[1], Kodithuwakku SP[2], Rajapaksha RNG[3]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, University of Peradeniya, Sri Lanka.
[2]Department of Animal Science, Faculty of Agriculture, University of Peradeniya, Sri Lanka.
[3]North Colombo Teaching Hospital, Ragama, Sri Lanka.

Correspondence:
Gihan MC
Senior Lecturer
Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Peradeniya, Sri Lanka.
: https://orcid.org/0000-0002-2494-6410

Abstract

Background: Ovulatory dysfunction accounts for 20-25% of the cases of infertility. The main treatment modality for anovulatory infertility is ovarian stimulation. Clomiphene citrate (CC) and letrozole (LET) are the drugs of choice but which is the best choice for first line treatment is debatable.

Objective: Compare the treatment outcome of anovulatory infertility by CC and LET.

Method: A prospective randomized controlled trial including two groups of anovulatory subfertile patients was carried out at a tertiary care center and patients were randomized to either CC 50 mg (n=127) which was the standard first line treatment used at the center as the control and LET 2.5 mg (n=121) as the trial drug which is the off labelled, yet currently prescribed for the anovulatory sub-fertile patients daily from the 2nd to 6th day of the menstrual cycle. Follicle number on day 12, endometrial thickness, pregnancy rates and multiple pregnancies were assessed. The data were analyzed using MINITAB 14.

Results: The mature follicles count (>18mm) on day 12 was not significantly different in two treatment groups (CC: 1.323± 0.935 and LET: 1.175±0.797). However, the mean endometrial thickness of the LET treated patients was significantly higher than the CC group (0.7691±0.0887 cm and 0.695± 0.134cm respectively). The clinical pregnancy rate of the LET group was significantly higher than the CC treated group (49% vs. 38%). There was no significant difference in the miscarriage rates (16% in both arms).

Conclusions: LET treatment enhances the endometrial thickness compared to CC with higher clinical and ongoing pregnancy rates. The higher pregnancy rates with LET may be due to its favorable effects on endometrial thickness and the receptivity owing to its less anti-estrogenic properties

Keywords: Clomiphene citrate, letrozole, anovulatory infertility, anti-estrogenic properties

INTRODUCTION

Infertility is the inability of a couple to conceive following 12 months of exposure to pregnancy. It is a common condition with a prevalence of 12-18 % among the women of age 15 to 34. The

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estimated women population at reproductive age with infertility is about 72 million of which about 40.5 million women are seeking the infertility medical care[1].

From the various female factor infertility, ovulatory dysfunction accounts for 20-25% of the cases of infertility. Ovulation is the result of a well-synchronized balance between hormones produced by the brain, hypothalamus, pituitary gland and ovary[2]. Any disruption of the complex interactions of the hormones from the hypothalamus-pituitary-ovarian axis can lead to ovulatory dysfunction. Ovulatory dysfunction is a term that describes a group of disorders in which ovulation fails to occur, or occurs on an infrequent or irregular basis[3]. Failure to ovulate is generally indicated by the absence of menstruation (amenorrhea) or infrequent menstruation (oligomenorrhoea). This condition is referred as anovulatory infertility.

Among the medical management options, clomiphene citrate (CC) and letrozole (LET) are the drugs of choice for ovarian stimulation but which one is the best choice as the first line treatment is still debatable. CC is a nonsteroidal triphenylethylene derivative that is known to exhibit both estrogenic agonist and antagonist properties and has been used as a pharmacological agent of choice in treating women with anovulatory infertility in many countries in the world but some has failed to ovulate with this[4][5]. Moreover, CC has an increased association with multiple-pregnancies due to resistant, multi-follicular development, and its peripheral anti estrogenic action on the endometrium and cervix has led to find a suitable alternative[6]. In the last decade, letrozole, an aromatase inhibitor (AI) has emerged as alternative ovarian stimulation agent and considered as a second line treatment for women resistant to CC[7]. Published literature confirms that LET has a definitive role in anovulatory women who have not responded to the CC therapy. Thus, use of LET in ovarian stimulation is becoming popular due to its customary dose of 2.5 mg, which elicits a monofollicular response and does not adversely affect either the endometrium or the cervical mucus, due to the absence of a peripheral estrogen receptor blockage[8][9][10]. There are some concerns about teratogenicity with the use of LET and unlike CC it is not approved by the United States Food and Drug Administration (FDA) for treatment of infertility. Aromatase inhibitors can also be effective as CC with significant higher cumulative birth rates[6][11][12][13][14]. Interestingly, still there is an ongoing debate whether CC or LET is better as first line treatment for the anovulatory infertility Although it is probable that the overall benefits of LET surpass CC, currently available data does not confirm such a view[9][15] . Thus, there is need for well-designed trials across all the ethnicities, treatment regimens for women with ovulatory dysfunction under different clinical settings.

Therefore, this study was designed to compare and evaluate the two drugs as a first line treatment in a group of anovulatory infertile women patient cohort in Sri Lanka, with regard to effects on follicular development, endometrial thickness during the implantation window, ongoing pregnancy and multiple pregnancy.

MATERIALS AND METHODS

The study was a prospective randomized controlled trial conducted at a tertiary care center in Sri Lanka. The CC was considered as the control drug since it has been in use in anovulatory treatment, however, since LET is still being used as an off labelled drug, we have used LET as the alternative drug to be evaluated with the control drug. Two parallel groups of anovulatory subfertile patients who attended the subfertility clinic, Teaching Hospital Ragama, Sri Lanka were recruited with informed consent. Those who were unable to achieve a pregnancy after a one year of regular unprotected sexual intercourse were considered as infertile. Anovulation was diagnosed in some patients by assessing mid-luteal progesterone levels and assessment of follicular development by serial trans-vaginal ultrasound scanning[15]. History of oligimennorrhoea was also used to support the diagnosis of anovulation.

The inclusion criteria were; Women under 40 years of age, with patent fallopian tubes. Females who are having fallopian tubal problems, uterine problems were excluded by performing a laparoscopy and chromotubation or a hysterosalpingogram. Females whom partners are

subfertile, females who were diagnosed to have endometriosis and couples fallen in to unexplained subfertility group were also excluded from the study. Patients who had major medical disorders and who were taking confounding medications were also excluded.

Randomization was done using a standard clinical randomization protocol[10][16][17][18][19] . The sample size was determined by using sample size calculation criterion described elsewhere keeping 10% of the dropout rate as well[16][17][20][21]. To calculate the sample size, the level of significant and power of test were set as 0.05% ($p<0.05$) and 0.8 (80%) respectively. According to this each arm should have at least 96 treatment cycles. A person other than the researcher did the randomization using simple block randomization by a computer-generated randomization list with random number generator option in SAS statistical package (SAS Inc. version 15.1 for windows). Depend on the randomization, a patient received either CC (comparison /control group) or LET (alternative/ test group).

Throughout the study, previously published treatment criteria were followed[10][16][20][21][22][23]. A randomly selected participant received clomiphene citrate 50 mg (n=127) daily from the second day to sixth day of the menstrual cycle or letrozole 2.5 mg (n=121) daily for the same period according to the number allocated by the software (single-blind approach). All the subjects were scanned transvaginally by the researcher himself on the twelfth day of the cycle to assess the follicular development and endometrial thickness using the vaginal probe of the ultra sound scanner (Aloka, Hitachi, Japan). Females with mature follicles were given with intramuscular 5000 IU of human chorionic gonadotropin (hCG) on the same day. The couples were advised to practice timed sexual vaginal intercourse after 24 to 36 hours of hCG injection. These patients were followed up further and number of pregnancies, multiple pregnancies and miscarriages were assessed. The study was carried out only for one cycle of ovulation induction due to time constraints. Population's baseline characteristics that are known or potential predictors of the outcome were also measured and the effects of confounding variables were considered. For this purpose, a data collection sheet was used. A student's t test, chi-square test or Fisher's exact test if any frequency count was <5 was used for testing differences between the two treatment groups. The data were analyzed using MINITAB 16 for Windows. The effect size for endometrial thickens and day 12 mature follicle counts were performed using Cohen's d and Hedges' g values calculation using standard formula.

RESULTS

The mean age of the CC and LET groups were 30.3 and 31.4 years respectively and the mean body mass index were 30.6 and 29.9 kg/m^2 respectively. The mean age and the body mass index of the subjects in the two groups were not significantly different. Furthermore, there was no significant difference in the duration of subfertility as well. The patients were followed up until the end of the second trimester.

Mature follicle counts

Both CC and LET equally induced ovaries to produce mature follicles at day 12 ultrasound scanning without significant difference in the mature follicle (>18 mm diameter) count (1.32±0.93 vs 1.17± 0.80) at(p =0.09, student's t test) (Figure 01).

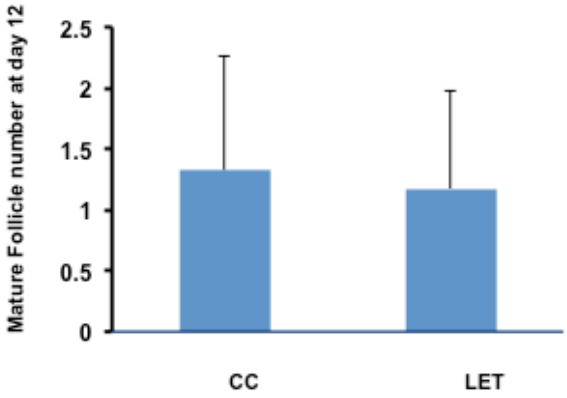


Figure 01: Mature follicles count with each treatment.

The values are in mm mean ± SD. CC= Clomiphene Citrate, LET= Letrozole.

Percentage of multiple follicle development (two or more than two) was slightly higher in CC treated patients (27%) than LET (24%) group, however, it was not significantly difference (p=0.08, Fisher's exact test). Moreover, among the multiple follicles-developed patients, CC group has slightly higher percentage for three or more follicles (8%) compared to the LET treated patients (5%) without any significant difference (p=0.07, Fisher's exact test). The effect size for mature follicle counts by Hedges' g and Cohen's d values were 0.17 for both tests.

Endometrial Thickness.

Endometrial thickness of the LET treated group was significantly higher (p=0.02, student's t test) than that of the CC treated group (8.0±0.08 vs 7.0±0.13 mm respectively) on the day of hCG, i.e., Day 12 (Figure 02). The effect size for endometrial thickness by Hedges' g and Cohen's d values were 0.66 and 0.65 respectively.

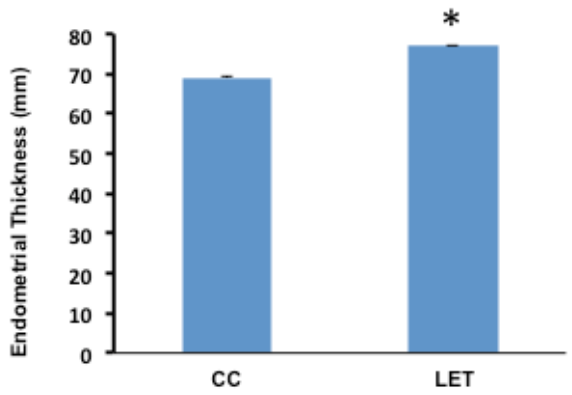
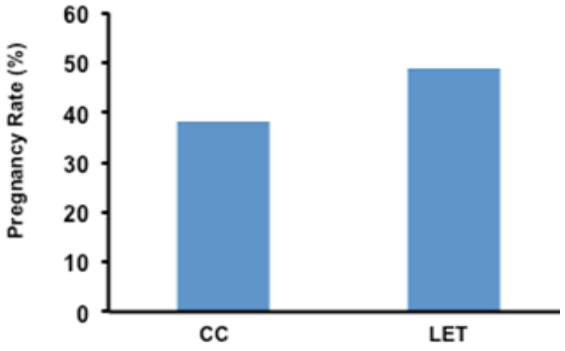


Figure 02: Endometrial thickness after the treatment.

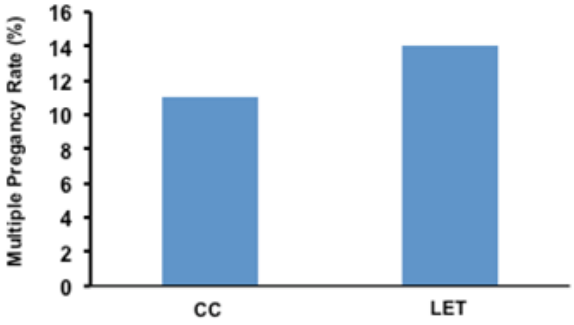
CC= Clomiphene Citrate, LET= Letrozole, * symbol indicates significant difference at p<0.05.

Pregnancy outcomes

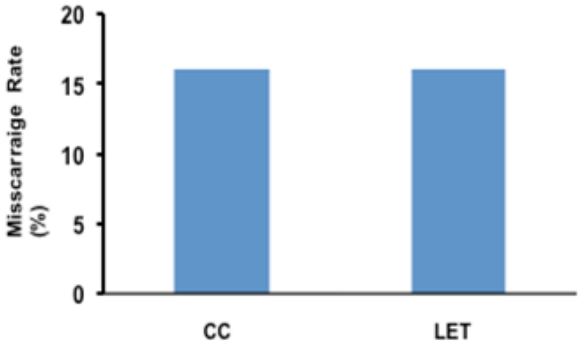
The ongoing pregnancy rate at the end of second trimester of the LET treated group was significantly higher (p=0.03, Fisher's exact test) than that of the CC treated group (49% vs. 38% respectively) (Figure 3A). The multiple pregnancies rate was significantly higher (p=0.04, Fisher's exact test) in LET treated group (14%) compared with the CC treated group (11%) (Figure 3B). The miscarriage rate was not significantly different (p=0.08, Fisher's exact test) between the two groups where both showing 16% (Figure 3C). The most of the pregnancy losses were recorded during the first trimester and no miscarriages were recorded during the second trimester period. Since the patients were not followed up to the term, the live birth rate data are not available.



A) Ongoing pregnancy rates after second trimester.



B) Multiple pregnancies rate.



C) Miscarriage rate up to second trimester.

Figure 3: Pregnancy outcomes of the two treatment groups.

DISCUSSION

Present study is the first prospective randomized study employed more than 100 patients for each arm to test suitability of LET also as a first line treatment in Sri Lankan patient cohort while looking at mature follicle development, endometrial thickness and ongoing pregnancy rates where only one study has been carried out using a small number of patient in which the study was limited to the endometrial thickness assessment after the treatments[24]. In the recent literature there are multiple studies comparing CC and LET in the other countries , however, diverse results can be observed[16][19][20][21][25][26][27]. Moreover, since CC has been used mostly to treat anovulatory infertility patients at the center as the first line treatment choice, we considered it as the control drug in this current trail while off labeled LET was considered as the alternative to be compared with CC making the trail as a RCT.

In the present study, both CC and LET treatment showed equal effects on the ovary in terms of mature follicle count. But LET treatment showed better results in terms of less multifollicle development and less number of multiple pregnancies which are comparable with previously published studies as well[20][28]. Moreover, present results did not show a significant change in the mean mature follicle size on day 12 scanning as well.

Treating unexplained infertility using letrozole (aromatase inhibitor) and CC resulted in favorable pregnancy outcomes with average miscarriage rates in many other parallel studies performed in different patient cohorts. Moreover, the safety of the drugs for both the mother and fetuses has also been well documented[29]. However, it's now well accepted that due to genetic background differences, patients from different parts of the world respond the subfertility treatments differently. Interestingly, there is only one study completed in Sri Lankan setting with small number of patients in the two arms previously without any information on endometrial aspect of the treatment outcomes[24]. Thus, present data may provide better insight on the use of both drugs in unexplained infertility conditions. Even though both clomiphene and letrozole increases release of gonadotropins with the effect on negative feedback loop, they have two distinct mechanisms of action[12]. This has a significant clinical importance.

Once the treatment with letrozole is over after five days, serum estrogen level increases drastically[30]. This has two important effects; it will block further FSH secretion preventing multiple follicular development and it will increase the production of cervical mucus and cause endometrial proliferation. Even though the present study results showed a slightly higher number of multiple follicles in the CC treated group, multiple pregnancy rate was slightly higher in the LET treated group, indicating the possibility of ovulation failure, fertilization failure, implantation failure or presence of antiestrogen effect of the CC treated group[14][30][31][32] [33]. However, a very recent study completed with large number of sample size has concluded that there is no significant difference between LET and CC in relation to mature follicle number, multiple follicle number, but LET has resulted significantly lower pregnancy outcomes[26].

Interestingly, the current study reported a desirable endometrial thickness with the treatment of LET which has also been observed by other studies as well[34][35]. The favorable response observed in terms of endometrial thickness could be due to the absence of antiestrogenic effects on the endometrium and also the aromatase inhibitory activity[34][35][36][37]. The similar observation has been made elsewhere for the endometrial thickness, however, in contract to our results no significant differences in both treatment in relation to pregnancy outcomes were reported[38]. Moreover, the effect size calculation too confirm the fact that impact of Letrozol is more for endometrial thickness rather than the mature follicle counts Interestingly, a similar regional study completed in India which may be genetically more similar to local cohort had shown no significant difference in the endometrial thickness with both the treatments[39]. Another recent study concluded that the gonadotropin only treatment is far superior than that of using CC or LET alone in anovulatory infertility which is contradictory to many others findings[26].

According to the present data, pregnancy outcomes are higher with ovulation induction when compared to other studies available in literature. Selection of pure anovulatory group for ovulation induction may be a reason for higher pregnancy rates. LET treatment performed better in terms of pregnancy outcomes compared to CC. Since CC is known to possess antiestrogenic effects on female reproductive tract, especially on the endometrium and uterine cervix which may lead to negative impact on pregnancy outcome in the present study[32][40][41]. The main undesirable impacts of the CC have been reported on endometrial thickness and making the cervical mucus hostile to sperms[42][43]. Moreover, 15 to 20% of the patients may develop clomiphene resistance[39]. However, some studies have reported better pregnancy outcomes with the CC treatment as well[44][45]. The less pregnancy rate with the CC in the present study may be due to presence of CC resistance and also due to antiestrogenic effects of CC on the endometrium which was evident by the less endometrial thickness observed compared to the other arm. It is also worth to note that, the present study has a limitation data of one cycle was included in the analysis, CC resistance must have been missed and possible prior exposure to CC was also not assessed in the present study since most of the medical history was based on recall memory of the patients. Ideally, three consecutive cycles with the treatment need to be followed up to identified as CC resistance[46]. The positive response observed in the present study from LET on overall treatment outcomes may be due to its absence of antiestrogenic effect on endometrial development in the patient cohort promoting optimal endometrial thickness and the receptivity. Similar to the present data higher clinical pregnancy rate with letrozole was reported elsewhere may be due to the absence of antiestrogenic effects on the reproductive tract with better endometrial thickness[31][41]. However, the present data from a Sri Lankan patient cohort with anovulatory infertility warrants further investigation on comparing CC and LET as a first line treatment taking many factors in to consideration with a comprehensive hormonal profiling, ovulation rate, ethnic background plus increase number of cycles to avoid any biasness due to CC resistance. Probably a stair-step up protocol could be clinically evaluated to avoid CC resistance which has been successfully used in PCOS conditions.

It is also worth to disclose that, there were few limitations in this study and most of them were inherent problems in local clinical setting. Firstly, clomiphene resistance in subjects was not evaluated and such patients were not excluded from the study as observation was done only for a single cycle of ovulation induction. Furthermore, the present study did not look at the ovulation rate following hCG injection due the logistical difficulties. Moreover, hormonal concentration measurements were not assessed in all the patients before or during the treatment cycle after ovulation induction due to less availability of the facility and due to the cost factor involvement. Specially the estrogen concentration could have been used to monitor the follicle development after the treatments. This study was conducted for a single dose of CC and LET. It would have been ideal to assess the clinical effectiveness for different doses in consecutive cycles. Moreover, a recent study reported that combination CC and LET would result better ovulation rates than LET alone indicating the possibility of combined treatments as well . Further, the subjects of the study were not followed up to the term; therefore, live birth rates were not compared between two groups. To increase the accuracy of the data and to come up with a more comprehensive conclusion, the study should have been conducted as a multicenter trial with a greater number of subjects. However, the overall outcome of the study proved that letrozole may be the better choice as first line drug for the local patients.

CONCLUSIONS

Treatment of anovulatory infertile patients with letrozole 2.5 mg from day 2 to day 6 of the cycle enhances endometrial thickness with significantly higher clinical and ongoing pregnancy rates compared to the clomiphene citrate 50mg treated patients for the same duration. Both treatments result no difference in mature follicle number, multiple pregnancies and miscarriage rate.

Thus, letrozole can be recommended as first line drug for ovulation induction in anovulatory infertility. However, letrozole being an off-label

drug, the clinician must discuss this treatment option with the patient prior to prescribe.

Author declaration
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Aouthors' contribution
MCG and SPK did the conceptualization of the study. MCG recruited patients and conducted the study including follow up data collection. RNGR was the clinical supervisor of MCG and he was the consultant in-charge. MCG wrote first draft of the manuscript and SPK revised the manuscript.

Ethics approval and consent to participate
The study protocol was approved by the ethical review committee of the Faculty of Medicine, University of Kelaniya, Sri Lanka.

Conflicts of interest
The authors declare that they have no competing interests.

Consent
Written consent was obtained before the data collection.

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