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Original Research Article

Clomiphene citrate plus N-acetyl cysteine versus letrozole for induction of ovulation in infertile patients with polycystic ovarian disease: a randomized clinical trial

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ABSTRACT

Background: Polycystic ovarian disease (PCOD), a common endocrine disorder with multisystem affection, is the most common cause of anovulatory infertility. Our objective is to evaluate the effect of using clomiphene citrate (CC) plus N-acetyl cysteine (NAC) versus letrozole in ovulation induction in infertile patients with PCOD.

Methods: Reproductive-aged infertile women either primary or secondary diagnosed as PCOD according to Rotterdam criteria, 2003 were considered for enrollment. Eligible women for were recruited and randomized (1:1) to receive either CC 100 mg plus NAC 600 mg (CC+NAC arm) or letrozole 5 mg (NCT03241472, clinicaltrials.gov). All medications were started from day 3 of the menstrual cycle for 5 days. The primary outcome was the ovulation rate in both groups. Secondary outcomes included the mid-cyclic endometrial thickness, ovarian hyperstimulation, and clinical pregnancy and miscarriage rates.

Results: One hundred ten patients were enrolled and randomized to CC+NAC arm (n=55) or letrozole (n=55). The ovulation rate in patients in letrozole arm was significantly higher than CC+NAC arm (71.8% versus 53.2%, p=0.01). Additionally, endometrial thickness was higher in letrozole arm (mean±SD: 11.46±1.61 versus 9.0±1.13, p=0.031). However, no statistical significant difference with regarding the ovarian hyperstimulation rate (1.8% versus 3.6%, p=0.157), clinical pregnancy rate [3/19 patients (27.3%) versus 19/55 (34.5%), p=0.409] and miscarriage rate [4/15 patients (26.7%) versus 19/55 (15.8%), p=0.317] in CC+NAC versus letrozole groups respectively.

Conclusions: Addition of NAC to CC in ovulation induction leads to comparable pregnancy rate as letrozole. However, letrozole produces high ovulation rate and the better mid-cyclic endometrial thickness.

Keywords: Clomiphene citrate, Induction of ovulation, Infertility, Letrozole, N-acetyl cysteine, Polycystic ovarian disease

INTRODUCTION

Infertility is defined as a couple's inability to become pregnant after one year of unprotected intercourse in women 35 years old and younger, and for six months in women over age 35 years. In any given year, about 15%

of couples in North America and Europe who are trying to conceive are infertile.¹

Polycystic ovarian disease (PCOD) is the commonest hyperandrogenic disorder in women and one of the most common causes of anovulatory infertility, with an

estimated prevalence of 4-7% worldwide.² It is an over-diagnosed and disproportionately treated condition. Lifestyle modification, weight loss, and exercise form the first line of treatment in infertile women with PCOD.³

Clomiphene citrate (CC) is a weak estrogen-like hormone that acts on the hypothalamus, pituitary gland, and ovary to increase levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH, which is also important in the process of ovulation) an increased level of FSH hormones improves the chances of growing an ovarian follicle that can then trigger ovulation. In women who ovulate irregularly, approximately 80 percent who take clomiphene will ovulate, and 30 to 40 percent of all women who take clomiphene become pregnant. These numbers apply to women who have taken up to three cycles of CC.⁴

In the study of Badawy et al, in women who have received CC with N-acetyl Cysteine (NAC), the number of mature follicles, improvement in endometrial thickness, and the increase in fertility rate were significantly higher than the group who have received CC alone, Ovulation rate improved significantly after the addition of NAC (17.9% versus 52.1%).⁵

Letrozole is a medication that is used for women with breast cancer. Letrozole also works for ovulation induction in women with PCOS. In 2014, researchers reported that in women with PCOD, the use of letrozole to induce ovulation resulted in higher live birth rates (eg, more women became pregnant and carried to term) than clomiphene.⁴

Therefore, the current study aims to compare the use of CC with NAC versus Letrozole for induction of ovulation in infertile women with PCOD.

METHODS

The current study was a randomized open-labeled controlled study conducted in Assiut Women Health Hospital between April 2017 and October 2018. The Institutional Ethical Review board approved the study. All patients signed informed written consent before participation in the study.

Patients were divided into two groups

- Group I: CC 100mg +NAC 600mg started from third day of cycle for 5 days
- Group II: Lertozole 5mg alone started from third day of cycle for 5 days.

Inclusion criteria

- All primary and secondary infertile women less than 39 years due to anovulation due to PCOD according to Rotterdam diagnostic criteria
- Primary or secondary infertility.

- Absence of galactorrhea
- Normal serum prolactin
- Normal Hysterosalpinography
- Their husband has Normal semen analysis.

Exclusion criteria

- Male factor infertility, tubal factor infertility
- Endocrinopathy as (Hypothyroidism, Hyperprolactinemia)
- BMI >35 Kg/m²
- Patients with previous ovarian surgery including drilling of the ovary.

The following was done to all study subjects

- Full history taking including personal, menstrual, obstetric, present, past and family history
- Clinical examination including, pulse, blood pressure, temperature, chest, heart and abdominal examination
- Breast examination for galactorrhea
- Gynecological examination
- Hormonal analysis in the form of FSH (Normal 3-10 mIU/ml), LH (normal: less than 7mIU /ml), and prolactin (2 to 29ng/ml) on 2nd of day of the cycle.

Ultrasound evaluation

- All patients were examined using trans-vaginal ultrasound to confirm anovulation one month before randomization
- On cycle day 12 all patients in both groups will be evaluated for the number of the follicle, the size of each follicle, and the endometrial thickness
- If one follicle reaches 18-24mm HCG trigger with (Chriomon 5000 IU) and timed intercourse will be schedule 24-36 hours, after HCG triggering. If there are more than 10 follicles in one or both ovaries no HGG triggering was prescribed to avoid hyperstimulation syndrome.

Randomization

Eligible women who gave their informed consent were randomized to one of the two groups. Randomization was conducted using a computer generated table of random numbers with allocation concealment. Allocation concealment was done using serially-numbered closed opaque envelope. Counseling for participation was done before recruitment. Once allocation was done, it was not changed.

The primary outcome was the ovulation rate in both groups. Secondary outcomes included the mid-cyclic endometrial thickness, ovarian hyperstimulation, clinical pregnancy and miscarriage rates.

Statistical analysis

Statistical analysis was performed using SPSS software version 20 (SPSS, Chicago, IL, USA). For Independent samples: Student's t-test was used for comparing normal distribution numerical data between two groups, and Chi square test for categorical data. P<0.05 is considered to be significant.

RESULTS

140 patients assisted for eligibility, 15 did not meet the inclusion criteria and 5 patients refused to participate. The remaining 120 patients were randomly assigned to the Letrozole Group (n= 60) and CC-“NAC” Group (n=60), the number of dropouts were five patients in each groups. All dropouts were due to either non-compliance to treatment or lost follow-up. The trial was completed by 55 patients in each group (Figure 1).

Both arms were comparable in age, parity, BMI, type and duration of infertility (Table 1).

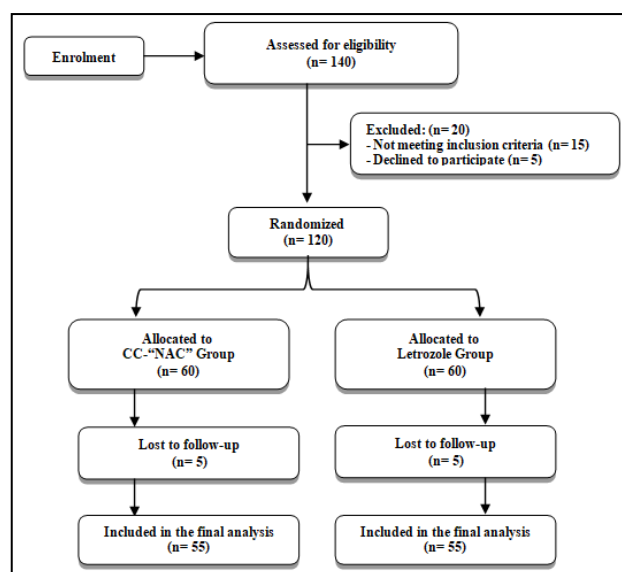


Figure 1: Flowchart of the participants.

Table 1: Baseline data of the studied groups.

	Group I (CC+NAC) (n=55)		Group II (Letrozole) (n=55)		p-value
	No.	%	No.	%	
Age in (years)					
Mean±SD	27.89±5.92		27.84±5.17		0.869
Range	18.0-38.0		19.0-38.0		
Residence					
Rural	47	85.5	39	70.9	0.065
Urban	8	14.5	16	29.1	
Type of infertility					
Primary	17	30.9	17	30.9	1.000
Secondary	38	69.1	38	69.1	
BMI in (Kg/ m²)					
Mean±SD	28.67±3.00		27.28±3.43		0.129
Range	24.2-31.8		22.2-30.5		
Duration of infertility in (years)					
Mean±SD	3.08±2.17		2.96±1.75		0.821
Range	1.0-15.0		1.0-10.0		

CC: clomiphene citrate, NAC: n-acetyl cystiene, BMI: body mass index.

The ovulation rate in patients in letrozole arm was significantly higher than CC+NAC arm (71.8% versus 53.2%, p=0.01). Additionally, endometrial thickness was higher in letrozole arm (mean±SD: 11.46±1.61 versus 9.0±1.13, p=0.031).

However, no statistical significant difference with regarding the ovarian hyperstimulation rate (1.8% versus 3.6%, p=0.157), clinical pregnancy rate [3/19 patients (27.3%) versus 19/55 (34.5%), p=0.409] and miscarriage rate [4/15 patients (26.7%) versus 19/55 (15.8%), p=0.317] in CC+NAC versus letrozole groups respectively.

DISCUSSION

Our results revealed higher ovulation rate and better mid-cyclic endometrial thickness with the use of letrozole for induction. On the other hand, Addition of NAC to CC in leads to comparable pregnancy rate as letrozole. There are many randomized controlled trials published in the literature but their results are conflicting. Some studies reported significant improvements in ovulation and pregnancy rate with CC after taking NAC in infertile women. Other studies reported significant improvements in ovulation and pregnancy rates with letrozole.

PCOS is a medical disorder that principally should be medically treated. Failure of CC even on maximal dose as a first line therapy for PCOS represents a real challenge for gynecologists.⁶ Many studies tried to combine another drug to CC to increase its efficacy.⁷ Others replaced it by an alternative medical or surgical treatment. Gonadotrophins therapy (GTs) is considered the best second line as it doesn't affect ovarian reserve and carries no risks of peritubal or periovarian adhesions.

A meta-analysis investigated 78 studies on the use of these medications in the infertility treatment of women with PCOS. Of these studies, 13 RCTs met the inclusion criteria. Six studies compared the use of letrozole versus CC and found that letrozole presented with a higher ovulation rate/patient (OR 2.90; 95% CI: 1.72- 4.88; $p < 0.0001$); however, no significant differences in the rate of ovulation per cycle or better pregnancy, live birth, multiple pregnancy or miscarriages rates were noted. Letrozole also did not obtain better results regarding clinical pregnancy or live birth rates compared with placebo or CC + metformin in women with CC-resistant PCOS. The results of the comparison of the effects of letrozole and anastrozole on ovulation and pregnancy rates in women with CC-resistant PCOS are controversial.⁸

Another prospective cross-over trial to compare CC plus NAC versus CC for inducing ovulation in patients with PCOD included 573 patients were treated with CC for one menstrual cycle versus 470 patients were treated with CC plus NAC for another cycle.⁵ Ovulation rate improved significantly after the addition of NAC (17.9% versus 52.1%). Although the number of mature follicles was more in the NAC group (2.1 ± 0.88 versus 3.2 ± 0.93), the difference was not statistically significant. The mean E2 levels (pg/ml) at the time of human chorionic gonadotropin injection, serum progesterone levels (ng/ml) on days 21-23 of the cycle, and the endometrial thickness were significantly improved in the NAC group. The overall pregnancy rate was 11.5% in the NAC group.

Letrozole can be recommended as first line treatment due to its higher ovulation, pregnancy, and live birth rate as well as lower multiple pregnancy rates, although the reluctance to adapt such new therapy is common in clinical practice.⁹⁻¹¹ The superiority of letrozole over clomiphene was stable in all sensitivity analyses including modifying the criteria of population (treatment naive), reporting strategies (reporting clinical pregnancy) and quality of included studies (low risk of randomization and allocation bias).

In our study, there were no significant differences in miscarriage rates in different comparisons; therefore, the superiority of letrozole over clomiphene in terms of live birth does not seem to be related to a decreased miscarriage rate.¹²

CONCLUSION

In conclusion, Comparable effects confirmed between both letrozole and CC-NAC with no clear difference confirmed between both groups. Although further studies are needed before aromatase inhibitors can be recommended for PCOS infertility, some potential advantages in letrozole treated patients warrant consideration.

- High ovulation rate
- Mono-ovulation in most cycles so less need to close monitoring by US
- Good endometrial thickness at time of ovulation triggering
- More pregnancy rate
- Short time to achieve pregnancy
- Decrease abortion rate
- Decrease multiple pregnancy rate
- Less side effects lead to more compliance to therapy
- Rapid clearance from the body so less likely to have anti estrogenic effect systemically or locally on endometrium and cervical mucus quality
- No accumulation of the medicine or its metabolite.

Letrozole is an efficient, safe ovulation induction agent and can be used as a first line ovulation inducing agent if the patient affords its price.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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