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Letrozole and metformin versus letrozole alone for ovulation induction in women with polycystic ovarian syndrome: a randomised controlled trial

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Abstract

Polycystic ovary syndrome is a syndrome with a complex interaction between metabolic, endocrine, genetic, and environmental factors. The aim of the study is to compare letrozole and metformin with letrozole alone for ovulation induction. This was a single blinded randomized controlled trial. Patients who met the inclusion criteria and consented for the study were recruited and randomized into study and control groups. The study group were placed on metformin 1000 mg daily and letrozole 7.5 mg daily from the second to the sixth day of the menstrual cycle, while the control group received letrozole 7.5 mg from the second day to the sixth day. Outcome measures recorded were ovulation, conception and pregnancy. The ovulation rate was 75.8% in metformin and letrozole group and 78.8% in letrozole alone group, conception rate was 42.4% and 33.3% respectively while pregnancy rate was 27.3% and 24.2% respectively. There was a higher ovulation rate in letrozole alone group than in combined letrozole and metformin, while conception rate and pregnancy rate was higher in the combined letrozole and metformin.

Key words: polycystic ovary, letrozole, metformin.

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Introduction

Polycystic Ovary Syndrome (PCOS) is the most common cause of anovulatory infertility and its etiology is related to a complex interaction between metabolic, endocrine, genetic, and environmental factors.[1] Insulin resistance and hyperinsulinemia play a role with hyperandrogenism in the development of metabolic alterations and anovulation in patients with PCOS.[2] The prevalence of PCOS ranges from 2.2% to 26% in various countries.[3] In Sub-Saharan Africa, the prevalence of PCOS range from 16-32%.[4] PCOS is characterized by ovulatory dysfunction, hyperandrogenism and polycystic ovary.[5,6]

The diagnosis of PCOS based on Rotterdam criteria, include two out of three criteria; abnormal ovulatory function , hyperandrogenism, and polycystic ovaries.[7,8] The first step in the treatment of PCOS is to restore ovulation.[1,8] The medical options include clomiphene, letrozole, metformin, and gonadotropins.[8-10] Metformin increases peripheral utilization of glucose and has a significant ovulation stimulatory effect compared with placebo.[4,11,12] Letrozole inhibit the negative feedback of estrogens on pituitary/hypothalamus and increase FSH secretion inducing ovulation.[9]

Several studies were carried out with different combinations of clomiphene, metformin and letrozole in ovulation induction.[8-14] The studies compared pregnancy and ovulation rates between letrozole, clomiphene and metformin in various combinations. But the studies did not carry out statistical test of association between ovulation/pregnancy rates and associated factors such as age, body mass index and duration of infertility. The objective of this study is to compare ovulation and pregnancy rates between women with PCOS who received letrozole and metformin compared to those who received letrozole alone and also to establish if there is an association between ovulation and factors such as age of patient, Body Mass Index (BMI) and duration of infertility.

Materials and Methods

Study location

The study was conducted at Aminu Kano Teaching Hospital (AKTH), Nigeria. Reproductive endocrinology clinics at AKTH are done once a week and a total of at least 40 patients are consulted weekly; 10-12 of them are PCOS patients.

Study population

The study was a Randomised Controlled Trial (RCT). Patients with at least two out of the three Rotterdam criteria: i) hyperandrogenism, testosterone >0.5ng/ml; ii) oligomenorrhea, cycle length of >35 days and or anovulation (day 21 progesterone <3 ng/ml); iii) polycystic ovary, presence of >12 follicles in each ovary, 2-9mm in diameter and or increased ovarian volume of 10 mls.[7,15-19]

Inclusion criteria

Inclusion criteria for the study were: i) PCOS patients with subfertility desiring pregnancy and willing and able to have timed intercourse; ii) PCOS patients with at least one patent fallopian tube and a normal uterine cavity, as determined by hysterosalpingography, or laparoscopy; iii) patients with a male partner with normal semen parameters, according to the World Health Organization (WHO) criteria; iv) patients who committed to having regular intercourse with their male partner with the intent of pregnancy.

Exclusion criteria

Exclusion criteria for the study were: Body Mass Index (BMI)>35 kg/m^2, additional causes of infertility, uterine fibroids, adenomyosis, pelvic surgery, hyperprolactinaemia, thyroid disease.

Sampling technique

Simple random sampling via computer generated random numbers. Patients were assigned serial numbers 1-80. The numbers were randomly placed into two groups and the researcher allocated patients into study and control groups based on which group their serial number falls.

Sample size determination

Minimum sample size required was calculated using the formula for RCT.[8]

$$n = \frac{(Z_{\alpha} + Z_{1-\beta})^2 - \{(p_1 q_1) + (p_2 q_2)\}}{(p_1 - p_2)^2}$$

where

n= minimum sample size in each group

Z_{α}= standard normal deviation corresponding to 5% level of significance, 1.96

$Z_{1-\beta}$= standard normal deviation corresponding to the power of the test to detect differences, set at 80%; the value obtained from the normal distribution table is 0.84

p_1= prevalence of ovulation in study group, 77%[1]

p_2=prevalence of ovulation in control group, 43%[1]

$$n = \frac{(1.96 + 0.84)^2 x \{(0.77)(0.23) + (0.43)(0.57)\}}{(0.77 - 0.43)^2}$$

$$n = \frac{7.84 \times 0.043}{0.1156}$$

n = 33

A total of 33 subjects were recruited for each group. Adding 20% for attrition, a total of 40 subjects were recruited in each group.

Ethical considerations

Approval for the study was obtained from the ethics committee of AKTH. Informed written consent was obtained from all participants.

Procedure

A questionnaire was filled containing patient's information and a number was randomly assigned to each patient. The patients were allocated to either the study or the control group using computer generated random numbers. A series of opaque envelopes numbered from 1 to 80 were prepared containing either letrozole and metformin (Group A) or letrozole only (Group B). Only the research assistant was aware of what group the patient belongs to.

GROUP A: patients received 1000 mg metformin (PANFOR SR) daily for three weeks before the onset of menses, on the second day of menses she commenced letrozole 2.5 mg three times daily (impregnil) for five days from day 2 of their menses.

GROUP B: patients commenced letrozole 2.5mg (impregnil) three times daily from the second day of menses for five days.

A patient with anovulation who does not have a spontaneous cycle were given norethisterone (Primolut N)^R 10 mg daily for 10 days to induce withdrawal bleeding; with onset of withdrawal bleeding, the research protocol is followed.

Follicular tracking was performed on days 10, 12 and 14 of the cycle. Once an ovarian follicle reaches ≥18 mm in size the patient was advised to have intercourse every other day for one week. Transvaginal ultrasound on day 16 was done to confirm ovulation. In case of delayed menstruation in a patient who had ovulated, β-HCG was assayed, a positive test indicates conception or chemical pregnancy and the patient was asked to stop all medications. Pregnancy was confirmed by presence of fetal cardiac activity on ultrasound by seventh week of gestation. If menses occured or serum β-HCG was negative, the patient continued metformin and participate in the second cycle for a maximum of three consecutive cycles.

Outcomes

Primary outcomes were defined as ovulation evidenced by corpus luteum identified on day 16 of the cycle. Secondary outcomes were chemical pregnancy, clinical pregnancy.

Statistical analysis

Data collected were analysed using SPSS version 20. Means and proportions of the socio-demographic variables of respondents were calculated and summarized using frequencies, percentages, means and standard deviations. Ovulation, conception and pregnancy were the dependent variables while independent variables included socio-demographic data of the participants.

Chi-square test or the Fisher's exact test was used to analyze factors associations. Risk ratios with 95% confidence intervals was calculated and compared between the groups. Test of significance, $p<0.05$ was considered statistically significant.

Results

A total of 97 women were invited, out of which 80 were randomized in two groups. Four participants were lost to follow-up (ML, n=1; L, n=3). Two women from the study group conceived on metformin before commencing letrozole. Eight women, four from each arm, discontinued medications. Six patients had to take norethisterone for 10 days to initiate withdrawal bleeding for induction cycle to begin. The remaining 66 participants (ML, n=33; letrozole, n=33) completed treatment as per protocol. Figure 1 shows flow of participants through the trial.

The mean age of participants was 28.8±5.9 years and mean BMI was 27.3±4.0 Kg/m^2.

The majority of the patients had tertiary level of education, were nulliparous and had infertility for less than 5 years (Table 1).

There was no statistically significant difference between the groups, p-value >0.05 (Table 2).

The ovulation rate was found to be similar in two groups, metformin and letrozole was 75.8%, 95% Confidence Interval (CI) (61.1-90.5) and letrozole was 78.8%, 95% CI (61.5-92.9). Conception rate was higher with metformin and letrozole than letrozole alone, (42.4%) and (33.3%) with 95% CI to be (25.1-58.9) and (16.9-49.1) respectively. Pregnancy rate was slightly higher with metformin and letrozole than with letrozole alone, (27.3%) and (24.2%) with 95% CI (20.3-51.7) and (9.5-38.5) respectively. There was no statistically significant difference in ovulation, conception and pregnancy rates, p-value >0.05 between the two groups (Table 3).

The total number of cycles was 172, 87 in metformin and letrozole group and 85 in letrozole only group. Ovulation rate per cycle in metformin and letrozole group was lower than letrozole only. Conception rate per cycle for metformin and letrozole was 16.1% and 12.9% respectively. Pregnancy rate was found to be higher in metformin and letrozole group, 13.7% than letrozole alone group, 9.4%.

Table 4 shows the ovulation rate for each drug per cycle for the three cycles. The denominator changes per cycle as patients conceive and are not included in subsequent cycle. A total of 87 cycles in letrozole and metformin group and 85 cycles in letrozole alone group were studied giving a total of 172 cycles.

Factors associated with ovulation were age, BMI and duration of infertility. There was no statistically significant association between age and ovulation, p>0.05. There was also no statistically significant association between BMI and ovulation, p-value >0.005. Similarly, there wasn't a statistically significant association between duration of infertility and ovulation (Table 5).

Table 1. Socio-demographic characteristics.

Variable	Study group n=33(%)	Control group n=33(%)	χ^2	p
Age (years)				
18-25	12 (36.4)	9 (27.3)		0.73†
26-35	19 (57.4)	21 (63.6)		
36-40	2 (6.1)	3 (9.1)		
Mean±SD 28.8±5.9				
Parity				
Nulliparous	26 (78.8)	24 (72.7)	0.33	0.57
Multiparous	7 (21.2)	9 (27.3)		
Education				
Primary or less	2 (6.1)	3 (9.1)		0.39†
Secondary	12 (34.6)	7 (21.2)		
Tertiary	19 (57.6)	23 (69.7)		
BMI (kg/cm^2)				
Normal	7 (21.2)	7 (21.2)	0.34	0.84
Overweight	18 (54.5)	16 (48.5)		
Obese	8 (24.2)	10 (30.3)		
Mean±SD 27.3±4.0				
Duration of infertility				
<5	23 (69.7)	17 (51.5)	2.285	0.13
≥5	10 (30.3)	16 (48.5)		

†Fishers exact test. SD, Standard Deviation; BMI, Body Mass Index

Discussion

This RCT compared ovulation induction agents among two groups, metformin and letrozole on one hand and letrozole alone on the other hand to compare effectiveness in terms of ovulation, conception and pregnancy, and to identify factors associated with ovulation.[20-30]

The mean age was found to be 28.8±5.9 years and mean duration of infertility to be approximately 5 years. This is similar to study by Davar *et al*. were the mean age was found to be 28.54±3.13 years & mean duration of infertility was 3.76 years.[31]

The majority of the patients were nulliparous (78.8%), similar to the findings in PPCOS II trial were nulliparous women were 87%.[21]

Ovulation rate was found to be slightly higher with letrozole alone which however was not statistically significant. This was similar to the findings of Liu *et al.* where they compared 4 groups (L, CC, CC+MET, L+MET);[32] no significant difference was noted among the four groups regarding baseline data of clinical manifestations, sex hormone, and insulin levels. The ovulation rate was significantly higher in group LE than CC group and no significant

Table 2. Outcomes.

Outcomes	Group A n=33(%)	Group B n=33(%)	χ^2	p
Ovulation			0.09	0.77
Yes	25 (75.8)	26 (78.8)		
No	8 (24.2)	7 (21.2)		
Conception			0.58	0.45
Yes	14 (42.4)	11 (33.3)		
No	19 (57.6)	22 (66.7)		
Pregnancy			1.15	0.28
Yes	12 (36.4)	8 (24.2)		
No	21 (63.6)	25 (75.8)		

Table 3. Outcomes per cycle.

Outcomes	Group A 87 cycles	Group B 85 cycles
Ovulation rate/cycle (rate)	60/87 69.0%	64/85 75.3%
Conception rate/cycle (rate)	14/87 16.1%	9/85 12.9%
Pregnancy rate/cycle (rate)	12/87 13.7%	8/85 9.4%

Table 4. Ovulation rate per cycle.

Outcomes	Group A 87 cycles	Group B 85 cycles
Ovulation rate first cycle	17/33 51.5%	22/33 66.7%
Ovulation rate second cycle	21/30 70%	21/27 77.8%
Ovulation rate third cycle	22/24 91.6%	21/25 84%
Total	60/87	64/85

Table 5. Factors associated with ovulation.

Variable	Group A				Group B			
	Yes	No	χ^2	p	Yes	No	χ^2	p
Age (years)				0.55†				0.43†
18-25	9 (27.3)	3 (9.1)			8 (24.3)	1 (3.0)		
26-35	15 (45.5)	4 (12.2)			15 (45.5)	6 (18.2)		
36-40	1 (3.0)	1 (3.0)			3 (9.1)	0 (0.0)		
BMI				0.56†				0.74†
Normal	6 (18.2)	1 (3.0)			6 (18.2)	1 (3.0)		
Overweight	12 (36.4)	6 (18.2)			13 (39.4)	3 (9.1)		
Obese	7 (21.2)	1 (3.0)			7 (21.2)	3 (9.1)		
Duration of infertility			0.14	1.00				0.69†
<5	17 (51.6)	6 (18.2)			14 (42.4)	3 (9.1)		
≥5	8 (24.2)	2 (6.1)			12 (36.4)	4 (12.1)		

†Fishers exact test. BMI, Body Mass Index.

difference was noted between the groups LE and CC, CC, and CC + MET, or LE and LE + MET in the pregnancy, abortion, and live birth rates.[32]

Similarly, Hurley *et al*. found no statistical association between metformin-letrozole and letrozole alone group.[33] There were no statistically significant differences in age, Anti-Müllerian Hormone (AMH) or BMI between the two groups. There were also no statistical differences in follicular recruitment or pregnancy rates (10% *versus* 13%, p=0.5663) when comparing the LE-M versus LE groups, respectively. They concluded that addition of metformin to LE does not improve follicular recruitment or pregnancy rates.[33] This higher ovulation rate could be attributed to the high dose of letrozole used, 7.5mg for both arms; this was similar to the findings of Pritts *et al*.[23] where higher doses of letrozole were association with higher ovulation rates without significant detrimental effect on endometrial thickness.

The pregnancy rate was 42.4% in metformin and letrozole group and 33.3% in letrozole alone group, there was no statistically significant difference between metformin and letrozole group although the rates were slightly higher for pregnancy in the metformin and letrozole group. This was similar to the findings in Sobrahbands study which showed higher pregnancy rate in metformin-letrozole group. The results of their findings was among overweight women.[22] This could also explain the finding in this study as majority of patients were overweight.

We found letrozole and metformin to be more effective than letrozole alone in women with PCOS. Although ovulation rate was found to be slightly higher in Letrozole alone group, conception and pregnancy rates were more likely after treatment with letrozole and metformin than with letrozole alone. This was similar to the findings by Legro *et al*.,[29] sustained reduction in androgen levels could be the reason of higher conception rate. Elgafore *et al*. reported that letrozole + metformin combination can have a success rate of ovulation of 90.6% and successful pregnancy in 34.5%.[34] Liu *et al*. reported a pregnancy rate of 57.9% in letrozole plus metformin and only 46.8% in patients who received letrozole alone.[32] Davar *et al*. reported a pregnancy rate of only 8.3%; a lower rate of pregnancy after letrozole and Metformin that is contrary to our findings.[35] The findings in Pakistan was high rate of pregnancy in patients receiving letrozole plus metformin versus letrozole alone, 56% in LE+ metformin group and 41% in letrozole group alone.[8] The better outcome of metformin in combination with other ovulation induction agents has been attributed to reduction in androgens observed in patients on metformin.[36] Netoro *et al*. concluded a review on use of metformin for ovulation induction and found that metformin has been proven to increase success rates and decreases complication rates in Anti-Retroviral Therapy (ART) and during ovarian stimulation when used as an adjuvant medication.[37]

There was no statistically significant association between age and ovulation between groups but there seemed to be a higher chance of conception in age groups 26-35 years. There was no statistically significant association between BMI and ovulation but ovulation was more likely in overweight patients than in obese patients. No statistically significant association between duration of infertility and ovulation.

Conclusions

The findings from this study showed a slightly higher ovulation rate in letrozole group than in combined letrozole and metformin group, while the conception and pregnancy rates were higher in combined letrozole and metformin group.

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Contributions: ARA, conceived the research, developed the methodology, and ensured the research design was appropriate; BAD, data collection, analysis, interpretation of the results, writing and editing of the manuscript; MY, led the investigation, ensuring accurate implementation of the study protocol, writing, editing and assisting in refining the final version of the study. All the authors have read and approved the final version of the manuscript, and agreed to be held accountable for all aspects of the work.

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Informed consent: written informed consent was obtained from all participants.

Patient's consent for publication: the patients gave their written consent to use their personal data for the publication of this case report and any accompanying images.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.