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Effects of Clomiphene Citrate Versus Letrozole on Semen Count and Motility in Men with Oligoasthenozoospermia in Osogbo, South-Western Nigeria: A Randomised Study

Akinbowale, Akin Akinyele [a*], Akinbowale, Busayo Temilola [b], Akinwale, Oladayo Damilola [c], Komolafe Monisayo [b], Bola-Oyebamiji Shekinat [d], I. Isawumi Adegboye [d] and Komolafe Johnson [d]

[a] Obstetric and Gyneacological Department, Osun State University Teaching Hospital, Osogbo, Nigeria.
[b] Nursing Department, Osun State University Teaching Hospital, Osogbo, Nigeria.
[c] Department of Nursing, Redeemer's University, Ede, Osun State, Nigeria.
[d] Department of Obstetrics and Gynaecology, Osun State University Teaching Hospital, Osogbo, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Background: Infertility is a major cause of socio-emotional and psychological burden world-wide and nearly half of all cases of infertility were as a result of male partner's related factors of which oligoasthenozoospermia is a major contributor. Currently, different treatments have been developed to manage this deficiency and improve semen parameters but no substantial results have been documented.
Aims: This study therefore aims at evaluating the effects of clomiphene citrate versus letrozole on semen count and motility in men with oligoasthenozoospermia in Osogbo, south-western Nigeria

**Corresponding author: E-mail: akinyeleakinbowale.aa@gmail.com;*

Study Design: A randomized control study carried out at the gynaecology clinic of LAUTECH teaching hospital, State specialist hospital and Ayomide Women's Health Specialist Hospital and IVF Centre Osogbo, Osun State.
Methodology: One hundred and forty (140) participants were randomized into the letrozole group and the clomiphene citrate group, with 70 participants in each arm of the study. The outcome measure includes the improvement in sperm concentration and motility (assessed at 4 and 8 weeks) following 3 months of alternate day administration of clomiphene citrate and letrozole by the participants. The study compared the improvement in semen concentration and motility following administration of Clomiphene citrate versus Letrozole among men with oligoasthenozoospermia. Data collected were analysed using Statistical Package for Social Statistics (SPSS-21) software and the level of significance was set at < 0.05.
Results: Letrozole and clomiphene caused significant improvement in sperm motility and concentration with letrozole having higher improvement in both sperm concentration and motility when compared to clomiphene citrate. There was 43.65% increased sperm concentration at 4 weeks and 48.24% increased at 8 weeks post-treatment in the letrozole group, while increased sperm concentration of 17.68% at 4 weeks post-treatment and 26.27% increment at 8 weeks post-treatment in the clomiphene citrate group was observed. Also, there was 33.24% increased sperm motility at 4 weeks and 42.09% at 8 weeks post-treatment in the letrozole group, and 14.30% increased sperm motility at 4 weeks and18.56% at 8 weeks post-treatment.
Conclusion: Sperm concentration and motility in men with oligoasthenozoospermiacan be improved with Letrozole and clomiphene citrate. Higher effect was observed in Letrizole group compared to clomiphene.

Keywords: Semen parameter; clomiphene citrate; letrozole; oligoasthenozoospermia,

1. INTRODUCTION

Infertility is a major source of socio-emotional and psychological burden worldwide; it is a sensitive issue in Nigerian culture as it remains a major cause of social stigma, marital disharmony, social neglect, and economic deprivation of the female partners. African men often equate sexual potency to fertility and sometime refuse medical evaluation [1]. Infertility occurs in about 15% of sexually active couple, and male factor infertility is responsible for 50% of all cases [2]. Male factor infertility is a major contributor to the burden of infertility in sub-Sahara Africa, causing marital disharmony and psychological distress among married couple [3]. Despite advances in the field of assisted Reproductive Technology [ART] for the management of male factor infertility, ART is still not readily available and where it is available, cost is a major setback especially intra-cytoplasmic sperm injection that can help men with severe abnormal semen parameters to have baby of their own [4-6]. More so, many couple prefers to have babies that are genetically their own thereby rejecting the option of sperm donor for artificial insemination [7].

In some cases of male infertility, the major cause is unknown indicating that men have an unexplained reduction of semen quality, a condition classified as idiopathic oligoasthenoteratozoospermia accounting for 25% of all cases [8]. In other words, idiopathic male factor infertility occurs when the possible cause of infertility could not be identified after thorough clinical and laboratory evaluation. More so, evidence has shown that various treatment and medical therapy had been instituted for those with idiopathic male factor infertility of which the use of antioxidants, selective estrogen receptor modulators and aromatase inhibitors were selectively instituted with resultant lower efficacy [9,10]. Anti-estrogen and aromatase inhibitors are considered effective because it provides negative feedback to the hypothalamus and pituatry. Anti-estrogen such as clomiphene blocks endogenous estrogen by binding to estrogen receptors in the hypothalamus and pituitary gland which subsequently leads to up-regulation of the hypothalamic-pituitary-gonadal axis witt increase in the level of gonadotropin release and stimulation of spermatogenesis [11,12].

Meta-analysis shows that estrogen antagonist (clomiphene citrate) is safe and has positive effects on sperm concentration and percent motility when compared to placebo. It also reduces the need for in-vitro fertilization and intra-cytoplasmic sperm injections, as intrauterine insemination becomes a viable option with improved semen parameters [13].

Letrozole on the other hands is a non-steroidal selective aromatase inhibitor that prevent aromatization of androgen to oestrogen by competitive reversible binding to the heme subunit of cytochrome P450 enzyme with subsequent increase level of circulating androgen [9-10]. Evidence showed that Letrozole is also being used for men with idiopathic infertility and has been shown to improve the testosterone/estrogen ratio, sperm concentration as well as sperm motility [10]. This is also beneficial in obese hypogonodal men to elevate the intra-testicular testosterone level [10,14].

Although, there are several studies on medical management of male factor infertility with varied reported efficacy. Nevertheless, there is no standard recommended therapy for management of those with idiopathic male factor infertility and no study has been conducted to compare the effectiveness of letrozole and clomiphene citrate in the treatment of male factor infertility. Therefore, this study aims at evaluating and comparing the effects of clomiphene citrate to that of letrozole in men with oligoasthenozoospermia.

1.1 Objective of the Study

1. To determine the level of improvement in semen concentration and motility following administration of clomiphene citrate.
2. To determine the level of improvement in semen concentration and motility following administration of Letrozole
3. To compare the improvement in semen parameter between administration of Clomiphene citrate to letrozole in men with oligoasthenozoospermia.
4. To review the side effect profile of both clomiphene citrate and letrozole

1.2 Hypotheses

H_0: There is no significant improvement in semen concentration and motility in men with oligoasthenozoospermia using letrozole compared to those using clomiphene citrate.

H_1: There is significant improvement in semen concentration and motility in men with oligoasthenozoospermia using letrozole compared to those using clomiphene citrate.

2. METHODOLOGY

2.1 Research Design

This study was a randomized control study carried out at the gynaecology clinic of LAUTECH teaching hospital, State specialist hospital and Ayomide Women's Health Specialist Hospital and IVF Centre Osogbo, Osun State 1st of April, 2018 to 31st of March, 2019. These settings were selected based on the patronage of male patients with oligoasthenozoospermia at the fertility clinic.

2.2 Population

The study population were men with abnormal semen count and motility that were evaluated for infertility at LAUTECH Teaching Hospital, State Specialist Hospital, Asubiaro and Ayomide Women's Health specialist Hospital and IVF Centre, Osogbo that were eligible and consented to take part in the study.

2.2.1 Inclusion criteria

Men with persistent abnormal semen count and motility at least two abnormal test results during infertility evaluation. In this study, abnormal semen count was taken as sperm count of less than 15million/ml on at least two occasions two weeks apart, and active motile sperm percentage of less than 32% on two assessmentsatleast two weeks apart [15].

2.2.2 Exclusion criteria

Men with obstructive azoospermia. chronic renal or liver failure, uncontrolled diabetes, normal semen parameters and those who are not interested in the study.

2.3 Sample Size Determination

The total number of patients that was recruited for the study was determined using the sample size formula for randomized control trial with outcome measure in continuous variable [16]. Estimated minimum sample size at 80% power and margin of error of 5% was calculated to be 64. A 10% attrition rate was anticipated, the adjusted minimum sample size was 70 in each arm of the study. Patients were recruited as they presented at the clinic and consented to take part in the study at the study centres.

2.4 Random Selection and Random Allocation

Block randomization of subjects into study groups was done using computer generated table of random number that gave equal chance

to all participants. A block of four possible combinations of letrozole and clomiphene citrate was done making a total of six possible blocks. The computer generated random number was used to pick from the blocks until the total sample size was achieved. All blocks generated were serialized and the numbers were written on a small paper that was put in a brown opaque envelope. Drugs were also packed into opaque brown envelopes with corresponding number. Participants were counselled, and informed consent were obtained, following which the subject picked an envelope that contain the number, it was subsequently opened and the corresponding drug was giving to the participant with appropriate instruction on dosage and possible side effects.

2.5 Recruitment of Participants

A total number of 140 patients with abnormal semen parameters following two consecutive semen analyses done at least two weeks apart were consecutively recruited into the study after obtaining informed consent from each participant. 40 participants were recruited from LAUTECH Teaching hospital, 46 participants were recruited from State specialist hospital, Asubiaro while 54 participants were recruited from Ayomide women's health and fertility centre. This was based on the numbers of male factor infertility that was seen at each centre in the year preceding this study. {Between 1st of April, 2018 to 31st of March, 2019). Each patient was given a detail brief about the study and sample collection.

2.6 Collection of Specimen (Spermato-zoa) for Semen Analysis

Each consenting patient at the gynaecology clinic of the hospitals used for the study took the randomized drug alternate day for 3 months (either 50mg of clomiphene citrate alternate day or 2.5mg of letrozole alternate day). Ejaculate (spermatozoa) was collected following 3 to 5 days of sexual abstinence from intercourse by masturbation into clean sterile screw cap plastic container at home (Those that had difficulty with self sample collection were assisted by their spouses) and the samples were brought to the hospital within 30 minutes of collection.

2.7 Storage, Transportation and Analysis of Specimen

Samples collected were kept close to the body surface during transportation to the hospital in order to maintain it close to the body temperature as much as possible. Analysis of the semen samples were done within one hour of its collection. The volume of the liquefied semen was measured using graduated cylinder and the pH was determined using a pH paper. The percentage progressive motility, non-progressive motility and non-motility was determined at 37^0C (turn the stage warmer on for 10 minutes), by placing a drop of well mixed liquefied semen on a slide (approximately 20µm deep), it was covered with a cover slip and count a total of 200 spermatozoa per replicate under a phase-contrast optics at x 200 or x 400 magnification and noting how many were motile. Then, calculate the average sperm motility.

The sperm count was performed by filling an improved Neubauer counting chamber with a well mixed and appropriate dilution of 10µl semen and then examine under phase-contrast optics x 200 or x 400 magnification, and count 200 spermatozoa and determine the numbers of rows that was counted in 2 aliquots. Determine the acceptability of the differences in the 2 aliquots and then calculate the sperm concentration [17]. All samples obtained from the study centres were analyzed at LAUTECH Teaching hospital Microbiology laboratory by medical laboratory scientist with the researchers' active involvement. Samples were taken at 4 weeks and 8 weeks after completion of treatment to determine the subjects' level of improvement.

2.8 Drug Procurement

Drugs that were used for this study were procured in bulk from importers and clomine (clomiphene citrate) manufactured by Baroque pharmaceuticals private limited India and imprenil (letrozole) manufactured by popular pharmaceutical limited Bangladesh were used for the study.

2.9 Data Analysis

The results of Investigation from the laboratory were entered into Statistical Package for Social Sciences (SPSS) version 21 software. Data was cleaned and a comparative analysis of the data was done. Descriptive statistics was used to compare baseline characteristics in a tabular form between the clomiphene citrate and letrozole groups. While inferential statistics of Chi-square test was used to determine significance of association between categorical variables, 2-independent samples t-test wasused

to assess mean difference in selected quantitative variables between two categories. Inferences on the hypotheses were drawn at 5% level of significance.

3. RESULTS

The total number of patients that were randomized for this study was 140, with 70 participants in each arms of the study. Seven patients were excluded from statistical analysis as 5 patients were lost to follow up [2] in the clomiphene citrate arm and 3 in the letrozole group]. Also, 2 patients could not continue with the study due to severe side effect (one in each arm of the study).

Table 1 shows the comparative socio-demographic parameters between the letrozole group and the clomiphene citrate group. Majority of the participants were between the ages of 20-40 years in the two groups with 35(53%) in the letrozole and 38(56.7%) in the clomiphene citrate arms. The mean age for the letrozole group was 38.46±1.44 and that for the clomiphene citrate arm was 37.74±2.17 with t-value of 0.509 and p-value of 0.114. Majority of the participants in both groups were from Yoruba ethnic group with 95.5% in the letrozole and 89.5% in the clomiphene citrate group with statistics test of χ^2=2.566 and p-value of 0.277. More so, majority of the participants had secondary level of education (Letrozole 28(42.2%); Clomiphene 28(41.8%)) in both groups and were professionals (Letrozole 26(39.4%); Clomiphene 27(40.3%)). The statistical test wereχ^2 = 0.025 with p-value 0.999 andχ^2 = 0.211 while the p-value was 0.900 for level of education and occupation respectively.

More than half of the participants had less than 5 years duration of infertility with (38)54.5% in the letrozole group and 3(552.2%) in the clomiphene citrate group. The statistical test was χ^2 = 3.192 with p-value of 0.445.The mean weight for the letrozole group was 70.33 ± 5.94kg and 70.46 ± 5.93kg in the clomiphene citrate group with t-test of 0.126 and p-value of 0.900. The average height of the participants was 1.61 ±0.04 metre for the letrozole group and 1.60 ± 0.05 metres in the clomiphene citrate group. The t-test was 1.108 and the p-value of 0.270. Furthermore, the pre-treatment sperm concentration of Letrozole and Clomiphene citrate were 10.24 ± 1.14 x$10^6$and 9.67 ± 0.96 x 10^6 respectively with t-test 0.959 and p-value of 0.399 while the pre-treatment sperm motility were 21.36 ± 1.48 and 22.79 ± 1.29 for letrozole and clomiphene citrate respectively with t-test of 1.925 and p-value of 0.051.

Table 2 shows the outcome measure in the clomiphene citrate group with a mean pre-treatment sperm concentration of 9.67±0.96x10^6 for sixty seven participants that were analyzed. The post-treatment sperm concentration at 4 weeks was 11.38±0.92x10^6 with an increment of 17.68% above the pre-treatment value that was observed among 44 participants, and the post-treatment sperm concentration at 8 weeks was 12.21±1.28x10^6 with an increment of 26.27% that observed among 49 participants. The pre-treatment sperm motility was 22.79±1.29. The post-treatment sperm motility at 4 weeks was 26.05±1.23 with an increment of 14.30% and the post-treatment sperm motility at 8 weeks was 27.02±1.24 with an increment of 18.56% above the pre-treatment value that was observed among 42 participants.

Table 3 shows the outcome measure in the letrozole group with the mean pre-treatment sperm concentration of 10.24±1.14x10^6 for sixty-six participants that were analysed. The sperm concentration at 4 weeks post-treatment was 14.71±1.15x10^6 with 43.65% increment that was observed among 50 participants and the sperm concentration at 8 weeks post-treatment was 15.18±1.14x10^6 with 48.24% increment observed among 54 participants. The pre-treatment sperm motility was 21.36±1.48. The sperm motility at 4 weeks post-treatment was 28.46±1.40 with 33.24% increment and the sperm motility at 8 weeks post-treatment was 30.35±1.42 with 40.09% increment that was observed among 48 participants.

Table 4 compares the outcome measure in both the letrozole and the clomiphene citrate group. The mean pre-treatment sperm concentration was 10.24 ± 1.14 x 10^6 for the letrozole group and 9.67 ± 0.96 x 10^6 for the clomiphene citrate group. The t-test was 0.959 and the p-value was 0.051. The sperm concentration for the letrozole group at 4 weeks post-treatment was 14.7 ± 1.15 x10^6, while that of the clomiphene citrate was 11.38 ± 0.92 x10^6 with the t-test of 2.934 and the p-value of 0.024. The motility at 4 weeks post treatment was 28.46 ± 1.40 for the letrozole group and 26.05 ± 1.23 for the clomiphene citrate group with t-test of 2.551 and p-value of 0.030. Also, the post-treatment sperm concentration at 8 weeks was 15.18 ± 1.14 x10^6 for the letrozole group and 12.21 ± 1.28 x10^6 for the clomiphene

group with t-test of 2.611 and p-value of 0.028 which was significant to that of pre-treatment value. The post-treatment sperm motility was 30.35 ± 1.42 for the letrozole group and 27.02 ± 1.24 for the clomiphene citrate group with t-test of 2.418 and p-value of 0.031.

Table 5 shows the side effect profile in both the letrozole and clomiphene citrate arm of the study.7(10.4%) headache as against 2(3%) in the letrozole group, loss of libido was 1(1.5%) in the letrozole arm, 9 participants in both letrozole and clomiphene citrate group had nausea, insomnia was reported by 5(7.6%) in the letrozole group and 2(3%) in the clomiphene citrate group, 6(10%) of the participants in the clomiphene citrate arm had dry mouth as against 4(6%) in the letrozole group, weakness was reported in 5(7.6%) of participants in the letrozole arm with 7(10.4%) in the clomiphene citrate arm, 2(3%) reported nervousness in the letrozole group and 1(1.5%) in the clomiphene citrate arm. Also, 4(6%) reported fatigue as side effect in the letrozole arm and 8(11.9%) in the clomiphene citrate arm.

Fig. 1 shows that majority of the participants had primary infertility which accounted for 40(60.6%) in the letrozole arm and 44(65.7%) in the clomiphene citrate arm of the study.

Table 1. Comparative Socio-demographic characteristics between the Study Groups

Variable	Letrozole	Clomiphene	Df	Test Statistics	p-value
Age Group					
20-40 years	35 (53)	38 (56.7)			
41-60 years	31 (47)	27 (40.3)	2		
60 years and above	0	2 (3.0)			
Mean age					
Tribe	38.46±1.44	37.74±2.17	2	χ^2=0.59	0.114
Yoruba	63 (95.5)	60 (89.5)		χ^2 = 2.566	0.277
Hausa	3 (4.5)	5 (7.5)			
Igbo	0	2 (3.0)			
Education Status					
None	5 (7.6)	5 (7.5)			
Primary	18 (27.3)	18 (26.9)	3	χ^2 = 0.025	0.999
Secondary	28 (42.2)	28 (41.8)			
Tertiary	15 (22.7)	16 (23.9)			
Occupation					
Artisan	21 (31.8)	19 (28.4)			
Trader	19 (28.8)	21 (31.3)	2	χ^2 = 0.211	0.900
Professional	26 (39.4)	27 (40.3)			
Duration of infertility					
<5 years	38 (54.5)	35 (52.2)			
5-10 years	24 (36.4)	26 (38.9)			
11-15 years	5 (7.6)	6 (9.0)	3	χ^2 = 3.192	0.445
16-20 years	1 (1.5)	0			
Weight	Mean ± SD	Mean ± SD			
	70.33 ± 5.94	70.46 ± 5.93		t-test = 0.126	0.900
Height	Mean ± SD	Mean ± SD			
	1.61 ± 0.04	1.60 ± 0.05		t-test = 1.108	0.270
Pre-treatment sperm concentration	10.24 ± 1.14 x10^6	9.67 ± 0.96 x 10^6		0.959	0.399
Pre-treatment sperm motility	21.36 ± 1.48	22.79 ± 1.29		1.925	0.051

Table 2. Shows the outcome measure in the clomiphene citrate group

Variable	Clomiphene	Percentage of increment	Number involved in Increment /[%] n=67
	Mean± SD		
Pre-treatment sperm concentration	9.67±0.96 $X10^6$		-
Post-treatment (4 weeks) sperm concentration	11.38±0.92 $X10^6$	17.68	44[65.7]
Post-treatment (8 weeks) sperm concentration	12.21±1.28 $X10^6$	26.27	49[73.1]
Pre-treatment sperm Motility	22.79±1.29		-
Post-treatment (4 weeks) sperm Motility	26.05±1.23	14.30	40[59.7]
Post-treatment (8 weeks) sperm Motility	27.02±1.24	18.56	42[62.7]

Table 3. Shows the outcome measure in the letrozole group

Variable	Letrozole	Percentage of Increment	Number involved in increment/[%] n=66
	Mean± SD		
Pre-treatment sperm concentration	10.24±1.14$X10^6$		-
Post-treatment (4 weeks) sperm concentration	14.71±1.15 $X10^6$	43.65	50[75.8]
Post-treatment (8 weeks) sperm concentration	15.18±1.14 $X10^6$	48.24	54[81.8]
Pre-treatment sperm Motility	21.36±1.48		-
Post-treatment (4 weeks) sperm Motility	28.46±1.40	33.24	44[65.7]
Post-treatment (8 weeks) sperm Motility	30.35±1.42	42.09	48[72.7]

Table 4. Compares the outcome measure in both clomiphene and letrozole groups

Variable	Letrozole	Clomiphene	T-Test	p-value
	Mean± SD	**Mean± SD**		
Pre-treatment sperm concentration	10.24±1.14 $x10^6$	9.67±0.96 x 10^6	0.959	0.399
Pre-treatment sperm motility	21.36±1.48	22.79±1.29	1.925	0.051
Post-treatment (4 weeks) sperm concentration	14.71±1.15 x 10^6	11.38±0.92 x 10^6	2.934	0.024*
Post-treatment (8 weeks) sperm concentration	15.18 ± 1.14 x 10^6	12.21 ± 1.28 $x10^6$	2.611	0.028*
Post-treatment (4 weeks) sperm Motility	28.46±1.40	26.05±1.23	2.551	0.030*
Post-treatment (8 weeks) sperm motility	30.35±1.42	27.02±1.24	2.418	0.031*

** The outcome measures are significant because the values are lesser than 0.05*

Table 5. Side effect profile of the respondents in both letrozole and clomiphene citrate groups

Variable	Letrozole		Clomiphene		χ^2	ρ
Headache	2(3.0)	64(97.0)	7(10.4)	60(89.6)	0.949	0.899
Loss of libido	1(1.5)	65(98.5)	0	67(100.0)	0.000	1.000
Hair loss	0	66(100.0)	0	67(100.0)	-	-
Nausea	9(13.6)	57(86.4)	9(13.4)	58(86.6)	1.647	0.542
Stooling	0	66(100.0)	0	67(100.0)	-	-
Body rash	0	66(100.0)	0	67(100.0)	-	-
Nose bleeding	0	66(100.0)	0	67(100.0)	-	-
Insomnia	5(7.6)	61(92.4)	2(3.0)	65(97.0)	1.374	0.377
Dry mouth	6(10.0)	60(90.0)	4(6.0)	63(94.0)	1.641	0.254
Weakness	5(7.6)	61(92.4)	7(10.4)	60(89.6)	1.590	0.299
Nervousness	2(3.0)	64(97.0)	1(1.5)	66(98.5)	0.921	0.881
Fatigue	4(6.0)	62(94.0)	8(11.9)	59(88.1)	1.671	0.221

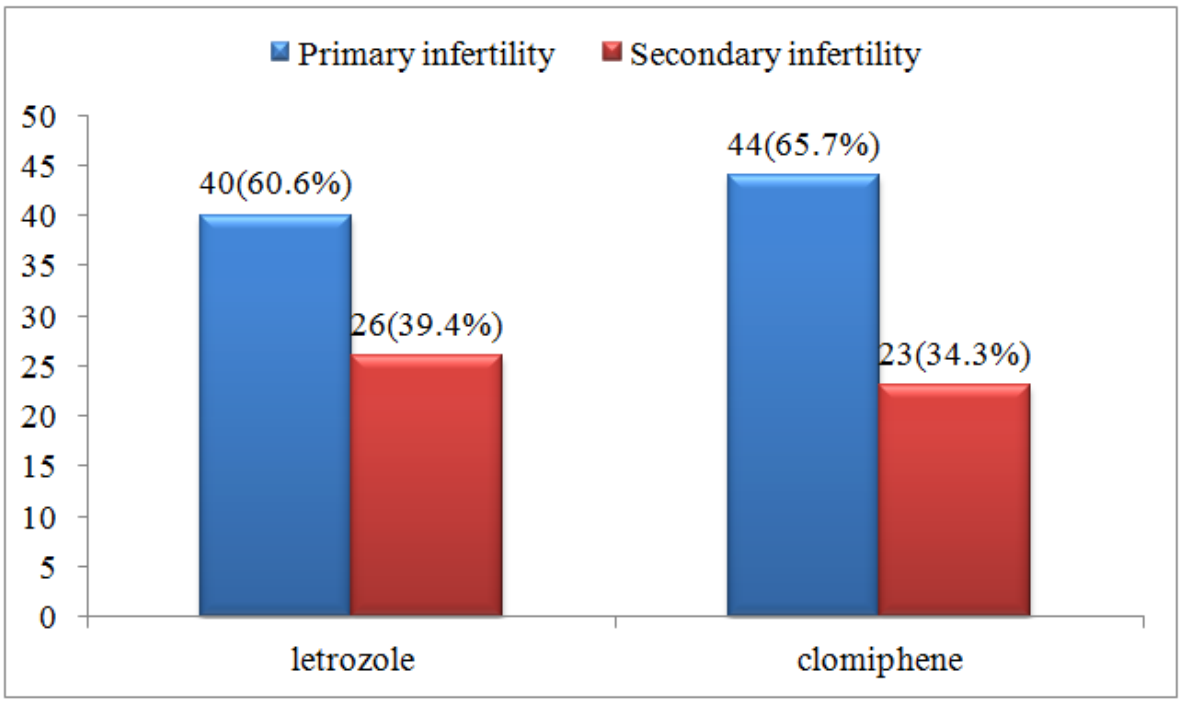

Fig. 1. Types of infertility in letrozole and clomiphene citrate group

4. DISCUSSION

The findings from the study demonstrated that the use of clomiphene citrate and letrozole were useful to increase semen parameters with letrozole having significant statistical edge over that of clomiphene citrate in term of increase in sperm concentration and motility. There was no significant difference between the socio-demographic characteristics between the participants in both the clomiphene citrate and the letrozole arm of the study, with majority of the participants having infertility for less than 5 years. In other words, the 2 drugs resulted in significant improvement in both sperm count and motility, however, the improvement observed from letrozole group appeared to be more pronounced and the difference was statistically significant [18].

The result from this study was in agreement with the report of [19] who reported significant increase in sperm count and motility following 6 months administration of 2.5mg daily of letrozole. Similarly, [20] reported improvement in sperm concentration and motility following usage of 2.5mg daily intake of letrozole among patient with non- obstructive azoospermia[64]. Also, [21] demonstrated improvement in sperm

concentration, motility and morphology following administration of letrozole. In the same vein, [22-30] reported 3 patients with azoospermia that subsequently demonstrated active spermatozoa with testicular biopsy following 3 months treatment with 2.5mg of letrozole. The outcome in this study also agrees with the study by [21] that demonstrated that 73% of the participants had improvement in semen parameters after 6 months administration of 2.5mg of letrozole and it is higher than the outcome achieved by [24] that demonstrated an improvement of 23.5% in semen parameters among azoospermic patient. The lower outcome in the study by [24] may be due to utilization of azoospermic patient instead of asthenozoospermic patient that was used in this study.

The findings in the clomiphene citrate group agreed with the findings of [25] that reported improvement in sperm concentration from 7.87 ± 2.64 millions/ml to 8.23 ± 3.08 million/ml following 3 months of treatment with clomiphene citrate and the sperm motility increased from 21.67 ± 6.99 % to 25.83 ± 9.92% in the same study [26]. However, the increase in sperm concentration was less than 5.24 millions/ml reported in meta-analysis by Chua et al who conducted a meta-analysis and reviewed 11 randomized control trials in which 5 of the studies used clomiphene citrate as the selective oestrogen receptor modulator, while the other ones utilised tamoxifen for their studies. Furthermore, the dosage of clomiphene citrate that was used ranges between 25 to 50 mg per day and the duration of treatment varied between 3 to 12 months in the review [27]. This could possibly account for the difference in the outcome when compared with the current study.

Also, the finding was less than an increase of 7.7 millions/ml reported by [28] in a meta-analysis done in 2015,in which 3 studies were reviewed with one of the study used clomiphene citrate in combination with vitamin E, and that could be the reason for the visible difference with this study. The study also agreed with the findings of [29] that reported improvement in semen parameter among 35 participants out of 53 [66%] that was treated with Clomiphene citrate for 3 months while the rest of the cohort noticed improvement in semen parameters between 6 to 15 months of therapy [30]. On the other hand, a double blind randomized control trial by WHO in 1992 using 25mg daily of clomiphene citrate for 6 months reported no improvement in pregnancy rate or semen parameters when compared to placebo [27] but the study has not been revisited since the time of its publication. There was a case report of 3 patients with severe oligozoospermia that became azoospermic following usage of clomiphene citrate, (possibly due to high dosage of clomiphene citrate that was used) and the semen parameters subsequently improve following discontinuation of the therapy [31-33].

The difference in outcome measures in both the clomiphene citrate and the letrozole groups may be due to the differences in the mechanism of action of both drugs as clomiphene citrate with its two isoforms (enclomiphene and zuclomiphene) acts by oestrogen receptor modulation, while letrozole act by reducing oestrogen concentration and subsequent reduction of negative feedback effect of oestrogen on the hypothalamus and the pituitary.

Both clomiphene citrate and letrozole were well tolerated with only one participant in the letrozole group discontinued the drug due to loss of libido (1.5%) which is similar to one person reported by [34]. Other reported side effects of letrozole include headache (3%), nausea in (13.6%), dry mouth (10%), fatigue (6%), which were different from 25%, 4.2%, 4.2% and 20.8% respectively reported by [31,34]. The observed reduced side effects in this study may be due to alternate day 2.5mg of letrozole that was used as against daily intake of 2.5mg in the previous studies [35-37].

The side effects reported for clomiphene citrate were nausea (13.4%), fatigue (11.9%), body weakness (10.4%), and headache (10.4%) that was mild except only one participant that had severe headache (1.5%) necessitating discontinuation of the drug. This is similar to the finding by [29,32] in their study on safety of clomiphene citrate among hypogonodal and sub-fertile men. Other minor side effects reported include dry mouth (6%), insomnia (3%) and nervousness.

The limitation of this study is that drugs used for this study were not produced locally making it difficult to blind the researcher however it is recommended that letrozole should be used in the treatment of men with oligoasthenozoospermia.

5. CONCLUSION

The findings of this study suggest that the use of letrozole and clomiphene citrate has a role to improve sperm count and motility in men with

oligoasthenozoopermia with letrozole demonstrating higher efficacy when compared to clomiphene citrate. Therefore, Letrozole and clomiphene citrate may be important adjuncts to other artificial reproductive techniques where it is necessary to improve semen count and motility that will help to improve the outcome of these procedures.There is also a need to increase research in the area of male factor infertility, such as the need to study combination of different modalities of medical management of male infertility in other to reduce this neglected scourge amongst men.

ETHICAL APPROVAL AND CONSENT

Ethical approval was obtained from the ethics and research committee of LAUTECH Teaching Hospital and it was used for the other 2 hospitals. Written consent was obtained from each participant after explaining the purpose and objective of the study to them and confidentiality was maintained.All principles governing ethical conduct was taken into consideration. The principles of benevolence and non- maleficence were also adopted in dealing with the participants.An increase in semen count of 25% above the highest count before the intervention was regarded as significant improvement while an increase of 10% in motility above the highest value before the intervention will be regarded as significant improvement [18].

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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