DOI: https://doi.org/10.54393/pjhs.v6i11.3372

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 11 (November 2025)

Original Article

OPEN ACCESS

Comparison of Letrozole and Clomiphene in Infertile Male Patients with Oligoasthenozoospermia

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ARTICLE INFO

Keywords:
Oligoasthenozoospermia, Letrozole, Clomiphene Citrate, Sperm Concentration, Sperm Motility

How to Cite:
Seerwan, M., Ilyas, M., Adnan, M., Muzammil, M., Saifullah, ., & Durrani, A. S. (2025). Comparison of Letrozole and Clomiphene in Infertile Male Patients with Oligoasthenozoospermia: Comparison of Letrozole and Clomiphene in Male Infertility. Pakistan Journal of Health Sciences, 6(11), 50-55. https://doi.org/10.54393/pjhs.v6i11.3372

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Received Date: 23rd July, 2025
Revised Date: 30th October, 2025
Acceptance Date: 7th November, 2025
Published Date: 30th November, 2025

ABSTRACT

Infertility often causes significant emotional distress, and in about 50% of cases, male factors such as oligoasthenozoospermia play a key role in the challenges you're facing. **Objectives:** To compare two medications, clomiphene citrate and letrozole, to see which one works better for improving sperm count and motility in men with oligoasthenozoospermia. **Methods:** This non-randomized controlled study was conducted at District Headquarter Teaching Hospital in D.I. Khan with 140 men diagnosed with oligoasthenozoospermia. Participants were divided into two groups of 70, receiving either letrozole or clomiphene citrate. Sperm concentration and motility were measured at three months, with improvements compared between the two groups. Statistical analysis was performed using SPSS version 21, with p-values <0.05 considered significant. **Results:** Both letrozole and clomiphene significantly improved sperm concentration and motility, with letrozole showing greater improvement in both parameters compared to clomiphene citrate. An increase of 48.23% in sperm concentration was observed in the letrozole group, while the clomiphene citrate group showed a 26.26% increase at 12 weeks post-treatment. Sperm motility improved by 42.08% with letrozole and by 18.55% with clomiphene citrate at the 12-week mark. **Conclusions:** Both letrozole and clomiphene citrate have been shown to improve sperm parameters in men diagnosed with oligoasthenozoospermia. The letrozole group showed a more significant effect than the clomiphene group.

INTRODUCTION

Worldwide, infertility causes substantial socio-emotional and psychological strain, and in Nigeria, it continues to be a sensitive issue, leading to social stigma, marital conflicts, neglect, and economic disadvantage for women. African men frequently link sexual potency with fertility, which can result in a reluctance to seek medical evaluation [1]. About 15% of sexually active couples are affected by infertility, with male infertility factors responsible for 50% of these cases [2]. Despite the development of advanced assisted reproductive technologies (ART) for male factor infertility, many couples still face barriers to effective treatment. ART remains largely inaccessible in many regions, and where available, its high cost-especially for ICSI-makes it difficult for men with severely impaired semen quality to have biological children [3-6]. In addition, the preference for genetically related children leads many couples to reject sperm donation as an option for assisted reproduction [7]. Male infertility is sometimes attributed to unknown causes, where men present with reduced semen quality without a clear explanation; this condition, known as idiopathic

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oligoasthenoteratozoospermia, represents about 25% of cases [8]. Idiopathic male infertility is diagnosed when a thorough clinical and laboratory assessment fails to reveal a specific cause for the impaired fertility. Furthermore, studies indicate that several therapeutic strategies have been applied to idiopathic male infertility, such as antioxidants, selective estrogen receptor modulators, and aromatase inhibitors; however, their effectiveness remains limited [9, 10]. The effectiveness of anti-estrogens and aromatase inhibitors is attributed to their ability to reduce estrogen feedback on the hypothalamus and pituitary, thereby enhancing endogenous testosterone synthesis. Clomiphene, an anti-estrogen, binds to estrogen receptors in the hypothalamus and pituitary, inhibiting the action of endogenous estrogen. This disinhibition enhances the hypothalamic-pituitary-gonadal axis, increasing gonadotropin secretion and promoting spermatogenesis [11, 12]. According to meta-analyses, clomiphene citrate, an estrogen antagonist, demonstrates a favorable safety profile and is associated with significant improvements in sperm concentration and motility relative to placebo. Clomiphene citrate enhances semen quality, reducing the reliance on IVF and ICSI while making intrauterine insemination a more viable treatment option [13]. Letrozole is a non-steroidal aromatase inhibitor that works by competitively binding to the heme subunit of cytochrome P450, preventing the conversion of androgens to estrogens and leading to elevated levels of circulating androgens. 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 [9, 10]. This is also beneficial in obese hypogonadal men to elevate the intra-testicular testosterone level [10, 14].

Although there are several studies on the medical management of male factor infertility with varied reported efficacy. Nevertheless, there is no standard recommended therapy for the 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. This study aims to evaluate the difference in semen parameter improvements between letrozole and clomiphene citrate in men diagnosed with oligoasthenozoospermia.

METHODS

This non-randomized controlled trial was carried out in the Department of Urology of District Headquarter Teaching Hospital, Dera Ismail Khan. The study was conducted from March to June 2025 after receiving ethical clearance from the Gomal Medical College, Dera Ismail Khan (Ref. No. 229/GJMS/JC). Men presenting with abnormal semen concentration and motility, assessed for infertility at the Urology Department of District Headquarter Teaching Hospital, Dera Ismail Khan, and who consented to participate, comprised the study population. Men with ongoing abnormal semen concentration and motility, as evidenced by at least two abnormal test results during infertility assessment. Abnormal sperm count in this study was considered as a sperm count below 15 million/mL on two separate occasions, at least two weeks apart, and a motility rate of active sperm lower than 34% on two separate assessments, spaced two weeks apart [15]. Men diagnosed with obstructive azoospermia, chronic kidney or hepatic failure, poorly controlled diabetes, normal semen profiles, or a lack of interest in participating were excluded from the study. The sample size for patient recruitment was determined based on the formula used for randomized controlled trials with continuous outcome measures [16]. Based on 80% statistical power and a 5% margin of error, the minimum required sample size was calculated to be 64. After adjusting for a projected 10% dropout rate, the final minimum sample size was increased to 70 per group by the convenience sampling technique. Eligible patients who presented at the clinic and agreed to participate were recruited at the respective study centers. Patients received comprehensive information regarding the study and the method of sample collection. SPSS version 21.0 was used for statistical processing. Data cleaning was conducted before performing a comparative analysis. Descriptive statistical methods were applied to compare baseline characteristics between the two treatment groups, with results displayed in tables. Inferential statistical methods included the Chi-square test to assess associations involving categorical data, while a two-sample t-test was used to determine differences in average values of specific quantitative measures between two classifications. Statistical decisions were based on a 5% significance level.

RESULTS

The study involved 140 patients, with 70 participants allocated to each of the two study arms. Out of the total participants, 9 were not included in the statistical evaluation. This included 3 in the letrozole arm and 4 patients in the clomiphene citrate arm who lost to follow-up and 2 patients who were unable to continue due to severe side effects (one in each study group). Most participants from both study arms fell within the 20 to 40-year age range, comprising 35 (43%) in the letrozole arm and 38 (56.7%) in the clomiphene citrate group. A majority of participants reported an infertility duration of under five years, including 56.06% (n=37) in the letrozole arm and 55.38% (n=36) in the clomiphene citrate arm. A value of 3.192 was obtained from the chi-square test, with a p-value of 0.445. Additionally, the baseline sperm concentration

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for the letrozole and Clomiphene Citrate groups was 10.23 ± 1.13 ×10^6 and 9.66 ± 0.95 ×10^6, respectively, with a t-test value of 0.95 and a p-value of 0.39. Similarly, the initial sperm motility was recorded as 21.35 ± 1.47 for letrozole and 22.78 ± 1.28 for Clomiphene Citrate, with a corresponding t-test of 1.92 and a p-value of 0.05 (Table 1).

Table 1: Comparative Socio-Demographic Characteristics Between the Study Groups

Variables		Letrozole	Clomiphene	Test Statistics	p-Value
Age Group (Years)	20-40	36 (54.54%)	37 (57.81%)	–	–
	41-60	30 (45.45%)	28 (43.75%)		
Duration of Infertility (Years)	<5	37 (56.06%)	36 (55.38%)	–	–
	5-10	29 (43.93%)	29 (44.61%)		
Pre-Treatment Sperm Concentration	–	10.23 ± 1.13 x 10^6	9.66 ± 0.95 x 10^6	0.95	0.39
Pre-Treatment Sperm Motility	–	21.35 ± 1.47	22.78 ± 1.28	1.92	0.05

The study presents the outcome measure for the letrozole group, showing a mean pre-treatment sperm concentration of 10.23 ± 1.13x106 among the 66 participants included in the analysis. At 12 weeks, this value rose to 15.16 ± 1.12 ×10^6, with a 48.23% increase observed in 53 participants. Before treatment, sperm motility was 21.35 ± 1.47. After 12 weeks, it reached 30.33 ± 1.40 (a 40.08% increase), based on results from 47 participants (Table 2).

Table 2: Outcome Measure in the Letrozole Group

Variables	Letrozole (Mean ± SD)	% of Increment	Participants Showing Improvement, n (%)
Pre-Treatment Sperm Concentration	10.23 ± 1.13 x 10^6	–	–
Post-Treatment (12 Weeks) Sperm Concentration	15.16 ± 1.12 x 10^6	48.23%	53 (80.30%)
Pre-Treatment Sperm Motility	21.35 ± 1.47	–	–
Post-Treatment (12 Weeks) Sperm Motility	30.33 ± 1.40	42.08%	47 (71.21%)

The study showed that, before treatment, the average sperm concentration in the Clomiphene Citrate group was 9.66 ± 0.95 ×10^6, based on the data from 65 participants. At 12 weeks post-treatment, the mean sperm concentration increased to 12.19 ± 1.26 ×10^6, reflecting a 26.26% improvement, as observed in 48 participants. Sperm motility before treatment was measured at 22.78 ± 1.28. At the 12-week mark following treatment, this value rose to 27.00 ± 1.22 18.55% increase based on observations from 41 participants (Table 3).

Table 3: Outcome Measure in the Clomiphene Citrate Group

Variables	Clomiphene (Mean ± SD)	% of Increment	Participants Showing Improvement, n (%)
Pre-Treatment Sperm Concentration	9.66 ± 0.95 x 10^6	–	–
Post-Treatment (12 Weeks) Sperm Concentration	12.19 ± 1.26 x 10^6	26.26%	48 (73.8%)
Pre-Treatment Sperm Motility	22.78 ± 1.28	–	–
Post-Treatment (12 Weeks) Sperm Motility	27.00 ± 1.22	18.55%	41 (63.07%)

The average sperm concentration before treatment was 10.23 ± 1.13 x 10^6 in the letrozole group and 9.66 ± 0.95 x 10^6 in the group treated with clomiphene citrate. The t-statistic was calculated as 0.95, with a corresponding p-value of 0.39. After 12 weeks post-treatment, the sperm concentration was 15.16 ± 1.12 × 10^6 in the letrozole group and 12.19 ± 1.26 × 10^6 in the clomiphene group. The t-test value was 2.61 with a p-value of 0.02, indicating a significant difference compared to the pre-treatment values. The pre-treatment sperm motility in the letrozole group was 21.35 ± 1.47, and in the clomiphene group was 22.78 ± 1.28, having a t-value of 1.92 and a p-value of 0.05. Following the treatment, sperm motility averaged 30.33 ± 1.40 in the letrozole group, compared to 27.00 ± 1.22 in the clomiphene citrate group. The difference was statistically significant, with a t-value of 2.41 and a p-value of 0.03 (Table 4).

Table 4: Compares The Outcome Measure in Both the Letrozole and The Clomiphene Groups

Variables	Letrozole (Mean ± SD)	Clomiphene (Mean ± SD)	t-Test	p-Value
Pre-Treatment Sperm Concentration	10.23 ± 1.13 x 10^6	9.66 ± 0.95 x 10^6	0.95	0.39
Post-Treatment (12 Weeks) Sperm Concentration	21.35 ± 1.47	22.78 ± 1.28	1.92	0.05
Pre-Treatment Sperm Motility	15.16 ± 1.12 x 10^6	12.19 ± 1.26 x 10^6	2.61	0.02*
Post-Treatment (12 Weeks) Sperm Motility	30.33 ± 1.40	27.00 ± 1.22	2.41	0.03*

DISCUSSION

Improvements in semen quality were observed with both clomiphene citrate and letrozole; however, letrozole was associated with a statistically greater increase in terms of increased sperm density and motility compared to clomiphene citrate. No statistically significant differences were observed in the sociodemographic profiles of participants between the clomiphene citrate and letrozole groups. The majority of individuals reported infertility duration of less than five years. While both drugs contributed to improved sperm parameters, letrozole produced a significantly greater enhancement in both quantitative and motility parameters, outperforming

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clomiphene citrate [17, 18]. The findings of this study were consistent with previous researchers, who observed a significant rise in sperm levels and their ability to move effectively after six months of daily 2.5 mg letrozole treatment [19]. These discrepancies between the use of clomiphene citrate and letrozole are connected with their pharmacological effects: clomiphene citrate acts on the estrogen receptors through enclomiphene and zuclomiphene, and letrozole decreases the level of estrogen, negative feedback on the hypothalamus and pituitary [20]. The results of the clomiphene group are also congruent with the previous studies that indicated that a three-month program resulted in an increase in sperm concentration and motility, but the extent of the improvement was smaller than the one reported in a meta-analysis of randomized controlled trials [21]. These differences could be related to the changes in dosage (2550 mg/day) and to the time of treatment (312 months) [22]. Both of the drugs were tolerated. In the group with letrozole, 1.5% stopped the treatment because of the decrease in libido; and the reported side effects such as headache (3%), nausea (13.6%), dry mouth (10%), and fatigue (6 per cent), were lower than the previous research where they were daily taking doses of 2.5mg of letrozole [23, 24]. The total increase in sperm concentration was less than a meta-analysis that had clomiphene citrate and vitamin E and hence combination therapy could produce a better result [25]. In their other reports, they saw an improvement in semen parameters in the majority of the patients in three to six months of treatment with clomiphene [26]. There was however, no significant difference in pregnancy rates or in semen quality between a six-month double-blind, placebo-controlled WHO trial of 25 mg/day clomiphene citrate. All the side effects of clomiphene citrate like nausea, fatigue, headache, and slight nervousness, were short-lived and tolerated [27, 28]. Regardless of the shortcomings such as a non-randomized design, a short 12-week follow-up and no pregnancy outcome data, the use of letrozole has potential in the management of oligoasthenozoospermia. Subsequent research must embrace randomized, parallel designs of follow-up of greater duration to determine hormonal and fertility outcomes.

The study's limitations include its non-randomized design, which may introduce bias, and the short follow-up period of 12 weeks, which doesn't assess long-term effects or pregnancy outcomes. It also lacked blinding, which could have influenced the results, and did not control for confounding factors like age and lifestyle. Additionally, the study focused only on sperm parameters and didn't explore long-term side effects or fertility outcomes, limiting the overall understanding of treatment efficacy. There is a growing need for further studies on male factor infertility. This includes researching various combinations of medical therapies for male infertility to address and reduce this overlooked health issue.

CONCLUSIONS

This study shows that letrozole and clomiphene citrate can help improve sperm quality in men with Letrozole showed better results than clomiphene citrate in treating oligoasthenozoospermia. Hence, letrozole and clomiphene citrate may play an important supportive role alongside other artificial reproductive methods. in cases where increasing semen concentration and motility is essential for better outcomes with these techniques.

Authors' Contribution

Conceptualization: MI
Methodology: MS
Formal analysis: MI
Writing and Drafting: MS, MA, MM, S, ASD
Review and Editing: MS, MI, MA MM, S, ASD

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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