Original Article

Efficacy and Safety of Letrozole in Improving Semen Parameters of Subfertile Men with Moderate-to-Severe Oligoasthenoteratozoospermia: A Placebo-controlled Randomised Trial

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Abstract

Background: Currently lack of consensus regarding the medical treatment of men with Oligoasthenoteratozoospermia (OATS). Letrozole is an aromatase inhibitor and may improve semen quality by stimulating hormone synthesis and spermatogenesis. There is lack of evidence on the efficacy and safety of letrozole as therapy for male infertility. **Aim:** To study the efficacy of letrozole in improving semen parameters, hormonal profile of participants with moderate-to-severe OATS and its side effects. **Settings and Design:** Randomised double-blinded placebo-controlled trials conducted in a tertiary care centre conducted between August 2021 and July 2023. Men with abnormal semen analysis reports between the age group of 21 and 45 years with moderate-to-severe OATS visiting the male infertility clinic were enrolled. **Materials and Methods:** Fifty-four men were randomised into two groups. Twenty-eight men in A (intervention group) received letrozole, and 24 men in Group B (control group) received a placebo after written informed consent. After 3 months, semen analysis and hormonal parameters were studied. **Statistical Analysis Used:** Data analysis was performed using SPSS version 19 (IBM). Associations between categorical variables in two groups were analysed using the Chi-square test or Fisher's exact test. Continuous variables were compared using the Mann–Whitney test, and independent Students' *t*-test and pre- and post-treatment comparisons of continuous variables were assessed using a paired *t*-test or Wilcoxon signed-rank test. **Results:** Total sperm count increased by 4.4 (2.8, 8.8) million per ejaculate, sperm concentration by 3.2 (1, 4.4) million/mL and progressive motility by 5.8 ± 7.3% compared to the placebo group, which was statistically significant (P = 0.001). The use of letrozole had minor side effects like headache and nausea. Letrozole use in men with OATS showed a significant improvement in follicle-stimulating hormone by 6.8 ± 5.5 mIU/mL, luteinising hormone by 6.3 ± 3.3 IU/L, testosterone by 193.3 ± 130 ng/dL, with P value of 0.001 and significant fall in oestradiol by 17.6 ± 7.9 pg/mL overall improving T/E ratio by 18.4 ± 8.8. **Conclusion:** Letrozole use may result in improving semen parameters in men with moderate-to-severe OATS. However, these findings need to be validated in larger trials.

Keywords: *Hormonal parameters, letrozole, Oestradiol and T:E ratio, oligoasthenoteratozoospermia, testosterone*

Introduction

The World Health Organization (WHO) revised glossary of assisted reproductive technology defines infertility as 'a disease characterised by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse'.[1] Male factor infertility is defined as 'Alteration in sperm concentration, motility or morphology in at least one sample of two sperm analyses, collected at least 1–4 weeks apart'.[2] It affects

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approximately 7% of all men and contributes to 40%–50% of infertility.[3]

Various drugs like androgens, clomiphene citrate, gonadotropins and aromatase inhibitors (AIs) have been tried to improve semen parameters.[4] Administration of androgens leads to suppression of hypothalamic–pituitary axis.[5] Clomiphene citrate being selective estrogen receptor modulator (SERM) showed variable results in improving semen parameters requiring more trials.[6] Pulsatile GnRH therapy and gonadotropins like follicle-stimulating hormone (FSH), luteinising hormone (LH) and human chorionic gonadotropin injections have been used to treat idiopathic male infertility, although these are costly and need frequent injections, which may not be affordable and acceptable for some patients.[7]

AIs, which inhibit aromatase and decrease conversion of testosterone to oestradiol, showed promising results in improving semen parameters, which are also cost-effective.[8] Letrozole is a non-steroidal, selective, potent, third-generation AI.[9] The number and quality of the studies focusing on AIs for male testicular dysfunction remain low; few randomised controlled studies and prospective cohort studies showed improvement in sperm parameters after letrozole treatment; side effects were loss of libido, cutaneous rash, headache and nausea.[10]

The current randomised, double-blind, controlled study tested the hypothesis that letrozole administration to moderate-to-severe Oligoasthenoteratozoospermia patients could increase their sperm count and hormonal parameters more significantly than a placebo.

Materials and Methods

This study was a single-Centre randomised, double-blinded, placebo-controlled trial conducted from August 2021 to July 2023 in the andrology clinic, women and Child Health, JIPMER. The Institutional Ethics Committee approved the study (Approval No: JIP/IEC/2021/052). The study was registered with www.ctri.nic.in (CTRI/2021/08/035725) on 17 August 2021.

The primary objective was to compare the efficacy of letrozole in improving semen parameters with placebo in men with moderate-to-severe Oligoasthenoteratozoospermia (OATS). The secondary objectives were to monitor the side effects of letrozole and to measure hormonal changes after letrozole treatment.

The study included men with moderate-to-severe OATS aged 21–45 years. OATS was defined according to the WHO 2021 guidelines[11] (oligospermia-sperm concentration is $<16 \times 10^6$/mL, asthenozoospermia-total motility <42%, teratozoospermia-normal morphology <4%). Oligozoospermia can be further classified as mild (between 10 and 15 million sperm/mL), moderate oligozoospermia (between 5 and 10 million sperm/mL) and severe oligozoospermia (<5 million sperm/mL).[12] Men with ejaculatory duct obstruction, reproductive tract surgeries, history suggestive of mumps orchitis, chronic tobacco consumption, alcohol abuse, ongoing medical treatment including gonadotropins, anabolic steroids, cancer chemotherapy, on antioxidants, leucocytospermia (white blood cell count more than 1 million/mL), severe varicocele (Grade 3 and 4) and previously diagnosed Klinefelter syndrome were excluded.

After written informed consent, participants were recruited. A detailed history was taken, and examination was done using a pre-designed pro forma. All were screened for hypertension and diabetes, and treatment was initiated and included in the study. Repeat semen analysis confirmed the diagnosis after 1–4 weeks. All semen analyses were performed by the same trained lab technician at the hospital. Hormonal evaluation with total testosterone, FSH, LH, prolactin, serum oestradiol and thyroid-stimulating hormone (TSH) was done in overnight fasting samples around 8:00 am to 10.00 am to rule out basic endocrine abnormalities. One part of the serum was used for FSH and LH assay on the same day, and the other part was stored at −80°C deep freezer to estimate testosterone by ELISA. Serum levels of total testosterone by ELISA using commercial kits from Calbiotech in stored serum samples. On the same day, FSH and LH, prolactin, TSH and estradiol were analysed by chemiluminescence using commercial kits from Beckman coulter in the DXI 600 immunoassay analyser in the biochemistry laboratory. Participants were divided into groups A and B, who received letrozole and placebo, respectively. The sample size was 27 in each group; considering the minimum expected difference in change in total sperm count between the control and experimental groups as 10 million/mL and standard deviation as 12 million/mL, the sample size was estimated to be 27 (with 10% of attrition) in each group at 5% level of significance and 80% power.[8]

After the initial evaluation, randomisation was done using the Rando ver 2.0 software, permuted block randomisation (the blocks of varying size 4, 6). Allocation concealment was done by serially numbered opaque sealed envelope technique by coguide from pharmacology department who is not involved in recruiting participants. A coguide from the pharmacology department prepared similar-looking placebo (shape and size) tablets containing the excipients alone, and drugs were administered double-blinded (both the patient and the investigator were blinded). The enrolment was started from 20 October 2021.

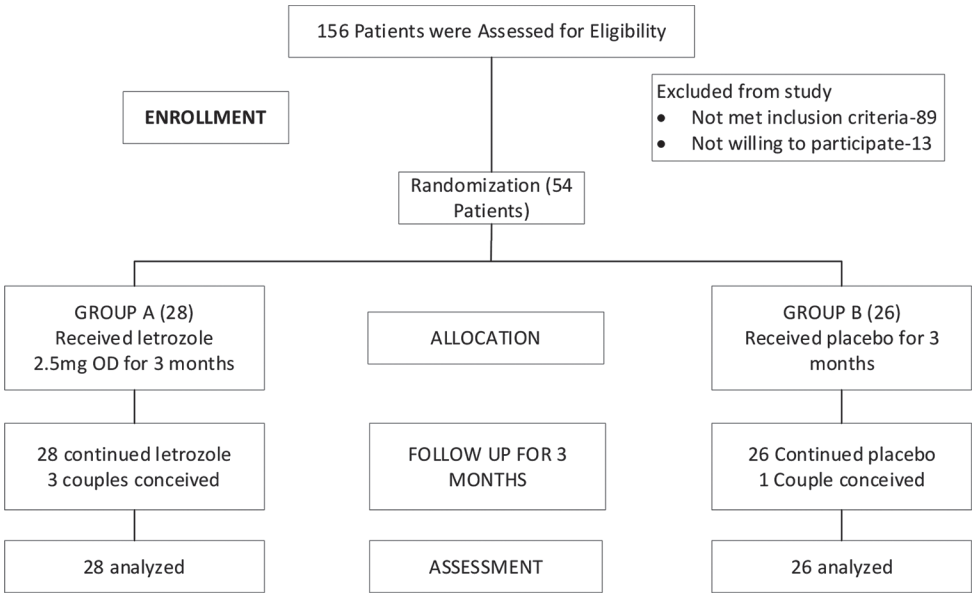

Figure 1: CONSORT diagram

Participants in Group A (intervention group) received oral tablets of letrozole 2.5 mg per day and in Group B received a drug with the placebo effect. All participants were given tablets for 3 months according to the allotted group and were instructed to take one tablet daily. The telephonic conversation was made every month to check for drug compliance and side effects.

After 3 months, repeat semen analysis and investigations (testosterone, FSH, LH and serum oestradiol) were done to check the improvement in semen parameters. Couples who conceived during the study period continued the drug for 3 months and were included in the study. The change in semen parameters and hormonal levels pre- and post-treatment were compared. Using telecommunication, patients were monitored regarding adherence to the drug and the occurrence of any side effects. Side effects include loss of libido, headache, fatigue, hair loss, dry mouth, nausea, nervousness, stomach discomfort, weight gain and rash. No scoring system was used to monitor side effects. Adherence to the Helsinki Declaration (ethical principles for medical research) was ensured throughout the study.

Statistical analysis

It was done in IBM SPSS Statistics 19. P <0.05 was considered statistically significant. Data were checked for normality using Kolmogorov–Smirnov test. The categorical variables were expressed as frequency and percentages. Continuous variables were expressed as standard deviation or median with interquartile range according to the normality assumptions. Associations between categorical variables in two groups were analysed using the Chi-square test or Fisher's exact test. Continuous variables were compared using the Mann–Whitney test and independent Student's *t*-test and pre- and post-treatment comparisons of continuous variables were assessed using a paired *t*-test or Wilcoxon signed-rank test.

Results

One hundred and fifty-six men were screened, and 102 men were excluded. Finally, 54 men with moderate and severe OATS were included in the study [Figure 1]. All 54 men completed 3 months of treatment. In the study, most of the participants had severe Oligoasthenoteratozoospermia, and five out of fifty-four participants had moderate Oligoasthenoteratozoospermia. In which three belong to the letrozole group and showed improvement in semen parameters. Three couples in the letrozole group and one couple in the placebo group conceived during the study period were asked to continue the tablets and were included in the study. The baseline demographic parameters are depicted in Table 1. The mean age of the sample population was 32 ± 4.13 years. Around 87% of couples had primary infertility. The study found that drivers were most observed among men with abnormal semen parameters. Among 54 men, 19 were drivers, while the remaining participants included four electricians, three teachers, five engineers, eight farmers and three welders.

Treatment with letrozole showed a significant ($P < 0.001$) fall in oestradiol and significant ($P < 0.001$) increase in FSH and LH, which in turn reflected by a substantial ($P < 0.001$) rise of serum testosterone and an overall increase in T:E ratio significantly ($P < 0.001$) [Table 2].

Semen parameters like total sperm count increased from 2.8 (1.0, 7.3) million per ejaculate to 8.8 (5, 12) million per ejaculate, sperm concentration increased from 1.5 (1, 3) million per mL to 5 (2.4,7), million per mL, progressive motility increased from 12.3 ± 8.9% to 18.2 ± 11.4% in letrozole group from pre-treatment to post-treatment samples [Table 2]. However, volume and morphology showed not much change in both the groups. Pre- and post-treatment semen analysis and most of hormonal parameters in the placebo group showed no significant change, as given in Table 3.

On comparing the delta change of hormonal parameters in the letrozole and placebo group, the letrozole group showed a significant increment of hormonal parameters with $P < 0.001$ for FSH (6.8 ± 5.5 mIU/mL), LH (6.3 ± 3.3 IU/L), testosterone (193.3 ± 130 ng/dL) and significant fall in oestradiol by 17.6 ± 7.9 pg/mL overall improving T/E ratio by 18.4 ± 8.8. On comparing the delta change of semen analysis in the letrozole and placebo group, the letrozole group showed a significant increment in total sperm count, sperm concentration and progressive motility [Table 4]. The side effects in the current study after letrozole administration were headache (6/28) and nausea (4/28), which were mild and relieved on medications. None of the studied patients developed allergic or severe adverse reactions to letrozole.

Table 1: Distribution of demographic and clinical characteristics of each group

	Letrozole (28)	Placebo (26)	*P*
Age (years), mean±SD	32±3.95	32±4.31	0.890
Primary infertility, *n* (%)	25 (89)	22 (84)	0.699
Married life (years), mean±SD	4±3.41	4±2.80	0.933
BMI (kg/m^2), mean±SD	26.2±3.4	24±3.1	0.323
Testicular volume, mean±SD	15±3.4	13±2.6	0.086
Smokers, *n*(%)	2 (7.1)	7 (26.9)	0.072
Alcohol, *n* (%)	7 (25)	7 (26.9)	0.872
Hypertension, *n* (%)	1 (3.6)	3 (11.5)	0.572
Diabetes, *n* (%)	3 (10.7)	2 (7.7)	0.572
Clinical pregnancy noted during study period	3	1	NA
Moderate OATS	3	2	NA
Severe OATS	25	24	NA

SD=Standard deviation, OATS=Oligoasthenoteratozoospermia, BMI=Body mass index, NA=Not available

Table 2: Distribution of pre- and post-treatment hormonal and semen parameters in the letrozole group

Letrozole group	Pre-treatment, mean±SD/median (IQR)	Post-treatment, mean±SD/median (IQR)	*P*
FSH (mIU/mL)	7.6±5.2	14.5±9.3	0.001
LH (IU/L)	4.9 (4.1–7.6)	12 (8–15.9)	0.001
Testosterone (ng/dL)	357.2±109.3	550.5±153.3	0.001
Oestradiol (pg/mL)	38.2±6	20.5±5.1	0.001
T/E ratio	9.5±2.9	27.9±8.7	0.001
Volume (mL)	2 (1.5–2.8)	2 (2–2)	0.302
Total sperm count (10^6 per ejaculate)	2.8 (1.0.7.3)	8.8 (5–12)	0.001
Sperm concentration (10^6 per mL)	1.5 (1–3)	5 (2.4–7)	0.001
Progressive motility (%)	12.3±8.9	18.2±11.4	0.001
Morphology (%)	2 (1–5.2)	3.5 (1–4.5)	0.638

Comparing means between pre- and post-treatment using paired *t*-test; comparing medians between pre- and post-treatment using Wilcoxon signed-rank test. SD=Standard deviation, IQR=Interquartile range, FSH=Follicle-stimulating hormone, LH=Luteinising hormone, T/E: Testosterone/oestradiol

Table 3: Distribution of pre- and post-treatment hormonal and semen parameters in the placebo group

Placebo group	Pre-treatment, mean±SD/median (IQR)	Post-treatment, mean±SD/median (IQR)	*P*
FSH (mIU/mL)	8.4±4.5	8.1±4.2	0.493
LH (IU/L)	3.3 (5.3–7.4)	6 (4–9)	0.094
Testosterone (ng/dL)	362.4±100.7	366.1±127.4	0.860
Oestradiol (pg/mL)	35±6.6	31.3±6.3	0.001
T/E ratio	10.6±3.3	12.2±5.1	0.041
Volume (mL)	2 (1–2.5)	2 (1–2.5)	0.586
Total sperm count (10^6 per ejaculate)	4 (2–6)	3 (1.8–6)	0.820
Sperm concentration (10^6 per mL)	2.1 (1–3)	2 (1–3.3)	0.866
Progressive motility (%)	14.1±9.8	15.3±12.4	0.447
Morphology (%)	2.5 (1–7.5)	1.5 (1–9)	0.874

Comparing means between pre- and post-treatment using paired *t*-test; comparing medians between pre- and post-treatment using Wilcoxon signed-rank test. SD=Standard deviation, IQR=Interquartile range, FSH=Follicle-stimulating hormone, LH=Luteinising hormone, T/E: Testosterone/oestradiol

Table 4: Comparison of change in hormonal and semen parameters in letrozole and placebo group

Comparison of change in both groups	Letrozole group, mean±SD)/median (IQR)	Placebo group, mean±SD)/median (IQR)	*P*
FSH (mIU/mL)	6.8±5.5	0.2±1.7	0.001
LH (IU/L)	6.3±3.3	0.9±2.5	0.001
Testosterone (ng/dL)	193.3±130	3.7±106.4	0.001
Oestradiol (pg/mL)	−17.6±7.9	−3.6±4.6	0.001
T/E ratio	18.4±8.8	1.5±3.7	0.001
Volume (mL)	0.1 (0.37–0.5)	0.1 (0.42–0.1)	0.269
Total sperm count (10^6 per ejaculate)	4.4 (2.8–8.8)	0.1 (2.1–2)	0.001
Sperm concentration (10^6 per mL)	3.2 (1–4.4)	0.0 (−1–1)	0.001
Progressive motility (%)	5.8±7.3	1.2±7.9	0.037
Morphology (%)	2.5 (1–7.5)	1.5 (1–9)	0.960

Comparing means between the letrozole and placebo groups using the independent Student's test; comparing medians between the letrozole and placebo groups using the Mann–Whitney *U*-test. SD=Standard deviation, IQR=Interquartile range, FSH=Follicle-stimulating hormone, LH=Luteinising hormone, T/E: Testosterone/oestradiol

Discussion

In this study, men presenting with severe OATS treatment with letrozole over 3 months significantly improved total sperm count, sperm concentration and progressive motility in letrozole group after 3 months of treatment, with corresponding rise in FSH, LH and testosterone, T:E ratio was found. The side effects were less severe and minor, like headaches and nausea. None of the studied patients developed allergic or severe adverse reactions to letrozole.

There is currently a lack of consensus regarding the treatment of men with OATS. Empirical treatment to raise FSH and LH in men with idiopathic oligospermia with clomiphene citrate and tamoxifen, have showed some improvement,[13] but due to their oestrogenic action, they have undesirable side effects.[14] Direct FSH injections used for treating male infertility showed positive effects on spermatogenesis, but these are of high cost and minimally invasive hence patients acceptance is less.[15]

As seen in SERM, AIs can increase endogenous testosterone without oestrogenic side effects.[16] Letrozole a highly potent AI in case of an infertile man with normal volume azoospermia and hypo spermatogenesis proven by testicular biopsy who took letrozole for 4 months showed spermatogenesis, documented with testis biopsy.[17] This is the case report of letrozole in male infertility.[17]

Our study examined the effects of letrozole on men with moderate-to-severe OATS. Participants had a mean age of 32 ± 4.13 years, a notable comparison to other studies, such as those by Saylam *et al*.[18] (34.9 ± 6.66 years) and Cavallini *et al*.[19] (median age of 44 years). The demographic differences may stem from variations in socioeconomic status and lifestyle habits.

In this study, primary infertility was prevalent, affecting 89% of the letrozole group and 84% of the placebo group, with both groups having a mean married life of 4 years. The impact of occupation on semen parameters was noted, particularly among drivers exposed to higher temperatures, which can affect spermatogenesis; 14% of participants were drivers, evenly distributed across groups. Smoking rates were comparable between groups, and alcohol consumption was similar, with 25% in the letrozole group and 26.9% in the placebo group.

Body mass index (BMI) was assessed due to its association with sperm count, revealing a mean BMI of 25 ± 3.1 kg/m² in both groups, while Cavallini *et al*.[19] reported a median BMI of 31.2 kg/m². Comorbidities such as hypertension and diabetes were equally distributed, minimising confounding factors. Basic hormonal parameters (FSH, LH, testosterone, oestradiol, prolactin and TSH) and semen parameters (volume, total sperm count, sperm concentration, morphology and progressive motility) were comparable between groups, strengthening the study's validity.

The primary outcome indicated that letrozole administration significantly improved total sperm count by 4.4 million per ejaculate, sperm concentration by 3.2 million per mL and progressive motility by 5.8 ± 7.3% compared to the placebo group, which showed no improvement. Morphology in both groups not changed significantly.

Regarding secondary outcomes, letrozole had minimal side effects; no patient reported loss of libido, which was the side effect in other studies where letrozole was used.[19,20] Six experienced headaches and four had nausea, which were manageable with symptomatic medications. Like other studies, participants experienced headache and nausea after letrozole use.[18,21]

Letrozole also significantly improved hormonal parameters: FSH increased by 6.8 ± 5.5 mIU/mL, LH by 6.3 ± 3.3 IU/L and testosterone by 193.3 ± 130 ng/dL,

while oestradiol decreased by 17.6 ± 7.9 pg/mL, resulting in a more favourable testosterone/oestradiol ratio, which is beneficial for spermatogenesis. However, there was some reduction in oestradiol levels even in the placebo group, even though not to the extent of the letrozole group. Probably due to psychological well-being by placebo treatment and lifestyle modification with reduction of weight and stress likely to reduction oestradiol.

Similar findings were reported by Cavallini *et al*.,[19] where the letrozole treatment group improved hormonal levels and sperm count compared to a placebo group. Gregoriou *et al*.[21] also observed improvements in seminal parameters among men treated with letrozole or anastrozole. Saylam *et al*.[18] reported a 20% pregnancy rate among oligospermic men after letrozole treatment. We have also observed three spontaneous conceptions during the letrozole group and one in the placebo group during the study period. Still, the follow-up of the pregnancy rate can be the root for future studies. The mild side effects observed were tolerable; no participants withdrew due to adverse effects, and there was no report of loss of libido, likely due to a lesser reduction in oestradiol compared to other studies.

In contrast, some participants in Cavallini *et al*.'s study[19] dropped out due to side effects, including loss of libido linked to reduced oestradiol levels. The findings from Kooshesh *et al*.[22] indicated similar mild side effects, which were generally well tolerated. Overall, the study supports the efficacy of letrozole in improving sperm parameters in men with OATS when maintaining a favourable safety profile.

The study's strength is that it is the first randomised controlled study conducted in India to study the efficacy of letrozole in improving sperm parameters in men with Oligoasthenoteratozoospermia to the best of our knowledge. Only a few participants on letrozole had minor side effects with no dropouts. The study's limitations are the short study duration and long-term outcomes like clinical pregnancy, pregnancy outcomes and live birth rate, which could not be studied.

Conclusion

This study found that letrozole administration in men with moderate-to-severe OATS leads to significant improvements in total sperm count, sperm concentration and progressive motility, with substantial hormonal changes compared to a placebo group. Based on the current study findings, letrozole use may result in improving semen parameters in men with moderate-to-severe oligoasthenoteratozoospermia. Letrozole is well tolerated, with minimal side effects; however, more extensive studies and validation are needed in different populations with different treatment durations and long-term outcomes.

Authors contribution

PU: Writing – review and editing, writing – original draft, methodology, investigation, formal analysis, data curation and conceptualisation. NSK: Writing – review and editing, supervision, project administration, methodology, investigation and conceptualisation. SM: Data curation, technical help and manuscript editing. NN: Data curation, technical/laboratory help and manuscript editing. SV: Writing – review and editing. AR: Writing – review and editing, methodology, results and statistical analysis.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

The datasets used for this study are available with the corresponding author on reasonable request for systemic review or IPD meta-analysis; the author team will be able to provide validate anonymous data.

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