

## The effectiveness of two different doses letrozole in ovulation induction – a comparative study

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**Introduction:** Letrozole is a third-generation selective aromatase inhibitor and an effective agent for ovulation induction. Even though it was used in Clomiphene Citrate failure cases, Clomiphene Citrate resistant women, for Intra-Uterine insemination, and also for mild stimulation for IVF/ICSI cases it has not gained its importance as a first-line drug for ovulation induction. **Objective:** To study the effectiveness of two different doses of Letrozole in ovulation induction and pregnancy rates and to calculate the proportion of Letrozole resistant and failure cases. **Materials and Methods:** One year Prospective, observational study was conducted on 120 study participants who were divided into two groups and were given either 2.5 or 5 mg of Letrozole respectively. **Results:** It was observed that 28 (46.67%) of 60 study participants in group I and 38 (63.33%) of 60 study participants in group II had ovulated. **Conclusion:** It is observed that there was no significant statistical difference in ovulation rates, Letrozole failure, and resistance rates in both groups. Though the endometrial growth was comparable in both study groups, it was observed that there was better follicular growth in study group II.

**Keywords:** Letrozole, Two different doses, Ovulation Induction, Letrozole Failure Rates, Letrozole Resistance Rates and Pregnancy Rates

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## Introduction

Infertility is generally defined as one year of unprotected intercourse without conception [1]. Some prefer the term sub-fertility to describe women or couples who are not sterile but exhibit decreased reproductive efficiency. Approximately 85-90% of healthy young couples conceive within one year, most of them within 6 months of marriage [2,3]. Infertility in general affects approximately about 10-15% of couples. The major causes of infertility include ovulatory dysfunction (20-40%), tubal and peritoneal pathology (30-40%), and male factors (30-40%). Uterine pathology is relatively uncommon and the remainder is largely unexplained. To some extent, the prevalence of each cause of infertility varies with age. Ovulatory dysfunction is more common in younger than in older couples, tubal and peritoneal factors have a similar prevalence, and male factors and unexplained infertility are observed somewhat more often in older couples [4,5]. The most common cause among ovarian factors is anovulation, and PCOS stands first in them.

Letrozole is a third-generation selective aromatase inhibitor that inhibits the production of Estrogen from Androstenedione and Testosterone substrates [6]. It was approved for use in 1997 for the treatment of postmenopausal breast cancer and by 2001 it has proven its role as an effective agent for ovulation induction [7]. Initially, Letrozole was used in patients with Clomiphene Citrate failure, Clomiphene Citrate resistance, patients who were going for intrauterine insemination, and also for mild stimulation for IVF/ICSI cases [8]. But Letrozole has not gained its importance as a first-line drug in the field of ovulation induction. Up till now, there has been a limited number of studies on the efficacy of different doses Letrozole used for ovulation induction. The aim of the present study was to evaluate the effectiveness of two different doses namely 2.5mg and 5mg doses of Letrozole in anovulatory patients.

## Materials and Methods

A prospective, observational study was conducted on 120 study participants who were divided into two groups Group I (2.5mg) and Group II (5mg) and was given 2.5 mg or 5 mg of Letrozole respectively. The study participants selected for the given study were distributed into two groups of 60 each. Serial assessment by ultrasound examination was per-

formed to note the response to the two doses of Letrozole on days 10, 12, and 14 of the menstrual cycle and the following parameters were measured and recorded - number of follicles, size of follicles, and endometrial thickness. All the patients who had a follicle size of  $\geq 18$ mm were administered a single dose of 5000IU Beta HCG and monitored for ovulation by ultrasound examination. Those patients who did not conceive were given four cycles of ovulation induction using Letrozole. Any incidence of Multiple Pregnancy or OHSS was noted and recorded. Based on the results obtained, the proportion of cases which were Letrozole resistant cases i.e. patients who did not ovulate in spite of Letrozole treatment, and the Letrozole failure cases i.e. patients who ovulated but failed to conceive after Letrozole treatment were analyzed. The ovulation rate pregnancy rates in the study population were calculated for the two doses of Letrozole.

### Inclusion Criteria

01. Patients between 20 to 40 years of age
02. Patients with bilateral patent fallopian tubes and normal HSG
03. Patients with partners having a normal semen analysis

### Exclusion Criteria

01. Married life < 6 months
02. Unprotected intercourse for < 6 months
03. Male infertility cases
04. Patients with any abnormalities detected in baseline scans

**Statistical Analysis** was done using the following statistical methods - Difference in ovulation and pregnancy rates analyzed as the difference in percentages, Statistical significance of such differences was assessed by chi-square test, Proportion of Letrozole failure and Letrozole resistant cases were commented upon, Level of significance is expressed as 'P' value < 0.05 taken as significant.

## Results

Following the statistical analysis, the results are tabulated as follows: The majority of the study participants were in the age group 18-25 yrs Group I (2.5mg) 63.33% and Group II (5mg) 58.33% respectively. Among the women who participated in the study most of them had normal BMI with

61.66% in the 2.5 mg study group and 45% in the 5 mg study group. The marital life of most of the patients who had participated in the study was less than 5 years with 60% in the 2.5 mg study group and 58.33% in the 5 mg study group. Primary infertility was the major cause of infertility in the study participants with 75% in the 2.5 mg study group and 66.66% in the 5 mg study group. On the whole, the study population had normal hormonal assay with high TSH observed in 35% and 21.67% of 2.5mg and 5mg. study groups respectively and high Prolactin levels were seen in 16.67% and 6.67% of patients in 2.5mg and 5mg study groups respectively.

**On day 10 of the cycle** majority of the patients in the 5mg group had more than 2 follicles 65% vs 58.33% of 2.5mg study group who had more than 2 follicles ( $p>0.05$ ). On day 10 of the cycle, the majority of the patients in the 5mg group had follicles of size  $\geq 14$ mm. 56.67% vs. 51.67% of the 2.5mg study group who had a follicle of size  $\geq 14$ mm ( $p>0.05$ ). On day 10 of the cycle, the majority of patients in the 5mg group had the endometrial thickness of  $\geq 7$ mm. 48.33% vs. 31.67% of 2.5mg study group who had the endometrial thickness of  $\geq 7$ mm ( $p>0.05$ ).

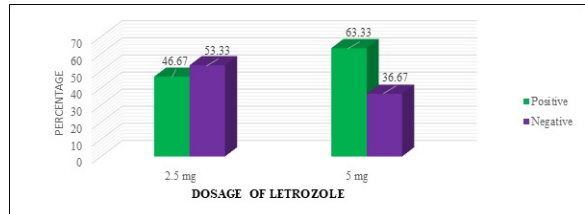
**On day 12** of the cycle, the majority of the patients in the 5mg. group had more than 2 follicles 71.67% vs. 61.67% of the 2.5mg study group who had more than 2 follicles ( $p>0.05$ ). On day 12 of the cycle, the majority of the patients in the 5mg group had follicles of size  $\geq 16$ mm. 63.33% vs. 53.33% of 2.5mg study group who had a follicle of size  $\geq 16$ mm ( $p>0.05$ ). On day 12 of the cycle, the majority of patients in the 5mg group had the endometrial thickness of  $\geq 8$ mm. 58.33% vs. 41.67% of 2.5mg study group who had the endometrial thickness of  $\geq 8$ mm ( $p>0.05$ ).

**On day 14** of the cycle, the majority of the patients in the 5mg group had more than 2 follicles 75% vs. 66.67% of the 2.5mg study group who had more than 2 follicles ( $p>0.05$ ). On day 14 of the cycle, the majority of the patients in the 5mg group had follicles of size  $\geq 18$ mm. 73.33% vs. 55% of 2.5mg study group who had a follicle of size  $\geq 18$ mm ( $p<0.05$ ). On day 14 of the cycle, the majority of patients in the 5mg group had an endometrial thickness of  $\geq 10$ mm. 66.67% vs. 53.33% of 2.5mg study group who had the endometrial thickness of  $\geq 10$ mm ( $p>0.05$ ).

**Ovulation Rates**

**Table-1: Ovulation Rate in Group I and II.**

Ovulation Cycle	2.5 mg Study Group		5 mg Study Group	
	Positive	Negative	Positive	Negative
Cycle 1	10 (16.66%)	50 (83.33%)	13 (21.67%)	47 (78.33%)
Cycle 2	11 (19.64%)	45 (80.36%)	16 (28.01%)	41 (71.99%)
Cycle 3	13 (24.07%)	41 (75.93%)	21 (39.62%)	32 (60.38%)
Cycle 4	15 (29.41%)	36 (70.59%)	22 (47.82%)	24 (52.18%)
Overall	28 (46.67%)	32 (53.33%)	38 (63.33%)	22 (36.67%)



**Fig-1: Overall Ovulation Rate in Group I and II.**

Among the study participants who were given 2.5 mg of Letrozole 10 (16.66%) out of 60 study participants had ovulation in cycle 1, 11 (19.64%) in 56 study participants ovulated in cycle 2, 13 (24.07%) out of 54 study participants ovulated in cycle 3 and 15 (29.41%) out of 51 study participants had ovulated in cycle 4. Overall 28 (46.67%) in 60 study participants had ovulated in the 2.5 mg. study group.

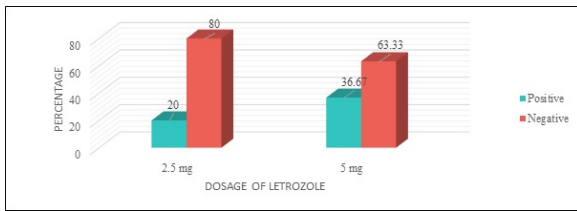
Among the study participants who were given 5 mg. of Letrozole 13 (21.67%) out of 60 study participants had ovulation in cycle 1, 16 (28.07%) in 57 study participants ovulated in cycle 2, 21 (39.62%) out of 53 study participants ovulated in cycle 3 and 22 (47.82%) out of 46 study participants had ovulated in cycle 4.

**Overall** 38 (63.33%) in 60 study participants had ovulated in 5 mg. study group. Using the Chi-square test to test the statistical significance of the difference p-value was obtained as 0.07. Since the p-value is  $>0.05$  the null hypothesis is accepted and there is no statistically significant difference between the ovulation rates of the two groups.

**Pregnancy Rate**

**Table-2: Pregnancy Rate Group I and II**

Pregnancy Cycle	2.5 mg Study Group		5 mg Study Group	
	Positive	Negative	Positive	Negative
Cycle 1	4 (40%)	6 (60%)	3 (23.07%)	10 (76.93%)
Cycle 2	3 (27.27%)	8 (72.73%)	5 (29.41%)	12 (70.59%)
Cycle 3	3 (23.07%)	10 (76.93%)	6 (30%)	14 (70%)
Cycle 4	2 (13.33%)	13 (86.67%)	8 (36.36%)	14 (63.64%)
Overall	12 (20%)	48 (80%)	22 (36.67%)	38 (63.33%)



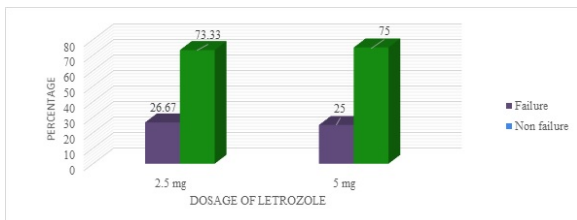
**Fig-2: Overall Pregnancy Rate Group I and II.**

Among the study participants who were given 2.5 mg. of Letrozole and had ovulated, 4 (40%) out of 10 ovulated women had conceived in cycle 1, 3 (27.27%) out of 11 ovulated women had conceived in cycle 2, 3 (23.07%) out of 13 ovulated patients had conceived in cycle 3 and 2 (13.33%) out of 15 ovulated patients had conceived in cycle 4. Overall 12 (20%) out of the 60 study participants conceived pregnancy in the study group who were given 2.5mg. of Letrozole.

Among the study participants who were given 5 mg. of Letrozole and had ovulated, 3 (23.07%) out of 13 ovulated women had conceived in cycle 1, 5 (29.41%) out of 17 ovulated women had conceived in cycle 2, 6 (30%) out of 20 ovulated patients had conceived in cycle 3 and 8 (36.36%) out of 22 ovulated patients had conceived in cycle 4. Overall 22 (36.67%) out of the 60 study participants conceived pregnancy in the study group who were given 5mg. of Letrozole.

Using the Chi-square test to test the statistical significance of the difference p-value was obtained as 0.04. Since the p-value is <0.05 the null hypothesis is rejected and there is a statistically significant difference between pregnancy rates of the two groups.

**Letrozole Failure Rates**

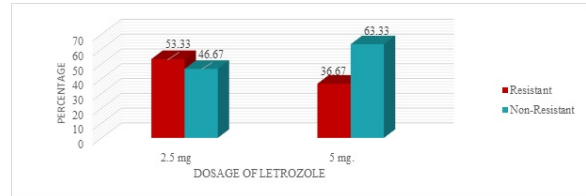


**Fig-3: Letrozole failure rate in the study population.**

In the above study among the patients who were given 2.5 mg. of Letrozole 16 (26.67%) were reported as Letrozole failure cases and among the group who were given 5 mg. of Letrozole 15 (25%) were reported as Letrozole failure cases.

Using chi-square to test the statistical significance of the difference p-value was found out to be 0.83 which is >0.05 and hence the null hypothesis is accepted. Therefore there is no statistically significant difference between Letrozole failure rates between 2.5 mg. and 5 mg. of Letrozole.

**Letrozole Resistance Rate**



**Fig-4: Letrozole resistance rate in the study population.**

In the above study among the patients who were given 2.5 mg. of Letrozole 32 (53.33%) were reported as Letrozole resistant cases and among the group who were given 5 mg. of Letrozole 22 (36.67%) were reported as Letrozole resistant cases.

Using chi-square to test the statistical significance of the difference p-value was found out to be 0.07 which is > 0.05 and hence the null hypothesis is accepted. Therefore there is no statistically significant difference between Letrozole resistance rates between 2.5 mg. and 5 mg. of Letrozole.

**Discussion**

Hundred and twenty women who satisfied the selection criteria were enrolled in the study and were divided into two groups. Group I comprised 60 women who were given 2.5 mg dosage of Letrozole for ovulation induction. Group II consisted of 60 women who were given 5 mg dosage of Letrozole for ovulation induction. It was observed in the above study that 28 (46.67%) in 60 study participants had ovulated in the 2.5 mg. study group while 38 (63.33%) in 60 study participants had ovulated in the 5 mg. study group. Using the Chi-square test to test the statistical significance of the difference p-value was obtained as 0.07. Since the p-value is >0.05 the null hypothesis is accepted and there is no statistically significant difference between the two groups. Similarly it was observed in the above study that 12 (20%) out of the 60 study participants conceived pregnancy in the study group who were given 2.5mg. of Letrozole while 22 (36.67%) out of the 60 study participants conceived pregnancy in the study group who were given 5mg.

Of Letrozole. Using the Chi-square test to test the statistical significance of the difference p-value was obtained as 0.04. Since the p-value is <0.05 the null hypothesis is rejected and there is a statistically significant difference between the two groups.

The present study was compared with the following previous studies:

In the study conducted by Elsharar et al [9] where 2.5mg of letrozole was given the ovulation rate was 50% and the pregnancy rate was 13.64% compared to 47.67% ovulation rate and 20% pregnancy rate observed in the current study with 2.5mg of Letrozole. In the study conducted by Begum et al [10] in the year, 2009 where patients were given 7.5mg of Letrozole the ovulation and pregnancy rates reported were 62.5% and 40.1% respectively vs 63.33% and 36.67% of ovulation and pregnancy rates being reported in the 5mg study group of the present study. In the study conducted by Al-Omari [11] et al in the year 2004 in which 2.5mg of Letrozole was given to the study participants the ovulation rate was 80% and pregnancy rate was 19% compared to 47.67% ovulation rate and 20% pregnancy rate observed in the current study with 2.5mg of Letrozole. In the study conducted by Atay et al [13] in the year 2006, the patients upon receiving 2.5mg of Letrozole reported an 82% ovulation rate and 22% pregnancy rate compared to 47.67% ovulation rate and 20% pregnancy rate observed in the current study with 2.5mg of Letrozole. In the study conducted by Bayar et al [14] in the year 2006 in which 2.5mg of Letrozole was given to the study participants the ovulation rate was 66% and pregnancy rate was 9% compared to 47.67% ovulation rate and 20% pregnancy rate observed in the current study with 2.5mg of Letrozole. In the study conducted by Badawy et al [15] in the year 2009 in which 5mg of Letrozole was given to the study participants the ovulation rate was 68% and pregnancy rate was 15% compared to 63.33% ovulation rate and 36.67% pregnancy rate observed in the current study with 5mg of Letrozole. In a study conducted by Tulandi et al [17] in the year 2006, 5mg. daily produced a higher number of ovulations than 2.5mg and the same has been reported even in the current study. The findings of this study are in contradiction to the findings observed in the study conducted at Mansoura University [18], Egypt in the year 2007 in which it was found that higher doses of Letrozole offered no significant advantage over the use of 2.5 mg Letrozole in terms of pregnancy rates. This

Study is in concurrence with the study conducted at McGill University [19] Canada where it was found that 5mg dose of Letrozole resulted in higher pregnancy rates compared to 2.5mg of Letrozole.

## Conclusion

Based on the findings of this study it may be concluded that there is no significant statistical difference in the ovulation rates, Letrozole failure rate, and resistance rates among women who were given 2.5mg and 5mg doses of Letrozole.

## What does the study add to the existing knowledge

Though the endometrial growth was similar in the two study groups, there was better follicular growth in the 5mg study group. The 5mg study group had a better and statistically significant difference in the pregnancy rates compared to the 2.5mg study group with no incidence of OHSS or Multiple pregnancies. Therefore 5mg dosage of Letrozole could be recommended compared to 2.5mg of Letrozole for ovulation induction based as it yielded better pregnancy rates.

## Author's contribution

**Dr. Susheela Gayam:** Concept, manuscript preparation

**Dr. Bhargavi Sajja:** Study design

**Dr. Mary Shashikala:** Data collection

**Dr. Neelima C.:** Statistical analysis

**Dr. Geeta Rani:** Manuscript preparation

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