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*Original Paper*

# Letrozole before TESE in Non-Obstructive Azoospermia, Does It Affect Sperm Retrieval Rate, A Retrospective Study

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***Abstract***

***Objective:*** *This study was designed to evaluate the effect of letrozole 2.5 mg, an aromatase inhibitor, on the sperm retrieval rate (SRR) by the testicular sperm extraction (TESE) procedures that was done for the treatment of males with non-obstructive azoospermia (NOA).*

***Materials and methods:*** *Data was collected retrospectively from males diagnosed with non-obstructive azoospermia who underwent TESE procedure in the duration between May 2010 until June, 2018. The collected data includes the age of the patient, body mass index (BMI), testicular volume, hormonal profile (FSH LH, prolactin, testosterone), and the use of letrozole preoperatively. Logistic regression was done to address the association of these parameters to the sperm's retrieval rate.*

***Results:*** *The study screaned 145 patients. Eighty patients fit the inclusion criteria and thus they were statistically analyzed. The use of letrozole was associated with negative TESE outcome (p=0.006), odd (0.154) CI 0.04-0.579. The other factors had no significant correlation to the TESE results.*

***Conclusion:*** *The evidence in this study showed an adverse effect of letrozole use on TESE results of those with high FSH.*

***Keywords***

*Non-Obstructive Azoospermia (NOA), TESE, letrozole*

## 1. Introduction

Azoospermia is the complete absence of sperm in the ejaculate. It presents in about 1% of general population and 10-15% of the population seeking medical evaluation (Cavallini, Beretta, & Biagiotti, 2011; Tiseo, Hayden, & Tanrikut, 2015).

Azoospermia can be due to non-obstructive (NOA), or obstructive (OA) conditions. Furthermore, NOA is subdivided into primary (hypergonadotropic hypogonadism), and secondary (hypogonadotropic hypogonadism) (Cavallini, Beretta, & Biagiotti, 2011; Abdel Raheem et al., n.d.).

Fertility chance for males with NOA may be improved by testicular exploration and sperm extraction methods (TESE or Micro TESE), where the extracted sperms are used for assistive reproduction methods like the in vitro fertilization Intracytoplasmic sperm injection (IVF-ICSI) (Abdel Raheem et al., n.d.).

Therefore TESE combined with ICSI has been frequently used as a therapeutic procedure for treating NOA (Schlegel & Su, 1997).

This study is designed to assess the effect of using letrozole before undergoing TESE procedure in males with NOA on the sperm retrieval rate.

Letrozole is a non-steroidal substance that reversibly binds and inhibits aromatase enzyme, leading to an increase in the endogenous testosterone synthesis without any changes in the circulating estrogen. Inhibiting estrogen can strongly stimulates LH production, which in turn increases the intratesticular and circulating testosterone level, leading finally to an increase in the sperm production (Cavallini, Beretta, & Biagiotti, 2011; Ribeiro et al., 2016; Jarow & Zirkin, 2005).

## 2. Study Design

Data was collected retrospectively from males with NOA who underwent TESE procedure in the duration between May, 2010 until June, 2018, at Jordan University Hospital (JUH). Clinical profile for all patients includes patient's age, testicular volume, hormonal profile (FSH, LH, testosterone and prolactin), duration of infertility and the use of letrozole pre- operatively.

The eligible patients were those with NOA presented with the absence of spermatozoa in the ejaculate in two different occasions, elevated level of follicular stimulating hormone (FSH) above seven mIU/ml and a testicular volume of less than fifteen ml on scrotal ultrasonography using the three-diameter technique ((length x width x height) x 0.71).

On the other hand, patient with any of the conditions below was excluded: complete AZFa or AZFb microdeletions, Klinefelter syndrome, FSH level less than 7 mIU/ml with a testicular volume more than 15 ml, severe systemic disease, hypogonadotropic hypogonadisms, complete retrograde ejaculation, or obstructive azoospermia which is manifested by a non-palpable vas deferens, history of vasectomy, or a dilated seminal vesicles.

In this study the primary end point is to test the association between the use of letrozole prior to TESE and the SRR. The secondary end points were presented by the predictive value (P-value) for the variables; patient's age, BMI, FSH level, and testicular volume on SRR.

The TESE procedure was done to all patients under general anesthesia, in which the testis is delivered through a median raphe incision, then a piece of the testicular tissue is taken from random incisions in each quadrant of the testis. If viable sperms are found in the collected tissue they are cryopreserved.

The statistical software package IBM SPSS Statistics 21 was used for statistical analysis. Patient demographics were analyzed descriptively. To detect the independent predictors of favorable outcome Multivariate Logistic regression was used. P-values were considered statistically significant if they were less than 0.05.

## 3. Results

The data of 143 patients were evaluated, a total of 63 were excluded; 54 had obstructive azoospermia, 5 had hypogondotropic hypogonadism, 2 complete retrograde ejaculation, and 2 had Klinefelter syndrome.

The remaining eighty patients involved in the study were classified according to the previous TESE results for two groups, “positive” with 45 patients (56.2%) and “negative” group with 35 patients (43.7%). The mean of age, BMI, testicular volume and hormonal profile were comparable in both groups (Table 1).

**Table 1. Demographic Data**

| | TESE result | | | | p value |
|---|---|---|---|---|---|
| | Negative (n=45) | | Positive( n= 35) | | |
| | Mean | Standard Deviation | Mean | Standard Deviation | |
| Age | 35 | 6 | 34 | 7 | 0.673 |
| BMI | 29.2 | 3.9 | 28.0 | 3.7 | 0.195 |
| LH | 7 | 4 | 9 | 5 | 0.121 |
| Testosterone | 5 | 3 | 5 | 2 | 0.737 |
| Prolactine | 11 | 12 | 11 | 5 | 0.349 |
| FSH | 19 | 10 | 21 | 19 | 0.854 |
| bilateral testicular volume | 10.2 | 3 | 9.8 | 4 | 0.426 |

A total of twenty two patients (27.5%) of both groups received letrozole 2.5 mg for three-month duration before undergoing TESE. data showed a negative SRR in 18 patients out of them, with only 4 patients gaining positive results (Table 2).

**Table 2. Patient Disposition**

| | | TESE results | | | |
|---|---|---|---|---|---|
| | | Negative (n=45) | | Positive (n=35) | |
| | | Count | N % | Count | N % |
| pre op letrozole | No | 27 | 46.6% | 31 | 53.4% |
| | Yes | 18 | 81.8% | 4 | 18.2% |

Regarding the predictive value of TESE outcome, logistic regression analysis (Table 3) showed statistical significance association between negative TESE outcome and the use of letrozole (p=0.006), odd (0.154) CI 0.04-0.579. The other factors had no significant correlation to the TESE results.

**Table 3. Binary Logistic Regression of the Association between the Age and the Infertility Duration of the Non-Obstructive Azoospermic Patients and TESE Positive Outcome**

| | B | Sig. | Odd | 95% C.I.for EXP(B) | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| letrozole use | -1.874 | .006 | .154 | .041 | .579 |
| LH | .107 | .129 | 1.112 | .969 | 1.277 |
| testosterone | .073 | .545 | 1.076 | .849 | 1.362 |
| Prolactin | -.017 | .557 | .983 | .929 | 1.041 |
| FSH | .002 | .929 | 1.002 | .962 | 1.043 |
| Age | -.010 | .817 | .990 | .906 | 1.081 |
| BMI | -.045 | .511 | .956 | .835 | 1.094 |

**4. Discussion**

Spermatogenesis is dependent on high intratesticular testosterone level, in addition to Sertoli cell stimulation. LH released by the anterior pituitary stimulates Leydig cells to increase Testosterone production which diffuses in the seminiferous tubules (Jarow & Zirkin, 2005; Walker & Cheng, 2005). Infertile men, especially those with non-obstructive azoospermia may have excess aromatase activity manifested by an increased serum T/E ratio (Schlegel, 2012).

Pavlovich et al. (2001) advocate a cut-point of 10 as the lower limit of normal T/E ratios in men (the units used were: Testosterone in ng/dL, and estradiol in pg/mL).

Medical therapy of infertile men aims to increase intratesticular testosterone and increase FSH production. Anastrazole (1 mg/day) and letrozole (2.5 mg/day)—an aromatase inhibitors—have been used in infertile men especially those with excess aromatase activity

Letrozole causes an increase in both gonadotropin and androgen levels in the blood and a decrease in the estrogen level. Those parallel effects seem to improve spermatogenesis in NOA men.

In Literature review the effect of using letrozole vary according to the cause of infertility. In Oligospermic patients, many authors reported on the improvement of spermatogenesis following the use of letrozole (Jarow & Zirkin, 2005; Walker & Cheng, 2005; Schlegel, 2012). Besides that, there are collaporating reports on letrozole efficacy in restoration of active spermatogenesis in azospermic men (Gregoriou et al., 2012; Patry et al., 2009; Saylam, Efesoy, & Cayan, 2011; Zhao et al., 2014; Kyrou et al., 2014). Table 4 summerizes the reports on letrozole effect in azospermic men.

**Table 4. Summary of the Reports on Letrozole Effect on NOA Patients**

| Reference | Study type | Included patients | Outcome after letrozole use |
|---|---|---|---|
| Patry et al. | case report | • 1 NOA patient<br>• normal FSH<br>• T/E <10 | The patient was converted to active spermatogenesis after 4 months of lezotrole use.<br>He remained azoospermic because of his simultaneous obstruction at the level of the epididymis. |
| Saylam et al. | prospective | • 17 NOA patient<br>• 10 oligospermia patient<br>• No comment on FSH<br>• T/E <10<br>• All treated with letrozole | Out of the 17 azoospermic patient, 4 (23.5%) presented spermatozoa in the ejaculate, while 13 (76.5%) remained azoospermic after letrozole treatment |
| Zhao et al. | case report | • 1 NOA patient<br>• high FSH<br>• T/E <10 | After taking letrozole for 3 months, semen analyses by computer-aided sperm analysis (CASA) revealed normal spermatogenesis |
| Kyrou et al. | case report | • 2 NOA patient<br>• normal FSH<br>• T/E <10 | Both were treated with letrozole for a period of 4 months (2.5 mg/48 h), resulting in normal spermatogenesis |
| Cavallini, 2013 | prospective | • 11 NOA patient<br>• 6 treated with letrozole, 5 treated with placebo<br>• T/E <10 | Spermatozoa were found in the ejaculate of all the NOA patients treated with letrozole for 3 months, while no spermatozoa could be found in the ejaculate of the NOA patients treated with placebo. |

Our result was contradictory to the previously published reports, in which letrozole use in the NOA had negative impact on spermatogenesis.

Out of the 80 patients in the current study, 22 patients were treated with letrozole. Only 4 (18.1%) had positive results. logistic regression analysis revealed significant association between the use of letrozole and the negative results (p=0.006), odd (0.154) CI 0.04-0.579.

Most of the previous reports were on patients with normal FSH. However, in our study the mean of FSH is 20.2 mIU/ml. This may indicate that the patient with normal FSH are most likely to benefit

from letrozole than those with high FSH.

Regarding the other parameters and their effect on SRR, The age was not found to have predictive value by Amer et al. (2018) and Ramasamy et al. (2014).

Furthermore, Bryson et al. (2014), Amer et al. (2018) and Li et al. (2017) observed that testicular volume of NOA patients did not affect the sperm retrieval rate (SRR).

While Ishikawa (2012) reported that the serum FSH could predict the TESE results, Li et al. (2017) found that FSH possessed low predictive values.

Our data demonstrated that neither age, BMI, serum FSH level nor testicular volume could predict the sperm retrieval rate when evaluated as the sole independent predictive factor.

The limitation of this study resides in it's nature as retrospective study as well as to the small sample size. We think that further researches are needed to evaluate the effect of letrozole in NOA men especially those with high FSH level.

## 5. Conclusion

The evidence in this study showed an adverse effect of letrozole use on TESE results of those with high FSH. Further researches are needed to address the patient's criteria who may benefit from this treatment.

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