ISSN: 2583-5386
DOI: doi.org/10.51219/JIH/mohamed-r-eletmany/50

URF PUBLISHERS
connect with research world

Journal of Integrated Health
https://urfpublishers.com/journal/integrated-health

Vol: 3 & Iss: 3

Research Article

The Efficacy of Aromatase Enzyme Inhibitor Administration before Microscopic Testicular Sperm Extraction (Micro TESE) in Men with Non-Obstructive Azoospermia

Mahdy B[1], Ali AF[2], Ibrahim HM[2] and Nada EA[3]

[1]Faculty of medicine, Luxor University, Luxor, Egypt

[2]Faculty of medicine, South Valley University, Qena, Egypt

[3]Faculty of medicine, Sohag University, Sohag, Egypt

Citation: Mahdy B, Ali AF, Ibrahim HM, et al. The Efficacy of Aromatase Enzyme Inhibitor Administration before Microscopic Testicular Sperm Extraction (Micro TESE) in Men with Non-Obstructive Azoospermia. *J Integrated Health* 2024;3(3): 272-277. DOI: doi.org/10.51219/JIH/mohamed-r-eletmany/50

Received: 31 July, 2024; **Accepted:** 05 August, 2024; **Published:** 07 August, 2024

***Corresponding author:** Dr. Mohammed R Eletmany, Chemistry Department, Faculty of Science, South Valley University, Qena 83523, Egypt, E-mail: mrmoham2@ncsu.edu

ABSTRACT

Background: Non-obstructive azoospermia (NOA) is a frequent cause of male infertility, and microsurgical testicular sperm extraction (micro-TESE) is an effective technique for sperm retrieval in NOA cases. While the use of hormone stimulation is recommended in cases of secondary hypogonadism, there is still debate surrounding its practice in men with NOA and primary hypogonadism prior to attempting surgical sperm retrieval. This study aimed at evaluating aromatase enzyme inhibitors (AEI) administration prior to micro-TESE.

Methods: The study included 80 male patients presenting to the Andrology Outpatient Clinic of South Valley University Hospitals between 2020 and 2023.

They were divided into 2 groups randomized by closed envelope:

Group (1) were subjected to AEI administration 3 months prior to micro TESE.

Control group (2) were not subjected to any treatment prior to micro TESE.

Results: 80 cases of micro-TESE were performed (56 unilateral and 24 bilateral) and testicular sperm retrieval rate (SRR) was 47.5%. There was no statistical difference in age, testicular size, clinical varicoceles and hormonal profiles between the two groups.

There were no significant differences in the outcomes of micro TESE, concentration of retrieved sperms and ICSI outcomes between groups. Hormonal levels for FSH, LH and prolactin before and after treatment in each group did not change significantly. Otherwise, significant increases in total testosterone levels were observed after treatment with AEI but not in the Control group.

Conclusions: Testicular microdissection is an effective and safe procedure for non-obstructive azoospermia patients, regardless of the different preoperative data. While hormonal treatment with AEI results in significant increases in total testosterone levels, it does not significantly impact the outcomes of micro-TESE, retrieved sperm concentration, or ICSI in men with NOA.

Keywords: Non-obstructive azoospermia, Micro-TESE, Testicular microdissection, Sperm retrieval rate, Aromatase enzyme inhibitors

List of Abbreviations: NOA: Non-obstructive azoospermia; TESE: Testicular sperm extraction; Micro-TESE: Microsurgical testicular sperm extraction; SRR: Sperm retrieval rate; ICSI: Intracytoplasmic sperm injection; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; TT: Total Testosterone; AEI: Aromatase Enzyme Inhibitors; ITT: Intra-Testicular Testosterone

1. Background

Non obstructive azoospermia (NOA) accounts for 60% of all azoospermia[1,2]. Microdissection testicular sperm extraction (micro-TESE), which allows detection of small regions of sperm production in the testes, combined with ICSI plays a pivotal role in the treatment of NOA[3].

Overall outcome data reports that microdissection testicular sperm extraction (micro-TESE) in men with NOA has reported sperm retrieval rates of up to 40-60%. Consequently, micro TESE is increasingly used as a first-line therapy for couples with infertility affected by NOA[4].

Age, testicular size, preoperative hormonal levels and clinical varicocele have been suggested to be predictive of the success of micro-TESE in some studies, while others have reported conflicting results[5,6].

It is common practice for endocrine stimulation therapies such as gonadotrophins and aromatase inhibitors to be used prior to micro-TESE to increase intra-testicular testosterone (ITT) synthesis with the aim of improving sperm retrieval rates; however, there is currently a paucity of data underpinning their efficacy[7].

Aromatase is present primarily in the adipose tissue, liver, testes, skin, and brain where it converts testosterone and other androgens to estradiol. Steroidal (testolactone) and non-steroidal (anastrozole, letrozole) aromatase inhibitors have been used to stimulate spermatogenesis in men with NOA[8]. Aromatase inhibitors inhibit the conversion of androgens to estrogens, thereby increasing serum testosterone and, presumably, the ITT levels. Furthermore, feedback inhibition of the pituitary and hypothalamus is decreased due to decreased serum estrogen levels, resulting greater gonadotropin release[9].

The aim of this study is to evaluate the efficacy of aromatase enzyme inhibitors administration prior to microscopic testicular sperm extraction in men with non-obstructive azoospermia and their effects on sperm retrieval rate and ICSI outcomes.

2. Materials and Methods

2.1. Patient selection

We collected data of 80 male adult patients with non-obstructive azoospermia who were referred to the male infertility outpatient clinic at Qena University Hospital and underwent microdissection testicular sperm extraction (micro-TESE) between April 2020 and February 2023. They were divided into two groups randomized by closed envelope:

Group (1) were subjected to aromatase enzyme inhibitor (AEI) administration 3 months prior to micro TESE.

Control group (2) were not subjected to any treatment prior to micro TESE.

Patients' age, medical history, testicular size, hormonal profile for follicle- stimulating hormone (FSH), luteinizing hormone (LH), prolactin and total testosterone (TT) before and after treatment, retrieved sperm concentration and ICSI outcomes were recorded.

Patients with obstructive azoospermia or other causes of male infertility, patients with a history of testicular cancer or who received chemotherapy or radiation therapy within the past 6 months were excluded from the study.

2.2. Surgical technique

All patients underwent the same surgical technique by an experienced male fertility surgeon. The surgical intervention was performed in 1-day surgery clinic under spinal anesthesia. A prophylactic antibiotic treatment was given and 1 week later the patients were all rechecked at outpatient clinic. Surgery was performed unilaterally on the larger testis, and when the testes volume was equal, the procedure was always performed on the right side. Briefly, the tunica vaginalis was opened following a midline scrotal incision. The testis was opened widely in an equatorial plane, revealing the testicular tissue. As a result, seminiferous tubules could be exposed widely in a natural manner that mimics intratesticular blood flow. The remaining steps of the operation were carried out under a 16-25x operating microscope. The tubules were dissected and the tissue samples were collected in separate containers filled with culture medium for immediate examination by an embryologist. Sperms are more likely to be found in tubules that are bigger and more whitish. Depending on the size of the testicles and the condition of the tubules, up to 15 biopsies may be collected. The procedure was repeated on the contralateral testis if no sperms were found in the first testis. Once all visible parenchymal regions were examined under a microscope or when additional dissection was deemed likely to endanger the testicular blood supply, the surgery was over. The micro-TESE procedure was considered successful if at least one motile spermatozoon was retrieved.

2.3. Data collection and analysis

Categorical variables were described by number and percent (No., %), where continuous variables described by mean and standard deviation (Mean ± SD). Chi-square test used to compare between categorical variables where independent samples T- test was used to assess the statistical significance of the difference between each two studied group means. The ANOVA test was used to determine whether there is a statistically significant difference between the means of three or more independent groups or not. The Paired-Samples T test was used to compare before and after treatment for each group. P value less than 0.05 was considered statistically significant, and P value more than 0.05 was considered statistically nonsignificant. All analyses were performed with the IBM SPSS 27.0 software.

3. Results

There were no statistically significant differences in age, right and left testicular volume between the two groups ($p = 0.794$, $p = 0.231$, $p = 0.481$) respectively **(Table 1,2 and Figure 1,2).**

Table 1: Age distribution among groups**.**

	AEI (n=40)	Control (n=40)	P. value
Age (years) Mean ± SD	40.75 ± 11.23	40.68 ± 10.15	0.794

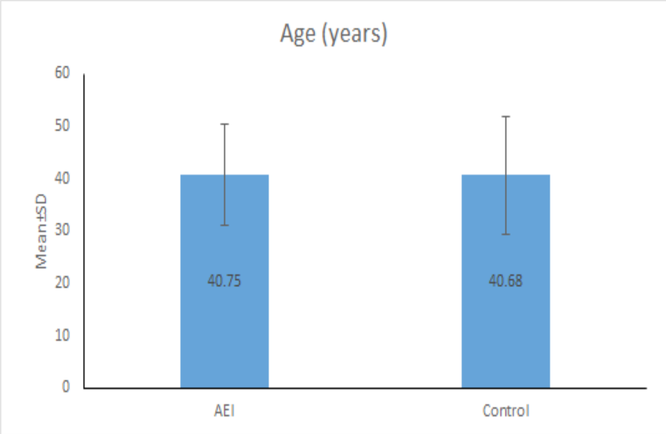

Figure 1: Clustered column chart showing (Mean ± SD) of age distribution between groups.

Table 2: Right & left testis volume distribution between groups.

	AEI (n=40)	Control (n=40)	P. value
Right testis volume (mL) Mean ± SD	8.65 ± 3.53	9.35 ± 3.72	0.231
Left testis volume (mL) Mean ± SD	8.75 ± 3.16	9.44 ± 4.01	0.481

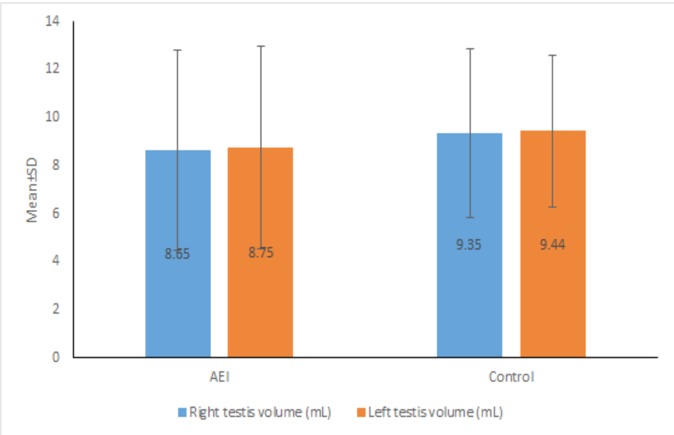

Figure 2: Clustered column chart showing Right & Left testis volume distribution between groups.

Regarding preoperative hormonal levels, there were no significant differences in FSH, LH, serum total testosterone, and serum prolactin levels between the two groups (p = 0.469, p = 0.331, p = 0.283, p = 0.172) respectively **(Table 3).**

Table 3: Preoperative FSH, LH, total testosterone and serum prolactin distribution between groups.

	AEI (n=40)	Control (n=40)	P. value
FSH (IU/L) Mean ± SD	13.89 ± 7.89	15.24 ± 18.8	0.469
LH (IU/L) Mean ± SD	6.38 ± 9.63	8.6 ± 8.34	0.331
Total Testosterone (nmol/L) Mean ± SD	4.29 ± 2.92	4.87 ± 2.34	0.283
Prolactin (ng/mL) Mean ± SD	14.29 ± 8.15	11.97 ± 5.79	0.172

Clinical varicocele was present in 18 patients at the time of examination with no significant differences between the two groups (p = 0.106) **(Table 4 and Figure 3).**

Table 4: Varicocele distribution between groups.

Varicocele	AEI (n=40)	Control (n=40)	P. value
No	32(80%)	30(75%)	0.106
Unilateral	6(15%)	2(5%)	
Bilateral	2(5%)	8(20%)	

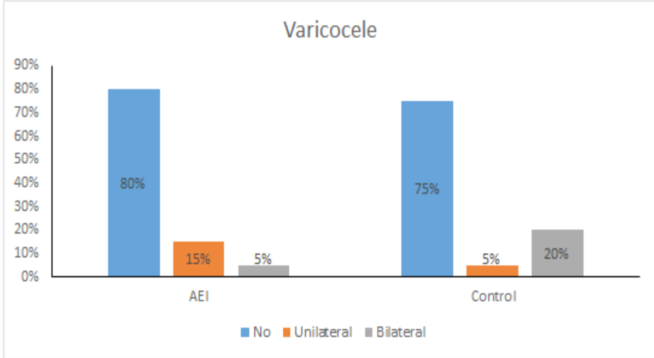

Figure 3: Clustered column chart showing (Percentage) of Varicocele distribution between the studied groups.

We performed 56 (70%) cases of unilateral micro TESE, 32 (40%) cases on the right side and 24 (30%) cases on the left side. The remaining 24 cases (30%) were bilateral. Our overall testicular sperm retrieval rate (SRR) was 47.5%. There were no significant differences in the outcomes of micro TESE between the two groups (p = 0.370) **(Table 5 and Figure 4).**

Table 5: Outcome of micro TESE distribution between groups.

Outcome of micro TESE	AEI (n=40)	Control (n=40)	P. value
Negative	19(47.5%)	23(57.5%)	0. 370
Positive	21(52.5%)	17(42.5%)	

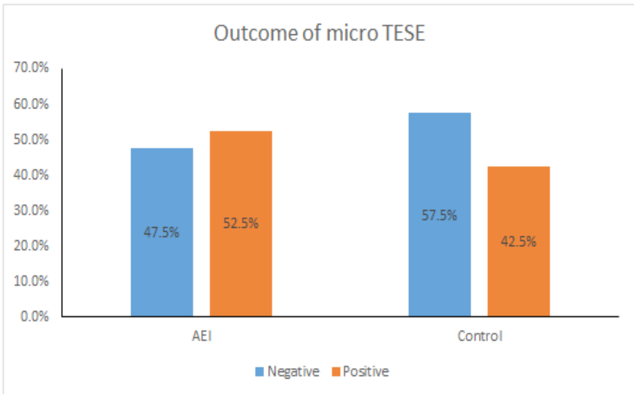

Figure 4: Clustered column chart showing (Percentage) of Outcome of micro TESE distribution between the studied groups.

The concentration of retrieved sperms did not differ significantly between the two groups (p = 0.385) **(Table 6 and Figure 5).**

Table 6: Concentration of retrieved sperms distribution between the studied groups.

	AEI (n=40)	Control (n=40)	P. value
No	14(35%)	17(42.5%)	0.385
Low	8(20%)	12(30%)	
Moderate	8(20%)	6(15%)	
Good	10(25%)	5(12.5%)	

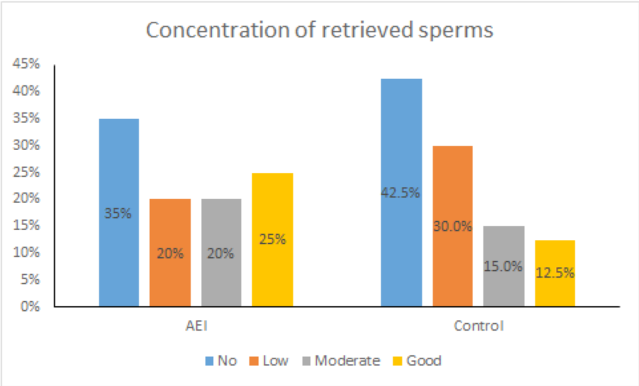

Figure 5: Clustered column chart showing (Percentage) of Concentration of retrieved sperms distribution between the studied groups.

No significant differences were found in ICSI outcomes between the two groups (p = 0.857) **(Table 7 and Figure 6)**.

Table 7: ICSI distribution between the studied groups.

	AEI (n=40)	Control (n=40)	P. value
ICSI			
No	10(25%)	12(30%)	0.857
Yes	30(75%)	28(70%)	

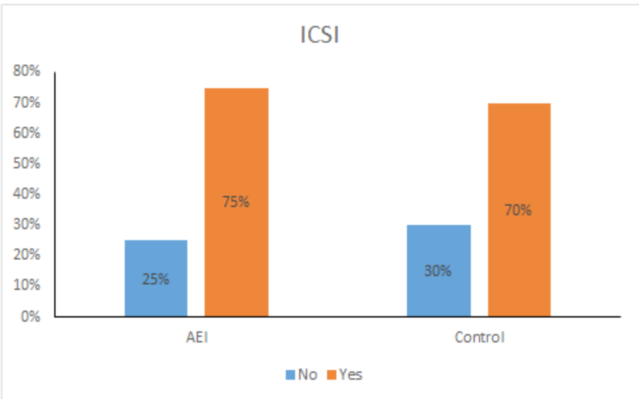

Figure 6: Clustered column chart showing (Percentage) of ICSI outcome distribution between the studied groups.

When comparing the difference in hormonal levels before and after treatment in each group; FSH, LH and prolactin did not change significantly. Otherwise, significant increases in total testosterone levels were observed after treatment within the AEI group (p = 0.003) but not in the Control group. When comparing the change in total testosterone levels between the groups, we noticed that there is a significant difference between the AEI group and the control group (p = 0.014) **(Table 8 and Figure 7 to Figure 10).**

Table 8: Before and after treatment data of FSH, LH, total testosterone and serum prolactin distribution between groups.

	AEI (n=40) Mean ± SD	Control (n=40) Mean ± SD	P1
FSH (IU/L)			
Before treatment	13.89 ± 7.89	15.24 ± 18.8	
After treatment	15.57 ± 11.42	16.59 ± 16.04	
Net (After-Before)	1.68 ± 12.41	1.35 ± 26.55	0.943
P2	0.396	0.749	
LH (IU/L)			
Before treatment	6.38 ± 9.63	8.6 ± 8.34	
After treatment	7.59 ± 5.09	7.57 ± 6.93	
Net (After-Before)	1.2 ± 10.98	-1.03 ± 9.18	0.327
P2	0.492	0.482	
Total Testosterone (nmol/L)			
Before treatment	4.29 ± 2.92	4.87 ± 2.34	
After treatment	5.57 ± 1.28	4.81 ± 1.4	
Net (After-Before)	1.28 ± 2.51	-0.06 ± 2.52	**0.014**
P2	**0.003**	0.876	
Serum prolactin (ng/mL)			
Before treatment	14.29 ± 8.15	11.97 ± 5.79	
After treatment	13.33 ± 5.25	10.65 ± 8.35	
Net (After-Before)	-0.97 ± 4.21	-1.27 ± 9.05	0.850
P2	0.155	0.391	

P1: Comparison between Net of AEI and Net of Control groups.

P2: Comparison between Before and After treatment for each group.

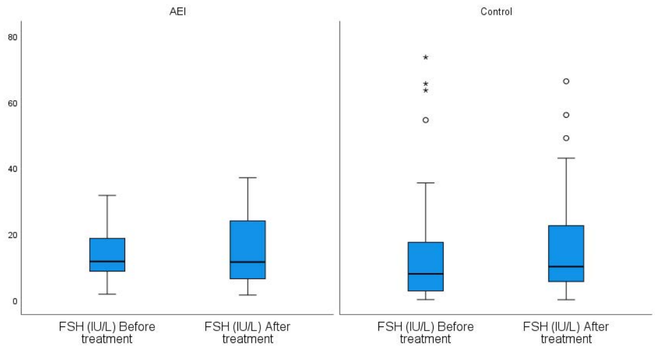

Figure 7: Boxplot chart showing distribution of FSH (Median, Q1 & Q3) before & after treatment between groups.

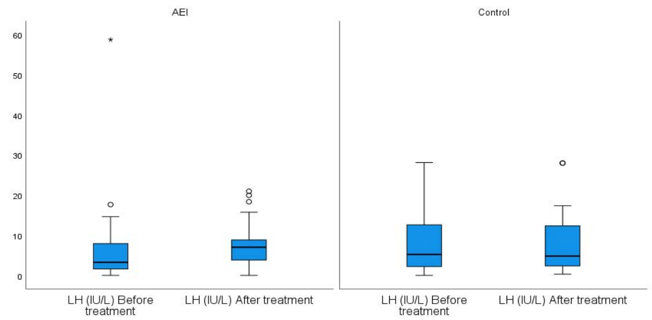

Figure 8: Boxplot chart showing distribution of LH (Median, Q1 & Q3) before & after treatment between groups.

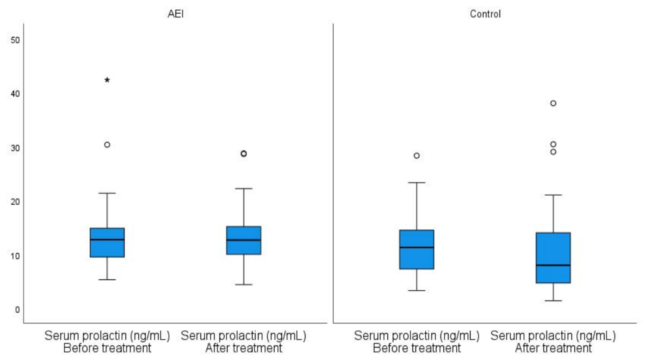

Figure 9: Boxplot chart showing distribution of Prolactin (Median, Q1 & Q3) before & after treatment between groups.

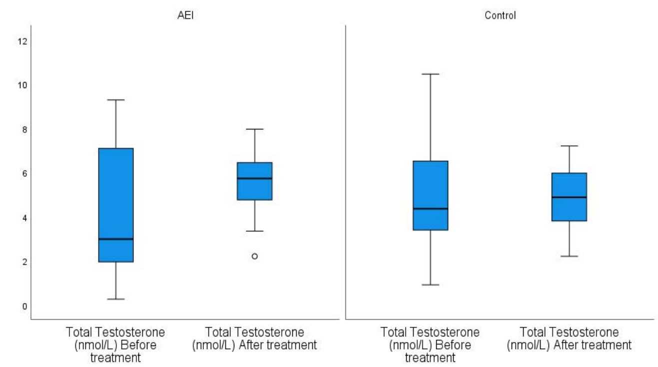

Figure 10: Boxplot chart showing distribution of Total Testosterone (Median, Q1 & Q3) before & after treatment between groups.

4. Discussion

Our overall SRR of 47.5% is consistent with the reported success rates for micro-TESE in NOA patients, which range between 40% and 60%. This consistency underscores the effectiveness of micro-TESE as a first-line treatment for NOA. However, the lack of significant improvement in SRR with AEI pre-treatment contradicts some previous studies that have suggested endocrine therapies can enhance spermatogenesis and increase SRR[10,11]. This discrepancy highlights the need for further research to delineate the specific patient populations or conditions under which endocrine therapies might be beneficial.

While age, testicular size and hormonal levels have been debated as predictors of micro-TESE success[12,13], We found no significant differences in age, testicular volume or preoperative hormonal levels among the two groups. Our findings contribute to the ongoing debate by indicating that preoperative endocrine profiles and testicular size alone may not be sufficient indicators of micro-TESE success.

Clinical varicocele has been suggested to negatively impact the results of micro-TESE by causing testicular damage and impairing spermatogenesis[14]. However, in our study, we found that these factors did not impact the results of micro-TESE. This finding is consistent with previous reports that have shown that varicocele repair does not necessarily improve the results of micro-TESE[15].

Our study observed significant increases in total testosterone levels in the AEI group, consistent with their known pharmacological effects[16]. However, the absence of a corresponding improvement in sperm retrieval suggests that while these agents effectively boost testosterone levels, this hormonal increase does not necessarily translate into enhanced spermatogenesis or improved micro-TESE outcomes. This finding is in line with some studies that question the efficacy of hormonal therapy in enhancing micro-TESE success[17].

The absence of significant improvements in SRR or ICSI outcomes with AEI pre-operative treatment challenges the current practice of routinely using these agents in NOA patients undergoing micro-TESE. Clinicians should consider these findings when devising treatment plans and setting patient expectations. While endocrine therapies may improve hormonal profiles, their utility in enhancing micro-TESE success remains unproven. This is particularly relevant given the cost, potential side effects, and the emotional burden associated with such treatments.

The sample size, while adequate to detect major differences, may not have been sufficient to uncover subtle effects of the treatments. Larger cohorts are needed to confirm these findings and elucidate the mechanisms underlying the variable response to endocrine therapies in NOA patients.

Additionally, exploring other potential predictive markers and adjunctive treatments could further optimize micro-TESE outcomes. Future research should investigate the molecular and genetic factors that might influence the response to hormonal therapy and the success of sperm retrieval. Understanding the pathways involved in spermatogenesis and how they are affected by endocrine treatments could provide valuable insights and lead to the development of more targeted therapies[18-24].

5. Conclusions

Testicular microdissection is an effective and safe procedure for cases of non-obstructive azoospermia despite the different preoperative characters. Age, testicular size, clinical varicocele and hormonal levels did not predict the success of micro-TESE. While hormonal treatments with AEI result in significant increases in total testosterone levels, it does not significantly impact the outcomes of micro-TESE, retrieved sperm concentration, or ICSI in men with NOA.

6. Competing interests

The authors have no competing interests.

7. References

1. Esteves SC, Miyaoka R, Agarwal A. An Update on the Clinical Assessment of The Infertile Male. Clinics 2011;4(66):691-700.
2. Jungwirth A, Giwercman A, Diemer T, Kopa Z, Dohle GR, Krausz C. European Association Of Urology Guidelines On Male Infertility: the 2012 Update. European Urology 2012;2(62):324-332.
3. Dohle GR, Krausz C. European Association of Urology Guidelines on Male Infertility: the 2012 Update. European Urology 2012;2(62):324-332.
4. Schlegel PN. Testicular Sperm Extraction: Microdissection Improves Sperm Yield with Minimal Tissue Excision. Human Reproduction 1999;1(14):131-135.
5. Tsujimura A, Matsumiya K, Miyagawa Y. Conventional Multiple or Microdissection Testicular Sperm Extraction: A Comparative Study. Human Reproduction, 2022;11(17):2924-2929.
6. Xu T, Peng LN, Lin X, Li J, Xu W. Predictors For Successful Sperm Retrieval of Salvage Microdissection Testicular Sperm Extraction (Tese) Following Failed Tese In Nonobstructive Azoospermia Patients. Andrologia. 2016;4(49):e12642.
7. Mahdy B, La Croce G, Roscigno M, Manica M, Da Pozzo L, Sacca A. Microsurgical Testicular Sperm Extraction: Predictive Factors and Outcomes for Men with Nonobstructive Azoospermia. Andrologia. 2024;6380023.
8. Tadros NN, Sabanegh ES. Empiric medical therapy with hormonal agents for idiopathic male infertility. Indian J Urol 2017;33(3):194-198
9. Knuth UA, Hönigl W, Bals-Pratsch M, Schleicher G, Nieschlag E. (1987). Treatment of severe oligospermia with human chorionic gonadotropin/human menopausal gonadotropin: A placebo-controlled, double blind trial. J Clin Endocrinol Metab 1987;65:1081-1087.
10. Raman JD, Schlegel PN. Aromatase inhibitors for male infertility. J Urol 2002;167:624-629.

11. Attia AM, Abou-Setta AM, Al-Inany HG. Gonadotrophins for idiopathic male factor subfertility. Cochrane Database Syst Rev 2013;23;(8):CD005071.
12. Schlegel PN. Aromatase inhibitors for male infertility. Fertil Steril. 2012;98(6):1359-1362
13. Saber-Khalaf M, Ali AF, Elsoghier OM. Predictive factors of successful testicular sperm extraction for non-obstructive azoospermia with a history of bilateral cryptorchidism and normal testosterone. Andrologia. 2022;54(1):e14284.
14. Ramasamy R, Padilla WO, Osterberg EC. A Comparison of Models For Predicting Sperm Retrieval Before Microdissection Testicular Sperm Extraction In Men With Nonobstructive Azoospermia. Journal of Urology, , 2013;2(189):638-642.
15. Ishikawa T, Kondo Y, Yamaguchi K, Sakamoto Y, Fujisawa M. Effect of Varicocelectomy On Patients With Unobstructive Azoospermia and Severe Oligospermia. BJU Int 2007.
16. Tsujimura A, Miyagawa Y, Fujita K, et al. Salvage Microdissection Testicular Sperm Extraction After Failed Conventional Tese for Patients with Non-obstructive Azoospermia. Journal of Urology, 2006;4S(175):454-454.
17. Hussein A, Ozgok Y, Ross L, Rao P, Niederberger C. Optimization of spermatogenesis-regulating hormones in patients with non-obstructive azoospermia and its impact on sperm retrieval: a multicentre study. BJU Int 2013.
18. Saylam B, Efesoy O, Cayan S. The effect of aromatase inhibitor letrozole on body mass index, serum hormones, and sperm parameters in infertile men. Fertil Steril 2011;95(2):809-811
19. Rashwan AK, Younis HA, Abdelshafy AM. Plant starch extraction, modification, and green applications: a review. Environmental Chemistry Letters 2024;1-48.
20. Elsagheer MA ,Wadea MK ,Ali NM ,Eletmany MR .Enhancing antioxidant status ,productive and reproductive performance for post-molt broiler breeders by using maca powder) lepidium meyenii .(Chelonian Conservation and Biology485-:(01)19;2024 .499
21. Selim MA ,Hassan EA ,Harb AEA ,Eletmany MR .Some spectral studies of New Derivatives of Nicotine ,Pyridazine ,Cinnoline Compounds .In7 th International Conference on Optical Spectroscopy ,Laser and Their Applications .Presented at the 7th International Conference on Optical Spectroscopy ,Laser and Their Applications ,NRC ,Cairo ,Egypt.2016
22. Eletmany MR .Development of New Organic Hole Transport Compounds for high Performances Dye-sensitized Solar cells. In1 st International Conference on Natural Resources and Renewable Energy) ICNRRE .(Presented at the1 st International Conference on Natural Resources and Renewable Energy)ICNRRE ,(South Valley University ,Hurghada ,Egypt2017 .
23. Eletmany MR, Abdellah IM, El-Shafei A. Sustainable Cotton Dyeing with Reactive Dyes for Enhanced Color Fastness and Durable Antimicrobial Properties. In NC Global Health Alliance Annual Conference, McKimmon Center on NC State’s campus 2023.
24. Eletmany MR, Hassan EA, Fandy RF, Aly KI. Synthesis and Characterization of Some New Benzoxazine Polymers with Their Industrial Applications. In 3rd Annual Conference of the Faculty of Science. Presented at the 3rd Annual Conference of the Faculty of Science, Faculty of Science, South Valley University, Qena, Egypt.