Efficacy of Human Chorionic Gonadotropin (HCG) and Aromatase Enzyme Inhibitor (AEI) Administration Prior to Microscopic Testicular Sperm Extraction (Micro TESE) in Men with Non-Obstructive Azoospermia

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Abstract

Background: Infertility affects 10-15% of couples, with both male and female factors contributing. Non-obstructive azoospermia (NOA) causes 60% of azoospermia cases, and micro-TESE with ICSI is a key treatment. Hormonal stimulation before micro-TESE may improve sperm retrieval, though its effectiveness is debated.

Objectives: To compare the efficacy of administering HCG and AEI before performing microscopic testicular sperm extraction

Patients and methods: This study involved 120 male patients with NOA from South Valley University Hospitals. Participants were randomly assigned into three groups: Group 1 received HCG treatment, Group 2 received aromatase enzyme inhibitors, and Group 3 was a control group with no treatment. All patients underwent a thorough evaluation. Microdissection TESE was performed, and postoperative data was compared between the 3 groups.

Results: The study compared demographic and clinical characteristics among three groups: HCG, AEI, and Control. No significant differences were observed in age, testicular volume, varicocele prevalence, or hormone levels. However, significant differences were found in sperm retrieval outcomes: 25% of the HCG group, 35% of the AEI group, and 80% of the Control group had no sperm retrieved ($p<0.001$). Moderate sperm concentration was significantly higher in the AEI group (20%) compared to HCG (5%) and Control (0%) ($p=0.003$), while good sperm concentration was higher in the HCG group (40%) compared to AEI (25%) and Control (0%) ($p<0.001$). No significant differences were found in ICSI usage across groups ($p=0.857$).

Conclusion: HCG and AEI prior to micro-TESE improves testosterone levels and sperm retrieval outcomes in men with NOA.

Keywords: Human Chorionic Gonadotropin; Aromatase Enzyme Inhibitor; Microscopic Testicular Sperm Extraction; Azoospermia.

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Introduction:

Infertility affects approximately 10-15% of couples in developed nations. The World Health Organization (WHO) defines infertility as the inability to conceive after one year of regular, unprotected intercourse, resulting in pregnancy and live birth. It is a medical condition that impacts both male and female partners' health and has broader public health implications. The emotional toll on infertile couples and the financial burden of assisted reproductive technologies are considerable **(Obeagu et al., 2023).**

Understanding the underlying causes of infertility is valuable not only for individual health but also for public health and healthcare systems. Identifying the reasons behind infertility can guide healthcare providers in offering accurate advice, reducing unnecessary treatments and their associated costs. Moreover, risks associated with assisted reproductive technologies (ART) can be better managed through thorough examination of both partners. Historically, traditional societies often believed that infertility was mainly caused by female factors, which led to extensive research on female reproductive health and disorders **(Salter et al., 2022).**

Non-obstructive azoospermia (NOA) is responsible for 60% of all azoospermia cases. Microdissection testicular sperm extraction (micro-TESE), which enables the identification of small areas of sperm production within the testes, is crucial in treating NOA when combined with intracytoplasmic sperm injection (ICSI). Sperm retrieval rates with micro-TESE in NOA cases have been reported to be between 40-60%. As a result, micro-TESE is increasingly becoming a preferred first-line treatment for couples facing infertility due to NOA. Several pre-surgical hormonal stimulation methods have been proposed to improve outcomes in NOA men before undergoing micro-TESE **(Achermann et al., 2021)**.

Endocrine stimulation treatments, including gonadotropins and aromatase inhibitors, are commonly used prior to micro-TESE to enhance intra-testicular testosterone production and improve sperm retrieval rates. However, the evidence supporting their effectiveness is limited. While hormone therapy is recommended for secondary hypogonadism, its use in men with NOA and primary hypogonadism before attempting surgical sperm retrieval remains controversial **(Mahdy et al., 2024)**.

This study aims to compare the efficacy of administering human chorionic gonadotropin and aromatase enzyme inhibitors before performing microscopic testicular sperm extraction in men with non-obstructive azoospermia.

Patients and Methods

This study involved 120 male patients who presented to the Andrology Outpatient Clinic of South Valley University Hospitals. The participants were randomly assigned into three groups through a closed-envelope method:

- **Group 1:** Patients received human chorionic gonadotropin treatment for three months prior to micro-TESE.
- **Group 2:** Patients received aromatase enzyme inhibitor treatment for three months prior to micro-TESE.
- **Group 3 (Control):** Patients did not receive any treatment before micro-TESE.

Study population:

- **Inclusion Criteria:** patients who were 18 years or older and diagnosed with non-obstructive azoospermia (NOA) based on the following diagnostic criteria **(Kaltsas et al., 2023):** at least two semen analyses, hormonal testing, and transrectal and testicular sonography. Serum FSH level > 12 IU/L and serum LH level > 8.6 IU/L
- **Exclusion Criteria:** Inability to understand the study or provide consent, inability to provide a semen sample, Unwillingness to undergo TESE or ICSI, Known obstructive azoospermia, History of prior testicular biopsy, Cryptozoospermia, Serum testosterone levels < 2.5 ng/mL.

Study procedures: All patients underwent the following:

Complete history taking including: personal history, medical history, family history, medication history and History of prior surgical procedures. The patient’s overall condition and vital signs were assessed. Evaluation of hair and fat distribution. The local examination involved the scrotal skin and testicular size/consistency.

Spermatic cord and penile examination were also performed.

Semen analysis (two samples to confirm azoospermia), Scrotal Doppler ultrasound and hormonal profile (FSH, LH, prolactin, and total testosterone levels) were done before and after treatment.

Microdissection TESE Procedure (Achermann et al., 2021):

- A midline scrotal incision was made, and the scrotal contents were carefully pushed out, with preference given to the side of the larger testis.
- The tunica vaginalis was opened, and the tunica albuginea of the testis was exposed. The procedure was then performed under an operative microscope.
- Once the tunica albuginea was opened, the testicular parenchyma was examined at magnifications of x12 to x18. Samples (5–10 mg) were excised from the larger, more opaque tubules.
- These samples were immediately checked for spermatozoa by placing a small droplet of tissue suspension on a glass slide and viewing it under a phase-contrast microscope at x200 magnification.
- If spermatozoa were not found in the initial sample, additional samples were taken from the same testis or, if necessary, from the opposite testis.
- Dissection was continued throughout the testicular tissue while maintaining the testicular blood supply.
- Once spermatozoa were retrieved or further dissection was deemed to risk damaging the testicular blood supply, the procedure was terminated.
- The best samples were collected in 5 mL of tubal fluid medium, centrifuged at 1800g, and carefully examined for the presence of even a single spermatozoon.

Ethical approval code: SVU-MED-DVA021-2-21-11-271.

Statistical analysis

performed using IBM SPSS (20.0). Quantitative variables were described by the mean, standard deviation (SD), and range, while qualitative variables were presented as frequencies and percentages. The Chi-square test was used to compare qualitative variables between groups, with the Fisher's exact test applied when any expected cell count was less than or equal to 5. The t-test was employed to compare parametric quantitative variables. Statistical significance was determined with a p-value < 0.05.

Results

The demographic and clinical characteristics of the studied groups (HCG, AEI, and Control) were compared. The mean age for the HCG, AEI, and Control groups was 39.35±9.66, 40.75±11.23, and 40.68±10.15 years, respectively, showing no significant difference (p=0.794). For testicular volume, the right testis volume was 7.88±4.17 mL in the HCG group, 8.65±3.53 mL in the AEI group, and 9.35±3.72 mL in the Control group, with no significant difference (p=0.231). The left testis volume was 8.43±4.22 mL in the HCG group, 8.75±3.16 mL in the AEI group, and 9.44±4.01 mL in the Control group, showing no significant difference (p=0.481). Regarding varicocele, 65% of the HCG group, 80% of the AEI group, and 75% of the Control group had no varicocele (p=0.303). Unilateral varicocele was found in 20% of the HCG group, 15% of the AEI group, and 5% of the Control group (p=0.133). Bilateral varicocele was present in 15% of the HCG group, 5% of the AEI group, and 20% of the Control group (p=0.132), with no significant differences observed across all groups **(Table 1, fig 1).**

Table (2):

For FSH levels, before treatment, the HCG group had 17.96±16.16 IU/L, the AEI group had 13.89±7.89 IU/L, and the Control group had 15.24±18.8 IU/L, with no significant difference (p=0.4691). After treatment, the HCG group showed 15.02±17.57 IU/L, the AEI group had 15.57±11.42 IU/L, and the Control group had 16.59±16.04 IU/L, also showing no significant difference (p=0.8965).

Regarding LH levels, before treatment, the HCG group had 9.28±9.19 IU/L, the AEI group had 6.38±9.63 IU/L, and the Control group had 8.6±8.34 IU/L, with no significant difference (p=0.3302). After treatment, the HCG group showed 7.5±4.37 IU/L, the AEI group had

7.59±5.09 IU/L, and the Control group had 7.57±6.93 IU/L, with no significant difference (p=0.9971).

For total testosterone levels, before treatment, the HCG group had 4.07±1.43 nmol/L, the AEI group had 4.29±2.92 nmol/L, and the Control group had 4.87±2.34 nmol/L, with no significant difference (p=0.2827). After treatment, the HCG group showed 4.96±1.33 nmol/L, the AEI group had 5.57±1.28 nmol/L, and the Control group had 4.81±1.4 nmol/L, with no significant difference (p=0.1074).

For serum prolactin, before treatment, the HCG group had 11.73±5.77 ng/mL, the AEI group had 14.29±8.15 ng/mL, and the Control group had 11.97±5.79 ng/mL, with no significant difference (p=0.2028). After treatment, the HCG group showed 11.01±7.97 ng/mL, the AEI group had 13.33±5.25 ng/mL, and the Control group had 10.65±8.35 ng/mL, with no significant difference (p=0.2106).

Table (3):

Regarding the concentration of retrieved sperm, 25% of the HCG group, 35% of the AEI group, and 80% of the Control group had no sperm retrieved, with a significant difference observed between the groups (p<0.001). For low sperm concentration, 30% of the HCG group, 20% of the AEI group, and 20% of the Control group were classified as having low sperm concentration, with no significant difference (p=0.4745). **Fig 2.**

In terms of moderate sperm concentration, 5% of the HCG group, 20% of the AEI group, and 0% of the Control group showed moderate sperm concentration, with a significant difference (p=0.003). For good sperm concentration, 40% of the HCG group, 25% of the AEI group, and 0% of the Control group had good sperm concentration, with a significant difference (p<0.001). Regarding ICSI, 65% of the HCG group, 70% of the AEI group, and 70% of the Control group underwent ICSI, showing no significant difference (p=0.857). **Fig 3.**

Table (1). Demographic and clinical data among the studied groups

Variables	**HCG (n=40)**	**AEI (n=40)**	**Control (n=40)**	**P. value**
Age (years)	39.35±9.66	40.75±11.23	40.68±10.15	0.794
Right testis volume (mL)	7.88±4.17	8.65±3.53	9.35±3.72	0.231
Left testis volume (mL)	8.43±4.22	8.75±3.16	9.44±4.01	0.481
Varicocele				
• **No**	26(65%)	32(80%)	30(75%)	0.303
• **Unilateral**	8(20%)	6(15%)	2(5%)	0.133
• **Bilateral**	6(15%)	2(5%)	8(20%)	0.132

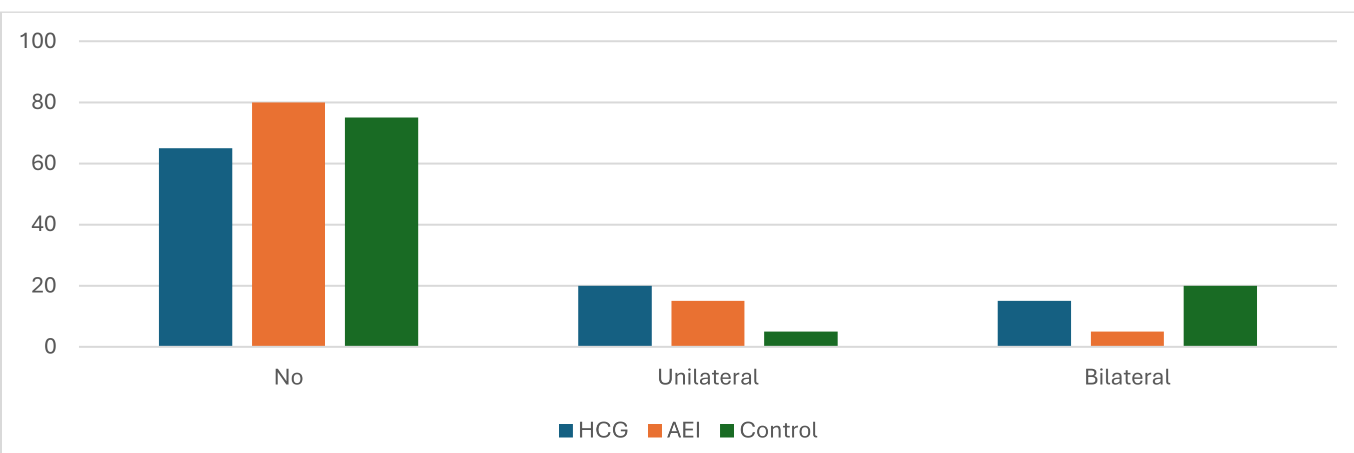

Fig 1. prevalence of the varicocele among the studied groups.

Table (2). Hormonal profile among the studied groups

Variables	HCG (n=40)	AEI (n=40)	Control (n=40)	P. Value
FSH (IU/L)				
• **Before treatment**	17.96±16.16	13.89±7.89	15.24±18.8	0.4691
• **After treatment**	15.02±17.57	15.57±11.42	16.59±16.04	0.8965
LH (IU/L)				
• **Before treatment**	9.28±9.19	6.38±9.63	8.6±8.34	0.3302
• **After treatment**	7.5±4.37	7.59±5.09	7.57±6.93	0.9971
Total Testosterone (nmol/L)				
• **Before treatment**	4.07±1.43	4.29±2.92	4.87±2.34	0.2827
• **After treatment**	4.96±1.33	5.57±1.28	4.81±1.4	0.1074
Serum prolactin (ng/mL)				
• **Before treatment**	11.73±5.77	14.29±8.15	11.97±5.79	0.2028
• **After treatment**	11.01±7.97	13.33±5.25	10.65±8.35	0.2106

Table (3). Outcome of micro TESE following among the studied groups

Variables	HCG (n=40)	AEI (n=40)	Control (n=40)	P. Value
Concentration of retrieved sperms				
• **No**	10(25%)	14(35%)	32(80%)	<0.001*
• **Low**	12(30%)	8(20%)	8(20%)	0.4745
• **Moderate**	2(5%)	8(20%)	0(0%)	0.003*
• **Good**	16(40%)	10(25%)	0(0%)	<0.001*
ICSI				
• **Yes**	26(65%)	28(70%)	28(70%)	0.857
• **No**	14(35%)	12(30%)	12(30%)	

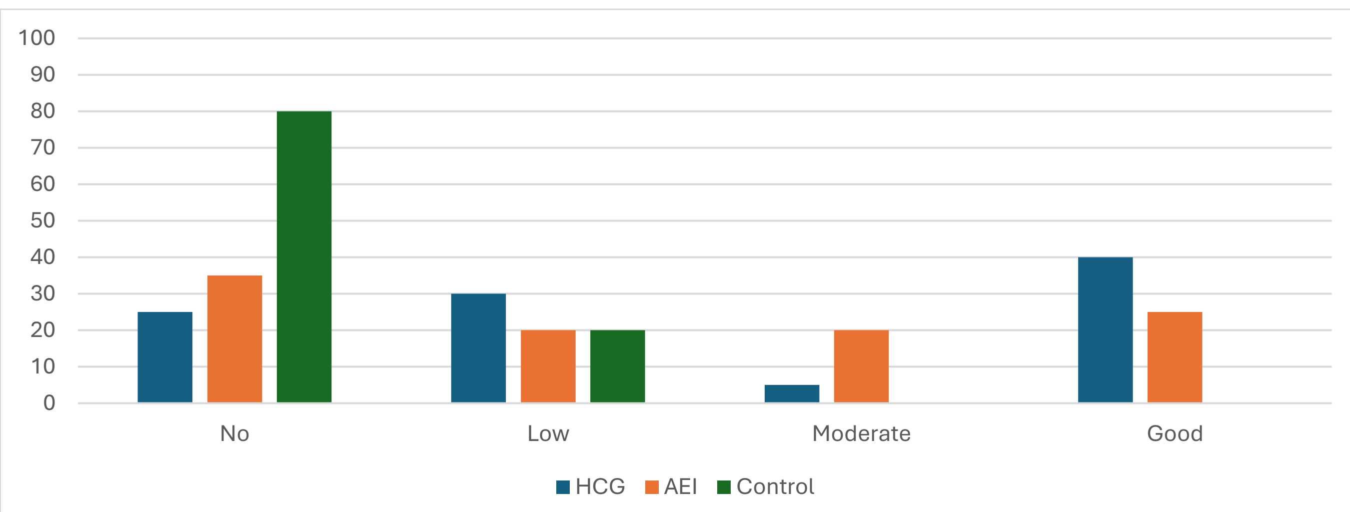

Fig 2. Concentration of retrieved sperm among the studied groups

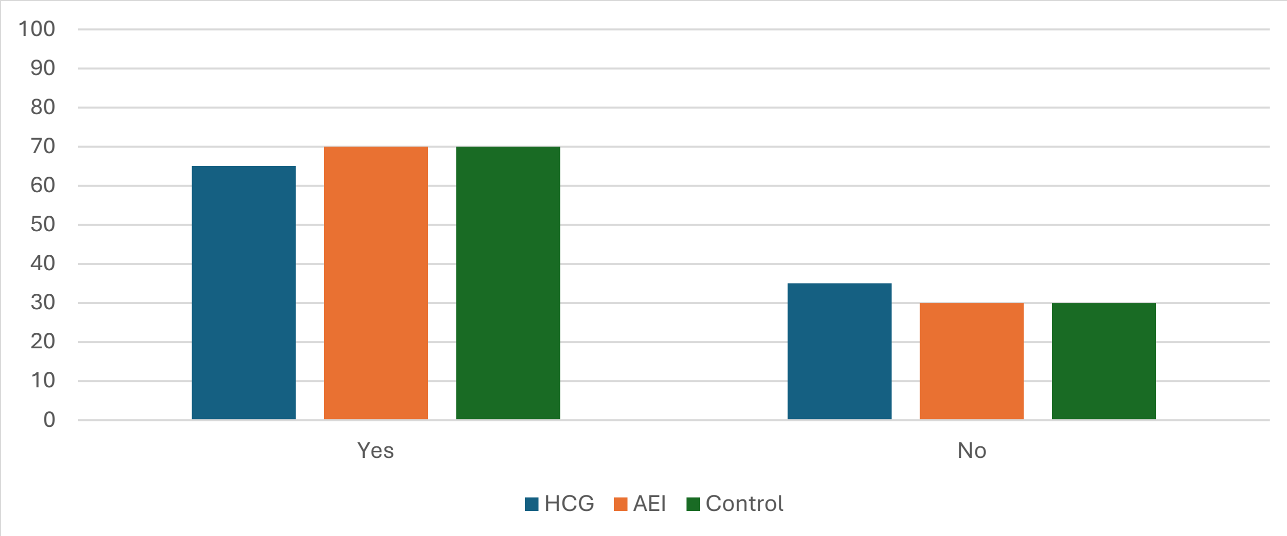

Fig 3. The need for ICSI among the studied groups

Discussion

Infertility is defined as the inability of a healthy woman to conceive after 12 months of regular, unprotected sexual intercourse. Male infertility refers to any health condition that hinders the ability to conceive, often due to abnormal sperm function or obstructions in ejaculation **(Assidi, 2022).** Among male infertility causes, azoospermia, the complete absence of sperm in the ejaculate, is the most severe form. Azoospermia is categorized into obstructive azoospermia (OA) and non-obstructive azoospermia (NOA), with the latter associated with testicular defects impairing sperm production **(Achermann et al., 2021).**

Microdissection testicular sperm extraction (mTESE) is considered the gold standard for sperm retrieval in NOA cases (Kaur et al., 2020). Endocrine stimulation therapies, such as gonadotropins and aromatase enzyme inhibitors (AEI), are commonly used prior to mTESE to enhance intra-testicular testosterone (ITT) levels, potentially improving sperm retrieval outcomes **(Mahdy et al., 2024).**

This study aimed to evaluate the efficacy of AEI administration before mTESE in men with NOA. The research was conducted at South Valley University Hospitals, involving 120 male patients divided into three randomized groups: Group 1 (HCG treatment), Group 2 (AEI treatment), and Group 3 (Control).

The study found no significant differences in age or testicular volume across the groups. Consistent with **Esteves (2015),** normal seminal volume and pH were observed, suggesting functional seminal vesicles and patent ejaculatory ducts in NOA patients.

Regarding hormonal levels, preoperative data showed no significant differences in FSH, LH, testosterone, or prolactin levels among the groups. Post-treatment, both HCG and AEI groups showed significant increases in total testosterone levels compared to the Control group, while prolactin levels remained unchanged. These findings are supported by previous studies **(Oduwole et al., 2021; Baburski et al., 2019).** HCG stimulates Leydig cells to produce testosterone, while AEIs prevent testosterone conversion to estrogen, leading to higher testosterone levels **(De Ronde & de Jong, 2011; Schlegel, 2012).**

Mahdy et al., (2024) similarly reported significant increases in testosterone levels after AEI treatment, with no changes in FSH, LH, or prolactin levels. **Coviello et al. (2005)** demonstrated that low dose hCG maintains normal intra-testicular testosterone levels, and **El Meliegy et al. (2018)** found that AEIs like anastrozole and letrozole effectively manage male infertility by increasing gonadotropin production.

The study found that sperm retrieval outcomes were significantly better in the HCG and AEI groups compared to the Control group.

Specifically, 25% of HCG patients, 35% of AEI patients, and 80% of Control patients had negative sperm retrieval outcomes. Positive results with HCG-based stimulation in NOA patients undergoing micro-TESE were also reported by **Khourdaji et al. (2018).**

Shiraishi et al. (2012) showed that HCG therapy increased sperm retrieval chances in men with prior negative micro-TESE outcomes. **Schiff et al. (2005)** found that men treated with anastrozole alone or in combination with HCG had successful sperm retrieval, supporting the efficacy of AEIs and HCG in improving outcomes. However, **Ramasamy et al. (2009)** did not observe a significant impact of pretreatment on success rates.

In contrast, **Mahdy et al., (2024)** reported no significant differences in micro-TESE outcomes between AEI and Control groups. Our study found a significant difference in sperm concentration between the HCG, AEI, and Control groups, with HCG showing the most positive results. One-Way ANOVA indicated significant differences between Control and HCG ($p < 0.001$) and Control and AEI ($p < 0.001$), but no significant difference between HCG and AEI ($p = 0.092$).

Kumar (2013) highlighted the role of HCG and FSH therapy in initiating spermatogenesis in men with hypogonadotropic hypogonadism, achieving positive sperm retrieval rates in 80% of treated men**. Tao (2022)** emphasized the role of hormonal balance in spermatogenesis, and **Shoshany et al. (2017)**, observed improvements in T/E ratios in men treated with anastrozole, though sperm concentration improvements were only seen in oligospermic men.

Regarding ICSI outcomes, no significant differences were found among the groups ($p = 0.857$), consistent with **Mahdy et al. (2024),** who also found no significant differences between AEI and Control groups regarding ICSI outcomes.

Conclusion

Our study highlights the effectiveness of administering human chorionic gonadotropin (HCG) and aromatase enzyme inhibitors (AEI) before microscopic testicular sperm extraction (micro-TESE) in enhancing total testosterone levels and improving sperm retrieval outcomes in men with non-obstructive azoospermia. Both treatments were more effective than the control group, which received no specific treatment. Among the two, HCG resulted in a higher sperm retrieval success rate. These results suggest that hormonal stimulation before micro-TESE could be a promising strategy to improve fertility treatment outcomes for men with non-obstructive azoospermia.

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