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Effects of Testicular Volume, Follicle Stimulating Hormone, Luteinizing Hormone and Presence of Varicocele On Successful Sperm Retrieval In Non-Obstructive Azoospermia

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ABSTRACT

The aim of the study was to evaluate the relation between the probability of positive sperm extraction with Testicular Sperm Extraction (TESE) and the clinical, laboratory and demographic features in a series of non-obstructive azoospermia (NOA) infertility patients who consulted to Urology Department in order to determine and inform couples who could not succeed and thus avoid unnecessary treatment.

Sixty-four patients with non-obstructive azoospermia were enrolled to the study. Demographical features and previous varicocele operation history were noted. In all cases serum levels of Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), genetic analysis and bilateral testicular volume were determined to find the correlation between probability of positive sperm extraction with TESE.

The incidence of NOA among all infertile men was 15.1%. TESE success rate in NOA was 29,6%. There were significant differences in FSH levels (p<0,001), LH levels (p=0,006), right testicular volume (p<0,001), and left testicular volume (p<0,001). The results were evaluated by ROC analysis. Success rate of TESE was decreased when FSH>8,9mIU/ml (sensitivity 80%, specifity68%), LH>4,25mIU/ml (sensitivity 76%, specifity 53%), right testicular volume<8,5ml (sensitivity84%, specifity56%) and left testicular volume<7,25ml (sensitivity 84%, specifity56%) in NOA. As there was no paramater with one hundred percent sensitivity, probability of positive sperm retrieval would stil exist in these patients.

In NOA cases increased FSH and LH levels, decreased testis volumes have negative effect at sperm retrieval. Chromosomal damages like Klinefelter Syndrome also decrease success rate. Determining groups with poor prognosis, may help prevention of patients from unnecessary processes, risks and costs.

Keywords: Male infertility, non-obstructive azoospermia, TESE

Introduction

Infertility is defined as the inability of a sexually active, non-contracepting couple to achieve pregnancy within one year (1). Infertility emerges as a significant health problem in about 20-35% of newly married couples and it is attributed to the male partner in up to half of the cases (2,3). Factors causing infertility in men include malnutrition, advanced age, prolonged exposure of the testicles to heat, systemic diseases, genetic disorders, tumors, stress, use of medication, chemical exposure, smoking and alcohol abuse, sexual disorders, congenital penis abnormalities, exposure to radiation, and congenital and endocrinologic diseases (4,5,6).

At present, the introduction of in vitro fertilization (IVF) and in parallel to this, the development of invasive and non-invasive sperm retrieval techniques have made it possible to obtain sperm from infertile men. Furthermore, the development of intracytoplasmic sperm injection (ICSI) procedure has provided a safe and effective treatment for male factor infertility (7,8,9). There are indications of use for ICSI in cases where epididymal and testicular sperm are used. It can also be used for patients with severe oligoasthenospermia (10).

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The incidence of nonobstructive azoospermia (NOA) among infertile male patients is 15% (11). In up to half of these patients, sperm can be retrieved from the testes (12,13). Studies have focused on investigating clinical and laboratory markers to increase the success of sperm retrieval by finding suitable patients, for whom sperm retrieval is possible and who can benefit from assisted reproductive technologies (ART).

This study aimed to predict the success of the procedure by evaluating clinical, laboratory, and demographic characteristics of patients with NOA, who underwent testicular sperm extraction (TESE) in the IVF and Reproductive Health Unit and by examining the possibilities of sperm retrieval with the TESE procedure; and to avoid the implementation of unnecessary procedures by identifying and informing couples for whom these procedures would fail.

Materials and Methods

The study included patients with NOA, who were admitted to our clinic due to infertility between 2006 and 2018 and who underwent TESE procedure in the ART center. A total of 423 patients presented with infertility were examined. Of these, 81 were found to have azoospermia based on the semen analysis performed according to the World Health Organization (WHO) 2010 standard semen analysis criteria. The patients' age, duration of unprotected sexual intercourse, history of previous varicocelectomy surgery, and follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were recorded. In our laboratory, the normal range of serum FSH and LH levels for men were determined to be 1.3–13.5mIU/mL and 1.1–8.7mIU/mL, respectively. Testicular and varicocele examinations were performed. Karyotype analysis and Y chromosome microdeletion assays were done and TESE results were evaluated. Patients refused to undergo the TESE procedure or those who already underwent TESE in an another center, those with missing information, and patients who had obstructive azoospermia according to their physical examination, laboratory, and medical imaging results were excluded from the study. A total of 64 patients who were eligible for the study and met the inclusion criteria were included in the study.

Genetic examinations of the patients were carried out by two different methods: chromosome and Y chromosome microdeletion assays. Cytogenetic study was performed for chromosome analysis. The chromosomes obtained at the end of these processes were analyzed using the GTG banding technique. For the Y chromosome microdeletion assay, regions on the Y chromosome which contained the investigated microdeletions using YDDS™ (Y Deletion Detection Systems, Promega, version 2.0,USA) were amplified with Polymerase Chain Reaction (PCR).

When performing TESE on patients, after the tunica albuginea was opened under the guidance of microscope at 40x magnification, more flexible, larger, and bright tubules were preferred. The samples were evaluated by biologists. If an adequate number of spermatozoa were not found, the tubular excision process was repeated. Before the TESE procedure was terminated, a second tubular sample was collected in a separate container for pathological examination. If no spermatozoa were found after all these procedures, the same procedures were repeated for the other testis.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 20.0 software and e-PICOS statistics software. Continuous data were expressed as mean±standard deviation, whereas categorical data were expressed as frequencies and percentage (%). The Kolmogorov-Smirnov test was used to determine whether the data was distributed normally. The Mann-Whitney U test was used for pairwise comparison of continuous data that did not follow a normal distribution, whereas the Student's t-test was used for pairwise comparison of continuous data following a normal distribution. The chi-square test was used to compare frequency data between two groups. Relationship between FSH, LH and testicular volumes was compared with Pearson correlation test. Receiver-Operating Characteristics (ROC) analysis was used to determine the appropriate cut-off point for independent markers and to calculate the sensitivity and specificity values. Logistic Regression Analysis was used to determine the independent marker or markers affecting sperm retrieval success with TESE. A p value of <0.05 was considered statistically significant.

Results

Azoospermia was detected in 81 (19.1%) of 423 patients presented to our clinic with infertility between 2006 and 2018. After patients with azoospermia whose clinical, laboratory, and imaging data was missing, or those who were not eligible for the study, and those with obstructive azoospermia were excluded, the remaining 64(15.1%) patients with NOA were evaluated. Sperm retrieval was successful in 19(29.7%) of the patients who underwent TESE procedure, whereas the TESE was negative in 45 (70.3%) of the patients.

The mean age of the patients was 34 (±5.9) years, and the median duration of unprotected sexual

Table 1. Demographic Characteristics

	n=64
Age, year (±)	34 (5,9)
Duration of unprotected sexual intercourse, year (min-max)	9 (1-22)
Right-side varicocele, n (%)	
None	50 (80,6)
Grade 1	8 (12,9)
Grade 2	2 (3,2)
Grade 3	2 (3,2)
Left-sidevaricocele, n (%)	
None	34 (55,7)
Grade 1	7 (11,5)
Grade 2	11 (18,0)
Grade 3	9 (14,8)
History of varicocelectomy, n (%)	17 (26,6)
Karyotype analysis	
Klinefelter syndrome	9 (14,1)
AZFc gene deletion	4 (6,3)

Table 2. Relationship between Hormone, Testicular Volume and TESE Success

	TESE Positive n=19	TESE Negative n=45	p
FSH (mIU/ml)	8,5±6,55	20,8±13,63	<0,001
LH (mIU/ml)	4,8±2,54	11,1±9,43	0,006
Right testicular volume (cm^3)	12,5±5,62	7,3±4,99	<0,001
Left testicular volume(cm^3)	13,3±7,06	7,1±5,29	<0,001

Table 3. ROC Analysis of Age, FSH, LH, Right and Left Testicular Volumes

	Cut-off value	AUC	%95Cl	p	Sensitivity (%)	Specificity (%)
Age	35	0,682	0,55-0,82	0,022	74	60
FSH	8,9	0,770	0,65-0,89	0,001	80	68
LH	4,25	0,725	0,60-0,85	0,005	76	53
Right Testicular Volume	8,5	0,751	0,61-0,89	0,002	84	56
Left Testicular Volume	7,25	0,764	0,64-0,88	0,001	84	56

intercourse was nine (1–22) years. Left-side grade I, II and III varicoceles were observed in 7 (11.5%), 11 (18.0%), and 9 (14.8) patients, respectively. No varicocele was identified on the right side alone in any patient. Among patients with left-sided varicocele, right-sided grade I, II and III varicoceles were observed in 8 (12.9%), 2 (3.2%), and 2 (3.2%) patients, respectively. History of varicocelectomy was present in 17(26.6%) of the patients. Chromosome analysis showed that nine (14.1%) patients had Klinefelter syndrome, whereas the Y chromosome microdeletion test revealed AZFc gene deletion in four (6.3%) patients. Table 1 presents the demographic characteristics of the patients.

Seventeen of the patients had previously undergone varicocelectomy. Left varicocelectomy was performed on 13 patients with a history of varicocelectomy, and it was learned that four patients had a history of bilateral varicocelectomy. Varicocele was not palpable on the examination of eight of the patients with a previous history of varicocelectomy, whereas varicocele was observed to persist in nine patients after varicocelectomy. Three and two of the patients

Table 4. Correlation Analysis of Right and Left Testicular Volumes, FSH and LH

		Right Testicular Volume	Left Testicular Volume	FSH	LH
Right Testicular Volume	r	1,000	,757**	-,511**	-,532**
	p	.	,000	,000	,000
Left Testicular Volume	r	,757**	1,000	-,644**	-,740**
	p	,000	.	,000	,000
FSH	r	-,511**	-,644**	1,000	,811**
	P	,000	,000	.	,000

Table 5. Logistic Regression Analysis of Right and Left Testicular Volumes, FSH and LH

	OR (%Cl)	p
FSH	0,88 (0,81-0,96)	0,003
LH	1,03 (0,83-1,27)	0,782
Right Testicular Volume	1,10 (0,97-1,27)	0,142
Left Testicular Volume	1,06 (0,93-1,21)	0,379

had a history of left and right orchiectomy, respectively.

Considering the demographic data of the patients, the duration of unprotected sexual intercourse and its distribution by the groups were evaluated. The patients were observed to be homogeneously distributed to the groups and there was no statistically significant difference between the groups.

The mean serum FSH (8.5±6.5mIU/mL) and LH (4.8±2.5mIU/mL) values of the TESE-positive patients were significantly lower than those of TESE-negative patients (20.8±13.6mIU/mL for FSH and 11.1±9.4mIU/mL for LH) ($p<0.001$ and $p=0.006$, respectively). The mean right testicular volume (12.5±5.6cm³) and left testicular volume (7.3±4.9cm³) of the TESE-positive patients were significantly higher than those of TESE-negative patients (right testicular volume:7.3±4.9cm³, left testicular volume:7.1±5.2cm³) ($p<0.001$ and $p<0.001$, respectively). The mean age of TESE-positive patients (36.6±5.6years) was significantly higher than that of TESE-negative patients (32.5±5.7years) ($p=0.011$). (Table 2)

The ROC curves of age, right and left testicular volume, and serum FSH and LH levels causing a significant difference in the comparison of the TESE-positive and TESE-negative groups. (Figures 1 and 2)

When the cut-off value for age was taken as 35 years, the sensitivity and specificity were found to be 74% and 60%, respectively, indicating that it was possible to predict the possibility of sperm retrieval in patients with NOA. In the ROC analysis, the sensitivity and specificity of right testicular volume were found to be 84% and 56%, respectively, when the cut-off value was taken as 8.5cm³ and when the cut-off value was taken as 7.25cm³, similarly, the sensitivity and specificity of left testicular volume were found to be 84% and 56%, respectively. These values indicated that the probability of sperm retrieval decreased significantly in patients with lower testicular volume than the above-mentioned volumes. When the cut-off value for FSH was taken as 8.9mIU/mL, its sensitivity and specificity were found to be 80% and 68%, respectively, and when the cut-off value was taken as 4.25mIU/mL, the sensitivity and specificity of LH were found to be 76% and 53%, indicating that sperm retrieval success would decrease in patients with FSH and LH levels higher than these cut-off values (Table 3).

When the correlations between right and left testicular volumes, FSH and LH were analyzed, a strong positive correlation was found between right testicular volume and left testicular volume ($r=0.757$, $p<0.001$). Both testicles were observed to be affected by pathogens causing spermatogenesis damage, together and to a similar extent in general. The right testicular volume was found to have a moderate negative correlation with serum FSH ($r=0.511$, $p<0.001$) and LH ($r=0.532$, $p<0.001$) levels. The left testicular volume was found to have a moderate negative correlation with serum FSH ($r=0.644$, $p<0.001$) level and strong negative correlation with serum LH($r=0.740$, $p<0.001$) level. A strong positive correlation was observed between serum FSH and LH levels ($r=0.811$, $p<0.001$) (Table 4). All these correlations showed that the general behavioral pattern of pathologies causing NOA reduced both testicular volumes, whereas increased serum FSH and LH levels.

Table 6. Relationship between Varicocele and TESE Success

	TESE Positive n=19	TESE Negative n=45	p
Varicocele Positive	9 (%33,3)	18 (%66,7)	0,586
VaricoceleNegative	10 (%27)	27 (%73)	

Table 7. The Effect of Varicocelectomy on TESE Success in Patients with Varicocele

	TESE Positive n=10	TESE Negative n=28	p
Varicocelectomy Positive	3 (%17,6)	14 (%82,4)	0,264
Varicocelectomy Negative	7 (%38,9)	11 (%61,1)	

Logistic regression analysis was performed with serum FSH and LH levels, right and left testicular volumes, which were found to be statistically significant in univariate analysis, in order to show the independent parameters affecting the success of sperm retrieval with TESE. As a result of this analysis, it was shown that the most powerful parameter that independently affects the success of sperm retrieval with the TESE procedure is the serum FSH level (Table 5). This result suggests that all parameters are independently associated with sperm retrieval success, but the main factor is serum FSH level, and other parameters have an effect by changing serum FSH level.

There was no statistically significant difference between varicocele and tese success (p=0.586). Similarly, there was no significant difference between patients with right-sided varicocele and those with left-sided varicocele in terms of sperm retrieval success. Patients with varicocele were divided into two groups according to whether varicocele was performed or not. There was no statistically significant difference between these two groups in terms of TESE success (p=0.264). (Table 6 and 7)

The chromosome and Y chromosome microdeletion assays performed on the patients with NOA revealed that nine (14%) of 64 patients had Klinefelter Syndrome. The microdeletion of AZF in Y chromosome was observed in four (6%) patients. Sperm retrieval with the TESE procedure was unsuccessful in all of the nine patients with Klinefelter Syndrome. While sperm retrieval was successful in two (50%) of the four patients with AZFc gene deletion, the procedure was unsuccessful in the other two (50%) patients. Sperm retrieval success could not be analyzed statistically in the patients with chromosomal damage since the low number of these patients eliminated the possibility to evaluate sperm retrieval success.

Discussion

Azoospermia is diagnosed in approximately 20% of infertile men, whereas patients with NOA constitute 15% of all infertile men (11,14). Similarly, 81 of the 423 patients who were admitted to the Urology Outpatient Clinic for infertility between 2006 and 2018 were diagnosed with azoospermia. This rate corresponds to 19.1% of the patients who were admitted to our clinic. While patients with NOA were considered sterile before the development of IVF techniques, it was observed that sperm could be retrieved with TESE in these patients and they could have children with sperm obtained through ICSI. It was seen that sperm could be obtained with the TESE procedure in 59% of the patients with azoospermia and who were thought to be unable to have children before the introduction of the TESE procedure. The success rate of sperm retrieval with the TESE procedure was reported to be similar percentage in some studies (15,16,17). In the present study, sperm retrieval was successful in 19(29.7%) of 64 patients with NOA. This rate differs significantly from study to study. In studies including only patients with normal karyotype, the success rates of the procedure have been found to be higher. In the literature, there are studies investigating whether it is possible to predict successful sperm retrieval before the procedure in patients scheduled for TESE procedure. In these studies, many parameters such as serum FSH levels, testicular volumes, genetic examinations and testicular pathologies have been examined; however, the predictive criteria have not been clearly determined yet (18).

Serum FSH levels and testicular volumes are among the most studied parameters. Increased FSH levels and small testicular volumes have been thought to be associated with testicular maturation arrest or testicular failure and FSH levels have been shown to

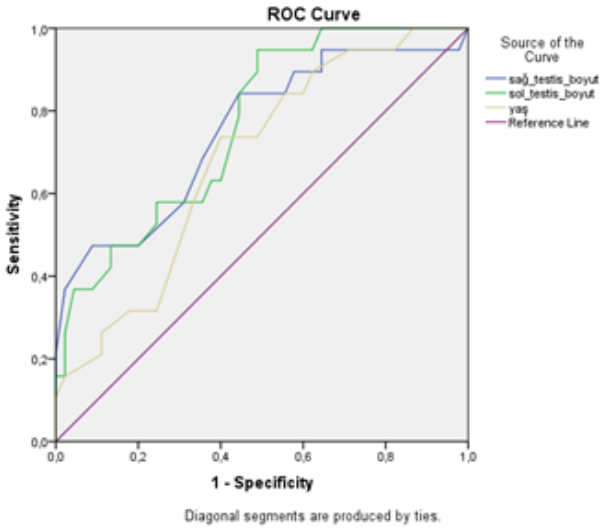

Fig. 1. ROC curve of age, right and left testicular volume

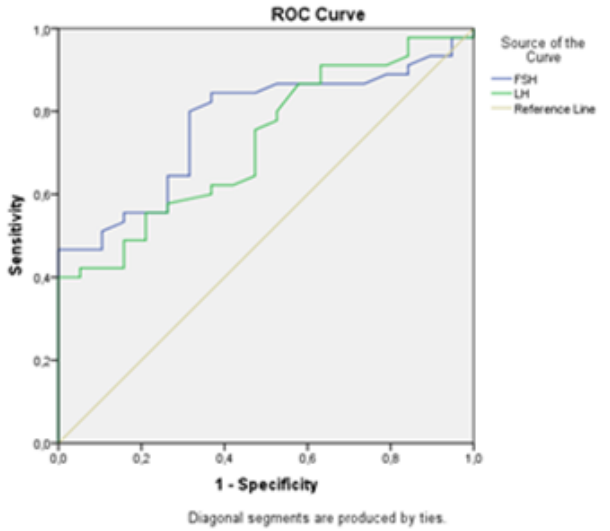

Fig. 2. ROC curve of serum FSH and LH levels

increase with the decreasing spermatogonia number. Moreover, spermatogonia production is known to occur even at very high serum FSH levels (18,19,20). Normal serum FSH levels do not indicate that the spermatogonia count is within normal limits and does not rule out spermatogenesis defects. Furthermore, sperm retrieval is possible in the presence of high serum FSH levels (1). In the present study, sperm could be obtained in the patients with high level FSH. There are also studies showing no statistical correlation between serum FSH levels and sperm retrieval rates with the TESE procedure (21). Unlike these studies, serum FSH levels were found to have an important role in predicting sperm retrieval success in the present study. The comparison of serum FSH levels of the patients and sperm retrieval rates showed a statistically significant difference. In the ROC analysis, when the cut-off value of serum FSH level was taken as 8.9mIU/mL, respectively. In a study by Vernaeve et al. calculated the cut-off value for FSH to be 25 mIU/mL and it was aimed to increase the negative predictive value of sperm retrieval success with the TESE procedure by taking low specificity value (22). In a study conducted by Guler et al. was taken as 12.7mIU/mL for FSH was found to be lower than the specificity value obtained in the present study. On the other hand, this specificity value was found to be closer to our study (16).

Serum LH values vary in patients with NOA. In the present study, the serum LH levels of the TESE-positive patients were found to be closer to normal values. However, the serum LH values of the TESE-negative patients can be higher. However, normal levels in cases where sperm cannot be obtained cause the serum LH level not to be used as a definite marker to predict sperm retrieval. In the present study, the comparison of serum LH levels and sperm retrieval success showed that the sperm retrieval success decreased in those with high serum LH levels. However, it is not possible to say that sperm retrieval will be successful for sure in patients with normal serum LH levels. When ROC analysis was performed LH level was taken as 4.25mIU/mL. It was observed that LH had lower sensitivity and specificity values than the ROC value of FSH. Pathologies that increase serum FSH levels also increase serum LH levels through a similar mechanism, and therefore, serum LH level accompanies the high serum FSH levels, particularly in cases where sperm retrieval is unsuccessful. In a study by Guneri et al., serum LH levels were found to have no statistically significant correlation with sperm retrieval success, but the increase in LH and FSH levels was observed to be correlated. In light of current data, serum LH level alone is insufficient to predict sperm retrieval success (17).

Regardless of being unilateral or bilateral, the decrease in testicular volume is associated with the spermatogenesis defect. The fact that testicular volume is generally below 15mL in patients with NOA also supports this information. Patients with a testicular volume below 5mL should be carefully examined in terms of karyotypic disorders or pathologies that may cause azoospermia (21,23). Similarly, in the present study, the mean right and left testicular volumes of the patients with NOA were found to be below normal testicular volume. The ROC analysis was performed to investigate the role of testicular volume in predicting sperm retrieval success. When the cut-off point was taken as 8.5mL for the right testicular volume and when the cut-off point was taken as 7.25mL, the sensitivity and specificity of left testicular volume in predicting sperm retrieval success, respectively. However,

regardless of the karyotype, sperm may not be found after the TESE procedure in patients with NOA, whose testicular volume is above these values and even within normal levels, and sperm can be obtained in patients with NOA whose testicular volume is below these values. The present study further showed that sperm could be obtained after TESE even from a patient with NOA with low testicular volume. For this reason, it is not possible to use the values obtained for testicular volume as a definite criterion to predict sperm retrieval success.

Although many studies have been conducted on varicocele, the contribution of varicocele and its treatment to fertility is still controversial since it has a standard definition. The incidence of varicocele is 19-41% among patients suffering from infertility (24). Similarly, 27(42%) of the 64 patients with NOA included in the present study had varicocele. When the patients with varicocele, right-sided varicocele and those with left-sided varicocele were evaluated in separate groups or together, no difference was observed between them in terms of sperm retrieval success. The reason why our patient group is heterogeneous and there is no standardization in our patients who underwent varicocelectomy, history of previous varicocelectomy has no effect on sperm retrieval success in patients with NOA. In contrast to the present study, a study by Tunc et al. found that sperm retrieval was successful underwent TESE five months after varicocelectomy in patients with NOA and varicocele who had a normal karyotype, respectively. In the present study, the patients who underwent varicocelectomy and patients with NOA who had varicocele but did not undergo varicocelectomy were compared. Furthermore, Tunc et al. only included patients with normal karyotype, whereas we also included those with chromosome defects, which reduced the sperm retrieval success rate in our study. Moreover, TESE was performed on patients five months after varicocelectomy in the study by Tunc et al., whereas there was no standardization for varicocelectomy dates in the present study. Another reason for the low success of TESE is that patients who had children after varicocelectomy were excluded and only those who had varicocelectomy and could not have children were included (25).

In the present study, karyotype and Y chromosome microdeletion assays were performed on 64 patients with NOA. Nine of the patients with NOA were found to have Klinefelter Syndrome (XXY). This rate, which corresponds to 14.1% of the patients with NOA in the present study, has been found to be 11% in other studies, similar to our study. While sperm retrieval was unsuccessful in all of the patients with Klinefelter Syndrome included in our study, the sperm retrieval rates for these patients have been reported to be up to 40% in the literature (26,27,28). When disorders other than numerical disorders in sex chromosomes such as Klinefelter Syndrome (47, XXY) were investigated, four patients were found to have Y chromosome microdeletion. This rate varies from the rates reported as 7%-18% in the literature. Compared to other studies, this rate was found to be lower in our study (6.3%). Y chromosome microdeletions are divided into subgroups according to the deleted region: AZFa, AZFb, and AZFc. Among these, AZFc deletion is the most common one, followed by the coexistence of AZFb and AZFc gene deletions 829,30,31). When the results of sperm retrieval with TESE procedure are evaluated, best sperm retrieval outcomes are known to be seen in patients with AZFc gene deletion (32). Due to the low number of patients, AZFc gene mutation was detected in four of our patients, whereas no AZFa and AZFb gene mutations were identified. Patients with AZFc gene mutation constitute 6.3% of NOA cases. The reason for our lower number of patients with Y chromosome microdeletion among the patients with NOA than the literature is that only patients with AZFc gene deletion were included in the study. In another study on Guneri et al., AZFa gene deletions were identified in one patient, whereas AZFb gene deletions were identified in five patients, AZFc gene deletions in eight patients, and AZFb+AZFc gene deletions in one patient. Similar to the present study, the ratio of patients with AZFc gene deletion to patients with NOA was found to be 6.7%. In the same study, sperm retrieval was successful in two (25%) of eight patients with AZFc gene deletion, while it was successful in two (50%) of the four patients in our study (16).

In conclusion, it is not possible to say that sperm retrieval will be successful for sure in patients with NOA using the existing markers. The present study showed that the chance of obtaining sperm decreased in the presence of Klinefelter Syndrome, high serum FSH and LH levels, and small testicular volumes. The risks and costs arising from the procedure can be avoided considering that the chance of obtaining sperm is lower in patients who have one, several, or all of these markers.

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