

Original Article

Impact of Varicocele Treatment on Sperm Recovery in Men with Non-Obstructive Azoospermia

Salem Swieb¹ , Miloud Elgmami² , Omar Alhaddad¹ ¹Faculty of Medicine, Misurata University, Misurata, Libya²Misurata Medical Center, Misurata, LibyaCorrespondence: s.swieb@med.misuratau.edu.ly

Keywords:Varicocele, Infertility,
Azoospermia.**ABSTRACT**

Varicocele, a condition characterized by dilated and tortuous veins within the pampiniform plexus, is observed in 10-20% of the general male population and is significantly more common in men with infertility, affecting 35-40% with primary infertility and up to 80% with secondary infertility. While its role in non-obstructive azoospermia (NOA) remains unclear, varicocele is present in approximately 5% of men with NOA, a severe form of male infertility that affects 10% of infertile men. to evaluate the improvement in semen quality and its outcome after varicocelectomy in non-obstructive azoospermic men. This study was a retrospective descriptive study; the study was conducted in Misurata Medical Center /Libya, and the National Infertility Center during the years January 2015 – January 2017. The study population was 20 patients diagnosed with non-obstructive azoospermia and varicocele. surgical varicocelectomy was performed in all cases, and after that, follow-up and sperm retrieval procedures were performed to retrieve sperm. The patients' ages ranged from 27 to 46 years; all of the cases were diagnosed with non-obstructive azoospermia and varicocele. there are 3 cases from the total 20 that got sperm on normal masturbation, and 5 cases got sperm by sperm retrieval procedures. the other 12 cases could not get sperm in the period from 3 to 24 months post-varicocelectomy. The results of our study indicate that infertile men with non-obstructive azoospermia NOA. and clinical and subclinical varicocele benefit from varicocelectomy and its harmless procedures for azoospermic patients. but in a high percentage, testicular sperm retrieval is mandatory

Introduction

Clinical varicocele is present in 10-20% of the general male population and is observed in 35-40% of men with primary infertility, increasing to up to 80% in those with secondary infertility [1,2]. It is defined as the dilation and tortuosity of veins within the pampiniform plexus, a venous network responsible for draining blood from the testicle. While varicocele is found in approximately 5% of men with non-obstructive azoospermia (NOA), its exact role in the pathophysiology of azoospermia remains unclear [3]. NOA, the most severe form of male infertility, affects about 10% of infertile men [4]. Before the advent of assisted reproductive technologies (ART), couples affected by NOA had limited options for conception, relying primarily on donor sperm. However, advances in ART, particularly intracytoplasmic sperm injection (ICSI) and microsurgical techniques for testicular sperm retrieval, have made biological fatherhood possible for approximately 20–40% of men with NOA [5]. Varicocele is rarely detected in boys under 10 years of age. The impact of varicocele on fertility and the benefits of its repair have been a subject of debate among andrologists for nearly 60 years, ever since Tulloch reported the first case of unassisted pregnancy following varicocele repair in 1952. Varicoceles are primarily diagnosed through physical examination and are classified using the Dubin system: grade 1 involves palpable varicose veins in the scrotum during the Valsalva maneuver, grade 2 involves palpable veins without the Valsalva maneuver, and grade 3 refers to varicose veins visible without any maneuver or manipulation. Clinical varicoceles are those detected during physical examination, while sub-clinical varicoceles, characterized by veins larger than 3 mm, are only observed through Doppler ultrasound with the Valsalva maneuver. Most studies on varicoceles utilize the Dubin system for classification [6].

As noted earlier, the presence of a varicocele does not necessarily lead to fertility issues. Many men with varicoceles show no signs of testicular dysfunction, although spermatogenesis is affected in a subset of patients. Therefore, the decision to treat a varicocele should be made cautiously to avoid unnecessary invasive procedures. According to the guidelines from the American Society for Reproductive Medicine (ASRM) Practice Committee, varicocele treatment should be considered when the following conditions are met: the couple is attempting to conceive; the varicocele is palpable during a physical examination; the couple has known fertility problems; the female partner has normal fertility or a potentially treatable cause of infertility, and time to conception is not a pressing issue; and the male partner has abnormal semen

parameters. It is important to note that untreated varicoceles can have a progressively harmful effect on the testes, potentially leading to irreversible infertility [7]. Even in cases where no testicular function abnormalities are detected, regular follow-up is recommended for patients with concerns about future fertility [7]. In healthy males, the temperature of the scrotum is approximately 2°C lower than the core body temperature. When testicular temperature rises to match core body temperature, there is a decrease in both sperm count and sperm quality. Although the precise mechanism by which elevated temperature affects spermatogenesis is not fully understood, the most widely accepted theory involves thermal damage to the DNA and proteins within the nuclei of spermatid tubule cells and/or Leydig cells [8].

Studies have reported that men with varicoceles and impaired sperm quality often exhibit elevated scrotal temperatures, and varicocelectomy has been shown to restore normal scrotal temperatures [9]. It has also been suggested that the reflux of catecholamines and their metabolites from the adrenal gland into left-sided varicoceles may cause vasoconstriction and reduced testicular function, although this finding has not been consistently observed [7,8]. Additionally, venous hypertension, caused by pressure on the gonadal venous valves from a hydrostatic column, may result in chronic vasoconstriction of testicular arterioles, leading to diminished testicular function [10]. This condition can cause persistent hypoperfusion, stasis, hypoxia, and subsequent dysfunction of the spermatid epithelium [11].

Oxidative stress (OS), secondary to elevated scrotal temperatures and the production of reactive oxygen species (ROS), is another important theory gaining increasing support as an explanation for the adverse effects of varicoceles on testicular function [11,12]. Blummer et al. reported that men with varicoceles exhibit impaired mitochondrial activity and sperm DNA fragmentation [13], and oxidative stress biomarkers have been shown to decrease following varicocelectomy [14]. Several prospective and retrospective studies have also demonstrated that varicocele repair is associated with reduced sperm DNA damage [15]. Tulloch was the first to report a spontaneous pregnancy after varicocelectomy in a couple with an azoospermic male [4]. Since then, varicocelectomy has become one of the most commonly performed surgeries for the treatment of male infertility. Azoospermia, defined as the complete absence of sperm in the ejaculate, must be confirmed by centrifuging a semen specimen at 3,000 g for 15 minutes at room temperature, followed by high-powered microscopic examination of the pellet [16]. Azoospermia, which can be classified as obstructive (OA) or non-obstructive azoospermia (NOA), is found in 15% of infertile men and occurs in 4-13% of men with clinical varicoceles [17]. This study aims to evaluate improvements in semen quality and reproductive outcomes following varicocelectomy in men with non-obstructive azoospermia, to explore the relationship between non-obstructive azoospermia and surgical varicocele repair, and to assess the outcomes of sperm retrieval procedures after varicocele repair.

Methods

Study Design and Setting

This retrospective descriptive study was conducted at Misurata Medical Center and the National Infertility Center in Libya, covering the period from January 2015 to January 2017.

Participants

Data were collected from 20 azoospermic infertile men who underwent comprehensive medical evaluations, including clinical examinations, hormonal assays, scrotal ultrasound, testicular sperm aspiration (TESA), testicular sperm extraction (TESE), and varicocelectomy. The study included all cases of non-obstructive azoospermia with clinical and subclinical varicoceles that underwent varicocelectomy (either high or low ligation) and subsequent sperm retrieval procedures during this period.

Procedures

Postoperative semen analysis was performed 3 to 12 months after surgery, with cryopreservation performed for those with positive sperm counts.

Testicular Sperm Aspiration (TESA)

TESA was conducted under local or general anesthesia. A 22-G butterfly needle was inserted into the testicular tissue, and suction was applied using a 20-ml syringe to aspirate fluid, which was then checked for sperm [18]. Though primarily used for men with obstructive azoospermia, TESA was also employed in non-obstructive azoospermic men in this study. This simple, non-surgical procedure – in which a specialist inserts a needle into the testicular tissue to aspirate fluid and cells, which are then examined in the lab for viable sperm, does not require specialized equipment or training. However, since the procedure is performed blindly, there is a risk of puncturing a tunical vessel, leading to hematocele, or causing intra-testicular hemorrhage due to multiple needles passes through the testicular tissue.

Testicular Sperm Extraction (TESE)

TESE was performed under general anesthesia. A scrotal incision was made to expose the testis, the tunica albuginea was incised, and a piece of testicular tissue was excised. The tunica was then sutured, and the incision was closed. This method yields a larger tissue sample and can be performed by any surgeon. However, it is an open surgical procedure, and there is a risk of damaging testicular vessels during the incision, closure, or tissue excision, as the testicular arteries are end-arteries. Both sperm retrieval procedures were performed in cases where no sperm were found in the ejaculate.

Statistical Analysis

Data entry and statistical analysis were performed using the Statistical Program for Social Sciences (SPSS). Descriptive statistics were employed, and results are presented as frequencies, with means ± standard deviations. A p-value was calculated for the data analysis.

Results

Age group, testicular size, and hormonal distribution

In this study, the age ranged from 27 to 46 years most frequent age group was from 30 to 40 years, in 50%. And about 60% of cases had diminished testicular size. These findings are seen in (Table 1).

Table (1). Distribution of age, testicular size, and hormonal findings

Variable	Case numbers and range
Age	From 20 -30 years, 7 cases, about 35% From 30-40 years, 10 cases, about 50% More than 40 years, 3 cases, about 15%
Normal testicular u/s size	It's 8 cases within normal size measurement About 40% of the total number
Decreased testicular u/s size	12 cases from the total of about 60%
FSH reading	Less than 15 mIU/ml. 5 cases More than 15 mIU/ml. 15 cases
Testosterone reading	Less than 2.5ng/ml 17 cases More than 2.5ng/ml 3cases

Table (2). Distribution of testicular sperm aspiration results

Testicular sperm aspiration TSA	Frequency	Percent %
Negative	12	60
Positive	8	40
Total	20	100
Chi - square = 0.80		P-value = 0.371

From the above table, we see that the value of chi-square equals 0.80 with p-value = 0.371, greater than 5%, which means that they are not statistically significant.

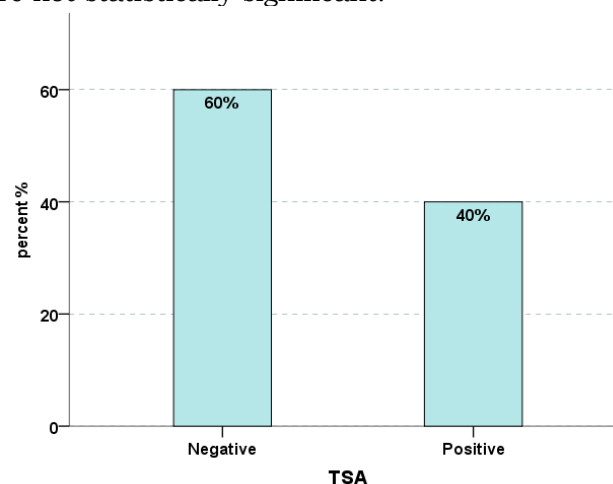


Figure 1. Distribution of testicular sperm aspiration results

Table 3. Distribution of the varicocelelectomy site

Site of Operation	Frequency	Percent %
low ligation	10	50
high ligation	10	50
Total	20	100

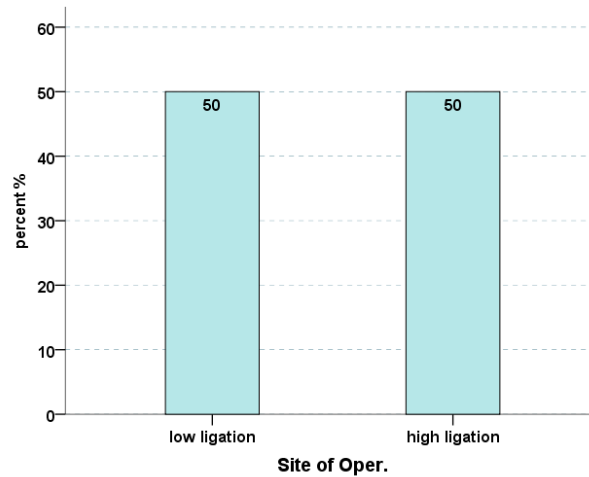


Figure 2. Distribution of the site of varicocelelectomy for non-obstructive azoospermia

Table 4. Frequency and percentage of varicocele grade

Degree of varicocele	Frequency	Percent %
2	6	30
3	7	35
4	7	35
Total	20	100

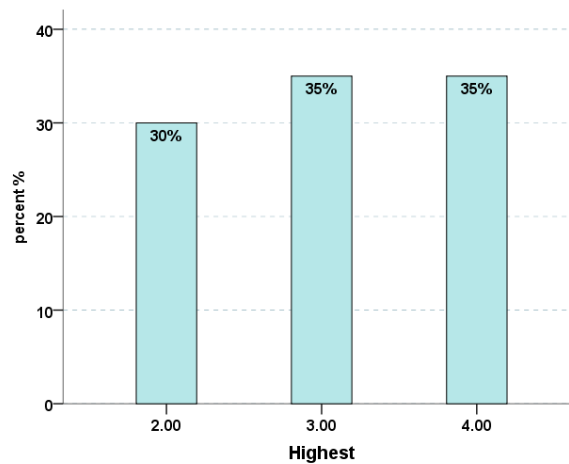


Figure 3. The grade and frequency of varicocele

Table 5. Distribution of the site of varicocelelectomy vs sperm retrieval procedures

TSA	Site of Operations		Total
	Low ligation	High ligation	
Negative	7	5	12
Positive	3	5	8
Total	10	10	20

Chi-square = 0.833 P-value = 0.361

No relationship between sperm retrieval procedures and the site of operation since the p-value is greater than 5%.

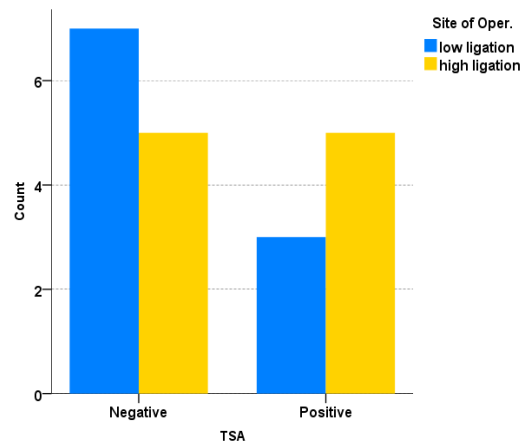


Figure 4. Site of operation and sperm retrieval procedures

Table 6. Highest grade of varicocele vs sperm retrieval

TSA	Highest			Total
	2.00	3.00	4.00	
Negative	6	3	3	12
Positive	0	4	4	8
Total	6	7	7	20

Chi-square = 5.714 P-value = 0.057

The table shows that the sperm retrieval and the highest grade of varicocele are not independent as 6% level of significance.

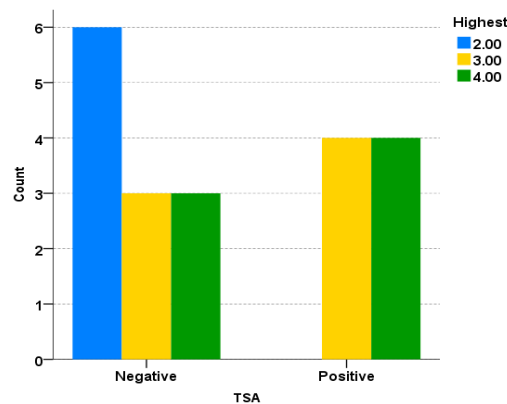


Figure (5). This diagram shows the results of the tables result showing the relationship between the degree of varicocele and the result of sperm retrieval procedures

Table (7). Summary for varicocelectomy and sperm retrieval

Site and grade of varicocele		Site and type of varicocelectomy	postoperative sperm ejaculate cryopreservation	postoperative sperm cryopreservation after TSA.TESE	Complication	ICSI trial success
Rt	Lt					
2	3	Bilateral high ligation	Negative	Positive	No	Failed 1st trial
3	3	Bilateral low ligation	Positive	-	-	Pass well ICSI
3	3	Bilateral high ligation	Negative	Negative	No	-
3	4	Bilateral low ligation	Negative	Negative	Hematoma	-
1	4	Bilateral low ligation	Negative	Positive	No	Pass well ICSI

2	2	bilateral low ligation	negative	negative	No	-
1	2	bilateral low ligation	negative	negative	Rt hydrocele	-
1	2	bilateral high ligation	negative	negative	No	-
3	3	bilateral high ligation	positive	negative	No	failed 1st trial
2	4	bilateral low ligation	positive	negative	No	pass well ICSI
1	2	bilateral low ligation	negative	negative	No	-
2	4	bilateral high ligation	negative	negative	varicocele recurrence	-
2	2	bilateral high ligation	negative	negative	No	-
3	3	bilateral high ligation	negative	negative	varicocele recurrence	-
3	4	bilateral high ligation	negative	positive	No	pass well ICSI
1	4	bilateral low ligation	negative	pv. after micro-TESE	No	-
2	3	bilateral high ligation	negative	negative	varicocele recurrence	-
3	3	bilateral low ligation	negative	positive	chronic pain	failed 1st trial
1	2	bilateral low ligation	negative	negative	No	-
2	4	bilateral high ligation	negative	negative	varicocele recurrence	-

Table (8). displays a logistic model to describe the relationship between the highest grade of varicocele and the TSA. It shows the positive relationship, so as the grade of varicocele increases, the probability of being positive (success) increases. In fact, the odds of getting positive results are 3:1 on average

Parameter	B	Std. Error	Hypothesis Test			Exp(B)	95% Wald Confidence Interval for Exp(B)	
			Wald Chi-Square	df	Sig.		Lower	Upper
(Intercept)	-4.627	2.3468	3.888	1	.049	.010	.000	.973
Highest	1.344	.7093	3.592	1	.058	3.836	.955	15.405

Discussion

The indications for varicocelectomy in men with non-obstructive azoospermia remain controversial. To our knowledge, this study consists of a pooled analysis addressing the potential benefits of varicocelectomy in men with non-obstructive azoospermia (NOA) and clinical varicocele, including sperm retrieval rates through testicular sperm aspiration (TESA) and testicular sperm extraction (TESE), as well as the presence of postoperative sperm in the ejaculate. Our results indicate that performing varicocelectomy in patients with NOA and clinical varicocele is associated with improved sperm retrieval rates [19].

Varicocele is known to have a detrimental effect on human spermatogenesis, and it is associated with male infertility. Historically, spermatogenesis has been induced and stimulated in some men following varicocele repair. Tulloch was the first to report a spontaneous post-varicocelectomy pregnancy in a couple with an azoospermic male. Since then, varicocelectomy has become the most frequently performed surgery for the treatment of male infertility [20].

In our research, all cases of azoospermia and negative sperm retrieval procedures before varicocele repair involved patients with varying degrees of varicocele. All cases underwent varicocelectomy subsequently. In three cases from the total of 20 patients, sperm appeared in the ejaculate within a period of 3 to 12 months

post-varicocele repair. These cases then underwent sperm banking and later trials of intracytoplasmic sperm injection (ICSI).

In five other cases, sperm could not be found through normal masturbation but were retrieved during sperm retrieval procedures, either through TESA or TESE. The highest percentage of varicocele cases was classified as grade 3 (about 35%) and grade 4 (also 35%). Around 50% of cases were in the age group of 30-40 years, and approximately 60% of cases had diminished testicular measurements on ultrasound. We found that most cases treated with high ligation achieved positive sperm results post-operatively. Five cases showed positive sperm results after high ligation, and three cases after low ligation varicocelectomy.

On the other hand, we found that the total of eight cases with positive results were associated with advanced-grade varicocele (grade 3 and grade 4). There is a direct correlation between the grade of varicocele and positive sperm outcomes.

Matthews et al. studied a cohort of 78 infertile men; 22 were azoospermic, and 56 were oligoasthenospermic. All patients underwent microvaricocelectomy. Post-operative semen analysis revealed that 55% of the azoospermic patients and 82% of the oligoasthenospermic patients had motile sperm. The pregnancy rate in the azoospermic group was 14% (versus 38% in the oligoasthenospermic group), and two spontaneous pregnancies occurred in the azoospermic group [1].

Beginning four months after varicocele repair surgery, Kim et al. examined 28 men with azoospermia and bilateral or unilateral varicoceles. Of the 28 men, 12 (43%) had sperm in their ejaculates, with a mean sperm count of $1.2 \pm 3.6 \times 10^6$ /ml at 24 months of follow-up. They reported two pregnancies following assisted reproductive technology (ART) treatment; however, there were no spontaneous pregnancies [21].

In a recently published prospective non-controlled study, Taha A. Abdel-Meguid reported the recovery of motile sperm in the ejaculate of 10 out of 31 (32.3%) men with NOA and clinically palpable varicoceles following subinguinal microsurgical varicocelectomy. Since 1952, numerous reports have been published on changes in sperm parameters and pregnancy rates in patients with NOA after varicocele repair. Based on these reports, 21-56% of men have motile sperm, and 0-15% of their partners achieve spontaneous pregnancies following varicocele repair. However, none of these studies included a control group [22].

Conclusion

The results of our study indicate that infertile men with non-obstructive azoospermia (NOA) and clinical or subclinical varicocele benefit from varicocelectomy. The procedure is safe for azoospermic patients; however, in a significant percentage of cases, testicular sperm retrieval is necessary.

References

1. Matthews GJ, Matthews ED, Goldstein M. Induction of spermatogenesis and achievement of pregnancy after microsurgical varicocelectomy in men with azoospermia and severe oligoasthenospermia. *Fertil Steril*. 1998;70(1):71-75.
2. Gorelick JI, Goldstein M. Loss of fertility in men with varicocele. *Fertil Steril*. 1993;59(3):613-6.
3. Esteves SC, Glina S. Recovery of spermatogenesis after microsurgical subinguinal varicocele repair in azoospermic men based on testicular histology. *Int Braz J Urol*. 2005;31(6):541-8.
4. Tulloch WS. Consideration of sterility; subfertility in the male. *Edinb Med J*. 1952;59(1):29-34.
5. Esteves SC. Clinical management of men with nonobstructive azoospermia. *Asian J Androl*. 2015;17(3):459-70.
6. Esteves SC, Miyaoka R. Sperm retrieval techniques for assisted reproduction. *Int Braz J Urol*. 2011;37(5):570-83.
7. Cozzolino DJ, Lipshultz LI. Varicocele as a progressive lesion: positive effect of varicocele repair. *Hum Reprod Update*. 2001;7(1):55-8.
8. Naughton CK, Nangia AK, Agarwal A. Pathophysiology of varicoceles in male infertility. *Hum Reprod Update*. 2001;7(5):473-81.
9. Fujisawa M, Yoshida S, Kojima K, Kamidono S. Biochemical changes in testicular varicocele. *Arch Androl*. 1989;22(2):149-59.
10. Jung A, Schuppe HC. Influence of genital heat stress on semen quality in humans. *Andrologia*. 2007;39(6):203-15.
11. Sofikitis N, Miyagawa I. Left adrenalectomy in varicocele rats does not inhibit the development of varicocele-related physiologic alterations. *Int J Fertil Menopausal Stud*. 1993;38(4):250-5.
12. Marmar JL. The pathophysiology of varicoceles in the light of current molecular and genetic information. *Hum Reprod Update*. 2001;7(5):461-72.
13. Shiraishi K, Takihara H, Matsuyama H. Elevated scrotal temperature, but not varicocele grade, reflects testicular oxidative stress-mediated apoptosis. *World J Urol*. 2010;28(3):359-64.
14. Agarwal A, Makker K, Sharma R. Clinical relevance of oxidative stress in male factor infertility: an update. *Am J Reprod Immunol*. 2008;59(1):2-11.
15. Blumer CG, Fariello RM, Restelli AE, Spaine DM, Bertolla RP, Cedenho AP. Sperm nuclear DNA fragmentation and mitochondrial activity in men with varicocele. *Fertil Steril*. 2008;90(5):1716-22.
16. World Health Organization. WHO laboratory manual for the examination and processing of human semen. 5th ed. Geneva: WHO Press; 2010.



17. Nasr-Esfahani MH, Abasi H, Razavi S, Ashrafi S, Tavalae M. Varicocele: semen parameters and protamine. *Fertil Steril*. 2009;91(4):1540-3.
18. Tournaye H, Clasen K, Aytoz A, Nagy Z, Van Steirteghem A, Devroey P. Fine needle aspiration versus open biopsy for testicular sperm recovery: a controlled study in azoospermic men with normal spermatogenesis. *Hum Reprod*. 1998;13(4):901-4.
19. Hamada A, Esteves SC, Agarwal A. Insight into oxidative stress in varicocele-associated male infertility: part 2. *Nat Rev Urol*. 2013;10(1):26-37.
20. Will MA, Swain J, Fode M, Sonksen J, Christman GM, Ohl D. The great debate: varicocele treatment and impact on fertility. *Fertil Steril*. 2011;95(3):841-52.
21. Kim ED, Leibman BB, Grinblat DM, Lipshultz LI. Varicocele repair improves sperm parameters in azoospermic men with spermatogenic failure. *J Urol*. 1999;162(3):737-40.
22. Abdel-Meguid TA. Predictors of sperm recovery and azoospermia relapse in men with nonobstructive azoospermia after varicocele repair. *J Urol*. 2012;187(1):222-6.