

# Effect of Varicocelectomy on Restoration of Spermatogenesis in Patients with Non-obstructive Azoospermia

## Non-obstruktif Azoospermik Erkeklerde Varikoselektominin Spermatogenez Restorasyonuna Etkisi

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### What's known on the subject? and What does the study add?

The efficiency of varicocelectomy is one of the challenging subject for patients with non-obstructive azoospermia. In this study, testicular volume and free testosterone levels were found to be predictive factors for recovery of spermatogenesis after varicocelectomy even though they have a weak association.

### Abstract

**Objective:** The aim of this study was to investigate the effect of varicocelectomy on spermatogenesis in patients with non-obstructive azoospermia (NOA) and the presence of clinical factors for re-spermatogenesis.

**Materials and Methods:** A total of 32 patients with clinically significant varicocele, who received the diagnosis of infertility, were included in this study. Microsurgical inguinal varicocelectomy and testicular biopsy were performed in all patients. After varicocelectomy, control spermogram samples were collected from patients at 3<sup>rd</sup>, 6<sup>th</sup> and 12<sup>th</sup> months. The role of age, testicular volume, hormone parameters and pathological findings in predicting re-spermatogenesis were investigated.

**Results:** The mean age of the patients who underwent surgery was 31.4±6.2 years. After varicocelectomy, sperm was detected in semen in 15.6% (5/32) of the patients. As a result of pathological evaluation, hypospermatogenesis, maturation arrest and germ cell aplasia were found in 34.4%, 31.2% and 34.4% of patients, respectively. The testicular volume was higher in patients with re-spermatogenesis (p=0,01). There was no statistically significant difference between responders and non-responders in terms of other investigated parameters.

**Conclusion:** Varicocelectomy is an acceptable modality of treatment for patients with NOA with clinically significant varicocele. On the other hand, appropriate patient selection is crucial. In this study, testicular volume was found to be a predictive factor for recovery of spermatogenesis after varicocelectomy.

**Keywords:** Infertility, Non-obstructive azoospermia, Varicocelectomy

### Öz

**Amaç:** Bu çalışmanın amacı obstruktif olmayan azospermisi (OOA) olan hastalarda varikoselektominin spermatogenez etkisini incelemek ve re-spermatogenez öngören klinik faktörlerin varlığını araştırmaktır.

**Gereç ve Yöntem:** Klinik anlamlı varikozel saptanarak infertilite tanısı alan 32 hasta çalışmaya dahil edildi. Bütün hastalara mikrocerrahi inguinal varikoselektomi ve aynı seansta testis biyopsisi uygulandı. Postoperatif 3, 6 ve 12. aylarda hastaların spermogram kontrolleri yapıldı. Yaş, testis hacmi, hormon parametreleri ve patolojik bulguların operasyon sonrası sperm üretimini öngörmede etkinliği araştırıldı.

**Bulgular:** Hastaların cerrahi zamanındaki ortalama yaşı 31,4±6,2 idi. Varikoselektomi sonrası hastaların %15,6 (5/32)'sinde spermogram ile sperm varlığı tespit edildi. Patolojik değerlendirme sonucunda sırasıyla %34,4, %31,2 ve %34,4 oranlarında hipospermatogenez, matürasyon arresti ve germ hücre aplazisi tespit edildi. Re-spermatogenez saptanan hastaların testis hacimleri daha büyüktü (p=0.01). Re-spermatogenez saptanan ve saptanmayan hastalar arasında araştırılan diğer parametreler açısından istatistiksel anlamlı fark yoktu.

**Sonuç:** Varikoselektomi, klinik olarak anlamlı varikozeli olmayan OOA olan hastalarda kabul edilebilir bir tedavi yöntemidir. Diğer taraftan doğru hasta profilinin seçimi çok önemlidir. Bu çalışmada varikoselektomi sonrası spermatogenezin öngörülmesinde testis hacminin prediktif değeri gösterilmiştir.

**Anahtar Kelimeler:** İnfertilite, Obstruktif olmayan azospermi, Varikoselektomi

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**Received:** 9.10.2018

**Accepted:** 6.12.2018

**Cite this article as:** Özman O, Çitgez S, Şimşekoğlu F, Selçuk B, Özden SB, Özkara H. Effect of Varicocelectomy on Restoration of Spermatogenesis in Patients with Non-obstructive Azoospermia. J Urol Surg 2019;6(2):130-134.

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## Introduction

Varicocele is one of the common causes of male infertility. It is seen in 15% of the normal population and in 40% of patients with infertility (1). Varicocelectomy is the most common surgical procedure for infertility. On the other hand, azoospermia is detected in 10–15% of infertile patients (2). The presence of varicocele is observed in 4–13% of azoospermic patients (3). This distinct clinical association has led to the idea that varicocele may be the cause of azoospermia and therefore the treatment of azoospermia with varicocelectomy may be possible. Tulloch (4) have shown for the first time that sperm can be detected in ejaculate after varicocelectomy in an azoospermic patient with varicocele. Even though half a century has passed after this report had been published, effect of varicocelectomy on patients with non-obstructive azoospermia (NOA) is still controversial. Criteria for decision making whether varicocelectomy should be performed or not for a patient diagnosed with clinically significant varicocele presenting with NOA is still ambiguous (5). It is important to identify patients in whom varicocelectomy will not be effective in order to prevent any delay in obtaining definitive results with assisted reproductive techniques. Clinical parameters are needed to help effective patient selection. Testicular biopsy may provide parameters for this purpose. Aboutaleb et al. (2) showed that patients with hypospermatogenesis were more likely to benefit from varicocelectomy. The predictive value of age, testicular volume and hormonal parameters, such as follicle stimulating hormone (FSH), luteinizing hormone (LH) and total testosterone (TT), has also not yet fully revealed. The aim of this study was to investigate the effect of varicocelectomy on spermatogenesis in NOA azoospermic patients and the presence of clinical factors for re-spermatogenesis.

## Materials and Method

After the ethics committee approval (ethical committee approval number: 83045809/604.01/02-171680), this prospective study including 32 patients prediagnosed with infertility presenting with varicocele and NOA was conducted between January 2016 and June 2018 in Cerrahpaşa Medical Faculty. The diagnosis of azoospermia was made by at least two spermograms made by the same biologist. None of the patients had physical examination and imaging findings in favor of obstruction. Spermogram samples were collected after a 3 days sexual abstinence. There were 3 weeks between two spermograms. The absence of sperm cells in centrifuged pellets was accepted as azoospermia. In addition, the patients were examined for the presence of clinically significant varicocele according to the World Health Organization criteria. Every patient in the study was examined by two different urologist for the presence of

varicocele. Bilateral varicocele was considered high-grade varicocele. Genetic evaluation was performed in all patients in accordance with the current European Urology Association guidelines for male infertility. Karyotype analysis and Y chromosome microdeletion assays were done. Serum levels of FSH, LH and TT were measured. Bilateral testicular volumes were determined by scrotal ultrasonography.

After the surgical intervention, control spermogram samples at 3<sup>rd</sup>, 6<sup>th</sup> and 12<sup>th</sup> months were examined by the medical biologist who made the preoperative evaluation. The patients were divided into two groups according to the presence of sperm in the spermogram after varicocelectomy. Two groups were compared in terms of age, testicular volume, FSH, LH, TT and pathological findings.

## Surgical Technique

Inguinal microsurgical varicocelectomy and testicular biopsy procedures were performed in all patients. A 3-cm skin incision was made in the groin region. After fascia incision, the spermatic cord was elevated with a Babcock clamp. A surgical microscope (Leica Microsystems®) was used for microsurgical technique. Dilated spermatic veins were ligated and transected. Lymphatics and arteries were preserved. Testicular biopsy was performed at the same session. The scrotal layers were dissected until the tunica albuginea was reached. A 1-cm transverse incision was performed on the anterior scrotal skin. and the testicular tissue was excised. All biopsies were evaluated by the same uropathologist.

## Statistical Analyses

Student's t-test and chi-square test were used for univariate statistical analyses of the collected data. The data was analyzed with the Statistical Package for the Social Sciences v. 16 (SPSS Inc, Illinois, USA). A p value of less than 0.05 was considered statistically significant.

**Table 1. Characteristics of patients**

Characteristic	All (n=32)	Responders (n=5)	Non-responders (n=27)	p
Age (year)	31.4±6.2	29.8±5.8	31.7±6.2	0.52
Testis volume (mL)	-	-	-	-
Right	7.5±3.4	9.4±3.5	7.2±3.4	0.09
Left	6.9±3.5	10.0±3.6	6.4±3.5	0.01
FSH (mIU/mL)	17.9±11.9	15.2±13.8	18.6±11.9	0.56
LH (mIU/mL)	8.4±3.6	7.4±4.5	8.6±3.6	0.51
Total Testosterone (ng/dL)	414.1±210.5	405.5±185.6	440.3±210.5	0.66

FSH: Follicle-stimulating hormone, LH: Luteinizing hormone

## Results

The mean age of the patients at the time of surgery was  $31.4 \pm 6.2$  years. The mean testicular volume and hormone profiles of the patients are summarized in Table 1. When the patients were divided into two groups according to the presence of sperm in postoperative spermograms, a statistically significant difference was found between the two groups in terms of median left and right testicular volume ( $p=0.01$  and  $p=0.09$ , respectively). Patients with recovery of spermatogenesis were found to have higher testicular volume. There was no statistically significant difference in age, FSH, LH and TT levels between responders and non-responders.

Grade 1, 2 and 3 varicocele was detected in 10 (31.3%), 19 (59.2%) and 3 (9.3%) patients, respectively. Bilateral varicocele was found in 34.4% of patients (11/32). One patient had right-sided, and the rest of the patients had left-sided varicocele. Two patients had secondary infertility and 5 patients had recurrent varicocele. The detailed varicocele examination findings of the patients are shown in Table 2. Two patients had a history of unilateral orchiectomy. Re-spermatogenesis was not observed after varicocele repair in these two patients. The only patient who underwent right varicocelectomy had a history of left orchiectomy.

Pathological examinations of the testicular biopsy specimens revealed hypospermatogenesis, maturation arrest and germ cell aplasia in 34.4%, 31.2% and 34.4% of patients, respectively. There was no statistically significant difference in pathological diagnosis between the responders and non-responders (Table 3).

There were no postoperative and peroperative complications associated with varicocelectomy performed concurrently with testicular biopsy. Patients were followed for 12 months postoperatively. During this follow-up period, the spermogram samples have yielded that 15.6% (5/32) patients had recovery of spermatogenesis. Re-spermatogenesis rates in 3<sup>rd</sup>, 6<sup>th</sup> and

12<sup>th</sup> months were 9%, 12.5% and 15.6%, respectively. Amongst these patients, 1 patient had hypospermatogenesis, 2 patients had maturation arrest and 2 patients had germ cell aplasia.

## Discussion

Currently, there is no known medical or surgical treatment for idiopathic azoospermia. Men with azoospermia due to spermatogenic failure can only have children with the help of surgical methods and assisted re-productive techniques. Varicocele is common in the community and varicocelectomy is the most common surgical intervention for varicocele-associated infertility (1). The coexistence of these two clinical conditions makes varicocelectomy a treatment option for azoospermia.

Matthews et al. (6) reported the presence of motile sperm in the ejaculate after varicocelectomy in 55% of 22 patients with azoospermia. Gat et al. (7) have shown that varicocelectomy may spare in more than 50% of azoospermic patients the need for testicular sperm extraction as preparation for intracytoplasmic sperm injection. In their study including 31 males, only 9.6% of patients had adequate motile sperm in the ejaculate after varicocelectomy (8). In a systematic review and meta-analysis of 468 NOA patients who underwent varicocelectomy, it was reported that sperm was found in postoperative ejaculates in 43.9% of 344 patients (9). In our study, sperm was detected in ejaculate in 15.6% of patients (5/32).

Conflicting data on the relationship between varicocele grade and postoperative re-spermatogenesis suggests that the relationship between varicocele and azoospermia may be more complex. Probably the toxic effects of varicocele over time reach a plateau where the restoration potential of spermatogenesis is completely eliminated. The high rates of re-spermatogenesis obtained by Matthews et al. (6) can be explained by the high grade and bilateral varicocele in the series. The rate of re-spermatogenesis in a study by Zampieri et al. (10), which only included azoospermic patients with grade 3 varicocele, was similar to that in the above study. In our series, only 3 patients had grade 3 varicocele, and the bilaterality rate was low (34.4%). It is deduced that sperm detection in our study would be lower than in other studies due to that particular reason. On the other hand, there are studies suggesting that there is no relationship between varicocele degree and post-varicocelectomy re-spermatogenesis (11,12). Finally, a meta-

**Table 2. Varicocele grades of groups**

Characteristic	Grade 1	Grade 2	Grade 3	p
Number of patients (n=32)	10 (31.3%)	19 (59.4%)	3 (9.3%)	-
Responders (n=5)	0 (0%)	5 (100%)	0 (0%)	0.52
Non-responders (n=27)	10 (37%)	14 (51.8%)	3 (11.2%)	-

**Table 3. Pathological findings**

Pathological diagnosis	All (n=32)	Responders (n=5)	Non-responders (n=27)	p value
Hypospermatogenesis	11 (34.4%)	1 (20%)	10 (37%)	-
Maturation arrest	10 (31.2%)	2 (40%)	8 (29.6%)	0.76
Sertoli cell only	11 (34.4%)	2 (40%)	9 (33.4%)	-

analysis of the data of five different studies showed that the rate of postoperative sperm retrieval was not increased with increasing varicocele grade. Varicocele may just be an incidental finding rather than an etiological element for most of the cases (5). Therefore, for appropriate patient selection, the parameters of the spermatogenic failure caused by varicocele should be enlightened.

In studies examining the relationship between NOA and varicocelectomy, certain predictive factors have been thoroughly researched. In the literature, some of the studies suggested that patients with a high level of FSH may not benefit from varicocelectomy (13). Ishikawa et al. (11) has conjectured that FSH was not a reliable parameter for predicting the outcome of varicocelectomy. In our study, lower FSH levels were found in patients who had viable sperms in their ejaculates after the surgery. However, no statistically significant difference was found in mean FSH levels between the two groups ( $p=0.56$ ). Similarly, other hormonal parameters did not show a significance to be used as predictive factors in future studies. Aboutaleb et al. (2) found no correlation between serum LH and TT levels and re-spermatogenesis after varicocelectomy. Similar results were obtained in our study.

The predictive value of testicular volume was also frequently investigated. In a study including NOA patients with grade 2 and 3 varicocele, no statistically significant relationship was found between post-varicocelectomy sperm production and testicular volume (14). Similar findings were found in a meta-analysis conducted in 2010 (15). Unlike reported cases in the literature, the testicular volume was higher in the re-spermatogenesis group compared to non-responder group in our study ( $p=0.01$ ).

In their meta analysis, Esteves et al. (9) reported that in 8 of the included studies, in a total of 161 patients, the rate of positive postoperative ejaculate in hypospermatogenesis patients was found to be statistically higher compared to those with sertoli cell only and maturation arrest. It was emphasized that the only prognostic factor to consistently predict obtaining viable sperm in an ejaculate collected after varicocelectomy was testicular histopathology. Amongst the patients responding to varicocelectomy in our study, 1 had histospermatogenesis, 2 had maturation arrest and 2 had germ cell aplasia. However, there was no statistically significant difference in pathological diagnosis between the responders and non-responders ( $p=0.76$ ).

### Study Limitations

In this study, we researched the effect of varicocelectomy on spermatogenesis in patients diagnosed with NOA and we defined the predictive factors favorable for recovery of spermatogenesis. Even though testicular pathology is found to be a relatively stronger predictive factor it is not always possible

to obtain biopsy samples manifesting the sperm production in the whole testes. Our study has certain limitations. Firstly, the number of patients was limited. Furthermore, the relatively low number of patients with advanced varicocele made it difficult to demonstrate the relationship between azoospermia and varicocele. Also it should not be forgotten that the number of studies performed on that particular patient group are few in the literature. In short, we believe that the results of this study will contribute to the literature. Future large-scale prospective studies are warranted.

### Conclusion

Varicocelectomy is an acceptable modality of treatment for non-obstructive azoospermic patients with clinically significant varicocele. On the other hand, appropriate patient selection is crucial. In this study, testicular volume was found to be a predictive factor for recovery of spermatogenesis after varicocelectomy.

### Ethics

**Ethics Committee Approval:** Ethical committee approval was given by Cerrahpaşa Medical Faculty (approval number: 83045809/604.01/02-171680).

**Informed Consent:** Consent form was filled out by all participants.

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions:

Surgical and Medical Practices: S.Ç., H.Ö., Concept: S.Ç., H.Ö., O.Ö., Design: O.Ö., S.Ç., Data Collection or Processing: M.F.Ş., S.B.Ö., B.S., Analysis or Interpretation: S.Ç., O.Ö., M.F.Ş., Literature Search: B.S., O.Ö., Writing: S.Ç., M.F.Ş., H.Ö., O.Ö.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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