

Should azoospermic patients with varicocele disease undergo surgery to recover fertility?

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SUMMARY

Introduction: Varicocele disease is well-known cause of infertility in men. The presence of spermatic varices veins create a hostile environment to spermatogenesis. It results in reduced quality of the sperm production and in some cases can determine a total absence of sperm. The varicocelectomy procedure in patients with non-obstructive azoospermia (NOA) can raise the rates of sperm in the semen analysis. A positive rate for sperm, even if very low, may be sufficient to enable the capture of sperm intended for in-vitro fertilization without the use of donor sperm.

Objective: To evaluate the raise of sperm in NOA patients with varicocele disease who were submitted to a bilateral procedure to recovery sperm production.

Method: We analyzed the sperm results of 25 NOA patients who undergone to a bilateral varicocelectomy procedure.

Results: From a total of 25 patients, three (12%) recovered sperm count four months after procedure. One year after the procedure, five (20%) patients recovered sperm production.

Conclusion: Patients with varicocele disease and azoospermia, without genetic changes or obstruction of the spermatic tract, should undergo surgical procedure to recover sperm.

Keywords: azoospermia, infertility, varicocele, surgery.

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INTRODUCTION

Should azoospermic patients with varicocele be operated? In cases of marital male infertility evaluation, absence of sperm on a sperm test is often a frustrating and devastating result for the couple. The azoospermic “couple” is referred to an assisted reproductive program many times already condemned to resort to the use of a sperm donor. However, something else can be offered to these patients. An etiological diagnosis should be performed and, depending on the cause, treatment options can be offered. The diagnosis of varicocele disease in an azoospermic patient justifies the resection of spermatic veins to improve spermatogenesis.

OBJECTIVE

To evaluate patients with non-obstructive azoospermia (NOA) and varicocele undergoing bilateral surgical correction for recovery of sperm production.

METHOD

In a retrospective study conducted from 2002 to 2015 at a private urologic service, we analyzed 25 patients with combined varicocele and azoospermia (the inclusion criteria). The patients had two consecutive sperm samples showing absence of sperm cells, collected within an interval of 3 to 5 days. The semen volume should be greater than 3 mL in the studied group. Physical examination identified presence of vas deferens and uni or bilateral varicocele. The results of laboratory tests of FSH, LH, total testosterone and fructose were within the normal range. All selected patients underwent karyotyping and Y-chromosome microdeletion analysis. All 25 patients underwent bilateral surgical repair of varicocele. Sub-inguinal approach assisted by loupe magnification was performed by the surgical team. They all received the pre-surgical guidelines and signed an informed consent form. Patients were discharged from the hospital on the same day as the surgical procedure. The

first sperm count was conducted 60 days after surgery, and subsequently repeated every 60 days.

RESULTS

Of the 25 patients, 10 (40%) presented bilateral varicocele on physical examination. Left varicocele was identified in nine (36%) patients, and six (24%) had right-sided varicocele only.

Sperm was found in three (12%) patients treated surgically, four months after the procedure. Six months after surgery, sperm was identified in five (20%) patients. After one year of follow-up, only five (20%) patients had sperm in the ejaculate (Table 1). None of the five patients presented testicular volume reduction in pre-op. The concentration of sperm in the patients operated reached 0.5 to 12 million/mL (Vr > 20 million/mL). Out of the total of 25 patients, three (12%) had changes in karyotype, and two (8%) had Y-chromosome microdeletions.

DISCUSSION

The male factor is responsible for about 40% of cases of marital infertility. A diagnosis of azoospermia is made in up to 15% of infertile men.^{1,2,4,6,7} Non-identification of sperm in the semen should always be investigated. A differential diagnosis between obstructive and non-obstructive azoospermia is fundamentally important for the treatment and prognosis of patients.^{1,2,4,8} FSH, LH, total testosterone and estradiol levels combined can demonstrate the testicular function. Last but not least, measuring the level of fructose in semen offers evidence for obstructive diagnosis.^{1,2,4,6,8}

Researching the medical history is crucial and can guide the diagnosis:

1. history of cryptorchidism in childhood and if and when it was corrected;
2. history of sexually transmitted diseases;
3. previous contact with gonadal-toxic agents or the use of exogenous androgen, very common in the absence of sperm;
4. story of retrograde ejaculation (in diabetics, patients with bladder voiding disorders, changes in patients undergoing prostatic surgeries) will identify patients with sperm in post-ejaculation urine analysis.

Karyotype analysis showed 15% of changes in azoospermic patients in the studied group. Regarding changes in karyotype, Klinefelter syndrome is one of the most frequent genetic alterations in azoospermic patients.^{1,5-7,12,13} Y-chromosome microdeletions can be expected in approximately 15 to 20% of patients with NOA. The Y-chromosome is responsible for determining the male gender and features three regions known as AZFa, AZFb, AZFc. That is where the information for the production and maturation of sperm cells can be found.^{1,5-7,12} This evaluation is truly important because patients referred for assisted reproduction can transmit genetic disorders in the absence of genetic counseling. These patients are unlikely to benefit from varicocelectomy.^{4,6,8,11-13}

On physical examination, identification of the vas deferens is fundamental. The presence of ectopic testicles or testicles with reduced volumes can be indicative of testicular failure or poor response to surgical procedure. These patients have a poorer prognosis.^{1,3,4,9}

Until recently, the presence of varicocele was not acknowledged in these patients. Varicocele repair should not be considered in obstructive seminiferous tubules. It has a prevalence of 15% in the general population and occurs in 30 to 40% of infertile patients.¹⁻⁴

A diagnosis is made during the physical exam with the patient being brought to a standing position, at room temperature. Doppler ultrasound can be used as a supplementary method.¹⁻³

Varicocele is a vascular disease that affects testicular veins. Its presence causes an inappropriate environment for the production and development of sperm.¹⁻⁴ The disease can change the concentration, motility, morphology and structure of sperm DNA.¹⁻⁴

Pathological sperm vein reflux leads to the accumulation of CO₂ and free radicals, lowering local concentrations of O₂, which affects the functioning of Leydig cells and Sertoli cells. These cells are responsible for the production of testosterone and sperm, respectively. The varicocele can cause atrophy and calcification, hindering cell development and espermatogenesis.^{1-3,5,6,11-13}

TABLE 1 Results of the sperm analysis after varicocelectomy.

Varicocele	Cases treated surgically	%	Sperm positive 4 th month	Sperm positive 6 th month	Sperm positive 12 th month
Bilateral	10	40			
Left	9	36	3 patients	5 patients	5 patients
Right	6	24			
Total	25	100	12%	20%	20%

Note that even one year after surgery, the rate of sperm recovery was not greater than 20%.

In the studied group, 25 patients underwent bilateral procedure, although only ten presented bilateral varicocele veins. Out of 25 patients operated, five (20%) benefited from varicocelectomy. Despite not reaching a minimum concentration of sperm, i.e. 20 million/mL, the recovery of spermatogenesis allowed the use of the patient's own semen for assisted fertilization techniques.^{5,6,8-10,13}

Semen cryopreservation was suggested to five patients. None of the patients who recovered some production presented testicular volume reduction, noting that testicular volume reduction can be a prognostic of poorer

results.^{1,8,9} Patients with no sperm found in the sperm control exam were referred to a human assisted reproduction service.

The five patients with genetic changes were advised of the possibility of choosing a sperm donor.

The other 15 patients with a diagnosis of idiopathic azoospermia were advised to undergo TESE, micro-TESE, TESA and PESA. These techniques are used to collect sperm from the testicle or epididymis. The sperm sample could be used for cryopreservation or assisted reproductive procedures (Table 2).^{1,7-9,12-16}

TABLE 2 Findings and actions after one year of varicocelectomy.

Varicoceles operated	n	%	Patients with sperm retrieved	With alterations in the karyotype	With Y-chromosome microdeletions	Idiopathic patients
Bilateral	10	40	5 patients	3 patients	2 patients	15 patients
Left	9	36				
Right	6	24				
Total	25	100	20%	12%	8%	60%
Actions			Cryopreservation of sperm	Use of sperm donor	TESA PESA TESE	
			Human reproduction service			

Note that 1/5 of the operated patients can use their own sperm.

CONCLUSION

Patients with varicocele and azoospermia and without genetic changes or obstruction should be treated surgically with varicocelectomy.

Although small, the postoperative recovery of sperm would allow the couple to undergo assisted reproductive procedures without the need of a sperm donor. Thus, patients with NOA associated with varicocele veins should be made aware of the small chance of success in recovering sperm production after surgery, and of the purpose of surgery.^{7-13,16}

CONFLICT OF INTEREST

The authors declare no conflict of interest.

RESUMO

Pacientes com azoospermia e varicocele devem ser submetidos à cirurgia para recuperar a fertilidade?

Introdução: A varicocele é sabidamente uma das causas de infertilidade nos homens. A presença de veias espermáticas dilatadas pode criar um ambiente hostil para a espermatogênese. Isso é causa de baixa qualidade e quantidade da produção do esperma; em alguns casos, pode determi-

nar uma ausência total de espermatozoides. O procedimento de varicocelectomia em pacientes com azoospermia não obstrutiva pode aumentar as taxas de espermatozoides na análise do sêmen. Uma taxa positiva para o esperma, mesmo se muito baixa, pode ser suficiente para permitir a coleta e destinar-se ao processo de fertilização *in vitro*. Isso sem a necessidade de usar esperma de doador.

Objetivo: Avaliar o aumento de espermatozoides em pacientes com varicocele associada à azoospermia não obstrutiva.

Método: Foram analisados os espermatozoides de 25 pacientes azoospermicos não obstrutivos submetidos a procedimento de varicocelectomia bilateral com magnificação microcirúrgica.

Resultados: De um total de 25 pacientes, em três (12%) ocorreu recuperação da contagem de espermatozoides quatro meses após o procedimento. Após um ano de procedimento, em cinco (20%) ocorreu a recuperação.

Conclusão: Pacientes com ausência de espermatozoides e varicocele, sem alterações genéticas, devem ser submetidos a tratamento cirúrgico a fim de recuperar a produção de espermatozoides.

Palavras-chave: azoospermia, infertilidade, varicocele, cirurgia.

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