Infertile men with varicocele alone and varicocele with coexistent non-obstructive azoospermia have completely different clinical, hormonal and sperm profiles.

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ABSTRACT: *Objective.* The aim of this study was to analyze the epidemiological, clinical, hormonal and sperm parameters in men with varicocele and to evaluate possible changes in sperm parameters after varicocelectomy.
Patients and Methods. We accessed clinical, hormonal, sperm and cytological parameters from medical records of the men examined in the outpatient infertility clinic between 1991–2005. Inclusion criteria were either clinically apparent varicocele or a history of varicocelectomy (Study 1). In a subgroup of men, data were available before and after varicocelectomy (Study 2).
Results. In 64% of men varicocele was the only cause of infertility, whereas in 36% other additional causes were found. There were statistically significant differences between men with varicocele only and idiopathic non-obstructive azoospermia (INOA) plus varicocele, regarding testicular volume, Follicle Stimulating Hormone (FSH) levels and sperm parameters (Study 1). In men with varicocele only, Sperm Index was the only parameter that showed statistically significant increase after varicocelectomy (Study 2).
Conclusions. Varicocele alone and INOA with coexistent varicocele have completely different clinical, hormonal and sperm profiles.

Key Words: Varicocele, Male infertility, Varicocelectomy, Varicocele repair.

INTRODUCTION

Infertility is a very common condition as it affects 15% of couples of reproductive age. In 40-50% of the cases infertility is exclusively or partly due to male factor[1]. The most common cause of male infertility is idiopathic, a condition in which one or more sperm parameters are abnormal with no identifiable cause[2]. The second most common finding in infertile men is varicocele; in a European study of 7802 infertile men[3] varicocele was found in 16.6%, whereas in a similar Greek study 21% of infertility was attributed to varicocele[4].

In 1952 Tulloch was the first to report improvement of sperm parameters and pregnancy achievement after bilateral varicocelectomy in an azoospermic man[5]. Several studies followed, so that varicocelectomy via ligation became the most common operation for male infertility. However, the pathogenesis and pathophysiology of varicocele as well as its relationship to infertility has not been fully elucidated. In addition, clinical trials concerning treatment effectiveness show conflicting results and varicocelectomy has been criticized especially under the light of Evidence-Based Medicine (EBM). The introduction of Intra-Cytoplasmic Sperm Injection (ICSI) as an effective method of assisted reproduction in cases of male infertility has questioned the methods used until now[6]. Therefore, varicocele still remains one of the most controversial issues in the field of Andrology.

The objectives of this study were to analyze the epidemiological, clinical, hormonal, sperm and cytological parameters in men with varicocele and to

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evaluate the changes in sperm parameters after varicocelectomy.

PATIENTS AND METHODS

Patients. Medical records of 925 men who were examined in the outpatient infertility clinic of the Unit of Reproductive Endocrinology between 1991 and 2005 were evaluated retrospectively. Men having either a clinically apparent varicocele on the day of physical examination or a surgically repaired varicocele in their personal history were included in the study (Study 1). In a subgroup of men, data were available before and after varicocelectomy, thus making possible to study the effects of the operation on sperm (Study 2).

In both studies of this work, emphasis was given to the presence of additional causes of male infertility on top of varicocele, especially Idiopathic Non-Obstructive Azoospermia (INOA). The diagnosis of INOA was considered in cases of men with decreased testicular volume (<15 cm^3), high Follicle Stimulating Hormone (FSH) values (at least twice the maximum normal value) and azoospermia or severe Oligo-Astheno-Teratozoospermia (OAT). In those cases, varicocele was considered a coincidental finding rather than the main cause of infertility.

Methods. Studied parameters included age of male and female partners, type and duration of infertility, testicular volume, side and grade of varicocele, side of varicocelectomy and time since operation, serum levels of FSH, Luitenizing Hormone (LH), prolactin and testosterone, sperm parameters and cytological findings of testicular FNA (Fine Needle Aspiration).

Semen samples were collected by masturbation after 3-5 days of abstinence from ejaculation. At least two semen samples were obtained from each man approximately 3 months apart. Semen analysis was performed manually and included measurement of the volume of the ejaculate and determination of the sperm concentration, motility and morphology according to the World Health Organization criteria[7]. Sperm concentration less than or equal to 20 10^6/mL, sperm motility at first hour less than or equal to 50% and normal sperm morphology less than or equal to 30% were considered abnormal.

On top of classic sperm parameters, Sperm Index (SI) was evaluated as well. SI offers a single number overview of the sperm quality, calculated by the formula: SI = sperm volume (mL) x sperm concentration (10^6/mL) x sperm motility at first hour (%) [World Health Organization (WHO) categories a and b] x normal sperm morphology (%)/10.000[8]. According to the WHO criteria for sperm parameters[7], SI values above 6 are considered normal.

All studied parameters were determined once in Study 1 men (before varicocelectomy in men who underwent operation) and twice in Study 2 patients (before varicocelectomy and approximately one year after).

Statistics. Data were described as median and interquartile range (IQR), due to non-parametric distribution of the values. Comparison between groups was performed by Mann-Whitney U test. Comparison within groups (before and after varicocelectomy) was performed by the Wilcoxon Signed Rank test. A p-value of less than 0.05 was considered statistically significant. Data analysis was made with the SPSS 13 software (SPSS Inc., Chicago, Ill.).

RESULTS

Study 1. Four hundred twenty-nine men met the inclusion criteria for Study 1. Of those, 277 (65%) were included because clinical varicocele was found during physical examination and the remaining 152 (35%) because they had a personal history of varicocelectomy.

Sixty-five percent of men had primary infertility, 25% had secondary infertility and 10% wanted to check their fertility status. The median duration of infertility was 3.0 years (IQR 3.5). Varicocele was found on the left side in 61% of men, on the right side in 4% and bilaterally in 35%. Of the men having a left varicocele, in 34 (11%) was of first grade (palpable after a Valsalva manoeuver), in 261 (85%) of second grade (palpable at the upright position) and in 12 (4%) of third grade (visible). Of the men having a right varicocele, in 22 (18%) was of first grade, in 103 (82%) of second grade, while no third grade varicocele was found. Regarding men with a history of varicocelectomy, operation on the left side had been performed on 84 (55%), on the right side on 3 (2%) and bilaterally on 65 (43%). The median time since varicocelectomy was 2.0 years (IQR 3.4). The epidemiological, clinical, hormonal and sperm parameters of all studied men are displayed in Table 1.

Table 1. Epidemiological, clinical, hormonal and sperm parameters of studied men. Data are described as median (IQR).

Age of the male (years)	33.0 (7.0)
Age of the female (years)	33.0 (8.0)
Mean testicular volume (cm^3)	23.0 (6.0)
FSH (mIU/mL)	6.8 (6.6)
LH (mIU/mL)	6.0 (4.6)
Prolactin (ng/mL)	6.6 (5.7)
Testosterone (ng/dL)	506 (285)
Sperm	
Volume (mL)	3.5 (2.1)
Concentration (10^6/mL)	19.0 (34.0)
Motility at first hour (%)	30.0 (40.0)
Normal morphology (%)	25.0 (28.0)

Table 2. Diagnostic classification of studied men.

Diagnosis	Number of men (n)	Percentage (%)
Varicocele only	272	64
Varicocele plus infection	77	18
Varicocele plus INOA	40	9
Varicocele plus cryptorchidism	16	4
Varicocele plus obstruction	7	2
Varicocele plus other causes	17	3
Total	**429**	**100**

Table 3. Clinical, hormonal and sperm parameters of men with varicocele only or INOA plus varicocele. Data are described as median (IQR).

Parameter	Varicocele only	Varicocele plus INOA	p-value
Mean testicular volume (mL)	23.5 (5.0)	13.5 (8.0)	< 0.001
FSH (mIU/mL)	6.5 (5.5)	16.2 (19.0)	< 0.001
LH (mIU/mL)	5.6 (4.3)	8.1 (8.2)	0.001
Prolactin (ng/mL)	6.0 (5.2)	10.7 (11.2)	0.007
Testosterone (ng/dL)	537 (250)	366 (353)	0.110
Sperm			
Volume (mL)	3.7 (2.0)	3.0 (1.5)	0.118
Concentration (10^6/mL)	23.0 (30.5)	0.6 (1.6)	< 0.001
Motility at first hour (%)	30.0 (39.0)	0.0 (5.0)	< 0.001
Normal morphology (%)	25.0 (31.0)	0.0 (10.0)	< 0.001
Sperm Index	6.5 (28.0)	0.0 (0.0)	< 0.001

Of the 429 men fulfilling the inclusion criteria, in 272 (64%) varicocele was considered as the only cause of infertility, whereas in the rest 157 (36%) an additional cause was found (Table 2). Two subgroups of men, those with varicocele only and those with INOA plus varicocele were further studied. Table 3 demonstrates the significant differences in the main clinical, hormonal and sperm parameters between men with varicocele only and men with INOA plus varicocele.

On table 4 sperm diagnoses are presented in men with varicocele only or INOA plus varicocele. Men with varicocele only had more frequently normal

Table 4. Sperm diagnoses in men with varicocele only or INOA plus varicocele. Data are described as number of men (percentage).

Sperm diagnosis	Varicocele only	Varicocele plus INOA
Normozoospermia	65 (28)	1 (3)
Asthenozoospermia only	26 (12)	0 (0)
Teratozoospermia only	6 (2)	0 (0)
Astheno-teratozoospermia	27 (12)	0 (0)
Oligo-Astheno-teratozoospermia		
Mild	41 (18)	3 (9)
Moderate	34 (15)	2 (6)
Severe	26 (12)	19 (56)
Azoospermia	3 (1)	9 (26)
Total	**228 (100)**	**34 (100)**

sperm parameters or mild OAT; on the contrary men with INOA plus varicocele had more frequently severe OAT or azoospermia (Chi-square, $p < 0.001$). Azoospermia was recorded in 23 men: 3 of them had varicocele only (1% of sperm diagnoses) and 9 had INOA plus varicocele (26% of sperm diagnoses).

A small number of men (n = 12) underwent testicular FNA. Cytological findings in men with varicocele only (n = 5) were normal spermatogenesis (n = 2, 40%), mild impairment (n = 2, 40%) and severe impairment of spermatogenesis (n = 1, 20%). Cytological findings in men with INOA plus varicocele (n = 6) were severe impairment of spermatogenesis (n = 1, 17%), incomplete maturation arrest (n = 1, 17%) and complete Sertoli Cell-Only Syndrome (SCOS) (n = 4, 66%) (Chi-square, $p < 0.05$).

Study 2. A total number of 152 men had a surgically repaired varicocele. Of them, adequate preoperative and postoperative data were available for 87. Sperm parameters and SI before and after the procedure are presented in Table 5. Of the 87 men who underwent varicocelectomy, 58 had a diagnosis of varicocele only and 12 INOA plus varicocele (Table 5). Subgroup analysis showed that in men with varicocele only, SI was the only parameter that showed statistically significant increase whereas in men with INOA plus varicocele sperm parameters and SI did not show any significant change after varicocelectomy.

DISCUSSION

The present study is based on the medical archive of a reference unit for male infertility in Greece, it comprises a large number of men and covers a 15-year period. Regarding the clinical parameters of men with varicocele, it is generally accepted that varicocele can cause a slight decrease in the volume of the ipsilateral testis, especially after a long-lasting presence[9]. In our study, the volume of the testes in men with varicocele only was well within normal range. On the contrary, in men with INOA plus varicocele the volume of both testes was significantly lower than in men with varicocele only. Regarding the hormonal parameters, varicocele is characterized by normal or slightly elevated FSH levels[10,11]. In our study, in men with varicocele only, FSH was within normal range, whereas in men with INOA plus varicocele FSH was significantly higher than in men with varicocele only.

As far as the relationship between varicocele and sperm quality is concerned, there is still controversy. The majority of men with varicocele has normal sperm parameters and remains fertile[12]. On the other hand, disorders of sperm quality are often found, such as mild or moderate asthenozoospermia, teratozoospermia or astheno-teratozoospermia[10]. In the present study, a considerable percentage of men with varicocele only (28.5%) had normal sperm parameters. More specifically, in men with varicocele only, normal sperm parameters were most commonly found, followed by mild OAT; completely different was the case in men with INOA plus varicocele, in which severe OAT and azoospermia prevailed. It should be emphasized that, in case varicocele does not affect sperm quality, is not considered a cause of male infertility and consequently varicocelectomy is not indicated.

One of the most interesting and debatable issues

Table 5. Sperm parameters and Sperm Index of men who underwent varicocelectomy before and after the procedure. Data are described as median (IQR).

Parameter	Before	After	*p*-value
All studied men (n = 87)			
Volume (mL)	3.2 (2.3)	4.0 (2.2)	1.000
Concentration (10^6/mL)	10.5 (25.1)	15.0 (32.5)	0.102
Motility at first hour (%)	15.0 (25.0)	20.0 (30.0)	0.038
Normal morphology (%)	16.0 (28.0)	24.0 (28.0)	0.181
Sperm Index	0.2 (2.8)	1.3 (13.5)	0.013
Men with varicocele only (n = 58)			
Volume (mL)	3.4 (2.6)	4.0 (2.0)	0.984
Concentration (10^6/mL)	12.0 (22.3)	20.0 (31.0)	0.072
Motility at first hour (%)	20.0 (20.0)	20.0 (37.0)	0.061
Normal morphology (%)	18.0 (29.0)	24.5 (30.0)	0.326
Sperm Index	0.4 (5.1)	2.0 (29.5)	0.037
Men with INOA plus varicocele (n = 12)			
Volume (mL)	3.5 (3.2)	3.6 (3.9)	0.593
Concentration (10^6/mL)	1.0 (8.5)	4.0 (12.1)	0.285
Motility at first hour (%)	0.0 (5.0)	10.0 (18.0)	0.344
Normal morphology (%)	0.0 (31.0)	5.0 (21.0)	0.279
Sperm Index	0.0 (0.0)	0.2 (0.5)	0.715

in the literature is the relationship between varicocele and azoospermia[13,14]. This subject is also clinically important, as azoospermic men with varicocele are quite often advised to proceed to varicocelectomy in order to restore spermatogenesis or, at least, use ejaculated spermatozoa for ICSI[15]. In our study, 23 cases of azoospermia were recorded, but only 3 of them could be attributed to varicocele only; the rest had additional causes of infertility, namely INOA, cryptorchidism, obstruction and chemotherapy. A recent uncontrolled study of azoospermic men[16] showed that varicocelectomy led to the report of ejaculated spermatozoa in at least one semen analysis postoperatively in 33% of them. Of those men, 55% relapsed into azoospermia within one year. Another retrospective study[17] showed that, while 22% of men with varicocele and non-obstructive azoospermia had some spermatozoa reported on a postoperative semen analysis at an average follow-up of 14.7 months, only 9.6% of them had viable spermatozoa in the ejaculate at the time of ICSI. An explanation for those poor results could be that varicocele is not the main cause of azoospermia or that its long-lasting presence causes irreversible testicular damage. Relapse of azoospermia after a short period of improvement could be due to a temporary induction of spermatogenesis or more possibly to the presence of cryptozoospermia even preoperatively.

Few men who met the inclusion criteria for this study were subjected to FNA. The cytological findings showed that there was milder damage in men with varicocele only than in men with INOA plus varicocele. Our interpretation of these data is that a cytological finding of SCOS does not necessarily mean that it was caused by varicocele. It is very likely that varicocele and primary testicular failure, such as INOA, can coexist.

One of the crucial questions regarding varicocele is whether varicocelectomy is followed by statistically significant improvement in sperm quality. Although there have been studies that showed significant improvement in semen parameters after varicocelectomy[18,19], their findings can not be fully accepted due to serious methodological disadvantages, such as lack of control groups and no report on pregnancy rate[20]. An important step was a meta-analysis written by Evers and Collins[21]. The authors reviewed nine prospective controlled studies with pregnancy rate as the main outcome[22-30]. The relative benefit in the group of thera-

peutic intervention was 1.10 (95% confidence interval 0.73 - 1.68), suggesting no significant benefit from the varicocele repair in infertile couples in whom varicocele was the only finding. The present work (Study 2) showed that in men with varicocele only, only Sperm Index increased significantly after varicocelectomy, still being in abnormal range. In men with INOA plus varicocele no parameter increased after varicocelectomy.

In this study, infertility could be attributed exclusively to varicocele in just 64% of the men presented with this condition or a personal history of it; in the remaining 36% an additional cause of male infertility was also found. We believe that an etiological diagnosis is the cornerstone in the therapeutic approach of male infertility. Therefore, it is of great importance to distinguish men with varicocele as the only cause of infertility from men with INOA and coincident varicocele. The presence of varicocele on clinical, ultrasound and sperm grounds should not be considered enough evidence to proceed to varicocelectomy. Important factors that should be taken under consideration are testicular volume, FSH and testosterone levels, FNA findings and finally and most importantly the age and FSH levels of the female partner as well as the presence of irreversible causes of female infertility[31].

In conclusion, we analyzed a large cohort of patients with varicocele and found that varicocele alone and INOA with coexistent varicocele have completely different clinical, hormonal, sperm and cytological profiles. In addition, varicocelectomy does not seem to be an effective treatment modality, especially in men with INOA plus varicocele. Further research should be focused on predictive factors of the success of varicocelectomy as well as the comparison between varicocelectomy and ICSI with cost-effectiveness and patients' preferences taken under consideration.

Οι υπογόνιμοι άνδρες με μοναδική διάγνωση την κιρσοκήλη και με διάγνωση κιρσοκήλη με συνυπάρχουσα μη αποφρακτική αζωοσπερμία παρουσιάζουν σημαντικές κλινικές, ορμονικές και σπερματικές διαφορές.

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ΠΕΡΙΛΗΨΗ: *Σκοπός.* Σκοποί της παρούσας μελέτης ήταν η ανάλυση των επιδημιολογικών, κλινικών και ορμονικών ευρημάτων, καθώς και των παραμέτρων του σπερμοδιαγράμματος των ανδρών με κιρσοκήλη και η σύγκριση των παραμέτρων του σπερμοδιαγράμματος πριν και μετά τη διόρθωση της κιρσοκήλης.

Υλικό και Μέθοδοι. Υλικό της μελέτης αποτέλεσαν τα φύλλα του ιστορικού των ανδρών που εξετάσθηκαν στο Ιατρείο Ανδρικής Υπογονιμότητας από το 1991 έως το 2005. Κριτήρια συμμετοχής στη μελέτη αποτέλεσαν η παρουσία κιρσοκήλης κατά την κλινική εξέταση του άνδρα ή το ιστορικό επέμβασης για διόρθωση της κιρσοκήλης.

Αποτελέσματα. Στο 64% των ανδρών η κιρσοκήλη τέθηκε ως η μοναδική διάγνωση, ενώ στο υπόλοιπο 36% βρέθηκε συνύπαρξη κιρσοκήλης με άλλα αίτια υπογονιμότητας. Οι άνδρες με μοναδική διάγνωση την κιρσοκήλη και οι άνδρες με διάγνωση ιδιοπαθή μη αποφρακτική αζωοσπερμία (ΙΝΟΑ) με συνυπάρχουσα κιρσοκήλη παρουσίαζαν στατιστικά σημαντικές διαφορές όσον αφορά στο μέγεθος των όρχεων, στις παραμέτρους του σπερμοδιαγράμματος και στα επίπεδα της FSH. Στην υποομάδα των ανδρών με μοναδική διάγνωση την κιρσοκήλη, η μόνη παράμετρος που παρουσίασε στατιστικά σημαντική αύξηση μετά την επέμβαση ήταν το Ολικό Λειτουργικό Κλάσμα (ΟΛΚ).

Συμπεράσματα. Οι άνδρες με μοναδική διάγνωση την κιρσοκήλη και αυτοί με ΙΝΟΑ και συνυπάρχουσα κιρσοκήλη παρουσιάζουν σημαντικές κλινικές, ορμονικές και σπερματικές διαφορές.

Λέξεις κλειδιά: Κιρσοκήλη, Ανδρική υπογονιμότητα, Διόρθωση της κιρσοκήλης.

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Abbreviations

FNA	Fine Needle Aspiration
FSH	Follicle Stimulating Hormone
ICSI	Intracytoplasmic Sperm Injection
INOA	Idiopathic Non-Obstructive Azoospermia
IQR	Interquartile Range
LH	Luitenizing Hormone
OAT	Oligo-astheno-teratozoospermia
SCOS	Sertoli Cell-Only Syndrome
SI	Sperm Index