Original Article

Subsequent impaired fertility (with or without sperm worsening) in men who had fathered children after a left varicocelectomy: A novel population?

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Abstract

Objectives: The objective of this paper was to assess whether the beneficial effects of a varicocelectomy on fertility are transitory or definitive after a first fathering.

Materials and Methods: This was a retrospective study which involved seven andrological centers. The files of 2223 patients who underwent subinguinal ligation of a high grade left varicocele for (oligo)±(astheno)±(terato)-spermia and infertility between January 1st, 2002 and January 1st 2013 were reviewed. Inclusion criteria for the patients were the following: Sperm count improvement and fathering a child after an uneventful left varicocelectomy; 745 patients were considered. Patients who had undergone three assessments for (in-) fertility: Before surgery, before the first fathering and after the first fathering were included in the study. Each assessment included: Clinical history, physical examination, two sperm analyses, bilateral scrotal Duplex scans, blood hormonal levels [follicle stimulating hormone (FSH), luteinising hormone (LH), testosterone (T) and prolactin (PRL)].

Results: Forty patients were finally studied; they all had an improved sperm count and had fathered once after surgery. Fifteen had fathered twice and still had their sperm count increased after the second fathering. Twenty-five patients could not father twice; 13 patients had their sperm count decreased after the first fathering and 12 did not. A decrease in testicular volume and an increase in FSH paralleled the worsening of sperm concentration, motility and morphology after fathering. No other differences could be observed between the groups.

Conclusions: Our data indicated that the beneficial effects of a varicocelectomy might be transitory in some cases.

Key Words: Male infertility, sperm analysis, varicocele, varicocele correction

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INTRODUCTION

Clinically detectable varicocele and/or high ecodoppler degree varicocele are recognized as causes of (oligo)±(astheno)±(terato)-spermia and male infertility for which surgery or embolization may improve sperm count and fathering in about 50-70% and 30-50% of patients, respectively.[1,2] Sperm parameters improved within 3-12 months after varicocele repair.[3-5]

The main causes of the decrease in sperm count after initial improvement are: Varicocele recurrence and/or other known clinically detectable causes of infertility: *i.e.* genital inflammation and/or drug administration, etc.[6,7]

The first Author began this multicenter retrospective study because he had found, by chance, two oligoasthenoteratospermic patients who had had their sperm count improved and who had fathered children after uneventful varicocele surgery, but who then had their sperm count decreased after fathering, in the absence of any clinically detectable cause of male infertility. The aim of this retrospective study was to better understand this occasional finding.

MATERIALS AND METHODS

One hundred and twenty-two Italian andrological centers were asked to participate. In order to be included in the study, the centers had to fulfil all the following criteria:

1. Andrological activity beginning from at least 1st January, 2002. The files were reviewed starting from this date until 1st January, 2013. The review started arbitrarily in 2002 because only since then have patient files been electronically collected
2. An initial diagnosis of male infertility, varicocele and of (oligo)±(astheno)±(terato)-spermia carried out with clinical history, physical examination, two sperm analyses,[8] bilateral scrotal Duplex scans and blood hormonal levels: *i.e.* follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL) and total testosterone (T)
3. Use of the same serology tests and the same range: FSH reference values: 1.5-12.4 mIU/ml; LH reference values: 1.0-10.0 mIU/ml; T reference values: 11-36 nmol/L and PRL reference values: 80-400 mIU/L. Serum concentrations of PRL, FSH and LH were measured using time-resolved immunofluorometric assays from Wallac, Turku, Finland. The sensitivities of the PRL, FSH and LH assays were 0.1mIU/L, 0.06 IU/L and 0.05 IU/L, respectively. In all the assays, the intra- and interassay coefficients of variation were <10%. Serum testosterone was measured using a radio-immuno assay (RIA) (Coat-a-Count from Diagnostic Products Corporation, Los Angeles, CA). The sensitivity of the Diagnostic Products Corporation testosterone assay was 0.23 nmol/L, and the intra- and interassay coefficients of variation were both <10%
4. Execution of genetic assessment (karyotype, y microdeletion and cystic fibrosis screening) in the patients with a sperm concentration $<5 \times 10^6$/ml[9,10]
5. Execution of surgery only on patients with 3rd, 4th or 5th degree varicocele.[1,2] The varicoceles were graded as follows using Duplex scans in all centers: grade 1: venous reflux with a Valsalva maneuver limited to the cranial portion of the cord, grade 2: reflux with Valsalva until the upper pole of the testicle, grade 3: reflux with Valsalva until the lower pole of the testicle, grade 4: reflux under basal conditions increased by Valsalva and grade 5: reflux under basal conditions which did not increase with Valsalva[11]
6. loop magnification subinguinal varicocelectomy (a microscope was never used)
7. repetition of the initial assessment (*i.e.*, clinical history collection, objective examination, hormonal levels, two semen analyses and scrotal duplex examination) at least 6-8 months after surgery and each time advice for (in) fertility was requested
8. assessment of female factors of infertility before surgery and each time advice for (in) fertility was requested[12]
9. the presence of an "expert laboratory" dedicated to sperm analyses in each center. An "expert laboratory" is defined as a laboratory which employs methods regarding quality assurance and quality control, which runs an internal quality control program and participates in external quality control programs aimed at reducing biological and analytical variability in accordance with international recommendations.[8,13]

Only seven centers fulfilled these criteria and were selected.

The Authors retrospectively reviewed the files of the patients who had been visited for left varicocele associated with (oligo)±(astheno)±(terato)-spermia and infertility. In total, 3311 patients were identified [Figure 1].

Inclusion criteria: (Oligo)±(astheno)±(terato) spermic patients who had their sperm count improved after a left varicocelectomy, subsequently fathered and who later attempted a second fathering were included in the study. Paternity among these men was assessed and confirmed, interviewing the male and female partners of each couple separately.

Patients were not admitted into the study if any of the following criteria were present before or during the course of the follow-up period: Presence of female factors of infertility (132 patients), seminal white blood cell concentration more than 10^6/mL, positive seminal cultural analysis or positive urethral swab chlamydia test and/or any symptom of genital inflammation (45 patients), hormonal alterations (16 patients), chromosomal aberrations (3 cases), drug, tobacco, or alcohol abuse (68 patients), ongoing medical treatment (gonadotropins, anabolic steroids, cancer chemotherapy: 2 patients), hydrocele and/or (delayed) atrophy of ipsilateral testicle and/or any other side effects from surgery (8 patients),[6] diabetes (2 patients), hypertension (2 patients), X-ray exposure in the previous

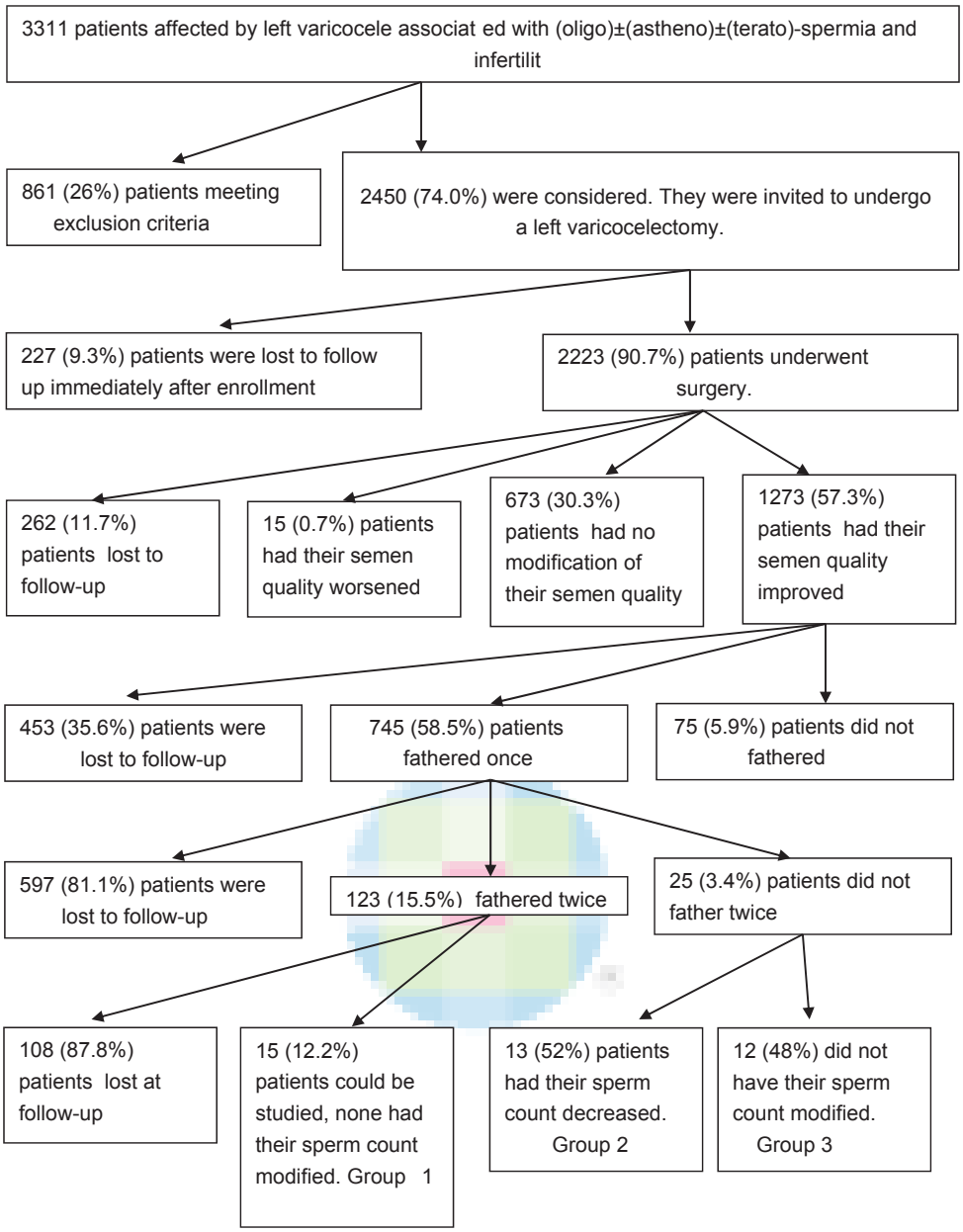

Figure 1: Description of patients affected by left varicocele associated with (oligo)±(astheno)±(terato)-spermia and infertility who underwent a left varicocelectomy during the period January 1, 2002 June 30, 2012 in seven andrological/urological centers. The study groups have been highlighted in bold

8 months (14 patients), testicular pathology (torsion, orchi-epididymitis, surgery, trauma or neoplasm: 10 patients), bilateral varicocele (242 patients), abnormal sperm appearance, consistency, liquefaction, volume and pH[8] (112 patients), and persistent or recurrent varicocele at duplex scrotal examination (205 patients).[9,10,14] Persistent varicocele is defined as any degree of venous reflux which occurred immediately after surgery; recurrent varicocele is defined as any degree of venous reflux which occurred at any time after surgery.[15]

Thus, 2450 patients were studied [Figure 1]. Two hundred and twenty-seven were lost to follow-up immediately after surgery; thus, 2223 patients underwent a left subinguinal varicocelectomy with loop magnification. Two hundred and sixty-two patients were lost to postoperatory follow up, 15 had their semen quality worsened after 6-8 months and 673 did not have their semen modified, while 1273 had their semen quality improved. The Pearson test was used to assess sperm count modifications in each patient, both in this case and throughout the paper.[16] This study investigated subsequent impaired fertility (with or without sperm worsening) in men who had fathered children and had had their sperm count increased after a left varicocelectomy; thus, only 1273 patients who had their sperm count improved after surgery were considered. Four hundred and fifty-three patients were lost

to follow up and 745 fathered once (mean gap in months between surgery and fathering ± standard deviation [s.d.]: 10.3 ± 4.1). Five hundred and ninety-seven of these were lost to follow up, 123 fathered twice (mean gap in months between the first and the second fathering ± s.d.: 41.0 ± 18.5). Fifteen of the latter spontaneously requested a complete assessment of (in-) fertility: *i.e.* two sperm analyses, bilateral scrotal Duplex scans and blood hormonal levels (thus, they could be enrolled in the study), and constituted Group 1. Their assessments were carried out after pregnancy induction (detected by measuring serum β-hCG on at least two occasions after a 14-day delay of menstrual cycle) with a median gap of 3.5 months from the last β-hCG measurement (range 2-5 months). Twenty-five patients could not father twice: 13 had their sperm count decreased (Group 2) and 12 did not have their sperm count modified (Group 3). Group 2 and Group 3 patients requested additional (in) fertility advice after the first fathering due to a delay in second fathering of >12 months.

The follow-up period of each patient extended from the first diagnosis of varicocele associated with infertility and impaired semen quality until the last (in) fertility assessment carried out after fathering.

Patient age, female age, duration of infertility, bilateral testicle volume before and after surgery and after fathering, time lag between fathering and the second request for advice for (in) fertility sperm concentration motility (class A+B World Health Organization [WHO] 1999 or class A WHO 2010),[8] morphology (strict criteria), ejaculated volume and the blood levels of FSH, LH, PRL and T were compared using *post hoc* non parametric median test comparison 'Holland test'.[17]

RESULTS

Demographic and clinical assessments of the patients studied are presented in Table 1.

No significant difference emerged among the three groups before and after surgery in terms of: Patient age, duration of infertility, time lag between surgery and fathering, bilateral testicle volume, ejaculate volume, blood hormones, and sperm concentration, motility and morphology.

A decrease in testicular volume and an increase in FSH paralleled the worsening of sperm concentration, motility and morphology of the Group 2 patients after the first fathering with respect to Groups 1 and 3. No significant difference could be observed in sperm count and in hormonal profiles between Groups 1 and 3 after the first fathering. The female partners of Group 3 were significantly older than those in Groups 1 and 2. No other significant differences were observed.

DISCUSSION AND CONCLUSIONS

Our data showed that some patients can father twice, and some others still struggled to conceive after a varicocelectomy, improvement of sperm count and a first fathering. One part of the latter had their sperm count worsened after the first fathering which paralleled the worsening of some clinical monitors of spermatogenesis (FSH and testicular volume) whereas another part did not have their sperm count and/or their clinical monitors of spermatogenesis worsened. The prevalence of each population cannot be calculated exactly because only 40 patients (3.1%) out of 1273 who had their sperm count improved after surgery could be fully assessed for (in-) fertility with clinical history collection, bilateral scrotal duplex examination, sperm count analyses and hormonal profiles. It is likely that the majority of the patients did not experience any late decline in semen quality because 123 fathered twice after surgery. This is a retrospective study, and the Authors could not have foreseen the need to review these data; thus, they regarded a complete assessment for (in-) fertility in these patients was not considered feasible. Fifteen of them spontaneously requested a complete assessment for (in-) fertility immediately after conceiving; thus, only the latter could be used for our research. This is a limitation of the present study, the retrospective nature of which did not allow means of limiting drop-outs who represented 96.9% of the cases studied.

A second limitation of the present study was that the seminal samples were examined in seven different laboratories; however, only andrological centers with "expert laboratories" were utilized (see the Material and Methods section) in order to limit the variations induced by different methods of semen analysis as much as possible.[8,13]

An additional limitation of this study was that we set out to describe Group 2 as having altered sperm parameters, and Groups 1 and 3 as not having altered sperm parameters. What is perhaps relevant is that there were no apparent differences between the groups, *i.e.* there were no preoperative factors which predicted the eventual outcome. Group 1 patients did not experience recurrent infertility but Groups 2 and 3 did; only one group (Group 2) had its semen deteriorated. Furthermore, all groups fit the guidelines for varicocele surgery.[1] No venous reflux was observed using bilateral scrotal Duplex scans in any group; thus, the hypothesis that a subtle recurrence/persistence of varicoceles may occur in the second group who developed infertility, granted testicular volume, FSH and sperm analysis could be discharged.

The FSH level of the patients studied was always within the range (reference values: 1.5-12.4 mIU/ml); however, it is a marker of spermatogenesis and of Sertoli cell function, and several

Table 1: Clinical and demographic characteristics of the population studied: 40 patients operated on for left varicocele who had their sperm count improved, fathered once after surgery and who attempted a second fathering. Fifteen succeeded (Group 1) and 25 did not. The latter patients were divided into two groups: 13 patients who had a significant decrease in their sperm count after fathering (Group 2) and 12 patients who had no significant variation of sperm concentration, motility and morphology after fathering (Group 3). Data are presented as medians and ranges (min-max)

	Group 1 (a)	Group 2 (b)	Group 3 (c)	*P*		
				a v/s b	b v/s c	a v/s c
Assessment before surgery						
Age (years)	36 (29-37)	34 (29-38)	35 (28-36)	n.s.	n.s.	n.s.
Duration of infertility (months)	17 (12-25)	18 (12-24)	18 (12-24)	n.s.	n.s.	n.s.
Bilateral testicle volume (cm^3)	28 (22-30)	26 (22-30)	27 (22-31)	n.s.	n.s.	n.s.
FSH (reference values: 1.5-12.4 mIU/ml)	6.5 (2.8-9.3)	6.3 (2.2-9.6)	7.0 (3.1-9.0)	n.s.	n.s.	n.s.
LH (reference values: 1.0-10.0 mIU/ml)	4.6 (2.0-6.2)	4.8 (2.1-6.3)	4.1 (2.0-7.0)	n.s.	n.s.	n.s.
T (reference values: 11-36 nmol/L)	23 (14-31)	22 (13-30)	24 (14-32)	n.s.	n.s.	n.s.
PRL (reference values 80-400 mU/L)	240 (98-414)	234 (100-412)	255 (98-407)	n.s.	n.s.	n.s.
Sperm concentration (millions/ml)	11.3 (4.1-20.6)	10.4 (3.2-18.3)	12.6 (5.4-20.1)	n.s.	n.s.	n.s.
Percentage of motile sperm (class A+B WHO 1999 or class A WHO 2010)	16 (0-33)	14 (0-30)	18 (0-36)	n.s.	n.s.	n.s.
Typical forms (strict criteria)	5 (0-9)	6 (2-8)	4 (1-7)	n.s.	n.s.	n.s.
Ejaculated volume ml.	3.5 (2-5)	3.5 (2.5-5)	3 (2.5-5)	n.s.	n.s.	n.s.
Assessment 6-8 months after surgery						
Bilateral testicle volume (cm^3)	30 (28-31)	29 (28-30)	30 (28-31)	n.s.	n.s.	n.s.
FSH (reference values: 1.5-12.4 mIU/ml)	4.9 (2.5-6.3)	5.1 (2.4-6.8)	4.7 (2.0-6.2)	n.s.	n.s.	n.s.
LH (reference values: 1.0-10.0 mIU/ml)	3.8 (2.2-6.0)	4.0 (2.1-6.2)	3.7 (2.0-5.8)	n.s.	n.s.	n.s.
T (reference values 11-36 nmol/L)	29 (16-35)	28 (15-34)	26 (15-31)	n.s.	n.s.	n.s.
PRL (reference values 80-400 mU/L)	242 (99-423)	234 (100-412)	255 (98-407)	n.s.	n.s.	n.s.
Sperm concentration (millions/ml)	38.2 (22.0-62.3)	36.7 (21.2-60.3)	35.8 (20.9-66.2)	n.s.	n.s.	n.s.
Percentage of motile sperm (class A+B WHO 1999 or class A WHO 2010)	64 (53-72)	62 (52-70)	66 (50-71)	n.s.	n.s.	n.s.
Typical forms (strict criteria)	16 (14-18)	16 (14-18)	16 (14-18)	n.s.	n.s.	n.s.
Time lag between surgery and fathering (months)	13 (6-17)	12 (6-18)	13 (6-18)	n.s.	n.s.	n.s.
Ejaculated volume ml.	3.5 (2-5)	3.5 (2.5-5)	3 (2.5-5)	n.s.	n.s.	n.s.
Female age at the time of the first assessment for (in-) fertility in years	30.1 (25.0-32.1)	32.4 (29.6-35.3)	35.3 (32.6-38.4)	n.s.	<0.046	<0.048
Assessment after the first fathering						
Time lag between the first fathering and this (in) fertlity assessment (months)	37 (29-57)	34 (24-52)	40 (26-61)	n.s.	n.s.	n.s.
Bilateral testicle volume (cm^3)	31 (28-31)	23 (21-30)	31.2 (27.4-32.2)	<0.032	<0.034	n.s.
FSH (reference values: 1.5-12.4 mIU/ml)	4.2 (2.2-6.0)	6.7 (2.4-9.8)	4.5 (2.0-5.9)	<0.029	<0.036	n.s.
LH (reference values: 1.0-10.0 mIU/ml)	3.9 (2.3-5.9)	4.6 (2.5-7.6)	3.9 (2.0-5.9)	n.s.	n.s.	n.s.
T (reference values 11-36 nmol/L)	26 (13-35)	24 (14-31)	29 (18-34)	n.s.	n.s.	n.s.
PRL (reference values 80-400 mU/L)	250 (90-386)	256 (92-415)	246 (102-387)	n.s.	n.s.	n.s.
Sperm concentration (millions/ml)	40.2 (22.0-70.1)	12.5 (4.3-17.2)	37.6 (21.2-68.3)	<0.031	<0.023	n.s.
Percentage of motile sperm (class A+B WHO 1999 or class A WHO 2010)	68 (54-72)	12 (0-23)	68 (54-72)	<0.035	<0.023	n.s.
Typical forms (strict criteria)	17 (15-19)	4 (0-8)	16 (14-18)	<0.025	<0.024	n.s.
Ejaculated volume ml.	3.5 (2-5)	3.5 (2.5-5)	3 (2.5-5)	n.s.	n.s.	n.s.
Female age at the time of the second assessment for (in-) fertility in years	33.2 (28.1-34.6)	35.2 (29.6-38.4)	38.6 (32.4-41.2)	n.s.	<0.041	<0.043

FSH: Follicle stimulating hormone, LH: Luteinizing hormone, PRL: Prolactin, T: Total testosterone, WHO: World Health Organization, n.s.: Not significant, v/s: Versus, a = patients who achieved a second fathering after surgery; b = patients who did not achieved a second fathering after surgery and who had their sperm count decreased, c = patients who did not achieved a second fathering after surgery and who did not have their count modified

studies have found that the risk of abnormal semen parameters is negatively correlated to sperm concentration, even for blood concentrations lower than the conventional upper limit of the reference interval.[18,19] Similarly, testicular volume is regarded as a clinical monitor of spermatogenesis which is negatively correlated with the reproductive activity of the testicle.[20]

Despite the large body of literature regarding varicocele surgery performed in (oligo)±(astheno)±(terato) spermic patients, we could not find any paper reporting a phenomenon such as this. Actually, when varicocelectomy is performed in non-obstructive azoospermic patients, semen samples obtained six months post-surgery revealed that about 20%-55%of the patients patients had sperm in their semen; however, a 12-month post-surgery semen sample analysis revealed about one half of these were again azoospermic, which the researchers posited may be only a temporary effect due to the induction of spermatogenesis, because of the severe impairment of gametogenetic process.[21] However no significant difference in sperm count and in current monitors of spermatogenesis could be found between the groups, and the phenomenon identified in this manuscript remains difficult to be understood.

When sperm count and monitors of spermatogenesis (FSH and testicle volume) do not worsen after fathering (Group 3 patients), female aging (in the absence of any other female factor of infertility) might explain difficulties in the second fathering;[22] at present, we cannot give any other explanation.

The following hypothesis could be postulated in the case that sperm count and monitors of spermatogenesis worsen after initial improvement and fathering. The association between varicoceles and male infertility has been known since the 1950s; however, the pathophysiology of the process remains uncertain. The proposed primary hypotheses involved hyperthermia, venous pressure, testicular blood flow, hormonal imbalance, toxic substances and reactive oxygen species.[23] However, these mechanisms are linked to venous varicosities and do not explain why only approximately one-third of patients with varicoceles are infertile. Microdeletions of the alpha-1 subunit of the sperm calcium channels in a proportion of dyspermic men with varicoceles suggest a genetic defect leading to abnormal acrosomal function. This finding seems to support a genetic "co-factor" hypothesis for the pathogenesis of (oligo)±(astheno)±(terato)-spermia associated with some varicoceles;[24] in fact, the altered genes identified in males with impaired spermatogenesis and a varicocele were: ACP'1' *B/*C, MT-ATP6, MT-ATP, CACNA1C, MT-CO1, MT-CO2 and MT-ND3.[25,26] The emerging hypothesis is that varicocele-associated dyspermia might be due to the combined effects of venous varicosities associated with gene defects.[24-26] This hypothesis might explain why only some patients with varicoceles are infertile: Only some varicoceles had altered the spermatogenesis-associated genes. This hypothesis might also explain the effects of surgery/embolization of varicoceles on the spermatogenetic process. Some varicoceles improve sperm count after surgery because their varicosity-related pathogenetic factors are chiefly preponderant with respect to genetic co-factors for determining dyspermia; others do not improve sperm count because their varicosity-related pathogenetic factors are not preponderant with respect to their genetic co-factors for determining dyspermia and, finally, still others improve sperm count provisionally after surgery because surgery might correct varicosity-related pathogenetic factors, but this correction might be shadowed by some kind of disruption of spermtogenesis related to moderately prepondrant genetic co-factors. We know that there is no proof that this type of mechanism occurred in the Group 2 patients; however, no other explanation is present in the literature to legitimize the transient beneficial effects of this type of surgery.

This was a retrospective study and, typically, a prospective design is ranked higher in the hierarchy of evidence than a retrospective design with regard to confounders, exposure and endpoints, due to the accuracy of the data collection. A retrospective design is a very time-efficient way of answering new questions using existing data while prospective studies are time-consuming; a study such as this one would have lasted a number of years.[27] As a partial compensation, multicenter studies (such as this one) have been recommended for retrospective research to allow comparisons among the data of each center in order to improve their reliability.[28] Furthermore, with regard to the centers, only those which used identical surgical and follow-up techniques were admitted to the study. Patient grouping could be carried out only "a posteriori"; thus, it was not possible to consider Group 2 as a "control" group. As a result of this, a "post-hoc" non-parametric test was used for data analysis.[6,16]

Our results might modify the current role of surgery for dyspermia associated with high grade varicoceles; however, it is not known to what degree since the prevalence of Group 1, 2 and 3 patients with respect to the general population of successfully operated on patients is unknown due to the limited number of cases which could be examined. Moreover, the patients studied should be considered a "selected" population because they were all late in fathering; thus, finding a relatively high number of dyspermic patients should be considered obvious. Even though additional studies are needed in this field, it is felt that informed consent to varicocele surgery should include a paragraph regarding the possible difficulty of fathering (associated or not with sperm count worsening) after an initial success.

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