

·Clinical Experience·

Induction of spermatogenesis in men with azoospermia or severe oligoteratoasthenospermia after antegrade internal spermatic vein sclerotherapy for the treatment of varicocele

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Abstract

Aim: To evaluate the treatment outcome of antegrade internal spermatic vein sclerotherapy in men with non-obstructive azoospermia or severe oligoteratoasthenospermia (OTA) as a result of varicocele. **Methods:** Between September 1995 and January 2004, 47 patients (mean age 33.8 ± 6.3 years) underwent antegrade internal spermatic vein sclerotherapy for the treatment of varicocele with azoospermia (14 patients) or severe OTA (33 patients). Testicular core biopsy was also performed in complete azoospermic patients who provided informed consent. The outcome was assessed in terms of improvement in semen parameters and conception rate. **Results:** Forty-two (89.4%) of 47 patients had bilateral varicocele. Serum follicle stimulating hormone (FSH) did not differ between patients with azoospermia and severe OTA. After the follow-up of 24.8 ± 9.2 months, significant improvement was noted in mean sperm concentration, motility and morphology in 35 patients (74.5%). Comparison between groups during the follow-up revealed significantly higher values of sperm concentration, motility and normal morphology in the severe OTA group. Pregnancy was achieved in 14 cases (29.8%). Testicular histopathology of the azoospermic patients with postoperative induction of spermatogenesis revealed maturation arrest at spermatid stage, Sertoli-cell-only (SCO) with focal spermatogenesis or hypospermatogenesis. None of the patients with pure SCO pattern or maturation arrest at spermatocyte stage achieved spermatogenesis after the treatment. Preoperative serum FSH levels didn't relate to treatment outcome. **Conclusion:** Antegrade internal spermatic vein sclerotherapy is an easy and effective treatment for symptomatic varicocele. It can significantly reverse testicular dysfunction and improve spermatogenesis in men with severe OTA, as well as induce sperm production in men with azoospermia, improving pregnancy rates in subfertile couples. (*Asian J Androl* 2006 Sep; 8: 613–619)

Keywords: varicocele; oligoasthenoteratospermia; azoospermia; sclerotherapy; spermatogenesis

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1 Introduction

Varicocele is a major cause of male infertility. Recent improvements in the diagnosis of varicocele with color Doppler ultrasonography, thermography and internal spermatic vein venography have increased the inci-

dence to 40% in men with primary infertility and up to 80% in men with secondary infertility [1]. Varicocele causes a progressive deterioration in testicular function and semen quality, ranging from oligozoospermia to complete azoospermia. The incidence of azoospermia or severe oligoteratoasthenospermia (OTA) in association with varicocele is common and is reported to range from 4.3% to 13.3% [2]. Although the efficacy of varicocele treatment in the management of oligozoospermic patients is well established [3], controversial results exist in the published literature with respect to varicocele treatment in patients with severe OTA or azoospermia [2, 4–6].

The present study aims to evaluate the bilaterality of varicocele in patients with non-obstructive azoospermia or severe OTA. Other aims are the evaluation of the improvement of semen quality and conception rate after antegrade internal spermatic vein sclerotherapy and the correlation of treatment outcome with the testicular histology patterns and endocrinology profiles in this particular patient cohort.

2 Materials and methods

2.1 Patients and diagnosis

Between September 1995 and January 2004, 47 patients (mean age 33.8 ± 6.3 years) with azoospermia or severe OTA as a result of varicocele were treated with antegrade internal spermatic vein sclerotherapy in our department. Table 1 lists the inclusion and exclusion criteria for treatment.

All patients underwent a baseline evaluation including detailed history, complete physical examination, hormone profile and genetic determination if needed. The volume,

position and consistency of the testes and epididymis were checked, and each spermatic cord was palpated in the standing position and during the Valsava maneuver. Only clinically detectable varicoceles were included in the present study. Varicocele grading was accomplished as follows: grade I, varicocele palpable only during Valsava maneuver; grade II, varicocele palpable in standing position; grade III, varicocele visible and palpable at rest. All patients underwent color Duplex scrotal ultrasonography, which confirmed the presence of varicocele. After obtaining informed consent, patients underwent internal spermatic vein antegrade sclerotherapy according to the technique described by Tauber and Johnsen [7]. The procedure was performed under local or general anesthesia. After surgical exposure of the spermatic cord with a vertical scrotal incision and opening of the external and internal spermatic fasciae, cannulation of a scrotal vein followed with venography, which confirmed the diagnosis in all 47 patients. Finally, sclerotherapy was accomplished with polidocanol (2 mL aethoxysclerol [4%], Kreussler, Germany). At the end of the procedure a phlebography ensured that all collaterals were sclerosed and ruled out failed injections and paravascular applications of the sclerosing agent.

In azoospermic patients after informed consent, open testicular biopsy was performed at the same time as varicocele repair. Biopsies were performed on the healthier appearing testis based on size and consistency. On the basis of standard qualitative interpretations of the hematoxylin and eosin sections, biopsies were classified as pure Sertoli-cell-only (SCO) pattern, maturation arrest at spermatocyte stage, maturation arrest at spermatid stage (Figure 1), SCO pattern with focal spermatogenesis, hypospermatogenesis, and normal spermatogenesis. The histological examination were performed by one pathologist at the pathological Institute of our hospital. The Hematoxyline-Eosin dye was used (Figure 1).

2.2 Semen analysis

Semen analysis was performed for three times before sclerotherapy with 3-day abstinence from sexual intercourse before semen collection. A minimum interval between all the analyses was 2 weeks. Postoperative evaluation included serial semen analyses with 3-month intervals in the first year after sclerotherapy and every 6 months thereafter. The semen analysis was performed according to the World Health Organization criteria [8]. Only men with azoospermia or severe OTA were enrolled. Azoospermia was confirmed by the absence of sperm in

Table 1. Study group inclusion and exclusion criteria for antegrade internal spermatic vein sclerotherapy. † According to World Health Organization criteria (1999) [8].

Inclusion criteria	Exclusion criteria
Infertility duration \geq 12 months	Genetic abnormality Obstructive azoospermia Cryptorchidism
Clinically detectable varicocele	History of testicular trauma Presence of systemic infection Endocrinopathy
Presence of azoospermia or severe oligoasthenoteratospermia†	Drug abuse Female partner proven infertility

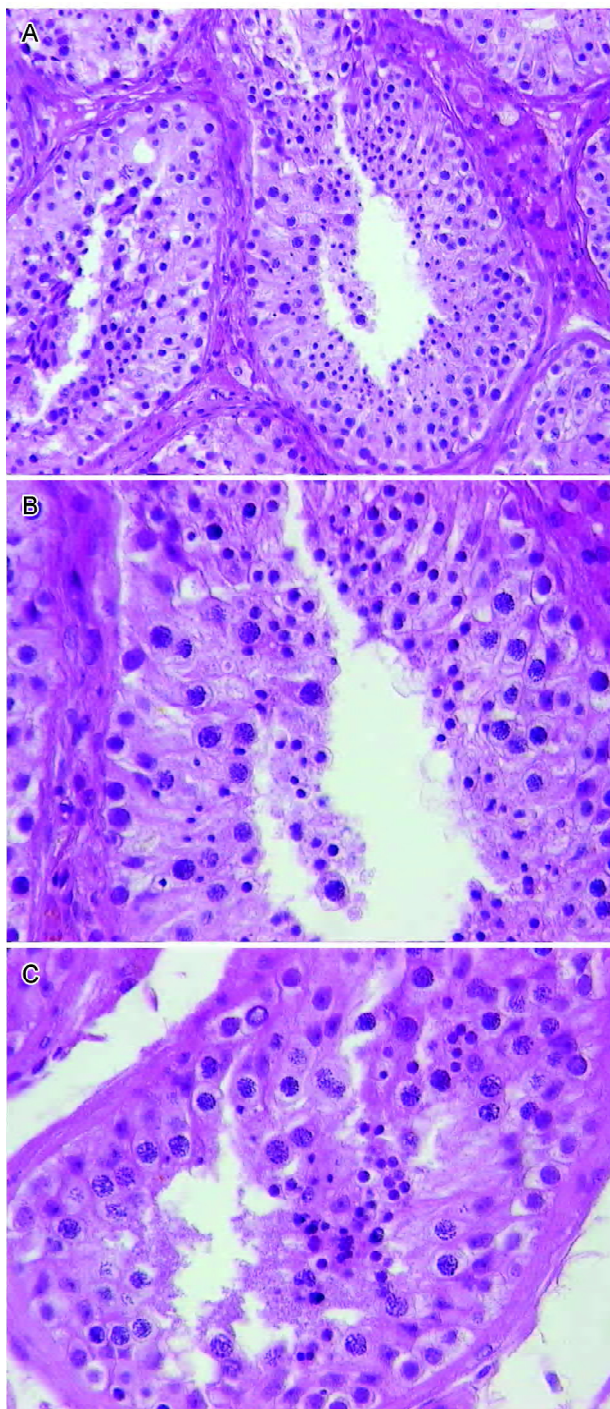


Figure 1. Histological finding with maturation arrest at the round spermatid stage. Microscopic view with different magnification (A, $\times 100$; B, $\times 200$; C, $\times 400$).

the centrifuged semen pellet. Severe OTA was defined as $< 1 \times 10^6$ total motile sperm/ejaculate in all analyses submitted. Man with a sperm density of $> 5 \times 10^6$ /mL

or $> 1 \times 10^6$ total motile sperm/ejaculate in any analysis was excluded. All men were fructose positive. This test was performed to rule out total obstruction of the ejaculatory ducts. Patients with azoospermia and post-sclerotherapy appearance of normal spermatozoa in at least one semen analysis were advised to consent to frozen storage of their semen because it is known that the appearance of spermatozoa post-varicocelectomy in azoospermic men with varicocele can be temporary [4]. Endocrinological evaluation was performed before sclerotherapy and it included serum follicle stimulating hormone (FSH) and testosterone.

2.3 Statistical analysis

Elaboration of data was accomplished by the Statgraphics Statistical Package (Manugistics, Rockville, MD, USA). Data were expressed as mean \pm SD. Normality was assessed using the Kolmogorov-Smirnov test. Comparison of the groups was performed by two-tailed signed-rank test or paired *t*-test as appropriate. Correlation was calculated according to Spearman's correlation coefficient. To compare the mean values between patients with azoospermia and severe OTA, we conducted an independent samples *t*-test after logarithmic transformation to achieve data-normality. $P < 0.05$ was considered statistically significant.

3 Results

The study group consisted of 14 (29.8%) patients with azoospermia and 33 (70.2%) patients with severe OTA. Of the all 47 patients, 42 (89.4%) underwent a bilateral procedure (12 out of 14 [85.7%] with azoospermia, 30 out of 33 [90.9%] with severe OTA), 4 (8.5%) underwent a unilateral left-sided procedure and 1 (2.1%) underwent a unilateral right-sided procedure. Of the 14 patients with azoospermia, 12 consented to open testicular biopsy. Testicular histopathology revealed SCO pattern in 2 patients, maturation arrest at spermatocyte stage in 1 patient, maturation arrest at spermatid stage in 4 patients, SCO pattern with focal spermatogenesis in 1 patient, and with hypospermatogenesis in 4 patients.

After postoperative follow-up of 24.8 ± 9.2 months, improvement was noted in mean sperm concentration, motility and morphology in 35 patients (74.5%).

In the azoospermia group, mean sperm concentration increased from zero (total sperm) before sclerotherapy to $3.1 \pm 1.2 \times 10^6$ /mL after sclerotherapy ($P < 0.05$, two-

tailed signed-rank test). Mean sperm motility increased to $2.2 \pm 1.9\%$ ($P < 0.001$, two-tailed signed-rank test), and mean sperm normal morphology to $7.8 \pm 2.2\%$ ($P < 0.01$, two-tailed signed-rank test). Of the 14 azoospermia patients, 7 (50%) had motile sperm observed in postoperative semen analyses, and 4 (28.6%) achieved posts-clerotherapy sperm counts of $> 1 \times 10^6/\text{mL}$.

In the group with severe OTA, mean sperm concentration increased from $0.4 \pm 0.2 \times 10^6/\text{mL}$ before sclerotherapy to $11.3 \pm 2.3 \times 10^6/\text{mL}$ after sclerotherapy ($P < 0.001$, paired *t*-test). Mean sperm motility rose from $11.8 \pm 2.7\%$ to $34.9 \pm 3.2\%$ ($P < 0.001$, paired *t*-test). Mean normal sperm morphology increased from $5.9 \pm 2.1\%$ to $16.1 \pm 2.0\%$ ($P < 0.001$, paired *t*-test). Of the 33 severe OTA patients, 29 (87.9%) demonstrated postoperative improvement in semen quality, and 19 (57.6%) achieved mean post-sclerotherapy sperm counts of $> 1 \times 10^6/\text{mL}$ and 10 (30.3%) patients achieved mean post-sclerotherapy sperm counts of $> 5 \times 10^6/\text{mL}$. Comparison between the two groups (Table 2) reveals that patients with severe OTA achieved significantly higher sperm concentration, motility and normal morphology values than patients with azoospermia in the follow-up period ($P < 0.001$ for all three variables, independent samples *t*-test).

Of the 47 patients, 14 (29.8%) have sired pregnancies leading to live births after antegrade sclerotherapy (Table 3) and 9 (19.1%) sired unassisted pregnancies and 5 (10.6%) contributed to assisted pregnancies (3 with intrauterine insemination and 2 with intracytoplasmic sperm injection [ICSI]). Two of the 14 patients with azoospermia (14.3%) and 7 of the 33 patients with severe OTA (21.2%) contributed to unassisted pregnancies.

Mean preoperative serum FSH levels were 17.6 ± 4.8 IU/L for the azoospermia group and 15.2 ± 3.9 IU/L for the severe OTA group ($P = 0.3$, independent samples

t-test, Table 3). Nine (64.2%) of 14 azoospermic patients and 17 (51.5%) of 33 severe OTA patients had preoperative elevated FSH levels, respectively. Preoperative FSH levels between men who did (14.8 ± 3.1 IU/L) and did not (19.4 ± 3.8 IU/L) show improvement in semen parameters after sclerotherapy were not significantly different ($P = 0.1$, independent samples *t*-test). Mean preoperative serum testosterone levels were 9.9 ± 5.8 nmol/L for the azoospermia and 11.2 ± 4.3 nmol/L for the severe OTA group ($P = 0.5$, independent samples *t*-test, Table 3). After the procedure, testosterone levels rose to 19.9 ± 7.4 nmol/L for the azoospermia and 22.1 ± 4.9 nmol/L for the severe OTA group ($P = 0.4$, independent samples *t*-test).

4 Discussion

Azoospermia and severe OTA are extreme testicular dysfunctions that occur in patients with varicocele and are a significant barrier to the male factor contribution to an unassisted pregnancy. Since the introduction of ICSI, testicular biopsy with testicular sperm extraction (TESE) has become an important therapeutic procedure for testicular sperm retrieval in non-obstructive azoospermic patients. Similarly, for men with severe OTA, who desire to contribute to a pregnancy with their own semen, options include ICSI with ejaculated sperm or with TESE. With either option, the couple relies on assisted pregnancy methods. The present study evaluates among other parameters the spontaneous pregnancy rates after antegrade sclerotherapy of the internal spermatic vein in patients with severe OTA or azoospermia as a result of varicocele. This procedure is proven to be safe, can be performed under local anaesthesia and has the advantage of lower cost and complication rates in comparison to other forms of surgical management for varicocele.

Table 2. Comparison of sperm concentration, motility and normal sperm morphology rates after internal spermatic vein sclerotherapy between patients with azoospermia and severe oligoasthenoteratospermia (OTA). †, Independent samples *t*-test.

Variable	Azoospermia (n = 14)	Severe OTA (n = 33)	P
Sperm concentration ($\times 10^6/\text{mL}$)	3.1 ± 1.2	11.3 ± 2.3	$< 0.001^\dagger$
Sperm motility (%)	2.2 ± 1.9	34.9 ± 3.2	$< 0.01^\dagger$
Sperm normal morphology (%)	7.8 ± 2.2	16.1 ± 2.0	$< 0.001^\dagger$

Table 3. Serum follicle stimulating hormone (FSH) and testosterone levels before sclerotherapy and postoperative pregnancy rates for women whose partners had azoospermia or severe oligoasthenoteratospermia (OTA). †, Normal, 1.0–8.0 IU/L; ‡, Normal, 9.1–55.3 nmol/L; §, Independent samples *t*-test.

Variable	Azoospermia (n = 14)	Severe OTA (n = 33)	P
Serum FSH (IU/L)†	17.6 ± 4.8	15.2 ± 3.9	0.3§
Serum testosterone (nmol/L)‡	9.9 ± 5.8	11.2 ± 4.3	0.5§
Number of pregnancies (%)	3 (21.4)	11 (33.3)	0.1§

Table 4. Comparison of financial cost, complications and pregnancy rates in patients after sclerotherapy and other varicocelectomy techniques. †Studies with azoospermia and severe oligoteratoasthenospermia (OTA).

	Pasqualotto <i>et al.</i> [4]†	Matthews <i>et al.</i> [5]†	Gat <i>et al.</i> [6]†	Johnsen <i>et al.</i> [18]	Rashid <i>et al.</i> [19]	Podkamenev <i>et al.</i> [20]
Procedure	Microsurgical repair	Microsurgical repair	Percutaneous embolization	Antegrade sclerotherapy	Laparoscopic ligation	Open ligation
Number of patients	15	78	101	2115	–	434
Financial cost	–	–	–	\$US57.49 unilateral	\$US6881 unilateral	\$US3317 unilateral
				\$US62.92 bilateral	\$US7099 bilateral	\$US4091 bilateral
Complications (%)	–	–	–	3.8	–	6.7
Hydrocele (%)	–	–	–	0	–	0.2
Pregnancy rates (%)†	6.6	31	34	–	–	22.2
						1.8

Table 4 presents a brief review of the published literature comparing the financial cost and complications after sclerotherapy and other commonly performed varicocelectomy techniques. It also presents published data concerning pregnancy rates after the treatment of varicocele in azoospermic men.

There is growing evidence that varicocele-induced severe OTA or even azoospermia is a result of bilateral disease in the majority of cases [4–6]. In our series, almost 90% of the patients had bilateral disease. In fact, severe semen deficiency expresses a bilateral testicular dysfunction. Previous studies have shown that varicocele is a bilateral disease in over 80% of varicocele-induced infertility [9]. The presence of vascular anastomoses between the right and left spermatic veins demonstrated by venography might explain the development of a secondary right varicocele when a left varicocele is present and vice versa [9]. Animal experimental studies in rabbits also demonstrate the development of secondary right varicocele in animals with iatrogenic left varicocele [10]. The main pathophysiologic pathway leading to semen abnormalities in humans is intratesticular hypoxia induced by high hydrostatic pressure of the internal spermatic vein [11]. This deleterious effect on semen seems to be a variable. This might explain why a subpopulation of men with varicocele are fertile at the time of diagnosis. In fertile patients, seminal molecular factors like decreased levels of cytokines-IL6 and increased seminal antioxidant capacity might also play a major role [12]. In the present series, the difference in

rates of bilaterality between the groups of patients with severe OTA and azoospermia was not statistically significant. Similar findings are noted by Matthews *et al.* [5] and Gat *et al.* [6], with overall bilaterality rates of 82% and 89%, respectively.

There is growing evidence that patients with varicocele-induced severe OTA and even azoospermia might benefit from varicocele repair [4–6, 13]. In a study published in 1998, Matthews *et al.* [5] reported that 55% of men with azoospermia had motile sperm observed in the ejaculate after inguinal microsurgical varicocelectomy and they even contributed to spontaneous pregnancies. This was followed by Kim *et al.* [13], who demonstrated motile sperm in 43% of azoospermic men after microsurgical inguinal varicocele repair, but no pregnancies by natural intercourse within 24 months. Others reported induction of spermatogenesis in 7 of 15 azoospermic men (47%) after microsurgical inguinal varicocele repair [4]. Gat *et al.* [6] observed significant improvement in sperm concentration, motility and morphology in 56.2% of patients with azoospermia and in 94.7% of patients with severe OTA after varicocele embolization treatment, with spontaneous pregnancy rates of 12% and 24%, respectively.

The present study agrees with previous reports indicating that men with azoospermia or severe OTA can benefit from varicocele repair. In our study, 74.5% of patients presented with improved semen parameters. Semen quality improved in 7 (50.0%) patients in the azoospermia group and in 29 (87.9%) patients in the severe OTA group, and 29.8% of the couples achieved preg-

nancy and live births, 64.3% of them unassisted. The positive effect of varicocele treatment on epididymal function, which has been clearly demonstrated in animal experimental studies [14] might have contributed significantly to the achievement of these high unassisted pregnancy rates. A positive effect was also observed in those still requiring assisted reproductive techniques, with only 2 (14.3%) pregnancies being established by ICSI procedure. Our results are in agreement with those of Matthews *et al.* [5] and Gat *et al.* [6], who also achieved high postoperative unassisted pregnancy rates with 58.8% and 62.5% of the pregnancies being unassisted, after microsurgical varicocelectomy and internal spermatic vein embolization, respectively. One serious drawback of the present study is the absence of a control untreated group to determine the true impact of antegrade sclerotherapy on the establishment of pregnancy in azoospermic patients. One recent randomized study including men with varicocele and decreased sperm parameters tried to answer this question without much success because of insufficient patient recruitment [15]. A drawback of that study was the exclusion of patients with severe OTA or azoospermia. A well-designed future prospective randomized study should provide patient stratification according to seminal parameters and age.

The issue of the role of preoperative FSH level as an outcome predictor after varicocele treatment has been addressed in several studies and the results are conflicting [5, 16]. According to the present analysis, postoperative semen parameters and contribution to pregnancy were unrelated to serum FSH levels. In contrast, testicular biopsy proved to be useful in identifying histologic patterns, which could relate to a favorable treatment outcome. The predictive value of testicular histopathology in the treatment outcome in men with complete azoospermia was first addressed by Matthews *et al.* [5], who concluded that the value of varicocele repair in men who have an SCO pattern in the testicular biopsy is uncertain. Kim *et al.* [13] demonstrate that testicular histopathology is the most important predictive factor of outcome in azoospermic patients after varicocele repair. They concluded that patients with SCO pattern and maturation arrest at spermatocyte stage showed no improvement, whereas 50.0% of complete azoospermic men with maturation arrest at spermatid stage and 55.6% of complete azoospermic men with hypospermatogenesis could achieve postoperative improvement. These findings were supported by others thereafter [4]. Recent developments

include the use of testicular tissue telomerase assay as a predictive parameter of the presence of spermatozoa in azoospermic men pre-varicocelectomy and post-varicocelectomy, a method that seems to be very promising in combination with the performance of testicular tissue mincing during biopsy to recover spermatozoa for freezing [17]. According to our results, none of the patients with complete azoospermia and SCO pattern or maturation arrest at spermatocyte stage could achieve spermatogenesis postoperatively, whereas 1 patient (100%) with SCO pattern with focal spermatogenesis, 2 patients (50%) with hypospermatogenesis and 2 (50%) with maturation arrest at spermatid stage presented with motile sperm in the ejaculate postoperatively. The presence of favorable histologic pattern in the majority of our patients (9 out of 12, 75%) could explain the high percentage of overall improvement in semen parameters of azoospermic patients in the current study.

Azoospermia or severe OTA represent testicular dysfunction, which is a result of bilateral varicocele in almost 90% of the cases. Treatment with antegrade sclerotherapy reversed testicular dysfunction and improved spermatogenesis in 50% of the patients with complete azoospermia and almost 90% of the patients with severe OTA. Adequate treatment might eliminate the need for TESE and ICSI in the majority of patients and achieve spontaneous pregnancy rates of 20%. Information regarding testicular histopathology might be an important adjunct in the preoperative counseling of azoospermic patients regarding treatment outcome, whereas preoperative FSH levels seem to be unrelated to treatment success. We recommend that varicocele repair be considered for all men with azoospermia or severe OTA who have a clinically palpable varicocele.

References

- 1 Gorelick JI, Goldstein M. Loss of fertility in men with varicocele. *Fertil Steril* 1993; 59: 613–6.
- 2 Czaplicki M, Bablok L, Janczewski Z. Varicocelectomy in patients with azoospermia. *Arch Androl* 1979; 3: 51–5.
- 3 Madgar I, Weissenberg R, Lunenfeld B, Karasik A, Goldwasser B. Controlled trial of high spermatic vein ligation for varicocele in infertile men. *Fertil Steril* 1995; 63: 120–4.
- 4 Pasqualotto FF, Lucon AM, Hallak J, Goes PM, Saldanha LB, Arap S. Induction of spermatogenesis in azoospermic men after varicocele repair. *Hum Reprod* 2003; 18: 108–12.
- 5 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: 71-5.
- 6 Gat Y, Bachar GN, Everaert K, Levinger U, Gornish M. Induction of spermatogenesis in azoospermic men after internal spermatic vein embolization for the treatment of varicocele. *Hum Reprod* 2005; 20: 1013-7.
 - 7 Tauber R, Johnsen N. Antegrade scrotal sclerotherapy for the treatment of varicocele: Technique and late results. *J Urol* 1994; 151: 386-90.
 - 8 World Health Organization. WHO Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction. Cambridge: Cambridge University Press; 1999.
 - 9 Gat Y, Bachar GN, Zukerman Z, Belenky A, Gornish M. Varicocele: a bilateral disease. *Fertil Steril* 2004; 81: 424-9.
 - 10 Sofikitis N, Miyagawa I. Effects of surgical repair of experimental left varicocele on testicular temperature, spermatogenesis, sperm maturation, endocrine function, and fertility in rabbits. *Arch Androl* 1992; 29: 163-75.
 - 11 Gat Y, Zukerman Z, Chakraborty J, Gornish M. Varicocele, hypoxia and male infertility. Fluid Mechanics analysis of the impaired testicular venous drainage system. *Hum Reprod* 2005; 20: 2614-9.
 - 12 Nallella KP, Allamaneni SS, Pasqualotto FF, Sharma RK, Thomas AJ Jr, Agarwal A. Relationship of interleukin-6 with semen characteristics and oxidative stress in patients with varicocele. *Urology* 2004; 64: 1010-3.
 - 13 Kim ED, Leibman BB, Grinblat DM, Lipshultz LI. Varicocele repair improves semen parameters in azoospermic men with spermatogenic failure. *J Urol* 1999; 162: 737-40.
 - 14 Okada H, Miyagawa I, Incze P, Ono K, Shimamoto K, Yamamoto Y, *et al.* Left varicocelectomy (LVRM) reverses the effect of varicocele on mechanisms and crosstalk between second messenger systems modulating the guinea pig sperm acrosome reaction (SAR). A novel experimental model for the study of varicocele. *J Urol* 1996; 155 (Suppl): N219.
 - 15 Krause W, Muller HH, Schafer H, Weidner W. Does treatment of varicocele improve male fertility? Results of the "Deutsche Varikozelenstudie", a multicentre study of 14 collaborating centres. *Andrologia* 2002; 34: 164-71.
 - 16 Marks JL, McMahon R, Lipshultz LI. Predictive parameters of successful varicocele repair. *J Urol* 1986; 136: 609-12.
 - 17 Giannakis D, Baltogiannis D, Tsoukanelis K, Loutradis D, Miyagawa I, Makrydimas G, *et al.* Role of testicular tissue telomerase assay for the prediction of the presence of testicular spermatozoa in azoospermic men with varicoceles, pre- and post-varicocelectomy. *Andrologia* 2004; 36: 111-22.
 - 18 Johnsen N, Tauber R. Financial analysis of antegrade scrotal sclerotherapy for men with varicoceles. *Br J Urol* 1996; 77: 129-32.
 - 19 Rashid TM, Winfield HN, Lund GO, Troxel SA, Sandlow JJ, Donovan JF. Comparative financial analysis of laparoscopic versus open varix ligation for men with clinically significant varicoceles. American Urological Association (AUA) 89th Annual Meeting; 1994 May 15-20; San Francisco, USA. California: *J Urol*; 1994.
 - 20 Podkamenev VV, Stalmakhovich VN, Urkov PS, Solovjev AA, Iljin VP. Laparoscopic surgery for pediatric varicoceles: Randomized controlled trial. *J Pediatr Surg* 2002; 37: 727-9.

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