Is it worthwhile to operate on subclinical right varicocele in patients with grade II–III varicocele in the left testicle?

Fábio Firmbach Pasqualotto,¹ Antônio Marmo Lucon,² Plínio Moreira de Góes,²
Bernardo Passos Sobreiro,² Jorge Hallak,² Eleonora Bedin Pasqualotto,¹ and Sami Arap²

Submitted March 29, 2004; accepted January 20, 2005

Purpose: To determine whether repair of subclinical varicoceles in the right testicle results in significant seminal improvement in patients with clinical left varicocele.

Methods: Patients were divided into two groups: Group I (unilateral varicocelectomy) and Group II (bilateral varicocelectomy—subclinical left varicocele). The mean sperm concentration before treatment was higher in Group I (21.01 ± 19.1) compared to Group II (5.7 ± 10.7) ($p = 0.04$).

Results: An increase in volume was detected in the left testicle of patients in Group I (17 ± 7.9 vs. 22.81 ± 8.2 ; $p = 0.04$) and in the right testicle of patients in Group II (18.4 ± 6.2 vs. 22.3 ± 6.5 ; $p = 0.04$). Although the mean postoperative sperm concentration in Group I increased slightly (25.7 ± 22.8), the mean sperm concentration in Group II increased significantly (30.32 ± 9.8 ; $p = 0.03$). Pregnancy rate was higher in Group II (66.7%) compared to Group I (33.3%).

Conclusions: Even a small, subclinical unrepaired varicocele continues to have a detrimental effect on bilateral testis function in a patient with grade II–III left varicocele.

KEY WORDS: Spermatozoa; semen; infertility; subclinical; varicocele.

INTRODUCTION

Clinical studies and laboratory research have provided convincing evidence that varicoceles may have a detrimental effect on spermatogenesis (1,2). In fact, semen quality uniformly declines in animals with induced varicoceles, even when only a left varicocele is produced (3). Furthermore, the varicocele does not only influence the physiology and the reproductive potential of the spermatozoa, but also the fertilizing capacity of the haploid male gamete (4). In a very elegant study, Sofikitis *et al.*, studying animal models, observed that the surgical repair of the secondary

right varicocele improved all semen parameters indicating the harmful consequences of the primary induced left varicocele on the right testis (5). Therefore, it appears that the primary left varicocele leads to a development of a secondary right varicocele due to activation of a tension reception within the wall of the left testicular vein.

There are many unresolved clinical questions related to varicoceles, for instance, as to whether subclinical varicoceles should be diagnosed and treated (6–15). Therefore, even though recent progress in diagnostic methods has revealed a higher incidence of subclinical varicoceles, the clinical significance of this is controversial as regards male infertility (1,2,16).

There are several studies showing that there is a significant improvement in semen parameters following varicocelectomy and in accordance with varicocele size (17–19). Marsman and Schats noted that

¹ University of Caxias do Sul, RS, Brazil.

² Divisão de Clínica Urológica, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, University of São Paulo, Brazil.

despite 59 articles on this subject in a 15-year period, there is still no consensus on the need to diagnose or as to indications for the treatment of subclinical varicoceles (11). The consensus is that bilateral surgical repair is indicated for large bilateral varicoceles.

A previous study has shown that subsequent right varicoectomy results in further improvement in semen analysis in 56% of infertile men who had previously undergone left varicoectomy and had a missed palpable right varicocele (20). In addition, Scherr and Goldstein recently showed that bilateral varicoectomy results in significantly greater improvement in postoperative seminal parameters than in cases of unilateral repair in patients with grades II and III left varicoceles associated with grade I right varicoceles (21).

When one side is palpable and the other side is subclinical, the question is as to whether to repair both sides. The purpose of this study was to determine whether it is worthwhile performing a bilateral varicoectomy in patients with left clinical and right subclinical varicoceles.

MATERIAL AND METHODS

The study was approved by the University of São Paulo review board and a written informed consent was obtained for all patients. In a prospective manner, one hundred and twelve patients with varicocele and primary infertility were evaluated between July 1999 and April 2001. The minimum duration of infertility required was defined as a failure to establish a pregnancy within 1 year with unprotected intercourse. No one of them was taking any antioxidants.

Of these 112 men with clinical varicocele, 50 patients had a grade II-III left varicocele without a clinical right varicocele. Testicular ultrasound was performed on the patients by only one physician specialist in ultrasound in order to measure the testicular size and detect subclinical varicoceles (diameter of the internal spermatic vein larger than 3 mm.) on the right side, resulting in 20 subclinical right varicoceles. The mean age of the wife at presentation was 30.3 ± 3.9 years. All women were normal based on history, hormonal levels and hysterosalpingogram.

All patients had at least two semen analyses obtained by masturbation after 2 to 5 days of abstinence and specimens were examined within one hour after collection and assessed for sperm concentration and motility. Levels of serum follicle-stimulating hormone, luteinizing hormone and testosterone were obtained for each patient.

Patients were divided into two groups according to the presence or not of a subclinical right varicocele: group I (left grade II or III varicoceles, $n = 30$) and group II (left II or III varicoceles and right subclinical varicoceles, $n = 20$).

No differences were seen in the mean age (32.5 ± 4.5 and 29.7 ± 3.6), levels of LH (5.2 ± 2.4 and 4.9 ± 1.8), FSH (6.9 ± 3.1 and 7.2 ± 2.9) and testosterone (617.2 ± 160.2 and 639.2 ± 190.3), nor in the mean volume of the right (18.79 ± 8.71 and 18.39 ± 6.27) or left testicles (17 ± 7.9 and 19.28 ± 8.9) between Groups I and II, respectively ($p > 0.05$).

The mean sperm concentration was higher in Group I (21.01 ± 19.1) as compared to Group II (5.7 ± 10.7) ($p = 0.04$). The mean sperm motility before treatment was the same in Groups I (43.5 ± 24.3) and II (39.4 ± 19.5) ($p = 0.08$). All patients in Group I underwent unilateral varicoectomy and those in Group II bilateral varicoectomy, either by the microsurgical subinguinal approach or by the inguinal approach without the use of magnification. Patients were operated by either FFP or JH, both specialists in male infertility treatment. The mean operating room time was higher in Group II (121.65 ± 33.07 min) as compared to Group I (72.75 ± 23.82 min; $p = 0.03$).

Two new semen analyses were performed on each patient at 6 and 12 months post operatively. Levels of FSH, LH and testosterone were assessed as well. The mean age $\pm$ Standard Deviation (*SD*) of the wives at presentation was 29.8 ± 6.95 . Pregnancy data was available for 36 patients (18 in each group) after a minimum of 18 months following the surgery.

Values are presented as the mean $\pm$ *SD*, with Student's *t*-test and the Wilcoxon paired test used for statistical evaluation. A chi-square test was used in order to compare pregnancy rates between Groups I and II. A value of $p < 0.05$ was considered statistically significant. Statistical calculations were performed with computer software (Statistical Package for Social Sciences, version 10.0 - SPSS inc., Chicago, IL, USA).

RESULTS

No improvement was seen in LH (5.9 ± 2.6 and 5.1 ± 1.8), FSH (6.5 ± 2.9 and 5.2 ± 3.1) and testosterone levels (671.3 ± 136.1 and 680.3 ± 143.2) either in Group I or Group II (Table I).

An increase in the volume was detected in the left testes of patients in Group I (22.81 ± 8.2 ; $p = 0.04$) and in the right testes of patients in Group II (22.3 ± 6.5 ; $p = 0.04$). However, no increase in volume was

Table I. Hormonal Levels Before and After Surgery in Patients Without (Group I) and with Subclinical (Group II) Right Varicoceles in Patients with Grade II–III Varicocele in the Left Testicle

Variables	Group I			Group II		
	Before surgery	After surgery	<i>p</i>	Before surgery	After surgery	<i>p</i>
LH	5.2 ± 2.4	5.9 ± 2.6	0.09	4.9 ± 1.8	5.1 ± 1.8	0.09
FSH	6.9 ± 3.1	6.5 ± 2.9	0.09	7.2 ± 2.9	5.2 ± 3.1	0.07
Testosterone	617.2 ± 160.2	671.3 ± 136.1	0.07	639.2 ± 190.3	680.3 ± 143.2	0.08

Note. *p* < 0.05 was considered significant.

seen either in the left testes of Group II (19.98 ± 8.5 ; $p = 0.08$), or in the right testes of Group I (19.45 ± 8.47 ; $p = 0.07$) (Table II).

The mean postoperative sperm concentration in Group I was slightly increased (25.7 ± 22.8), whereas that in Group II increased significantly (30.32 ± 9.8 ; $p = 0.03$). The mean sperm motility remained the same in Groups I (39.5 ± 19.4 ; $p = 0.08$) and II (41.2 ± 18.9 ; $p = 0.09$) (Table III). The pregnancy rate was higher in Group II (12/18; 66.7%) than in Group I (6/18; 33.3%, $p = 0.04$).

DISCUSSION

There are many studies in the literature suggesting an acquired, apparently progressive infertility due to the varicocele (22,23). In fact, varicocelectomy has become the most commonly performed operation in male infertility (1,2,22,24–26). However, couples have to be counseled that they will have to wait for at least 12 months following varicocelectomy before deciding to proceed with any type of assisted reproductive technique (ART) (27,28).

The increased prevalence of varicoceles amongst men with secondary infertility suggests that this vascular lesion has a progressive rather than static effect upon male infertility. These studies also conclude that while the incidence of varicoceles in men with secondary infertility is higher than in men with primary infertility, the serum concentrations of FSH is also significantly higher in men with secondary

infertility, suggesting a greater degree of seminiferous tubular damage over time (22). On the other hand, the observed increase in the prevalence of varicoceles may be due either to an absolute increase in the number of men with varicoceles who have secondary infertility or a relative increase due to a reduction of other etiologies that cause male infertility. Another factor which may affect the interpretation of these studies is the fertility potential of the spouse, greatly reduced with advancing age (24,25).

The exact mechanism by which an incidental varicocele becomes pathological remains unclear (29). Recently, studies have demonstrated the role of oxidative stress in men with varicocele and infertility (30).

A topic of considerable debate over the years has been as to whether varicocele size affects outcome of varicocele repair (1,2,6,12,17). This is of considerable importance since early reports have suggested that varicocele size had no impact upon subsequent pregnancy rates, leading to the conclusion that very small varicoceles, even subclinical ones, should be identified and treated (8,9,31). The progressive rather than static effect of a varicocele upon male infertility suggests that, over time, the presence of a subclinical varicocele may result in abnormalities in the semen analysis and subsequently infertility.

A number of studies have looked for specific markers of testicular injury in infertile men with clinical varicoceles (29). Even though Dubin and Hotchkiss have described specific findings of

Table II. Testicular Size Before and After Surgery in Patients Without (Group I) and with (Group II) Subclinical Right Varicoceles in Patients with Grade II–III Varicocele in the Left Testicle

Variables	Group I			Group II		
	Before surgery	After surgery	<i>p</i>	Before surgery	After surgery	<i>p</i>
Right testicle	18.79 ± 8.71	19.45 ± 8.47	0.07	18.39 ± 6.27	22.3 ± 6.5	0.04
Left testicle	17 ± 7.9	22.8 ± 8.2	0.04	19.28 ± 8.9	19.98 ± 8.5	0.08

Note. *p* < 0.05 was considered significant.

Table III. Sperm Concentration and Motility Before and After Surgery in Patients Without (Group I) and with (Group II) Subclinical Right Varicoceles in Patients with Grade II-III Varicocele in the Left Testicle

Variables	Group I			Group II		
	Before surgery	After surgery	<i>p</i>	Before surgery	After surgery	<i>p</i>
Sperm concentration (X 10 ⁶ /mL)	21.01 ± 19.1	25.7 ± 22.8	0.06	5.7 ± 10.7	30.32 ± 9.8	0.03
Sperm motility (%)	43.5 ± 24.3	39.5 ± 19.4	0.08	39.4 ± 19.5	41.2 ± 18.9	0.09

Note. *p* < 0.05 was considered significant.

germinal cell hypoplasia and premature sloughing of immature forms within the lumina of the seminiferous tubules in their study of 88 subfertile men with varicoceles, most of the reported changes in testicular histology and semen quality seen in these men are largely nonspecific (32). Varicoceles not only have deleterious effects on the hormonal aspects of spermatogenesis but also in decreased function through testicular hyperthermia, reflux of toxic metabolites and seminiferous tubular hypoxia secondary to venous stasis (3,29). Since in our series of patients no differences in the hormonal levels were found between patients with and those without right subclinical varicoceles when a clinical left grade II-III varicocele was present, we argue that a subclinical varicocele does not impaired hormonal levels.

The accuracy of diagnosis must be taken into account when subclinical varicocele repair is addressed (1,16). It is well known that there is no "gold standard" for the diagnosis of varicoceles. The detection of a clinical varicocele requires an adept clinician, a warm room and a co-operative patient for proper diagnosis. Given the subjective character of a clinical examination, non-invasive diagnostic testing (e.g. ultrasonography) has been employed to attempt to quantify varicocele size in patients with clinical varicocele and to evaluate the presence or not of a subclinical varicocele in the right side. Ultrasound has also been valuable in following the regression of varicoceles after repair. With the widespread application of scrotal ultrasonography and colour Doppler imaging, varicoceles are being reported in up to 91% of subfertile cases, most of whom were previously regarded as having idiopathic etiology (33). This dramatic increase in the incidence of bilateral varicoceles in infertile patients as compared to that previously reported is largely due to cases of overlooked right varicocele (21).

Relative ipsilateral testicular atrophy is a specific finding in men with left varicoceles; however, because men with varicocele and prior fertility also may have associated atrophy of the testicle, this finding

alone does not appear to be predictive of fertility status. Pinto *et al.* reported that the difference between right and left testicular volume was lower in fertile men without varicoceles than in either fertile or infertile men with left varicoceles (34). Zini *et al.* examined the influence of varicoceles on testicular size with ultrasound measurements of testicular volume (14). The authors showed that a clinical left varicocele can impact negatively on left testicular volume and a subclinical varicocele also is associated with decreased left testicular volume. Even though no differences were seen in the right testicle volume between the groups evaluated, the right testicle was lower in patients with subclinical varicocele compared to the other group. Of utmost importance, in our series, an improvement was detected after surgery in the left testes of patients without right subclinical varicocele and right testes of patients with right subclinical varicoceles. The fact that the left testicular volume increased in patients with only left varicocele and did not increased in patients with left clinical varicocele and a right subclinical varicocele is unknown. Therefore, a varicocelectomy performed in a patient with subclinical varicocele may increase testicular size. These results suggest that, even though the surgery was performed in infertile adult men, the varicocelectomy procedure may increase the testicle size and this fact, in turn, may be the reason for the surgery's leading to an improvement in semen analysis.

CONCLUSIONS

In our study, we detected that the mean postoperative sperm concentration significantly increased when the right subclinical varicocele was repaired, suggesting that, in patients with left clinical varicocele, scrotal ultrasonography may be employed to detect whether or not a subclinical right varicocele is present. If a right subclinical varicocele is present in patients with a left clinical varicocele, a bilateral varicocelectomy should be performed to treat these patients. Further studies must be done

to compare unilateral or bilateral varicocelectomy in patients with left clinical varicocele and right subclinical varicocele.

REFERENCES

1. Jarow JP, Sharlip ID, Belker AM, Lipshultz LI, Sigman M, Thomas AJ, *et al.*: Best practice policies for male infertility. *J. Urol.* 2002;167:2138–2144
2. Weidner W, Colpi GM, Hargreave TB, Papp GK, Pomerol JM: EAU guidelines on male infertility. *Eur Urol* 2002;42:313–322
3. Sofikitis N, Miyagawa I: Bilateral effect of varicocele on testicular metabolism in the rat. *Int J Fertil* 1994;39:239–247
4. Sofikitis NV, Miyagawa I, Incze P, Andrighetti S: Detrimental effect of left varicocele on the reproductive capacity of the early haploid male gamete. *J Urol* 1996;156:267–270
5. Sofikitis NV, Takahashi C, Nakamura I, Hirakawa S, Miyagawa I: Surgical repair of secondary right varicocele in rats with primary left varicocele: effects on fertility, testicular temperature, spermatogenesis, and sperm maturation. *Arch Androl* 1992;28(1):43–52
6. Dubin L, Amelar RD: Varicocele size and results of varicocelectomy in selected subfertile men with varicocele. *Fertil Steril* 1970;21:606–609
7. Yarbrough MA, Burns JR, Keller FS: Incidence and clinical significance of subclinical scrotal varicoceles. *J Urol* 1989;141(6):1372–1374
8. McClure DR, Khoo D, Jarvi K, Hricak H: Subclinical varicocele: the effectiveness of varicocelectomy. *J Urol* 1991;145:789–791
9. Dhabuwala CB, Hamid S, Mogissi KS: Clinical versus subclinical varicocele: improvement in fertility after varicocelectomy. *Fertil Steril* 1992;57(4): 854–857
10. Howards SS: Subclinical varicocele. *Fertil. Steril.* 1992;57(4): 725–726
11. Marsman JW, Schats R: The subclinical varicocele debate. *Hum Reprod* 1994;9:1–8
12. Jarow JP, Ogle SR, Eskew A: Seminal improvement following repair of ultrasound detected subclinical varicoceles. *J Urol* 1996;155:1287–1290
13. Yamamoto M, Hibi H, Hirata Y, Miyake K, Ishigaki T: Effect of varicocelectomy on sperm parameters and pregnancy rate in patients with subclinical varicocele: a randomized prospective controlled study. *J Urol* 1996;155:1636–1638
14. Zini A, Buckspan M, Berardinucci D, Jarvi K: The influence of clinical and subclinical varicocele on testicular volume. *Fertil. Steril.* 1997;68: 671–674
15. Unol D, Yeni E, Verit A, Karatas OF: Clomiphene citrate versus varicocelectomy in treatment of subclinical varicocele: a prospective randomized study. *Int J Urol* 2001;8(5):227–230
16. Jarow JP: Effects of varicocele on male fertility. *Hum Reprod Update* 2001; 7(1):59–64
17. Steckel J, Dicker AP, Goldstein M: Relationship between varicocele size and response to varicocelectomy. *J Urol* 1993;149:769–771
18. Schlesinger MH, Wilets IF, Nagler HM: Treatment outcome after varicocelectomy. *Urol Clin North Am.* 1994;21:517–529
19. Kamal KM, Javeri K, Zini A: Microsurgical varicocelectomy in the era of assisted reproductive technology: influence of initial semen quality on pregnancy rates. *Fertil Steril* 2001;75:1013–1016
20. Amelar RD, Dubin L: Right varicocelectomy in selected infertile patients who have failed to improve after previous left varicocelectomy. *Fertil Steril* 1987;47:833
21. Scherr D, Goldstein M: Comparison of bilateral versus unilateral varicocelectomy in men with palpable bilateral varicoceles. *J Urol* 1999; 162:85–88
22. Witt MA, Lipshultz LI: Varicocele: A progressive or static lesion? *Urology* 1993; 42: 541–543
23. Cozzolino DJ, Lipshultz LI: Varicocele as a progressive lesion: Positive effect of varicocele repair. *Hum. Reprod. Update* 2001;17:55–58
24. Kamischke A, Nieschlag E: Varicocele treatment in the light of evidence-based andrology. *Hum. Reprod. Update* 2001; 7(1): 65–69
25. Silber SJ: The varicocele dilemma. *Hum. Reprod. Update* 2001; 7(1): 70–77
26. Redmon JB, Carey P, Pryor JL: Varicocele—the most common cause of male factor infertility. *Hum. Reprod. Update* 2002;8(1):53–58
27. Daitch JA, Bedaiwy MA, Pasqualotto EB, Hendin BN, Hallak J, Falcone T, *et al.*: Varicocelectomy improves intrauterine insemination success rates in men with varicocele. *J Urol* 2001;165:1510–1513
28. Pasqualotto FF, Lucon AM, Hallak J, Goes PM, Saldanha LB, Arap S: Induction of spermatogenesis in azoospermic men after varicocele repair. *Hum. Reprod.* 2003;18:108–112
29. Naughton C, Nangia A, Agarwal A: Pathophysiology of varicoceles in male infertility. *Hum Reprod Update* 2002;7:473–481
30. Pasqualotto FF, Sharma RK, Nelson DR, Thomas AJ Jr, Agarwal A: Relationship between oxidative stress, semen characteristics and clinical diagnosis in men undergoing infertility investigation. *Fertil Steril* 2000;73:459–464
31. McClure RD, Hricak H: Scrotal ultrasound in the infertile man: detection of subclinical unilateral and bilateral varicoceles. *J Urol* 1986;135:711–715
32. Dubin L, Hotchkiss RS: Testis biopsy in subfertile men with varicocele. *Fertil Steril* 1969;20:51–57
33. Resim S, Cek M, Fazlioglu A, Caskurku T, Gurbuz G, Sevin G: Echocolor doppler ultrasonography in the diagnosis of varicocele. *Internat Urol Nephrol* 1999;31:371–382
34. Pinto KJ, Kroovand L, Jarow JP: Varicocele related testicular atrophy and its predictive effect upon fertility. *J Urol* 1994;152:788–790