

# Semen profile, testicular volume, and hormonal levels in infertile patients with varicoceles compared with fertile men with and without varicoceles

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**Objective:** To assess semen analysis, testicular volume, and hormone levels in fertile and infertile patients with varicoceles and fertile men without varicoceles.

**Design:** Retrospective study.

**Setting:** Academic medical center.

**Patient(s):** Patients were divided into three groups: fertile men with varicoceles (n = 79), infertile men with varicoceles (n = 71), and fertile men without varicoceles (n = 217).

**Intervention(s):** None.

**Main Outcome Measure(s):** Levels of LH, FSH, and total T and testicular volume in fertile and infertile men with varicoceles and fertile controls without varicoceles.

**Result(s):** LH (IU/L) and T (ng/dl) levels were not statistically different across the three groups. FSH levels were significantly higher in infertile men with varicoceles ( $7.8 \pm 7.6$  IU/L) than in the fertile men with varicoceles ( $3.5 \pm 2.1$  IU/L) or in fertile men without varicoceles ( $3.5 \pm 1.9$  IU/L). The right testicle was smaller in infertile patients with varicoceles ( $18.7 \pm 8.3$  cm<sup>3</sup>) than in fertile men with varicoceles ( $25.2 \pm 13$  cm<sup>3</sup>) or in fertile men without varicoceles ( $24.9 \pm 10.7$  cm<sup>3</sup>). In addition, the left testicle was smaller in infertile men with varicoceles ( $17.6 \pm 8.9$  cm<sup>3</sup>) than in fertile men with varicoceles ( $21.6 \pm 7.8$  cm<sup>3</sup>) or in fertile men without varicoceles ( $23.4 \pm 8.3$  cm<sup>3</sup>). Sperm concentration was lower in infertile men with varicoceles ( $33.7 \pm 23.3 \times 10^6$ /mL) than in fertile men with varicoceles ( $101.8 \pm 76.6 \times 10^6$ /mL) or in fertile men without varicoceles ( $111.8 \pm 74.2 \times 10^6$ /mL). In addition, sperm motility was lower in infertile men with varicoceles ( $37.2\% \pm 23.9\%$ ) than in fertile men with varicoceles ( $53.9\% \pm 17.4\%$ ) or fertile men without varicoceles ( $58.9\% \pm 15.8\%$ ).

**Conclusion(s):** Infertile patients with varicoceles have higher levels of FSH, smaller testes, and lower sperm concentration and motility compared with controls with or without varicoceles. No statistical differences were seen in the variables evaluated among the fertile men with incidental varicoceles detected at physical examination and those without varicoceles. (Fertil Steril® 2005;83:74–7. ©2005 by American Society for Reproductive Medicine.)

**Key Words:** Testis, semen, varicocele, hormones, infertility

Although the incidence of varicoceles in the male general population is roughly 15%, it has been implicated as a factor responsible for infertility in as much as one-third of the infertile population (1–4). Many clinicians believe that varicoceles exert a progressive deleterious effect over time (5, 6). The increased prevalence of varicoceles among men with secondary infertility suggests that this vascular lesion has a progressive rather than static effect on male infertility (4–7). It was found that of 259 patients with primary infertility, 50% were found to have varicoceles, while in 259 patients with secondary infertility 69% were found to have varicoceles (5).

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Similar findings were observed in a study of 888 infertile men, of whom 94% of men with secondary and 35% of men with primary infertility had varicoceles (7). Therefore, a patient who is considered fertile today may not be in the future.

This difference in the incidence of varicoceles in the two populations (primary and secondary varicoceles) was significant, indicating an acquired and apparent progressive rate of infertility due to the presence of the varicoceles (5, 6, 8). They (5, 6) also concluded that the serum concentration of FSH is significantly higher in men with secondary infertility, which suggests a greater degree of seminiferous tubular damage over time. On the other hand, the observed increase in the prevalence of varicoceles may be due to either an absolute increase in the number of men with varicoceles who have secondary infertility or a relative increase due to a reduction in other etiologies that cause male factor infertility (4, 9–11). In addition, men with varicoceles who are ex-

posed to cigarette smoking may have an additional risk for the development of testicular damage (12). The fertility potential of the spouse, which is greatly reduced with advancing age, is another factor that may affect the interpretation of these studies (13).

The exact mechanism by which an incidental varicocele becomes pathological remains unclear (14–18). Varicoceles may produce a gradual temporal loss of normal spermatogenesis over time as a result of a raised intratesticular temperature and subsequent progressive germ cell injury. The role of oxidative stress in men with varicoceles and infertility has recently been demonstrated (19, 20). Furthermore, varicoceles do not only influence the physiology and the reproductive potential of the spermatozoa, but also the fertilizing capacity of the haploid male gamete (21).

In a very elegant study, Sofikitis and Miyagawa observed that the surgical repair of an experimental varicocele in the rabbit can significantly improve the parameters that indicate the harmful effects of the varicoceles on the testicles (22). In addition, Sofikitis et al., studying animal models, observed that the surgical repair of the secondary right varicocele improved all semen parameters that indicate the harmful consequences of the primary induced left varicocele on the right testis (23). Therefore, it appears that the primary left varicocele leads to a development of a secondary right varicocele because of activation of a tension reception within the wall of the left testicular vein.

Men who presented for infertility evaluation were reevaluated because of persistent fertility problems and presented a statistically significant deterioration in sperm density and motility in a study published by Chehval and Purcell (8). On the other hand, it was recently demonstrated that semen quality in men with initially asymptomatic varicoceles showed no change over a long time when compared with controls without varicoceles (14).

In current medical practice, impairment of semen parameters, in particular, a decrease in sperm count, sperm motility, and morphologically normal spermatozoa with an increase in head abnormalities, suggests that a varicocele may be present (2, 3, 15–18). Studies evaluating the hormone levels in infertile men with varicoceles have shown that the development of hormonal dysfunction of the Leydig cells may be caused by compensatory proliferation and hyperplasia of some of those cells (17, 18). Contradictory findings have been published in the literature about the T levels after varicocelectomy (17, 18, 24).

The purpose of our study was to evaluate sperm concentration and sperm motility according to the World Health Organization (WHO) criteria (25), the levels of LH, FSH, and total T, and testicular volume in fertile and infertile men with varicoceles and fertile men without varicoceles.

## MATERIAL AND METHODS

This study was approved by the Institutional Review Board, and the patients involved gave their informed consent. The

records of 71 infertile patients with clinical varicoceles, 79 fertile men with clinical varicoceles, and 217 fertile men without clinical varicoceles between January 1999 and February 2001 were evaluated. Fertile men with and without incidental varicoceles were recruited from our database of men who sought vasectomy for sterilization purposes. All of them were 25 years old or older and had at least two children according to a protocol carried out in our university hospital.

The minimum duration of infertility required was defined as a failure to establish a pregnancy within 1 year with unprotected intercourse. A basic infertility evaluation including a detailed history and a complete physical examination was undertaken. Testicular volumes were evaluated in all patients with calipers by the same investigator (FFP).

Semen samples were collected from all patients after at least 48 hours of sexual abstinence in sterile containers and allowed to liquefy at 37°C for 30 minutes and analyzed for sperm concentration and percentage motility according to WHO criteria. Serum FSH, LH, and T levels and testicular volume were also assessed in all the patients. No patients were taking vitamin C or E and four who had pyospermia were treated before varicocele repair.

Values are presented as mean  $\pm$  SD, with Student's *t*-test and the Wilcoxon paired test used for statistical evaluation.  $P < .05$  was considered statistically significant. Statistical calculations were performed with computer software.

## RESULTS

Infertile patients with varicoceles had a lower mean age ( $28.7 \pm 6.9$  years) than the fertile men with varicoceles ( $35.5 \pm 6.1$  years;  $P = .04$ ) or the fertile men without varicoceles ( $34.9 \pm 6.1$  years;  $P = .04$ ). However, no differences were seen between fertile men with and without varicoceles ( $P = .234$ ) (Table 1).

The right testicle was smaller in infertile men with varicoceles ( $18.7 \pm 8.3$  cm<sup>3</sup>) than in fertile men with ( $25.2 \pm 13$  cm<sup>3</sup>) or without varicoceles ( $24.9 \pm 10.7$  cm<sup>3</sup>) ( $P < .05$ ). No statistical differences were seen between fertile men with and without varicoceles ( $P = .185$ ). In addition, the left testicle was smaller in infertile men with varicoceles ( $17.6 \pm 8.9$  cm<sup>3</sup>) than in fertile men with ( $21.6 \pm 7.8$  cm<sup>3</sup>) or without varicoceles ( $23.4 \pm 8.3$  cm<sup>3</sup>) ( $P < .05$ ). No statistical differences were detected between fertile men with or without varicoceles ( $P = .429$ ).

LH and T levels were not statistically different across the three groups ( $P > .05$ ). FSH levels were significantly higher in infertile patients with varicoceles ( $7.8 \pm 7.6$  IU/L) than in fertile men with ( $3.5 \pm 2.1$  IU/L) or without varicoceles ( $3.5 \pm 1.9$  IU/L) ( $P < .05$ ). No statistical differences were seen between fertile men with and without varicoceles ( $P = .128$ ).

Sperm concentration was lower in infertile men with varicoceles ( $33.7 \pm 23.3 \times 10^6$ /mL) than in fertile men with ( $101.8 \pm 76.6 \times 10^6$ /mL) or without varicoceles ( $111.8 \pm$

TABLE 1

Variables evaluated in infertile men with varicoceles, fertile men with varicoceles, and fertile men without varicoceles.

Variables	Incidental varicocele	<i>P</i> <sup>a</sup>	Infertile men with varicoceles	<i>P</i> <sup>b</sup>	Fertile men without varicoceles (group C)	<i>P</i> <sup>c</sup>	Incidental varicocele
Age (years ± SD)	35.5 ± 6.1	.03	28.7 ± 6.9	.04	34.9 ± 6.1	.234	35.5 ± 6.1
FSH (IU/L ± SD)	3.5 ± 2.1	.04	7.8 ± 7.6	.04	3.5 ± 1.9	.128	3.5 ± 2.1
LH (IU/L ± SD)	4.5 ± 2.2	.265	4.3 ± 1.9	.451	4.7 ± 2.1	.785	4.5 ± 2.2
T	574.2 ± 98.2	.856	540.36 ± 94.5	.673	590.72 ± 112.6	.650	574.2 ± 98.2
Left testicle (cm <sup>3</sup> )	21.6 ± 7.8	.04	17.6 ± 8.9	.03	23.4 ± 8.3	.429	21.6 ± 7.8
Right testicle (cm <sup>3</sup> )	25.2 ± 13	.02	18.7 ± 8.3	.03	24.9 ± 10.7	.185	25.2 ± 13
Sperm concentration (×10 <sup>6</sup> /mL)	101.8 ± 76.6	.02	33.7 ± 23.3	.02	111.8 ± 74.2	.867	101.8 ± 76.6
Sperm motility (%)	53.9 ± 17.4	.04	37.2 ± 23.9	.04	58.9 ± 15.8	.698	53.9 ± 17.4

Note: *P* < .05 was considered significant.

<sup>a</sup>Comparison between incidental varicocele and infertile men with varicocele.

<sup>b</sup>Comparison between infertile men with varicocele and fertile men without varicocele.

<sup>c</sup>Comparison between fertile men without varicocele and incidental varicocele.

Pasqualotto. Parameters detected in patients with varicoceles. *Fertil Steril* 2005.

74.2 × 10<sup>6</sup>/mL) (*P* < .05). No statistical differences were seen between fertile men with and without varicoceles (*P* = .867). In addition, sperm motility was lower in infertile men with varicoceles (37.2% ± 23.9%) than in fertile men with (53.9% ± 17.4%) or without varicoceles (58.9% ± 15.8%) (*P* < .05). No statistical differences were detected between fertile men with and without varicoceles (*P* = .698).

## DISCUSSION

It has been proposed that the aging process could provide an explanation for a decline over time in semen quality (26). In our study, the infertile patients with varicoceles had a lower mean age than the fertile men with varicoceles or the fertile men without varicoceles with no differences between fertile men with and without varicoceles. Therefore, even if aging is one of the causes for semen quality impairment, this is not an issue in this study because the group of infertile men was younger than the other two groups.

Although there are some reports showing that varicoceles disturb the Leydig cell function, resulting in a decrease in T biosynthesis (17, 18, 24), in our study, LH and T levels were not statistically different across the three groups of patients evaluated. However, in our study, FSH levels were significantly higher in the infertile patients with varicoceles than in the fertile men with or without varicoceles, with no differences between these two groups. The highest levels of FSH seen in infertile patients with varicoceles could certainly be related to the lower sperm concentration, lower sperm motility, and decreased testicular volume in these patients.

The mechanism by which an incidental varicocele becomes pathological remains unclear (17–20, 27–29). Vari-

coceles may induce a gradual temporal loss of normal spermatogenesis over time as a result of raised intratesticular temperatures and subsequent progressive germ cell injury or loss (17, 18). Recently, studies have demonstrated the role of oxidative stress in infertile men with varicoceles (19, 20, 28, 29). Another possible mechanism by which an incidental varicocele may subsequently impair sperm production was proposed in a Sprague-Dawley rat model (30). The investigators found that the varicocele may act as a cofactor in association with certain gonadotoxins, producing a greater degree of injury in the varicocele-associated testicle than in the testicle not associated with a varicocele (30). A varicocele could then predispose the testis to further noxious insults, exposure to which would most likely increase over time. Recently, Evers and Collins did a systematic review of seven studies that they identified by searching Medline and a register of controlled trials (31). They observed that varicocele treatment was not effective in trials restricted to male subfertility with clinical varicoceles or in those that included men with subclinical varicoceles or normal semen analysis. However, this systematic review, done with a meta-analytical method, might have had insufficient power to detect small effects because of the small number of patients in some subgroups. In addition, surgical ligation is an option in the management of patients with painful varicoceles (32).

To eliminate interobserver variation, testicular volumes were assessed by the same physician (FFP) in all patients. A multicenter study conducted by WHO found that varicoceles (mostly on the left side) were associated with relative left testicular hypotrophy when compared with the contralateral testicle (33). Lipshultz and Corriere demonstrated that left

testicular size in men with varicoceles was significantly decreased compared with that of a control group of men (34). In addition, Pinto et al. reported that the difference between right and left testicular volume was lower in infertile men without varicoceles than in either fertile or infertile men with a clinical left varicocele (35). However, this finding alone does not appear to be predictive of fertility potential in men with clinical varicoceles. In our series of patients, both testicles were smaller in infertile men with varicoceles than in fertile men with or without varicoceles. In addition, no statistical differences were detected between fertile men with or without varicoceles.

A decrease in semen quality, not only in sperm concentration and percent motility, but also in morphologically normal spermatozoa, is often found in infertile men with varicoceles. In our series of patients, sperm concentration and percent motility was lower in infertile men with varicoceles than in fertile men with or without varicoceles. In addition, sperm motility was lower in infertile men with varicoceles than in fertile men with or without varicoceles. Also, no differences were detected in sperm concentration and sperm motility in the fertile group, irrespective of the presence or absence of varicoceles.

These data are of clinical importance because they show that the presence of a clinical varicocele does not rule out fertility in men. Varicoceles may cause damage to the testicles but not to all of them. The decision for performing a varicocelectomy or not should be tailored to the semen profile and not to the presence or absence of this clinical entity.

## REFERENCES

- Redmon JB, Carey P, Pryor JL. Varicocele—the most common cause of male factor infertility. *Hum Reprod Update* 2002;8:53–8.
- Jarow JP, Sharlip ID, Belker AM, Lipshultz LI, Sigman M, Thomas AJ, et al. for the Male Infertility Best Practice Policy Committee of the American Urological Association. *J Urol* 2002;167:2138–44.
- 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;75:1013–6.
- Jarow JP, Coburn M, Sigman M. Incidence of varicoceles in men with primary and secondary infertility. *Urology* 1996;47:73–6.
- Witt MA, Lipshultz LI. Varicocele: a progressive or static lesion? *Urology* 1993;42:541–3.
- Cozzolino DJ, Lipshultz LI. Varicocele as a progressive lesion: positive effect of varicocele repair. *Hum Reprod Update* 2001;17:55–8.
- Gorelick JJ, Goldstein M. Loss of fertility in men with varicocele. *Fertil Steril* 1993;59:613–6.
- Chehval MJ, Purcell MH. Deterioration of semen parameters in men with untreated varicocele: evidence of progressive testicular damage. *Fertil Steril* 1992;57:174–7.
- Jarow JP. Effects of varicocele on male fertility. *Hum Reprod Update* 2001;7:59–64.
- Kamischke A, Nieschlag E. Varicocele treatment in the light of evidence-based andrology. *Hum Reprod Update* 2001;7:65–9.
- Silber SJ. The varicocele dilemma. *Hum Reprod Update* 2001;7:70–7.
- El-Mulla KF, Kohn FM, El Beheiry AH, Schill WB. The effect of smoking and varicocele on human sperm acrosin activity and acrosome reaction. *Hum Reprod* 1995;10:3190–4.
- Silber SJ, Nagy Z, Devroey P, Camus M, Van Steirteghem AC. The effect of female age and ovarian reserve on pregnancy rate in male infertility: treatment of azoospermia with sperm retrieval and intracytoplasmic sperm injection. *Hum Reprod* 1997;12:2693–700.
- Lund L, Larsen SB. A follow-up study of semen quality and fertility in men with varicocele testis and in control subjects. *BJU* 1998;82:682–6.
- Schatte EC, Hirshberg SJ, Fallick ML, Lipschultz LI, Kim ED. Varicocelectomy improves sperm strict morphology and motility. *J Urol* 1998;160:1338–40.
- Vazquez-Levin MH, Friedmann P, Goldberg SI, Medley NE, Nagler HM. Response of routine semen analysis and critical assessment of sperm morphology by Kruger classification to therapeutic varicocelectomy. *J Urol* 1997;158:1804–7.
- Su LM, Goldstein M, Schlegel P. The effect of varicocelectomy on serum testosterone levels in infertile men with varicoceles. *J Urol* 1995;154:1752–5.
- Segenreich E, Israilov S, Shmuele J, Niv E, Banil J, Livne P. Evaluation of the relationship between semen parameters, pregnancy rate of wives of infertile men with varicocele, and gonadotropin-releasing hormone test before and after varicocelectomy. *Urology* 1998;52:853–7.
- Naughton C, Nangia A, Agarwal A. Pathophysiology of varicoceles in male infertility. *Hum Reprod Update* 2002;7:473–81.
- 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;73:459–64.
- 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;156:267–70.
- 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.
- 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;28:43–52.
- Cayan S, Kadioglu A, Orhan I, Kandirali E, Tefekli A, Telloglu S. The effect of microsurgical varicocelectomy on serum follicle stimulating hormone, testosterone and free testosterone levels in infertile men with varicocele. *BJU International* 1999;84:1046–9.
- World Health Organization. WHO laboratory manual for the examination of human semen and sperm-cervical mucus interaction. Cambridge: Cambridge University Press, 1999.
- Kidd SA, Eskenazi B, Wyrobek AJ. Effects of male age on semen quality and fertility: a review of the literature. *Fertil Steril* 2001;75:237–48.
- Marmar JL. The pathophysiology of varicoceles in the light of current molecular and genetic information. *Hum Reprod Update* 2001;7:461–72.
- Pasqualotto FF, Lucon AM, Hallak J, Saldanha LB, Góes PM, Arap S. Induction of spermatogenesis in azoospermic men undergoing varicocele repair. *Hum Reprod* 2003;18:108–12.
- Sharma RK, Pasqualotto FF, Nelson DR, Thomas AJ Jr, Agarwal A. ROS-TAC is a novel marker of oxidative stress. *Hum Reprod* 1999;14:2801–7.
- Peng BC, Tomashefsky P, Nagler HM. The cofactor effect: varicocele and infertility. *Fertil Steril* 1990;54:143–8.
- Evers JL, Collins JA. Assessment of efficacy of varicocele repair for male subfertility: a systematic review. *Lancet* 2003;361:1849–52.
- Peterson AC, Lance RS, Henry ER. Outcomes of varicocele ligation for pain. *J Urol* 1998;159:1565–7.
- World Health Organization. The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. *Fertil Steril* 1992;57:1289–92.
- Lipshultz LI, Corriere JN. Progressive testicular atrophy in the varicocele patient. *J Urol* 1977;117:175–6.
- Pinto KJ, Kroovand L, Jarow JP. Varicocele related testicular atrophy and its predictive effect upon fertility. *J Urol* 1994;152:788–90.