

## ORIGINAL PAPER

# The effect untreated right subclinical varicocele on the outcomes of contralateral left clinical varicocelectomy in infertile patients

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## Summary

**Purpose:** The management of infertile patients with unilateral subclinical varicocele (SCV) and contralateral clinical varicocele (CV) remains controversial. We aimed to evaluate the effect of untreated SCV on the outcome of contralateral clinical varicocelectomy in infertile patients with oligoasthenozoospermia (OA).

**Materials and methods:** Infertile patients with the diagnosis of OA who underwent left varicocelectomy were retrospectively evaluated. While all patients in the study had left clinical varicocele (LCV), some patients had concomitant right SCV. Patients were divided into two groups according to the presence or absence of a right SCV accompanying LCV as group 1; (LCV n = 104) or group 2; (LCV with right SCV, n = 74). Patients were evaluated with spermogram parameters, pregnancy rates and serum levels of follicle stimulating hormone, luteinizing hormone, total testosterone at the first year of the follow-up.

**Results:** The mean sperm concentration increased significantly in both groups. However, group 1 showed significantly greater improvement than group 2. The ratio of progressive motile sperm in group 1 was increased significantly whereas no significant change was shown in group 2. Both the spontaneous pregnancy rate and the pregnancy rate with ART were statistically lower in the group of patients with right SCV. No statistically significant difference was detected in serum hormone levels in both groups after varicocelectomy operations.

**Conclusions:** Untreated right SCV may have adverse impact on the outcomes of left clinical varicocelectomy. In this context, the right testis can be considered in terms of treatment in patients with right SCV accompanying left CV.

**KEY WORDS:** Infertility; Subclinical Varicocele; Varicocelectomy.

Submitted 24 November 2023; Accepted 5 December 2023

## INTRODUCTION

According to the World Health Organization, the overall prevalence of primary infertility ranges between 3.9% and 16.8%, and up to 60% of infertility cases have been reported to be associated with men (1-2). Varicocele is the most common curable cause of male infertility and present in nearly 25% of men with abnormal semen quality and 35% of men with primary infertility (3-4). Varicocele can be classified as clinical or subclinical based on the radiological and clinical criterions. *Clinical varicocele* (CV) is diagnosed

by physical examination and graded into three as grade I (dilated veins palpable with Valsalva), grade II (dilated veins palpable during rest but not visible) and grade III (dilated veins visible and palpable during rest (5)). *Subclinical varicocele* (SCV) is the abnormal dilatation of the veins of the pampiniform plexus that cannot be detected by physical examination but can be diagnosed by imaging modalities (6). Although CV is diagnosed by physical examination, physical examination can be unsatisfactory or confusing due to factors such as a patient's history of scrotal surgery, coexisting hydrocele, obesity, or improper examination. As such, the *European Association of Urology* (EAU) guideline recommends that imaging studies must be used to confirm the diagnosis in infertile men with CV (7). At the present time, scrotal *color Doppler ultrasound* (CDUS) has become the most widely used imaging technique for the diagnosis and classification of both CV and SCV (5, 6). Although US and European guidelines recommend that treatment should only be offered for palpable varicoceles in infertile males, different trials have reported conflicting results demonstrating the benefits of repairing subclinical varicocele (6, 9-10). According to EAU, varicocelectomy should only be performed in patients with CV, impaired semen analysis and infertility lasting  $\geq 2$  years (11). Although isolated unilateral SV in infertile patients is not at all an indication for varicocele repair, the management of infertile men with unilateral SV and contralateral CV remains a controversial issue and there is no consensus on whether bilateral varicocele repair is superior to unilateral varicocele repair in patients with *left clinical varicocele* (LCV) and right SCV (12-13). Reported conflicting outcomes may be due, in part, to the small study size, different study designs, and the effect of varicocelectomy techniques in different studies. For infertile patients with left CV and right SCV, it is worthwhile to study whether bilateral or unilateral surgical repair should be performed.

In the present study, we performed a retrospective study of oligoasthenospermic infertile patients diagnosed with solitary LCV or LCV with RSV. We compared the improvement in spermogram parameters after left varicocelectomy between the two groups of patients. We aimed to determine whether the presence of an untreated right SCV influenced the spermogram parameters after left clinical varicocelectomy.

## MATERIALS AND METHODS

This retrospective study includes one hundred seventy-eight primary infertile males with the findings of oligoasthenospermia (oligospermia and asthenospermia) in at least 2 consecutive semen analyses. Primary infertility is defined as never been involved in a conception and the failure to obtain a natural pregnancy at least 12 months of following regular unprotected sexual intercourse.

The study protocol was reviewed and approved by the Institutional Review Board of Health Science University, Dışkapı Training and Research Hospital (No. 143/07).

The study was performed according to the Declaration of Helsinki.

As per our protocol, recurrent varicocele, secondary infertility, necrospermia, endocrinopathy, history of orchitis and cryptorchidism, use of vitamins or hormonal supplements, abnormal peripheral karyotype, Y chromosome microdeletion and cases whose partners have got fertility problems were excluded from the study. Patients with severe oligoasthenospermia (TMSC < 1x10<sup>6</sup>/mL) and azoospermia were also excluded from the study. A medical history was taken, and a scrotal examination was performed by the same physician in an upright position during normal breathing and Valsalva manoeuvres. Two consecutive spermograms were performed before the treatment and at the first year of the treatment. Pregnancy rates were recorded at the first year control visit. Semen samples were acquired by masturbation following three days of abstinence. Data including scrotal examination, medical history and two consecutive spermograms at baseline and at the first year of the treatment, were retrieved from the electronic patient folders.

Spermogram analysis data were recorded as the average of two semen samples. Semen samples were analysed for volume, sperm count, concentration, motility, morphology, viability. Oligoasthenospermia is defined according the criteria's which were recognized by the WHO in 2010 (normal total sperm count,  $\geq 39 \times 10^6$ , normal sperm concentration  $\geq 15 \times 10^6$ /mL, and normal typical morphology > 4%, normal progressive motility > 32% (14). CV was diagnosed by physical examination and graded according to Dubin grading system (grade I to III). Scrotal CDUS was used to diagnose SCV and to confirm CV. The diagnostic criterion of a SCV is the presence of dilated veins in the pampiniform plexus > 2 mm, demonstrating reflux during the Valsalva manoeuvre on CDU without any physical examination finding (15). Patients were divided into groups as group 1 (LCV and right testis without varicocele n = 104) or group 2 (LCV with RSV, n = 74) according to whether LCV was associated with right SCV or not. Patients in both groups underwent left microsurgical subinguinal varicocelectomy. Primary endpoint of the study was to compare the groups in terms of seminal response, and pregnancy rates following varicocelectomy. Secondary endpoint of the study was to compare the changes in testicular volume and serum hormone profile between the groups at the first year of the surgery.

All measurement data are presented as the mean SD with paired or unpaired Student-t test used for statistical evaluation. The chi-square test was used to compare sperm parameters. One-sample Kolmogorov-Smirnov was used to test the normal distribution. Analysis of the data obtained

in this study was performed with computer software (*Statistical Package for Social Sciences, version 10.0; SPSS, Chicago, IL*). As a result of Kolmogorov-Smirnov normality test, since the distribution of the measurements was suitable for normal distribution, the number of data was sufficient, and there were no outliers, tests that provided the parametric test approach were applied ( $p > 0.05$ ).

## RESULTS

A total of 178 primary infertile males with impaired semen parameter who went unilateral left varicocelectomy were retrospectively evaluated. Of the 178 patients, 104 were in group 1 and 74 were in group 2. The demographic and baseline characters of the patients were presented in Table 1. The mean age of the patients was  $33.1 \pm 6.2$  years in the group 1 and  $32.6 \pm 6.4$  years in the group 2 ( $p = .326$ ). The group 1 and group 2 had an infertility duration of  $30.4 \pm 4.6$  and  $32.6 \pm 4.1$  months which revealed no statistical difference ( $p = .422$ ). The baseline seminal parameters including mean sperm concentration, progressive motility, normal sperm morphology and viability were comparable between the two groups. In addition, no statistically significant differences were observed in terms of, right and left testicular volume and serum

**Table 1.**

Baseline data of the infertile patients in both groups.

	Group 1 (n = 104)	Group 2 (n = 74)	P value
	X $\pm$ s.d. ( $\mu$ -IQR)	X $\pm$ s.d. ( $\mu$ -IQR)	
Age	33.10 $\pm$ 6.20 (32.50-5.70)	32.60 $\pm$ 6.40 (31.80-5.50)	.326
Infertility period (months)	30.40 $\pm$ 4.60 (30.20-7.10)	32.60 $\pm$ 4.10 (31.40-6.90)	.422
Left Varicocele Grade			
Grade 1 (n)	10 (10%)	7 (9%)	.876
Grade 2 (n)	60 (58%)	41 (55%)	.549
Grade 3 (n)	34 (33%)	26 (35%)	.343
Sperm Concentration x10 <sup>6</sup> /mL	5.50 $\pm$ 1.90 (5.90-1.50)	4.42 $\pm$ 1.73 (4.75-1.30)	.234
Progressive Motile (a+b) (%)	19.20 $\pm$ 4.93 (20.50-5.00)	18.41 $\pm$ 3.72 (19.00-6.50)	.767
Normal sperm morphology (%)	8.42 $\pm$ 2.57 (8.70-2.50)	7.68 $\pm$ 1.93 (8.00-3.00)	.876
Sperm viability (%)	56.00 $\pm$ 11.22 (57.30-10.50) (22.50-6.50)	52.00 $\pm$ 10.83 (53.50-9.50) (24.20-6.00)	.432
Testis Volume (mL) (Right)	14.6 $\pm$ 3.6 (14.50-3.50)	14.1 $\pm$ 3.4 (15.60-3.00)	.232
Testis Volume (mL) (Left)	13.75 $\pm$ 2.80 (14.20-4.00)	14.01 $\pm$ 3.40 (14.50-3.00)	.384
FSH level (mIU/mL)	8.40 $\pm$ 4.30 (8.50-3.50)	7.70 $\pm$ 4.70 (8.00-4.00)	.321
LH level (mIU/mL)	6.40 $\pm$ 1.10 (6.50-1.50)	5.80 $\pm$ 0.90 (6.00-1.00)	.156
TT (ng/dL) (median)	406.23 $\pm$ 202.25 (417.00-75.00)	432.47 $\pm$ 287.23 (438.00-87.00)	.146

*For Left Varicocele Grade 15% of expected cell counts less than 5.*  
 $\mu$ , Population Mean; IQR, Interquartile Range; FSH, Follicle Stimulating Hormone; LH, Luteinizing Hormone; TT, Total Testosterone.

**Table 2.**  
Change in sperm parameters and pregnancy rates in both groups following left varicolectomy.

	Group 1 (n = 104)		P	Group 2 (n = 74)		P	p Po 1-2
	Pre-operative X ± s.d. (μ-IQR)	Post-operative X ± s.d. (μ-IQR)		Pre-operative X ± s.d. (μ-IQR)	Post-operative X ± s.d. (μ-IQR)		
Sperm Concentration (10 <sup>6</sup> /mL)	5.52 ± 1.90 (5.70-4.00)	24.30 ± 5.32 (24.10-7.00)	.002	4.40 ± 1.72 (5.00-3.00)	13.21 ± 2.90 (12.50-5.50)	.045	.032
Progressive Motility (%)	19.21 ± 4.90 (19.50-6.50)	46.31 ± 9.44 (49.5-10.20)	.013	18.40 ± 3.71 (17.50-4.50)	26.11 ± 5.40 (28.30-7.50)	.042	.026
Normal sperm morphology (%)	8.40 ± 2.50 (8.50-4.00)	14.20 ± 3.70 (15.00-5.50)	.532	7.60 ± 1.90 (8.40-2.50)	10.9 ± 5.91 (10.40-3.00)	.446	.342
Sperm viability (%)	50,00 ± 11.20 (55.20-14.50)	69,00 ± 16.80 (70.5-15.50)	.034	48,00 ± 10.80 (52.55-12.20)	56,00 ± 12.4 (58.70-13.0)	.048	.047
Pregnancy rates(n)		48(46%)			20 (27%)		.018
Spontaneous		42 (40%)			18 (24%)		
ART		6 (6%)			2 (5%)		

*For Pregnancy rates 18% of expected cell counts less than 5.  
μ, Population Mean; IQR, Interquartile Range; ART: Assisted Reproductive Technology.*

FSH, LH and TT levels between the two groups before the surgery. The changes of semen parameters in the first year after left varicolectomy in the two groups are shown in Table 2. There were statistically significant increases in sperm concentration, and progressive motility, viability in both groups, while the normal morphology remained unchanged for both groups after the varicolectomy. After the surgery, the mean sperm concentration increased significantly in both groups, but the improvement in group 1 was significantly greater than the group 2 (increased to  $24.3 \pm 5.3$  in group 1 versus  $13.2 \pm 2.9$  in group 2, respectively,  $p = .032$ ). In addition observed changes in progressive sperm motility, (to  $46.3 \pm 9.4$  in group 1, versus to  $26.1 \pm 5.4$  in group 2,  $p = .026$ ), viability (to  $69 \pm 16.8$  in group 1 versus to  $56 \pm 12.4$  in group 2,  $p = .047$ ) were more statistically significant in group 1 compared to group 2. In the first-year control of varicolectomy, the pregnancy rate was 46% in group 1, while this rate was 26% in group 2. A statistically signifi-

**Table 3.**  
Change in bilateral testicular volume and hormone profile in both groups following left varicolectomy.

	Group 1 (n = 104)		P	Group 2 (n = 74)		P	p Po 1-2
	Pre-operative X ± s.d. (μ-IQR)	Post-operative X ± s.d. (μ-IQR)		Pre-operative X ± s.d. (μ-IQR)	Post-operative X ± s.d. (μ-IQR)		
Testis Volume (ml) (Right)	14.6 ± 3.6 (14.8-2.50)	14.4 ± 3.40 (14.5-2.50)	.734	14.1 ± 3.4 (14.3-3.00)	14.2 ± 2.6 (14.0-2.50)	.956	.876
Testis Volume (ml) (Left)	13.7 ± 2.8 (13.9-3.20)	14.2 ± 3.10 (14.0-3.00)	.646	14.3 ± 3.2 (14.7-3.50)	14.4 ± 2.8 (15.0-2.80)	.845	.640
FSH level (mIU/mL)	13.6 ± 4.30 (13.5-4.00)	12.2 ± 4.90 (12.0-6.00)	.221	12.7 ± 4.7 (12.5-4.50)	11.6 ± 3.9 (12.0-4.00)	.134	.244
LH level (mIU/mL)	15.4 ± 4.10 (16.5-5.00)	14.5 ± 4.20 (15.0-5.00)	.642	14.8 ± 0.9 (15.5-2.0)	14.6 ± 4.00 (14.0-4.00)	.934	.784
TT (ng/dl) (median)	290 ± 168 (300-90)	310 ± 176 (325-100)	.634	305 ± 187 (310-100)	340 ± 202 (355-120)	.440	.510

*μ, Population Mean; IQR, Interquartile Range; FSH, Follicle-Stimulating Hormone; LH, Luteinizing Hormone; TT, Total Testosterone.*

cant difference was observed between the groups in both spontaneous pregnancy rates and pregnancy rates with ART ( $p = .018$ ). There was no significant change in testicular volume and serum hormone levels after surgery in both groups.

## DISCUSSION

In this retrospective, non-randomized study, we aimed to show the effect of untreated SCV on the outcome of contralateral varicolectomy for LCV. We showed less improvement in semen parameters and also lower pregnancy rates in the group of patients with right SCV and LCV compared to patients with LCV following left varicolectomy. Varicocele is one

of the leading cause of impaired spermatogenesis and the most common correctable cause of male infertility (16). The main purpose of varicolectomy in male infertility is to improve the semen parameters, achieve natural conception, and reduce the level of assisted reproductive technology. Several studies have suggested that varicolectomy has a beneficial effect on sperm parameters and fertility status in infertile men only with palpable varicocele (3-17). According to EAU and AUA guidelines, varicolectomy should only be performed in infertile men with CV and abnormal spermiogram (18, 19). Recently, due to the increasing popularity of CDUS, the diagnosis of SCV has increased. The increase in the detection rate of bilateral varicocele is mainly due to the neglect of the detection of SV in previous reports (20). The impact of SCV on the sperm parameters is still debated and the clinical significance of repairing sonographically detected varicocele is controversial regarding male infertility (5, 21). Since previous trials have reported that varicocele size had no effect

on pregnancy rates, leading to the conclusion that very small varicoceles, even SCV should be diagnosed and treated (6, 22).

Evidence that varicocele size does not correlate with pathology in testicular structure or sperm parameters is supported by the demonstration that SCV also may have a damaging effect on the spermatogenesis (23). SCV may be a milder form of CV with the same pathogenic mechanism and the results showed that 28% of SCV in adolescent patients progressed to CV (24-25). *Dhabuwala et al.* showed that seminal response and fertility were improved after subclinical varicolectomy and suggested that SCV may have similar deleterious effects as CV (6). In contrast

to these studies, it has been suggested that the improvement in semen parameters after the surgical treatment of SCV is associated with lower success rates compared to CV surgery (26). A review evaluating three randomized clinical trials emphasized no evidence of benefit following varicocelectomy in infertile men with SCV (27). Likewise, Jarow et al. showed that the improvement in semen quality after subclinical varicocelectomy was statistically lower than CV repair and pointed out that the benefit from subclinical varicocelectomy is questionable (28).

Although there is no prominent consensus on the management of SCV, another issue discussed in the literature is the management of infertile patients with unilateral SCV accompanying contralateral CV. We did not perform right subclinical varicocelectomy in the group of patients with right SCV as recommended by current guidelines, and we assessed the results of left varicocelectomy in both groups of patients. In our study, spermiogram parameters (e.g., concentration, progressive motility, motility,) were significantly improved after left varicocelectomy in patients with left CV. Significant improvement was shown only in sperm concentration and progressive motility in patients with right SCV and left CV. Statistically better improvement in sperm parameters including concentration, progressive motility, total motility were shown in left CV patients compared to patients with left CV and right SCV at the first year of the surgery. A trial including one hundred forty-five infertile males with left CV or left CV with right SCV investigated the seminal response following either unilateral or bilateral varicocele repair. The authors showed that patients who underwent bilateral varicocele repair had more significant improvement in semen parameters (sperm concentration and progressive motility) and had higher spontaneous pregnancy rate compared to patients those underwent left varicocele repair (29). In a recent meta-analysis including six hundred thirty-seven patients of either left CV or left CV with right SCV, improvement in spermiogram parameters following bilateral varicocelectomy or unilateral varicocelectomy were compared (30). Statistically significant improvement in progressive sperm motility, sperm morphology was reported in favour of the bilateral varicocelectomy group. However, no statistically significant differences were revealed in sperm concentration between two groups. In a randomized controlled study, more significant changes in seminal response were shown in bilateral varicocelectomy compared to unilateral left varicocelectomy in infertile males with left CV and right SCV (31). Subsequent right varicocelectomy improved semen quality in 56% of patients, with a pregnancy rate of 43% in selected infertile patients those with no improvement in sperm parameters following left varicocelectomy. A recent study evaluating the outcomes bilateral varicocelectomy reported that, bilateral varicocele was found to be as high as 98.5% after radiologic assessment and subclinical varicocelectomy may be useful to avoid disease recurrence and optimize treatment outcomes (32). Contrary to these findings, Grasso et al. claimed that the benefit of repairing right SCV associated with left CV was not substantial, given the possible additional morbidity and additional operative time (33). Secondary endpoint of the study was to compare the changes in testicular volume and serum hormone profile

between the groups. There were no significant differences in bilateral testicular volume between the two groups at baseline and the first year of surgery. Similar to the negative effect of CV on testicular volume, it has been reported in previous studies that testicular volume decreases in SCV (34). Although Pasqualotto et al. did not observe an increase in mean left testicular volume in patients with left CV and right SCV who underwent bilateral varicocelectomy, they observed a significant increase in the mean volume of right testis following bilateral varicocelectomy (35). They suggested that the varicocelectomy may increase the testicle size and this may be the reason for the surgery's leading to an improvement in semen analysis. We evaluated hormone profile at baseline and compared the serum hormone levels at the first year of postoperative period. Neither preoperative abnormalities nor significant changes in serum hormone levels following varicocelectomy were observed in either group of our study. Zheng et al. indicated that SCV did not affect hormone levels, as they were unable to find statistical differences in hormone levels between patients with left CV only and right SCV with left CV (36).

Our study has some limitations which need to be considered while evaluating its findings. First, it is a retrospective study that can be affected by all potential weaknesses stemming from its retrospective design. Second, according to current guidelines, we performed left varicocelectomy only in the bilateral varicocele group and assessed the deleterious effect of SCV on sperm quality, rather than subclinical varicocelectomy direct impact.

## CONCLUSIONS

The topic of whether to repair or not to repair the ipsilateral SCV in patients with contralateral CV is still controversial. Untreated right SCV may have detrimental effects on sperm parameters.

This hypothesis should be supported by the larger case studies with the outcomes of right SCV repair in patients with accompanying left CV.

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**Conflict of interest:** The authors declare no potential conflict of interest.