

# Varicocele and the outcomes of microdissection testicular sperm extraction in non-obstructive azoospermia: a case-control study

## Abstract

**Purpose:** The effect of varicocele and varicocele repair on microdissection testicular sperm extraction (micro TESE) outcomes is controversial.

**Methods:** A retrospective case-control study of non-obstructive azoospermia patients undergoing micro TESE at a tertiary-care hospital.

**Results:** Varicocele was less likely to be present in successful micro TESE cases than their unsuccessful controls (OR=0.55). However, this finding was not statistically significant ( $p=0.19$ ). Similarly, repair of varicocele was associated with higher odds of having successful micro TESE (OR=9.00), although the association was insignificant ( $p=0.07$ ).

**Conclusion:** Varicocele and varicocele repair may not be significant associates of success in NOA patients undergoing micro TESE.

**Keywords:** varicocele, micro tese, non-obstructive azoosperm

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## Introduction

Despite the advances in the management options,<sup>1-3</sup> no adequate sperm retrieval can be achieved in a considerable proportion of non-obstructive azoospermia (NOA) patients.<sup>4</sup> Besides the technical improvements, optimization of the patient's clinical status is one possible means by which the outcomes of sperm retrieval procedures could be improved. For example, lifestyle changes and habitual modifications (e.g. smoking cessation) may enhance spermatogenesis prior to extraction.<sup>5</sup> Hormonal optimization has also been attempted, although with varying success rates.<sup>6,7</sup> One possible optimization intervention is varicocele repair.<sup>8</sup> Varicocele is a relatively common pathology,<sup>9</sup> found in around 5%-10% of azoospermia cases.<sup>10</sup> Its negative effects on fertility has been recognized;<sup>11</sup> a study of over 9000 men presenting to infertility clinics indicated a significant association between varicoceles and abnormal semen findings, testicular-volume parameters, as well as other parameters of testicular function.<sup>12</sup> Others have suggested varicocele to be age-related with a progressively detrimental effect on fertility.<sup>13</sup> Correcting varicocele may result in improved fertility.<sup>14,15</sup> In 1952, Tulloch reported the first post-varicocele-repair spontaneous pregnancy, suggesting its potential positive effect on infertility outcomes.<sup>16</sup> A prospective randomized clinical trial of infertile men with palpable varicocele showed higher likelihood of semen-characteristics improvement and spontaneous pregnancy in repaired vs. conservatively-treated varicoceles.<sup>17</sup>

Despite these reports, the benefits of varicocele repair in NOA remains a debatable matter,<sup>18</sup> as the current evidence also indicates the lack of any effect of varicocele repair on infertility.<sup>19,20</sup> Of note, a recent systematic review identified relevant limitations of the overall evidence that would justify this procedure in sub fertile men.<sup>21</sup> While microdissection testicular sperm extraction (micro TESE) offers the best chances of sperm retrieval in NOA,<sup>2,3</sup> the effect of varicocele

and its repair on micro TESE outcomes is controversial. Of the few available reports, some suggested better outcomes when repaired,<sup>10,22</sup> while others showed no added benefit.<sup>20</sup> In this study, we attempt to investigate the association between varicocele (and varicocele repair) and the outcomes of micro TESE in NOA patients.

## Case presentation

This is a retrospective, case-control study. The relevant data were collected through retrospective chart review of NOA patients treated under the care of the Urology Department of our tertiary referral center during the period Aug 2009-Aug 2015. Cases were defined as NOA patients who underwent micro TESE in whom the operation resulted in successful retrieval of at least one sperm. The controls were selected from the pool of NOA patients for whom micro TESE resulted in no sperm retrieval (i.e. micro TESE was unsuccessful) within the study period. Cases were matched with controls based on age, serum testosterone levels and histopathological diagnosis. One standard deviation was allowed as the matching criterion of tolerance for each of age (6.85 years) and testosterone (6.83 nmol/L). Histological subtype was an exact match. The intended ratio of patients to controls was 1:2. Random selection of eligible controls was applied for each case, where possible.

Varicocele and its repair status served as the "exposure" variable in this study. The presence of varicocele was determined by ultrasonographic assessment of the spermatic veins and pampiniform plexus using the following criteria: dilated veins >3 mm and/or the presence of reflux.<sup>23-25</sup> Varicocele repair status was identified from the enrolled patients' records available at the hospital. Study findings were summarized using frequencies, means and standard deviations. Comparisons were made between the different populations using Student's t-, Chi-square and Fisher's exact tests, as appropriate. Odds ratios, along with their 95% confidence interval (95%CI) were

calculated for each of the explored relationships. All analyses were conducted using Statistical Package for Social Sciences (SPSS) v22.0. Armonk, NY: IBM Corp. A  $p < 0.05$  was considered significant.

### Ethical consideration

The study was reviewed and approved by the Research Advisory Council (RAC), the institutional review board at our institution.

### Discussion

A total of 32 cases and 56 controls were matched, and thus, included in the analysis. The mean age of the studied patients was 35.5 years, with a range of 24 to 53. Overall, sertoli-cell only syndrome

constituted the major histological pattern seen in dissected testes (77.3%). Demographic, hormonal and ultrasonographic characteristics of, and micro TESE outcomes in, the study population are shown in Table 1. Table 2 & Table 3 shows the distribution of varicocele and varicocele repair, respectively, among cases and controls. There was a 45% reduction in the odds of having ultrasonographic evidence of varicocele in successful micro TESE cases compared to unsuccessful controls (OR=0.547; 95%CI=0.224-1.341). However, this decrease was insignificant ( $p=0.186$ ). Likewise, varicocele repair was not significantly different between cases and controls in whom varicocele is present ( $p=0.066$ ), despite being associated with 9 times higher odds of having successful than unsuccessful micro TESE outcomes (OR=9.000; 95%CI=0.919-88.162).

**Table 1** Sample characteristics and micro TESE outcomes

#	Variable	Mean±SD (n) – Cases Frequency (%) –Cases	Mean±SD (n) – Controls Frequency (%) – Controls	Mean±SD (n) – overall Frequency (%) – overall	P value (Cases vs Controls)
1	Age	36.28±6.73 (32)	35.09±6.21 (56)	35.52±6.39 (88)	0.403
2	BMI	31.49±7.02 (32)	31.88±8.40 (56)	31.74±7.89 (88)	0.822
3	Thyroid stimulating hormone (TSH)	2.62±2.04 (31)	2.44±1.67 (51)	2.51±1.81 (82)	0.654
4	Follicular stimulating hormone (FSH)	17.08±10.57 (32)	21.82±18.4 (56)	20.10±16.10 (88)	0.128
5	Luteinizing hormone (LH)	10.36±6.05 (32)	12.28±8.56 (56)	11.58±7.76 (88)	0.266
6	Prolactin	11.15±6.84 (32)	10.52±4.29 (55)	10.75±5.34 (87)	0.603
7	Estradiol (E2)	98.95±55.83 (12)	126±78.91 (20)	116.16±71.45 (32)	0.299
8	Testosterone	11.16±5.44 (32)	10.81±5.72 (56)	10.93±5.59 (88)	0.781
10	US volume	(n=32)	(n=56)	(n=88)	>0.05
	Normal	23 (71.9)	41 (73.2)	64 (72.7)	
	Small	9 (28.1)	15 (26.8)	24 (27.3)	
11	US varicocele present	(n=32)	(n=56)	(n=87)	-
	Right	6 (18.8)	9 (16.4)	15 (17.2)	
	Left	15 (48.4)	19 (33.9)	34 (39.1)	
	Right or left	15 (48.4)	19 (33.9)	34 (39.1)	
12	Varicocele Repair	(n=32)	(n=55)	(n=88)	-
	Yes	5 (15.6)	1 (1.8)	6 (6.8)	
	No	27 (84.4)	55 (98.2)	82 (93.2)	
13	Bone marrow transplantation	(n=32)	(n=55)	(n=87)	>0.05
	Yes	1 (3.1)	1 (1.8)	2 (2.3)	
	No	31 (96.9)	54 (96.4)	85 (96.6)	
14	Chromosomal analysis	(n=5)	(n=11)	(n=16)	>0.05
	Normal	4 (80)	8 (72.7)	12 (75)	
	XXY, 47	1 (20)	3 (27.3)	4 (25)	
15	Pre-treatment with clomiphene or B-HCG	(n=32)	(n=56)	(n=88)	>0.05
	Yes	2 (6.25)	11 (19.6)	13 (14.7)	
	No	30 (93.75)	45 (80.4)	75 (85.3)	
16	Micro TESE Outcome	(n=32)	(n=56)	(n=88)	N/A
	Positive	32 (100)	0 (0)	32 (36.4)	
	Negative	0 (0)	56 (100)	56 (63.6)	

Table Continues...

#	Variable	Mean±SD (n) – Cases Frequency (%) –Cases	Mean±SD (n) – Controls Frequency (%) – Controls	Mean±SD (n) – overall Frequency (%) – overall	P value (Cases vs Controls)
17	Histopathology	(n=27)	(n=48)	(n=75)	>0.05
	Sertoli-cell syndrome	20 (74.1)	38 (79.2)	58 (77.3)	
	Hypospermatogenesis	5 (18.5)	6 (10.7)	11 (14.7)	
	Maturation arrest-early	2 (7.4)	4 (7.1)	6 (8)	
	Maturation arrest-late	0 (0)	0 (0)	0 (0)	
18	Sperm motility	(n=29)	N/A	N/A	N/A
	Motile	10 (34.5)			
	Non-motile	19 (65.5)			
19	Number of straws frozen	3.22±2.24 (32)	N/A	N/A	N/A

**Table 2** Varicocele distribution among successful-micro TESE cases and unsuccessful controls

	Varicocele	No varicocele
Successful micro TESE	15	16
Unsuccessful micro TESE	19	37

**Table 3** Varicocele repair distribution among successful-micro TESE cases and unsuccessful controls with documented varicocele

	Repaired	Not repaired
Successful micro TESE with varicocele	5	10
Unsuccessful micro TESE with varicocele	1	18

Varicocele may affect around 15% of the general population,<sup>26</sup> 35% of primary infertility patients,<sup>27</sup> and even a greater proportion of secondary infertility cases.<sup>28,29</sup> It has received much attention because of the potential improvements of fertility outcomes after its repair. In fact, varicocele is believed to be among the most common correctable etiologies of infertility in men.<sup>9</sup> Vascular perfusion appears to affect the quality of spermatogenesis.<sup>30</sup> Indeed, several reports have shown associated derangements in semen parameters when varicocele is present,<sup>11,12</sup> and shown improvements when varicocele is corrected.<sup>8,10,14,15,22,31,32</sup> However, this association is not consistent. Several reports showed no benefit of varicocele repair on infertility<sup>19,33</sup> and on micro TESE outcomes.<sup>20</sup> A recent systematic review indicated evidence of fertility improvements after treatment of varicocele to be inadequate.<sup>21</sup>

In this paper, we found no difference between cases and controls in either varicocele or varicocele repair. Such findings may be an extension to the broader controversy concerning the effect of varicocele and varicolectomy on fertility. It should be noted that the inconsistency may represent an otherwise multifaceted disease that needs a closer scrutiny; recent meta-analyses have suggested the repair's effect to be dependent on the underlying predominant histological pattern found on the testicular tissue biopsy.<sup>34,35</sup> With having sperm in the ejaculate or spontaneous pregnancy as the successful outcome, Weedon et al.<sup>34</sup> showed patients with hypospermatogenesis and late maturation arrest to have a significantly higher likelihood of success than those with sertoli-cell only or early maturation arrest histology. Similarly, Aboutaleb et al.<sup>36</sup> showed the improvements in semen analysis parameters after varicolectomy to be present in hypospermatogenesis histology but not in maturation arrest or sertoli-

cell only pattern. To account for this observation, histological subtype was exactly matched between cases and each of their corresponding controls in this study. The majority of the cases showed sertoli-cell only histological pattern, which may have accounted for the lack of significant effect of varicocele repair on micro TESE outcomes that was observed in this study.<sup>36</sup>

Several limitations are to be acknowledged. First, the number of patients in both cases and controls arms is small. Second, “exposure” in this case-control design was defined by ultrasonographic criteria, which may differ in some cases from clinical counterpart; previous reports suggested doubtful benefit of subclinical-varicocele repair on fertility outcomes.<sup>33,37</sup> Third, not many patients underwent varicolectomy, and thus, it may limit the power of detection of the association between varicocele repairs with micro TESE outcomes. Finally, since this was a retrospective study, selection bias between cases and controls may exist. However, none of the clinical, radiological, or histopathological parameters were significantly different between the cases and control groups (Table 1). While this paper focused on NOA patients, the addition of a third “normal-fertility” control group, and investigating whether varicocele distribution is comparable to that of NOA patients may have provided insight into the varicocele’s true effect on fertility in the studied population.

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## Conflicts of interest

The author declares there is no conflict of interest.

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