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# Does Varicocele Repair Improve Male Infertility? An Evidence-Based Perspective From a Randomized, Controlled Trial

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### Abstract

**Background:** Randomized controlled trials (RCTs) addressing varicocele treatment are scarce and have conflicting outcomes.

**Objective:** To determine whether varicocele treatment is superior or inferior to no treatment in male infertility from an evidence-based perspective.

**Design, setting, and participants:** A prospective, nonmasked, parallel-group RCT with a one-to-one concealed-to-random allocation was conducted at the authors' institution from February 2006 to October 2009. Married men 20–39 yr of age who had experience infertility  $\geq 1$  yr, had palpable varicoceles, and with at least one impaired semen parameter (sperm concentration  $< 20$  million/ml, progressive motility  $< 50\%$ , or normal morphology  $< 30\%$ ) were eligible. Exclusions included subclinical or recurrent varicoceles, normal semen parameters, and azoospermia. Sample size analysis suggested 68 participants per arm.

**Intervention:** Participants were randomly allocated to observation (the control arm [CA]) or subinguinal microsurgical varicocelectomy (the treatment arm [TA]). Semen analyses were obtained at baseline (three analyses) and at follow-up months 3, 6, 9, and 12. The mean of each sperm parameter at baseline and follow-ups was determined.

**Measurements:** We measured the spontaneous pregnancy rate (the primary outcome), changes from baseline in mean semen parameters, and the occurrence of adverse events (AE—the secondary outcomes) during 12-mo follow-up;  $p < 0.05$  was considered significant.

**Results and limitations:** Analysis included 145 participants (CA:  $n = 72$ ; TA:  $n = 73$ ), with a mean age plus or minus standard deviation of  $29.3 \pm 5.7$  in the CA and  $28.4 \pm 5.7$  in the TA ( $p = 0.34$ ). Baseline characteristics in both arms were comparable. Spontaneous pregnancy was achieved in 13.9% (CA) versus 32.9% (TA), with an odds ratio (OR) of 3.04 (95% confidence interval [CI], 1.33–6.95) and a number needed to treat (NNT) of 5.27 patients (95% CI, 1.55–8.99). In CA within-arm analysis, none of semen parameters revealed significant changes from baseline (sperm concentration [ $p = 0.18$ ], progressive motility [ $p = 0.29$ ], and normal morphology [ $p = 0.05$ ]). Conversely, in TA within-arm analysis, the mean of all semen parameters improved significantly in follow-up versus baseline ( $p < 0.0001$ ). In between-arm analysis, all semen parameters improved significantly in the TA versus CA ( $p < 0.0001$ ). No AEs were reported.

**Conclusions:** Our RCT provided level 1b evidence of the superiority of varicocelectomy over observation in infertile men with palpable varicoceles and impaired semen quality, with increased odds of spontaneous pregnancy and improvements in semen characteristics within 1-yr of follow-up.

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## 1. Introduction

Infertility affects 10–15% of couples endeavoring to conceive, with male infertility contributing to nearly 50% of cases [1]. Varicoceles are the most prevalent abnormal physical finding in male infertility, with a prevalence of 19–41% of men with primary infertility and 45–81% of men with secondary infertility [1,2].

Although varicocele repair procedures have been extensively practiced over several decades in the domain of male infertility, the fundamental question regarding their beneficial effect on male fertility remains unresolved. Numerous conflicting individual reports and systematic reviews on outcomes of varicocele treatment have been published in the literature, with many studies claiming improvements in pregnancy rates and semen characteristics [2–10] and other reports denying any benefit [11–16]. Despite randomized controlled trials (RCTs) being considered the gold standard and most powerful tool in contemporary clinical research [17], a number of systematic reviews concluded that properly conducted RCTs addressing varicocele treatment are quite scarce and have contradictory outcomes [2–4,11,12]. In addition, RCTs can yield biased results if they lack methodologic rigor [17]. In the era of evidence-based medicine (EBM), it seems inappropriate to either widely practice or reject varicocele treatment based solely on outcomes of inadequately designed studies or conflicting expert opinions.

The current study undertook to determine the superiority or inferiority of varicocele treatment versus no treatment in infertile men with palpable varicoceles and impaired semen quality by addressing the effects on pregnancy rates and semen characteristics in a prospective, randomized, controlled, parallel fashion, providing level 1b evidence in this regard.

## 2. Materials and methods

### 2.1. Setting

The study was conducted at the authors' institution between February 2006 and October 2009. The study received ethical committee approval, and informed consent was obtained from each participant prior to enrollment.

### 2.2. Study design

The study was designed in a prospective, one-to-one concealed-to-randomization, controlled, parallel-group, nonblinded, open-label fashion.

### 2.3. Outcome measures

The primary outcome measure was determining spontaneous pregnancy rate during a 12-mo period after receiving the allocated intervention. Secondary outcomes were changes from the mean baseline of each semen parameter (sperm concentration, motility, normal morphology) and the occurrence of adverse events (AEs) during the designated 12-mo period.

### 2.4. Sample size

To estimate the sample size prior to commencing the study, an effect size of 21.5% improvement in pregnancy rate within 1 yr following varicocele repair was postulated. The effect size was based on previous studies [5,6,14,16] that had similar inclusion–exclusion criteria but diverse pregnancy outcomes concluding superiority [5,6] versus nonsuperiority of varicocele treatment [14,16]. The mean pregnancy rate in these studies was 38.5% in treated patients versus 17.05% in nontreated patients. To accomplish a statistical power of 80% and by setting the alpha level at 5%, a sample size of 68 patients per arm was essential in double-sided testing. We determined a sample size of 75 patients per arm, allowing up to seven patients to drop out.

### 2.5. Inclusion criteria

Married, overall healthy men 20–39 yr of age who had had infertility for >1 yr of unprotected intercourse, clinically palpable unilateral or bilateral varicoceles (grades 1–3), and impaired semen quality (at least one of the following semen characteristics: sperm concentration <20 million/ml, progressively motile sperm <50%, or morphologically normal sperm <30%) were considered eligible for the study.

### 2.6. Exclusion criteria

Patients with unilateral or bilateral subclinical or recurrent varicoceles, normal semen parameters, azoospermia, an abnormal hormonal profile, additional causes of infertility, significant medical diseases, smoking, occupational heat exposure, female partner  $\geq 35$  yr of age, associated female factor infertility, or unstable marriage were deemed ineligible. Patients who refused randomization were excluded from study entry. Patients who explicitly elected or rejected surgery or initially elected to have an observation period before considering surgery afterwards were excluded as well to avoid undermining the randomization process.

### 2.7. Baseline period

Palpable varicoceles on physical examination were further documented by scrotal ultrasound. All patients underwent three-semen analyses within a 3-mo baseline period, with as constant a number of days of sexual abstinence (3–5 d) as possible. Patients were instructed to avoid using any medications that might affect their semen quality or fertility potential throughout the baseline and study periods.

### 2.8. Randomization and allocation to intervention

Eligible patients were offered the option of receiving immediate varicolectomy or observation for 1 yr with subsequent reevaluation of the management plan and possible delayed varicolectomy. Eligible patients who declared willingness to equally accept either option on a random basis were enrolled as participants and were allocated at a balanced one-to-one ratio to either immediate varicolectomy (the treatment arm [TA]) or observation (the control arm [CA]). A simple random allocation sequence was computer generated and concealed by an independent research assistant. Randomization–allocation concealment to both investigators and participants was ascertained by using sequentially numbered opaque envelopes containing the assigned intervention. However, neither the participants nor the investigators were blinded to the intervention after allocation.

### 2.9. Interventions

TA patients underwent subinguinal microsurgical varicolectomy with arterial and lymphatic sparing [7] within a maximum of 4 wk following

the last baseline semen analysis. CA patients were allocated to observation only.

**2.10. Follow-up**

Participants were followed for 12 mo after the day of surgery (TA) or the day of the last baseline semen analysis (CA). Any pregnancy that might occur during the study period was documented. Repeated semen analyses were obtained at follow-up months 3, 6, 9, and 12. All participants were assessed for adverse effects (AEs) throughout study period, while TA patients were evaluated at the 6-mo follow-up, with physical examination and scrotal ultrasound to assess varicocele recurrence, hydrocele formation, and testicular size.

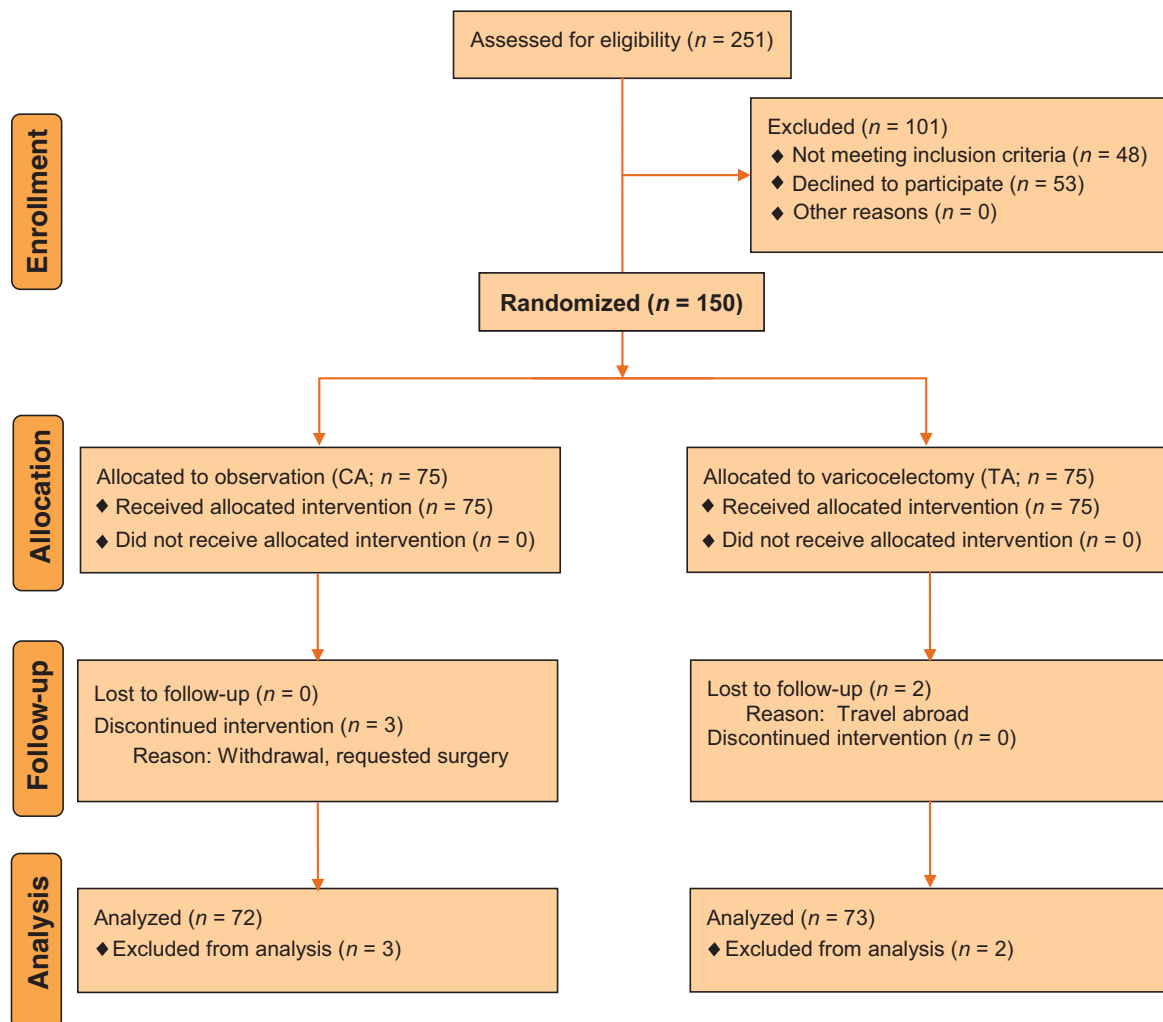
**2.11. Statistical analysis**

Unpaired Student *t* test for between-arm analysis, paired student *t* test for within-arm analysis, and Fisher exact tests for dichotomous variables were performed using SPSS v.16.0 software (SPSS, Chicago, IL, USA). A two-tailed *p* value <0.05 was considered statistically significant. The mean plus or minus standard deviation (SD) of each semen parameter was calculated for the three-semen analyses conducted

during the baseline period, then for the 12-mo follow-up semen analyses. The number needed to treat (NNT; reciprocal of absolute risk difference) was calculated for the dichotomous outcome of spontaneous pregnancy, representing the number of patients to be treated to achieve an extra pregnancy. The confidence interval (CI) around the NNT was calculated using the Schulzer method.

**3. Results**

Initially, 150 participants were randomly and equally allocated to either the TA or CA. Two participants in the TA and three participants in the CA were excluded from analysis, leaving the final number analyzed at 145 participants. The Consolidated Standards of Reporting Trials chart (Fig. 1) demonstrates the flow of participants through the trial. The mean age plus or minus SD was 29.3 ± 5.7 yr of age in the CA and 28.4 ± 5.7 yr of age in the TA, with an insignificant difference (*p* = 0.34). Baseline demographic, clinical, and semen characteristics of the analyzed patients in both arms were comparable with insignificant differences (Tables 1 and 2).



**Fig. 1 – Consolidated Standards of Reporting Trials flow chart for the trial. CA = control arm; TA = treatment arm.**

**Table 1 – Baseline characteristics of the treatment and control arms**

Parameter	CA (n = 72)	TA (n = 73)	p value
Age of participants, yr	29.3 ± 5.7	28.4 ± 5.7	0.34
Age of wife, yr	25.8 ± 4.3	25.3 ± 4.1	0.47
Duration of infertility, mo	17.8 ± 4.9	18.5 ± 5.1	0.40
Infertility, no. (%)			
Primary	38/72 (52.8)	40/73 (54.8)	>0.99
Secondary	34/72 (47.2)	33/73 (45.2)	>0.99
Varicocele, side, no. (%)			
Unilateral, left	53/72 (73.6)	53/73 (72.6)	>0.99
Unilateral, right	0/72 (0)	0/73 (0)	>0.99
Bilateral	19/72 (26.4)	20/73 (27.4)	>0.99
Total sides	91	93	-
Varicoceles (n = 93) grade, no. (%)			
Grade 1	36/91 (39.6)	38/93 (40.9)	>0.99
Grade 2	30/91 (33)	28/93 (30.1)	>0.99
Grade 3	25/91 (27.5)	27/93 (29)	>0.99

CA = control arm; TA = treatment arm.

Spontaneous pregnancy was achieved in 13.9% of the CA compared to 32.9% of the TA, with an odds ratio (OR) of 3.04 (95% CI, 1.33–6.95) and an NNT of 5.27 patients (Table 3). The mean age of wives who achieved pregnancy was 26.1 ± 4.4 yr of age in the CA versus 27.2 ± 4.6 yr of age in the TA—an insignificant difference ( $p = 0.52$ ; 95% CI, -2.37 to 4.59).

Semen parameter changes are shown in Table 2. In CA within-arm analysis, none of the semen parameters revealed significant changes from baseline, with  $p = 0.18$  for sperm concentration,  $p = 0.29$  for progressive motility, and  $p = 0.05$  for normal morphology. Conversely, in TA within-arm analysis, the mean of all semen parameters improved significantly during follow-up versus baseline ( $p < 0.0001$ ). In between-arm analysis, all semen parameters improved significantly in the TA versus the CA ( $p < 0.0001$ ). No AEs were reported in either the TA or CA, and none of the TA patients demonstrated evident recurrent varicocele, hydrocele formation, or changed testicular size during follow-up.

#### 4. Discussion

In the realm of EBM, although RCTs are considered the gold standard and best tool in evaluating health care interventions, providing level 1 evidence [17], only a few clinical situations can be managed in a real EBM setting in urology [18]. Few RCTs addressing the effect of varicocele repair on pregnancy outcome and semen characteristics have been published in the literature, with most of them subject to major criticism [2–4]. Ficarra et al, in their systematic review of available RCTs addressing the treatment of varicoceles for male infertility, reported that some RCTs included men with subclinical varicoceles or normal semen parameters, while others had poor methodologic quality, poor recruitment, significant drop-outs after randomization, or inadequate statistical power [4]. They concluded that the current literature does not provide enough data to draw any favorable or adverse conclusions, and data from

**Table 2 – Changes in semen parameters in both arms**

Semen parameter	Within-arm analysis* CA (n = 72)		Within-arm analysis* TA (n = 73)		Between-arm analysis**	
	Mean ± SD (range)	p	Mean ± SD (range)	p	p	D (95% CI)
Sperm concentration, million/ml	17.5 ± 6 (9.1–27.2)	-	18.1 ± 5.8 (8.5–34.8)	-	0.5	0.66 (-1.3 to 2.6)
	17.2 ± 6.4 (8.5–28.4)	0.18	32.2 ± 10.6 (13.3–46.6)	<0.0001	<0.0001	15 (12.1–17.9)
Motility, %	26.1 ± 11.9 (16–57)	-	25.3 ± 12.8 (15–55)	-	0.7	-0.8 (-4.9 to 3.3)
	25.8 ± 12.5 (15–55)	0.29	41.0 ± 10 (25–60)	<0.0001	<0.0001	15.2 (11.5–18.9)
Normal morphology, %	30.9 ± 4.2 (26–42)	-	31.2 ± 4.1 (27–40)	-	0.62	0.34 (-1.0 to 1.7)
	31.1 ± 4.2 (26–40)	0.05	39.1 ± 4.5 (33–49)	<0.0001	<0.0001	8.03 (6.6–9.5)

CA = control arm; TA = treatment arm; SD = standard deviation; D = mean difference; CI = confidence interval.  
\* Paired *t* test.  
\*\* Unpaired *t* test.

**Table 3 – Pregnancy rates in both arms**

	Within-arm analysis		<i>p</i>	Between-arm analysis		
	CA ( <i>n</i> = 10 of 72)	TA ( <i>n</i> = 24 of 73)		D	OR	NNT
Pregnancy, % (95% CI)	13.9 (7–24)	32.9 (22–45)	0.01	19 ± 0.8 (5.19–32.78)	3.04 (1.33–6.95)	5.27 (1.55–8.99)
Age of pregnant wives, yr ± SD (95% CI)	26.1 ± 4.4	27.2 ± 4.6	0.52	1.11 (–2.37 to 4.59)	–	–

CA = control arm; TA = treatment arm; D = mean difference; CI = confidence interval; OR = odds ratio; NNT = number needed to treat.

ongoing studies should provide more information on this topic [4].

In the current study, concealed randomization–allocation at a one-to-one balanced ratio was implemented to eliminate selection bias. Stringent inclusion–exclusion criteria were adopted in an attempt to ensure better homogeneity and comparability of baseline characteristics in the trial arms, to reduce the risk of imbalance resulting from confounding factors, and consequently to better identify and quantify the effect size of intervention. Similarly, to eliminate age as a confounder and obviate the controversies regarding fertility potential and outcomes of varicolectomy in younger or older age groups [19–22], we limited our study to couples with males between 20 and 39 yr of age and females younger than 35 yr of age. Likewise, patients with subclinical or recurrent varicoceles, normal semen parameters, or azoospermia were considered ineligible. We did not include patients who requested specific management—whether observation or varicolectomy—to avoid undermining the randomization process. In addition, sample size analysis was performed prior to recruiting patients to ensure adequacy of the study's statistical power. Establishing the traditionally accepted 80% statistical power with 5% alpha level conferred reliability to our significantly positive findings. To further support the reliability of our findings, although a study with lesser power (from a statistical viewpoint) may allow a small positive effect size to be overlooked, a less powered study would advocate treatment if significant effects were observed [16].

Because pregnancy is the ultimate goal for infertility patients, we adopted spontaneous pregnancy rate as the primary outcome measure, while changes in semen parameters were used as a secondary outcome. Investigations using semen parameter changes as the primary outcome measures for the efficacy of varicocele treatments provide only indirect evidence, given that pregnancy is the only outcome parameter at venture [2–4]. Besides, semen parameters demonstrate extensive intra- and interindividual variability and overlapping between fertile and infertile men [23,24]. In our study, with a comparable mean age among females capable of conceiving in both arms, spontaneous pregnancy was documented in 13.9% of the CA versus 32.9% of the TA, a difference that is statistically significant ( $p = 0.01$ ) and favoring repair of varicoceles. Patients in the TA have an appealingly higher OR of 3.04 (95% CI, 1.33–6.95) for achieving spontaneous pregnancy compared to the CA. The magnitude of effect and clinical importance of varicolectomy is further conveyed by the NNT of 5.27 patients (95% CI, 1.55–8.99), meaning that we

need to treat 5.27 patients to achieve an extra spontaneous pregnancy within 1 yr after varicolectomy. Our pregnancy outcomes are consistent with previous studies, supporting the beneficial effects of varicocele repair on the fertility status of males with palpable varicoceles and impaired semen quality [3,4].

In two independent meta-analyses reviewing RCTs, Ficarra et al. [4] reported a pregnancy rate of 36.4% and 20%, while Marmar et al. [3] reported 33% and 15.5% pregnancy rates in patients who underwent varicocele treatment compared to no treatment, respectively. Contrary to our findings, Nieschlag et al, in an RCT comparing varicocele treatment to counseling, found pregnancy rates not significantly different in both groups (29% vs 25%, respectively) at the end of the 12-mo study period, suggesting that counseling is as effective as treatment in achieving pregnancy [14]. Although that study was methodologically sound, it has a high dropout rate of 38.4%, jeopardizing its findings. Similarly, Evers and Collins systematic reviews [11,12] found no difference in the odds of pregnancy in varicocele-treated patients compared with no treatment, suggesting no benefit for varicocele treatment. However, in their meta-analyses, they included patients with subclinical varicoceles or normal semen characteristics. In addition, the lack of difference may be the result of not reporting pregnancy as a main outcome variable. Including large studies reporting only limited pregnancy data may give these studies more weight and would cause the overall conclusion to be weighted toward no effect [3].

Despite extensive variations in sperm characteristics, several studies linked better pregnancy outcomes to better semen parameters [2]. The chances of pregnancy in a Danish report increased with increasing sperm density up to 40 millions/ml [25]. Similarly, normal sperm motility [26] and sperm morphology [27] were identified as powerful discriminators differentiating between fertile and infertile men. In a meta-analysis to determine the efficacy of varicolectomy in improving semen parameters in infertile men with palpable varicoceles and abnormal semen analysis, all semen parameters improved significantly following varicolectomy [2]. In our study, superior improvements of semen characteristics in the TA versus the CA were evident. In within-arm analysis, all semen parameters improved significantly in the TA ( $<0.0001$ ), while none of these parameters showed significant change in the CA. In addition, in between-arm analysis, semen characteristic changes in the TA were significantly different ( $<0.0001$ ) from the CA, favoring treatment.

Our findings endorse the belief that varicocelectomy is an effective treatment for improving semen parameters in infertile men with clinically palpable varicoceles [2]. Besides the evident superiority of varicocele repair in our study, none of the patients in either arm encountered any AE, further supporting the previously reported safety of subinguinal and microsurgical procedures with arterial and lymphatic sparing [7–9,28].

For practical reasons, this study was conducted as open label without masking to either participants or investigators, with the inherent bias of unmasking [17]. However, assessing objective rather than subjective outcomes in our study might reduce such bias.

## 5. Conclusions

Our study provided an evidence-based endorsement (level 1b evidence) of the superiority of varicocele repair over observation in infertile men with palpable varicoceles and impaired semen quality. The study exhibited the beneficial effect of varicocelectomy on the odds of spontaneous pregnancy and improvements in semen characteristics within 1 yr.

**Author contributions:** Taha A. Abdel-Meguid had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Abdel-Meguid.

*Acquisition of data:* Abdel-Meguid, Al-sayyad, Tayib, Farsi.

*Analysis and interpretation of data:* Abdel-Meguid.

*Drafting of the manuscript:* Abdel-Meguid.

*Critical revision of the manuscript for important intellectual content:* Abdel-Meguid, Al-sayyad, Tayib, Farsi.

*Statistical analysis:* Abdel-Meguid.

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