Microsurgical Varicocelectomy Treats Male Infertility

Improves Testosterone Levels As Well

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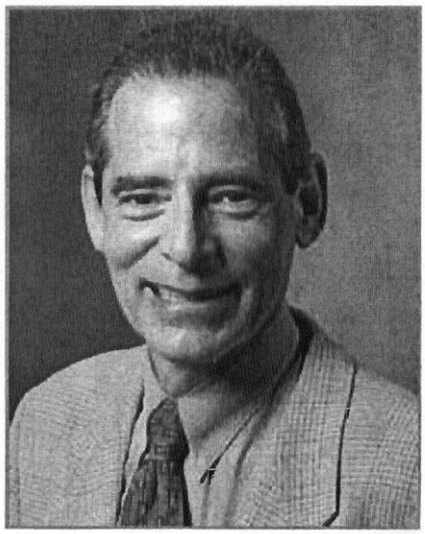

Dr. Marc Goldstein

Microsurgical repair of varicoceles is known to improve semen quality and result in two to three times higher pregnancy rates compared to no treatment or other medical approaches for varicocele. *(1)* However, newer research shows that varicoceles are also associated with low testosterone levels and that microsurgical repair significantly increases serum testosterone levels in more than two-thirds of men. Thus, even men who are not concerned with fertility may benefit from this surgical treatment.

Varicoceles are found in approximately 15% of the general male population but in a higher percentage of infertile men who have never fathered a child (35%) or who once fathered a child but are now infertile (81%). *(2,3)*

How Do Varicoceles Cause Male Infertility?

The exact cause of infertility among men with varicocele is not clearly understood, however, researchers believe that varicoceles interfere with the countercurrent heat exchange mechanism in the testicles. "As the arteries to the testicles approach each testicle, they become very tightly wound like a radiator coil and are normally surrounded by a fine network of veins. This network helps exchange heat," explained Dr. Goldstein, Surgeon-in-Chief of Male Reproductive Medicine and Surgery and Director of the Center for Male Reproductive Medicine and Microsurgery at the NewYork-Presbyterian Hospital/Weill Cornell Medical Center. If the veins become enlarged because of higher pressure in the veins or poorly functioning valves, the heat exchange mechanism does not work properly causing elevated intratesticular temperature and impairing their ability to make sperm.

In addition to the effects on fertility, research by Dr. Goldstein and others has shown that the elevated intratesticular temperature caused by varicoceles can impair the testes' ability to make testosterone by negatively affecting testicular Leydig cell function. Thus, varicocele may put men at risk for the adverse effects of low testosterone level, such as low sex drive, erectile problems, decreased muscle strength, osteopenia/osteoporosis, and depression.

A Study That Supports This Theory

Dr. Goldstein and colleagues performed a retrospective chart review on 327 men ages 18-70 years who had undergone

subinguinal microsurgical varicocelectomy for clinically palpable varicoceles. *(4)* These men had significantly lower serum testosterone levels compared with a control group of men with or without varicoceles who did not undergo the procedure (416 Â± 164 ng/dL versus 469 Â± 192 ng/dL, P<0.001). This association was not altered by patient age. Compared with baseline, the patients' serum testosterone levels were significantly higher after microsurgical varicocelectomy (358 Â± 126 ng/dL versus 454 Â± 168 ng/dL, P<0.001). In addition, 70% of men who underwent the procedure showed an increase in serum T levels post-operatively. The findings were presented at the 2007 annual meeting of the American Society for Reproductive Medicine and are expected to be published shortly.

What is a Microsurgical Varicocelectomy?

Dr. Goldstein uses the mini-incision, subinguinal microsurgical varicocelectomy with delivery of the testicle. The gubernacular veins and external spermatic perforators are also inspected and divided. Gubernacular veins in particular have been shown to cause of up to 10% of varicocele recurrences. The testicle is then returned to the scrotum and the spermatic cord is placed on a large Penrose drain. He then inspects the spermatic cord under a microscope and divides and ligates or clips all dilated internal spermatic veins. Postoperatively, venous return is via the deferential (vasal) veins, which drain into the internal pudendal veins and usually have competent valves. This approach allows the varicoceles to be removed while preserving the testicular artery, which is only 0.5-1.5-mm in diameter. The magnification also allows for identification and preservation of the lymphatics surrounding the testes, which reduces the risk of hydrocele. The procedure was pioneered by Dr. Goldstein *(5)* as well as Joel L. Marmar, MD, of Robert Wood Johnson Medical School, Camden, New Jersey.

Patients who respond best to varicocelectomy are those with large varicoceles in whom the veins can be felt and seen from the outside (ie, grade III varicoceles). Varicoceles first appear in adolescence and worsen slowly over time. Dr. Goldstein advocates repairing large varicoceles when they first appear in adolescents because "it is much easier to prevent future infertility than to treat it once the damage has already occurred." The sooner varicoceles are repaired the better the chance of halting future damage, he said.

NewYork-Presbyterian Hospital/Weill Cornell Medical Center, has the largest experience in the world in the use of microsurgical techniques for the treatment of male reproductive disorders, including varicocelectomy and vasectomy reversals, Dr. Goldstein said. "Very few major IVF [in vitro fertilization] centers have a reproductive urologist on staff. If a man has any sperm at all, they bypass the male altogether and start IVF. Here, physicians from the male and female reproductive divisions work together as a team to provide optimal care for the couple rather than just treating one partner separately." In at least half of these couples, the man could be treated and the couple could achieve a pregnancy without IVF, notes Dr. Goldstein. "We can use simpler, more economical treatments that are easier for women like IUI (intrauterine insemination) or a natural conceived pregnancy." In addition, for men who have zero sperm count, varicocelectomy can allow for enough sperm to be produced in their semen to allow for IVF or, if they remain at zero sperm count, can improve sperm production enough inside the testicle that it can be extracted with an operating microscope (microdissection testicular sperm extraction) for use in IVF/Intracytoplasmic sperm injection.

Faculty Contributing to this Article:

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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 ± 5.7 in the CA and 28.4 ± 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 ≥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 varicocelectomy or observation for 1 yr with subsequent reevaluation of the management plan and possible delayed varicocelectomy. 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 varicocelectomy (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 varicocelectomy with arterial and lymphatic sparing [7] within a maximum of 4 wk following

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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).

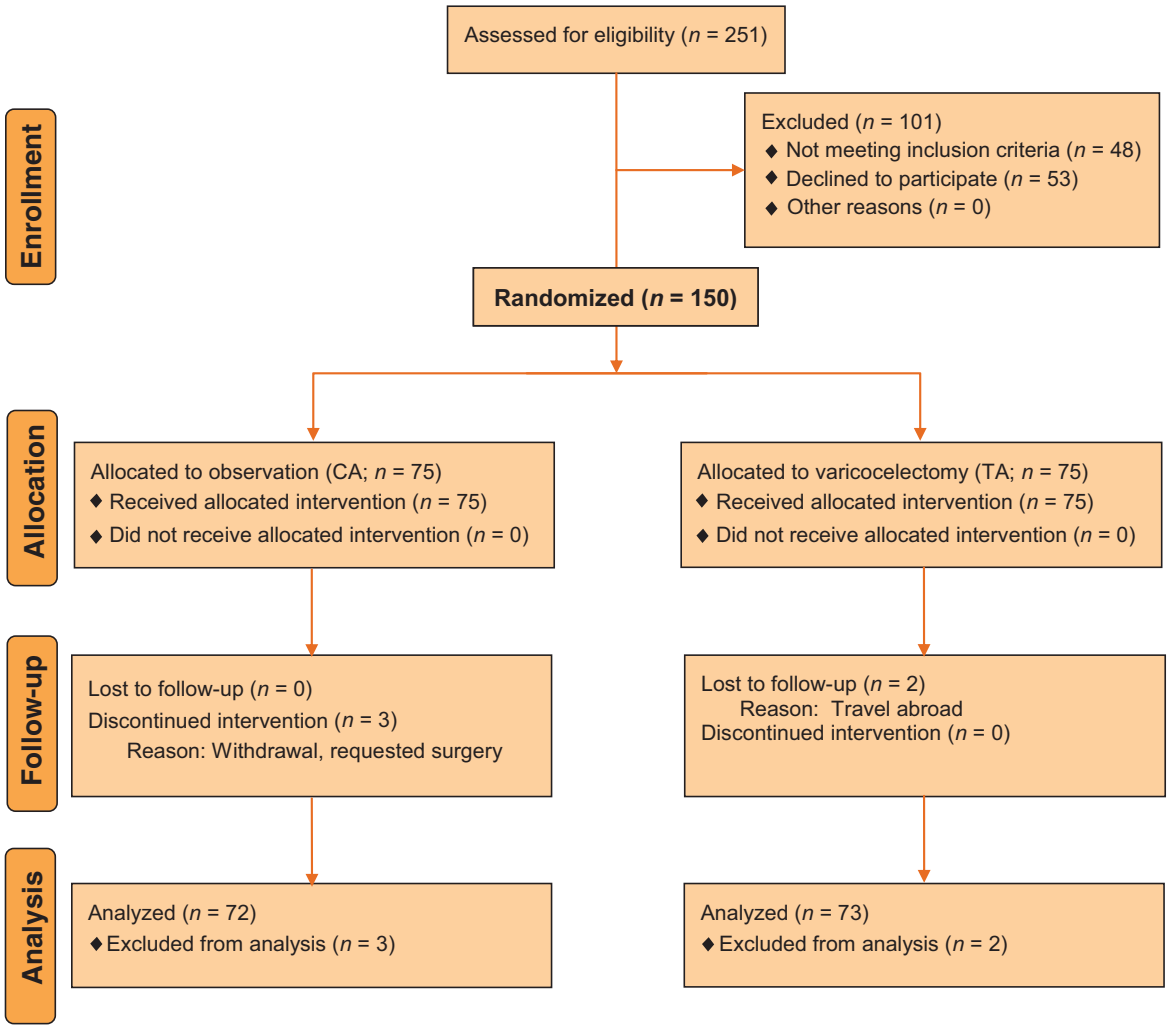

Fig. 1 – Consolidated Standards of Reporting Trials flow chart for the trial.
CA = control arm; TA = treatment arm.

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	D (95% CI)	Mean ± SD (range)	p	D (95% CI)	p	D (95% CI)
Sperm concentration, million/ml								
Baseline	17.5 ± 6 (9.1–27.2)	–	–	18.1 ± 5.8 (8.5–34.8)	–	–	0.5	0.66 (−1.3 to 2.6)
Follow-up	17.2 ± 6.4 (8.5–28.4)	0.18	−0.22 (−0.54 to 0.1)	32.2 ± 10.6 (13.3–46.6)	<0.0001	14.1 (12.9–15.4)	<0.0001	15 (12.1–17.9)
Motility, %								
Baseline	26.1 ± 11.9 (16–57)	–	–	25.3 ± 12.8 (15–55)	–		0.7	−0.8 (−4.9 to 3.3)
Follow-up	25.8 ± 12.5 (15–55)	0.29	−0.25 (−0.71 to 0.21)	41.0 ± 10 (25–60)	<0.0001	15.75 (14.1–17.4)	<0.0001	15.2 (11.5–18.9)
Normal morphology, %								
Baseline	30.9 ± 4.2 (26–42)	–	–	31.2 ± 4.1 (27–40)	–	–	0.62	0.34 (−1.0 to 1.7)
Follow-up	31.1 ± 4.2 (26–40)	0.05	0.21 (0.003–0.413)	39.1 ± 4.5 (33–49)	<0.0001	7.89 (6.5–9.3)	<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.

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Table 3 – Pregnancy rates in both arms

	Within-arm analysis		Between-arm analysis			
	CA (n = 10 of 72)	TA (n = 24 of 73)	p	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 varicocelectomy 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 varicocelectomy—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 varicocelectomy 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 varicocelectomy. 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 varicocelectomy in improving semen parameters in infertile men with palpable varicoceles and abnormal semen analysis, all semen parameters improved significantly following varicocelectomy [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.
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Undergoing varicocele repair before assisted reproduction improves pregnancy rate and live birth rate in azoospermic and oligospermic men with a varicocele: a systematic review and meta-analysis

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Objective: To evaluate how varicocele repair (VR) impacts pregnancy (PRs) and live birth rates in infertile couples undergoing assisted reproduction wherein the male partner has oligospermia or azoospermia and a history of varicocele.
Design: Systematic review and meta-analysis.
Setting: Not applicable.
Patient(s): Azoospermic and oligospermic males with varicoceles and in couples undergoing assisted reproductive technology (ART) with IUI, IVF, or testicular sperm extraction (TESE) with IVF and intracytoplasmic sperm injection (ICSI).
Intervention(s): Measurement of PRs, live birth, and sperm extraction rates.
Main Outcome Measure(s): Odds ratios for the impact of VR on PRs, live birth, and sperm extraction rates for couples undergoing ART.
Result(s): Seven articles involving a total of 1,241 patients were included. Meta-analysis showed that VR improved live birth rates for the oligospermic (odds ratio [OR] = 1.699) and combined oligospermic/azoospermic groups (OR = 1.761). Pregnancy rates were higher in the azoospermic group (OR = 2.336) and combined oligospermic/azoospermic groups (OR = 1.760). Live birth rates were higher for patients undergoing IUI after VR (OR = 8.360). Sperm retrieval rates were higher in persistently azoospermic men after VR (OR = 2.509).
Conclusion(s): Oligospermic and azoospermic patients with clinical varicocele who undergo VR experience improved live birth rates and PRs with IVF or IVF/ICSI. For persistently azoospermic men after VR requiring TESE for IVF/ICSI, VR improves sperm retrieval rates. Therefore, VR should be considered to have substantial benefits for couples with a clinical varicocele even if oligospermia or azoospermia persists after repair and ART is required. (Fertil Steril® 2016;106:1338–43. ©2016 by American Society for Reproductive Medicine.)
Key Words: Varicocele, varicocele repair, varicocelectomy, assisted reproductive technology, male factor infertility

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Infertility affects approximately 15% of couples and is defined as the inability of a sexually active couple to achieve pregnancy within 1 year (1, 2). A male factor is present within an estimated 50% of infertile couples, and a varicocele can be detected in >35% of the men in these relationships (2). Although a prior meta-analysis has shown improvement in pregnancy (PRs) and live birth rates in natural cycles after varicocele repair (VR), there is not a consensus regarding additional benefit to fertility beyond natural conception (3–6).

Advancements in assisted reproductive technology (ART) have brought the additional value of VR into question. With the advent of IVF and then intracytoplasmic sperm injection

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(ICSI) came the ability to achieve pregnancy with far fewer sperm than are necessary with IUI. Because VR improves semen parameters, it offers the ability to help couples with severe oligospermia and even azoospermia avoid costly ART strategies (7, 8). For those who still require ART despite VR, there may also be the benefit of improved semen quality through reduction of deleterious effects such as reactive oxygen species and DNA fragmentation (9, 10).

At present, few studies have addressed the question of how VR versus having a persistent untreated varicocele impacts the live birth and pregnancy outcomes of patients with oligospermia and azoospermia who pursue ART. The goal of this systematic review and meta-analysis is to provide a comprehensive analysis of the current data and a context for how to counsel infertile couples and fellow practitioners trying to determine the value of VR in the era of ART.

MATERIALS AND METHODS

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were used in the design and execution of this study. Institutional Review Board approval was not required for this study.

Literature Search and Inclusion Criteria

A literature search was performed through PubMed using the primary search terms "varicocele," "varicocelectomy," "male infertility," and "assisted reproductive technology." Our inclusion criteria were that the articles represent original research evaluating couples with men who have semen parameter abnormalities and a clinical varicocele who did or did not undergo a VR. Furthermore, the studies were required to report on fertilization rates, PRs, or live birth rates and whether or not ART of any type was used. Articles not available in English were excluded. Each of the selected studies was further evaluated for quality and risk of bias. Specifically, the study design and data collection method for each article was systematically screened. Verification bias and selection bias were additionally considered for each study to confirm the results were applicable for the specific outcomes in this meta-analysis.

Data Analysis

Six of the seven articles reported on IVF outcomes and were included in the meta-analysis (11–16). One of the articles included data only for IUI and was excluded from the meta-analysis (17). The results from this study were included as part of the systematic review. To assess the possible associations between the outcome variables (pregnancy, live birth, and sperm retrieval) and status of varicocele (repaired vs. persistent), counts of success and failure of each outcome for the varicocele treatment groups were obtained from the existing literature. Odds ratios (OR) for the success of the respective outcome variable for VR versus untreated varicocele were computed for the individual studies. Due to small and zero counts in some of the studies and for the sake of consistency across analyses, each OR for the individual studies has an associated 95% exact confidence interval (CI) for purposes of inference.

For the meta-analyses combining multiple studies, conditional logistic regression was used for each outcome variable with study as a stratification variable. When goodness-of-fit statistics indicated heterogeneity among the studies (residual score test, $P<.20$), a rescaling factor was used to modify the standard errors to prevent underestimation of the variation and account for overdispersion. The rescaling factors are based on an unstratified generalized estimating equation approach to an overdispersed logistic model with both study and treatment as covariates. Ninety-five percent CIs and P values based on Wald test statistics incorporating the rescaled standard errors were computed for the meta-analysis OR. All analyses were done in SAS v9.3.

RESULTS

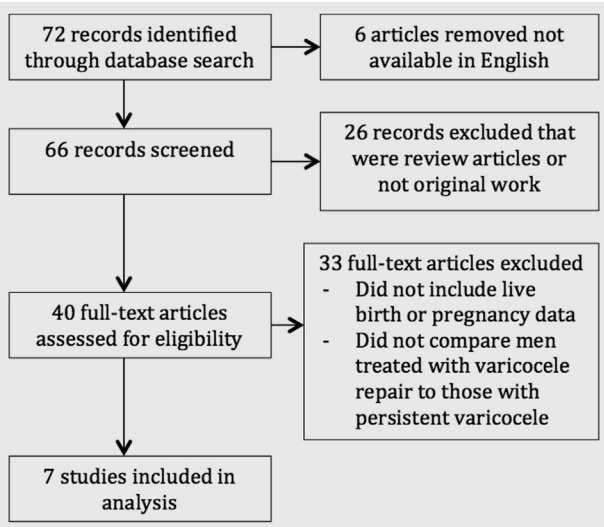
Literature Search

The literature search resulted in 72 articles for review. Six articles were not available in English and were excluded. Twenty-six articles were either review articles or did not represent original work. Of the remaining 40 articles, 7 reported on fertilization rates, PRs, or live birth rates among men with a clinical varicocele and abnormal semen parameters who subsequently underwent VR (11–17). Supplemental material provides a list of the 33 excluded articles. Two of the articles included only men with grade III varicocele, whereas the other five articles included all grades of clinical varicocele (13, 15). Each of these seven studies was retrospective and met our requirements for study quality. These results are summarized in Figure 1 and pertinent characteristics of each study are reviewed in Table 1.

Pregnancy Rate

All seven articles included data on PR. Of the four articles reporting on men with oligospermia undergoing IVF or IVF/ICSI, three studies (11, 12, 14) showed a statistically

FIGURE 1



Literature search results.

Kirby. ART outcomes after varicocele repair. Fertil Steril 2016.

TABLE 1

Study characteristics.

Author/year	Varicocele grade	Semen analysis characteristics	ART method	Cohort size
Gokce/2013	All grades	Oligospermia asthenospermia, teratospermia (any combination of)	IVF/ICSI	306
Esteves/2010	All grades	Oligospermia asthenospermia, teratospermia (any combination of)	IVF/ICSI	242
Pasqualotto/2012	Only grade III	"Poor semen parameters"	IVF/ICSI	248
Ashkenazi/1989	All grades	"Subfertile Semen"	IVF	22
Haydardedeoglu/2010	Only grade III	Nonobstructive azoospermia	IVF/ICSI with TESE	269
Inci/2009	All grades	Nonobstructive azoospermia	IVF/ICSI with TESE	96
Daitch/2001	All grades	Oligospermia asthenospermia, teratospermia (any combination of)	IUI	58

Note: ART = assisted reproductive technology; ICSI = intracytoplasmic sperm injection; TESE = testicular sperm extraction.

Kirby. ART outcomes after varicocele repair. Fertil Steril 2016.

significant increase in PR among those who had undergone VR. The remaining article (13) did not show a statistically significant difference in PR associated with VR. As a group, the meta-analysis did not show a statistically significant difference in PR for men with oligospermia; however, there was a trend toward higher PRs associated with VR (OR = 1.695, P=.073).

Of the two articles evaluating men with azoospermia who underwent testicular sperm extraction (TESE) with IVF/ICSI, neither illustrated a statistically significant difference in PRs between the VR and untreated varicocele groups (15, 16). However, when combining these two studies, the meta-analysis showed a statistically significant improvement in PR favoring VR (OR = 2.336, P=.044). The summary meta-analysis of all six of these studies including men with oligospermia and azoospermia showed an overall increase in PR among those undergoing VR compared with those with untreated varicocele (OR = 1.760, P=.011). Table 2 provides the ORs and CIs in tabular format and Figure 2 illustrates these results as a forest plot.

The only study reporting IUI outcomes did not illustrate a statistically significant improvement in PR associated with VR (OR = 1.989, 95% CI 0.565–8.834). This was not included in the group IVF analysis.

Live Birth Rate

Six of the seven articles included data on live birth rate (11–13, 15, 16). Of the three articles reporting on men with oligospermia undergoing IVF/ICSI, two (11, 12) showed a statistically significant increase in live birth rate among those who had undergone VR. The remaining article (13) did not show a statistically significant difference in live birth rates when comparing the VR and untreated varicocele groups. Meta-analysis showed a statistically significant difference in live birth rate favoring VR for men with oligospermia (OR = 1.699, P=.042).

Of the two articles (15, 16) evaluating men with azoospermia and with varicocele who underwent TESE with IVF/ICSI, neither alone illustrated a statistically significant improvement in live birth rate among men who underwent VR. Combining the data from these two studies in meta-analysis, there appears to be a strong trend toward improvement in live birth rate favoring VR, as this finding narrowly missed statistical significance (OR = 2.208, P=.052). The meta-analysis of all five IVF studies also shows an increase in live birth rate among those undergoing VR compared with those with untreated varicocele (OR = 1.761, P=.002). Table 2 provides the ORs and CIs in tabular format and Figure 2 illustrates these results as a forest plot.

The Daitch et al. (17) study, which was the only study reporting IUI outcomes, illustrated a statistically significant

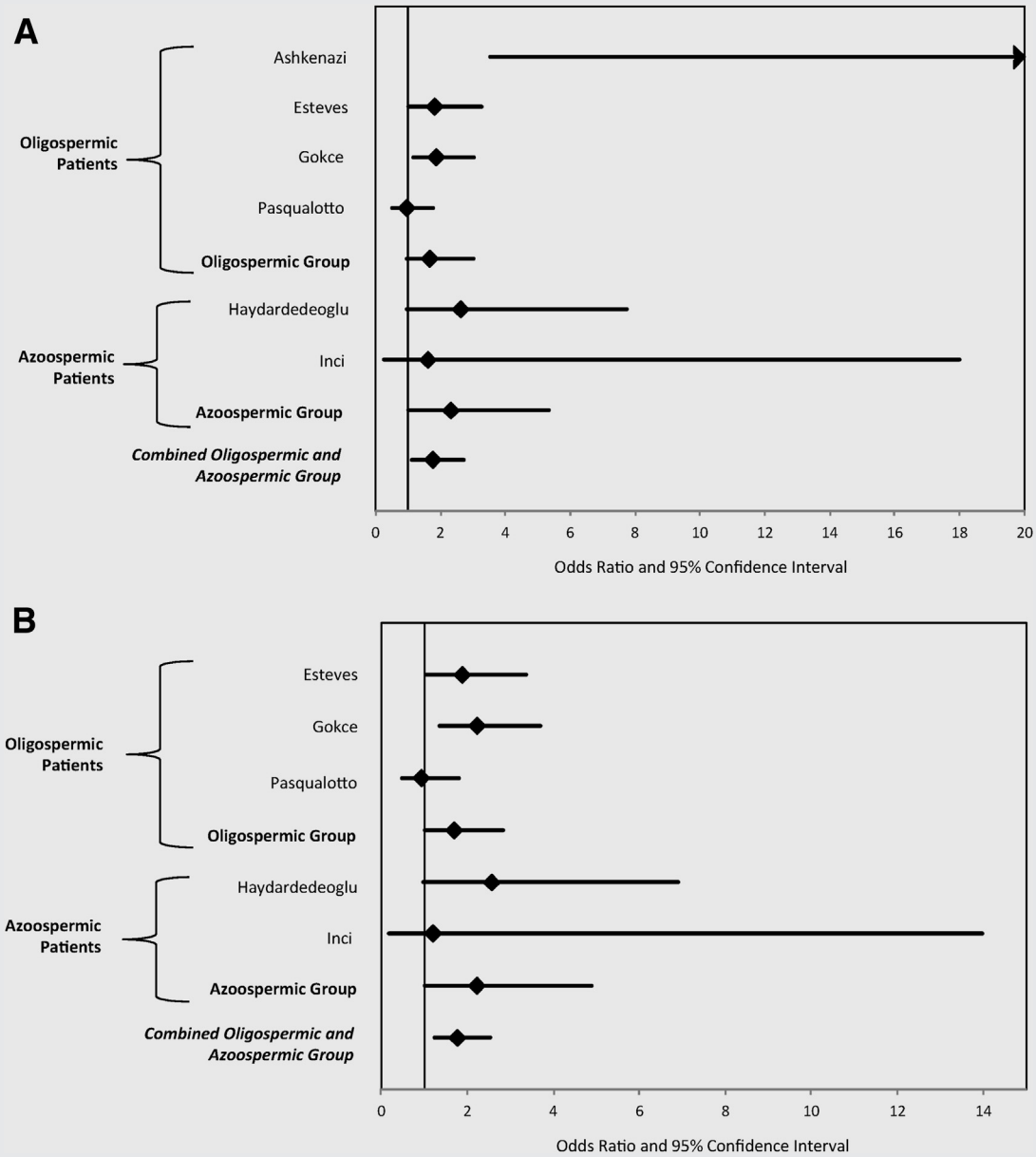
TABLE 2

Odds ratios comparing varicocele repair with persistent varicocele.

Patient group	Odds ratio	95% confidence interval	*P* value
A. Pregnancy rate			
Oligospermia			
Ashkenazi	Infinity	(3.526, Infinity)	
Esteves	1.829	(1.026, 3.275)	
Gokce	1.872	(1.155, 3.035)	
Pasqualotto	0.96	(0.522, 1.792)	
Oligospermic group	1.695	(0.951, 3.020)	.0733
Azoospermia			
Haydardedeoglu	2.621	(0.947, 7.743)	
Inci	1.604	(0.244, 18.108)	
Azoospermic group	2.336	(1.022, 5.342)	.0444
Combined oligospermia and azoospermia	1.760	(1.139, 2.720)	.0109
B. Live birth rate			
Oligospermia			
Esteves	1.873	(1.038, 3.365)	
Gokce	2.227	(1.348, 3.697)	
Pasqualotto	0.915	(0.475, 1.802)	
Oligospermic group	1.699	(1.020, 2.831)	.0417
Azoospermia			
Haydardedeoglu	2.559	(0.971, 6.903)	
Inci	1.212	(0.179, 13.993)	
Azoospermic group	2.208	(0.994, 4.904)	.0518
Combined oligospermia and azoospermia	1.761	(1.223, 2.537)	.0024

Kirby. ART outcomes after varicocele repair. Fertil Steril 2016.

FIGURE 2



(**A**) Forest plot for pregnancy rates. (**B**) Forest plot for live birth rates.

Kirby. ART outcomes after varicocele repair. Fertil Steril 2016.

improvement in live birth rate associated with VR (OR = 8.360, 95% CI = 1.170–363.002). This study was not included in the group analysis.

Sperm Retrieval Rate

Of the two articles (15, 16) reporting on azoospermic men undergoing TESE with IVF/ICSI, one reported an improvement in sperm retrieval rates associated with VR. As a group, meta-analysis demonstrated that the sperm retrieval rate was improved among those having undergone VR (OR = 2.509, P=.0001).

DISCUSSION

To our knowledge, this article represents the first meta-analysis evaluating how VR impacts ART outcomes for patients with azoospermia and oligospermia. The impact of VR is an important reproductive medicine topic for every fertility specialist, particularly given the observation that treatment of the male factor is underused (18). In addition, considering the financial burden associated with ART, it is critical to know whether VR confers some additional benefit, even if natural conception is not achieved after the repair.

The present study is a unique meta-analysis because it evaluates the data regarding men with oligospermia and azoospermia. It is important to consider these two groups both individually and as a whole given the proposed pathophysiology of infertility in men with varicocele. Specifically, VR has been shown to decrease the high sperm DNA fragmentation rates and reactive oxygen species associated with varicoceles, and this type of DNA damage has been associated with worse outcomes in ART treatments (10, 19–21). Although patients with oligospermia and nonobstructive azoospermia may represent a similar population along a continuum versus entirely unique populations, oxidative stress likely plays a role in each.

It is not entirely clear why varicocele may impact pregnancy and live birth rates differently in the individual azoospermic and oligospermic patient populations. Although there was not sufficient data to incorporate the impact of VR on specific semen parameters into the analysis, a generalized improvement in semen quality is likely a contributing factor to these improvements. Perhaps there are events during the early phases of pregnancy that are impacted by sperm damage and oxidative stress that are unique to the process of transit through the epididymis and vas deferens. Evidence has suggested that the impact of DNA fragmentation may not be fully realized until later in pregnancy, thus leading to higher miscarriage rates (22). The present findings of improved live birth rates but unchanged PRs among patients with oligospermia do fit such a hypothesis. Although this meta-analysis cannot provide specific answers to these questions, it does illustrate that, although patients with oligospermia and azoospermiac requiring ART benefit from VR, the value may materialize through different mechanisms. The variability in outcomes across these two populations reinforces the need for further study into how VR impacts semen quality and ART outcomes.

Although analysis of the individual groups showed unique impacts on PRs and live birth rates, VR was uniformly associated with improved ART outcomes in the combined analysis of men with oligospermia and azoospermia. These improvements highlight the most important finding from this study from the perspective of counseling patients. The decision to pursue VR is often complex and requires the consideration of multiple factors that include patient age, desire for multiple children, baseline semen characteristics, cost, timing, and tolerability of ART. Many couples pursue VR with the hope of avoiding the need for ART. However, for couples requiring IVF despite VR, this meta-analysis demonstrates that these couples still benefit with respect to live birth and PRs with ART.

This study does have limitations to be considered. Each of the studies in this review was retrospective and thus represented lower quality evidence relative to prospective and randomized trials. In addition, the reviewed studies did not uniformly provide data on objective semen quality characteristics and therefore limited our ability to provide correlation between our findings and hypotheses of how VR impacts ART outcomes. Correlating VR with clinical outcomes and semen parameters including additional advanced semen studies such as DNA fragmentation may help to further characterize how VR impacts ART results. In addition, there was inconsistency and heterogeneity across the studies with respect to varicocele grade reporting. The possibility of a dose-response relationship between varicocele grade and ART outcomes may be missed in the absence of such data.

Whereas the findings suggest some difference in how VR impacts oligospermic and azoospermic patients, those differences may also represent inadequate sampling. The *P* values for live birth and pregnancy outcomes among the individual groups were each relatively close to our significance threshold of .05 (.073, .044, .042, .052). Greater sampling would likely provide clarity and significance to these trends.

In conclusion, this systematic review and meta-analysis provides evidence that in infertile couples undergoing ART, wherein the male partner has a diagnosis of oligospermia or nonobstructive azoospermia and a varicocele, that VR results in improved PRs and live birth rates. Sperm retrieval rates are higher in patients who have persistent nonobstructive azoospermia after VR requiring TESE for IVF/ICSI. Counseling couples with male factor infertility secondary to a varicocele should include these additional benefits of VR in the era of ART.

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COMPARISON OF BILATERAL VERSUS UNILATERAL VARICOCELECTOMY IN MEN WITH PALPABLE BILATERAL VARICOCELES

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ABSTRACT

Purpose: The left varicocele is usually larger in men with bilateral varicoceles. We hypothesized that most of the benefit of varicocelectomy would derive from repair of the larger varicocele. To test this hypothesis we prospectively compared the effect of unilateral versus bilateral microsurgical varicocelectomy in men with large (grade III) or moderate (II) left varicocele associated with small but palpable (I) right varicocele.

Materials and Methods: A total of 91 patients were prospectively followed and included in the study. Of the patients 65 underwent bilateral and 26 underwent unilateral left repair. All patients underwent preoperative and postoperative semen analysis.

Results: Motile sperm concentration increased from 12.1 ± 1.7 to 23.7 ± 31.8 (95.8% change) in the bilateral group compared with an increase from 19.5 ± 21.4 to 27.8 ± 34.8 (42.6% change) in the unilateral group ($p < 0.05$). Similarly, sperm concentration increased from 23.8 ± 29.5 to 48.6 ± 61.3 (157.6% change) in the bilateral group compared with an increase from 41.1 ± 40.9 to 59.5 ± 66.7 (44.8% change) in the unilateral group ($p < 0.05$).

Conclusions: Bilateral varicocelectomy resulted in significantly greater improvement in postoperative seminal parameters than unilateral repair in patients with grades II to III left varicocele associated with grade I right varicocele. Even a small, unrepaired palpable right varicocele continues to have a detrimental effect on bilateral testis function. Men with bilateral palpable varicoceles require bilateral repair.

KEY WORDS: varicocele, microsurgery, semen, infertility

The association between male subfertility and varicoceles has been known for the last century.[1] In addition, the association between the presence of a varicocele and a decline in semen parameters with time has been documented.[2,3] Recently the microscopic surgical anatomy of varicoceles,[4,5] and microsurgical artery and lymphatic sparing techniques have been described.[6–8] The reported incidence of varicocele in the general and subfertile populations is influenced by the method of examination. In the general population the incidence is between 15 and 18% on physical examination,[9] and 18 and 35% on scrotal sonography and color flow Doppler imaging, respectively.[10]

Improvement in semen parameters has been significant following varicocelectomy and related to varicocele size.[11–13] Men with large varicoceles have poorer preoperative semen quality but demonstrate greater postoperative improvement than those with small or medium varicoceles.[12,13] The consensus is that bilateral surgical repair is indicated for bilateral large varicoceles.[14] The ability of high resolution ultrasound to detect even smaller, subclinical varicoceles led to studies of the benefit of the repair. Although some believe that benefit is derived from repairing such a varicocele,[15] more recent evidence suggests that it does not result in statistically significant improvement in semen parameters.[13] When 1 side is palpable and the other is subclinical the question becomes whether to repair both sides.

In 1 study 70% of patients with unilateral varicocele on examination had bilateral varicoceles on sonography.[16] Subsequent right varicocelectomy resulted in further improvement in semen analysis in 56% of infertile men who had previously undergone left varicocelectomy and had a missed palpable right varicocele.[17] In patients with bilateral palpable varicoceles, consisting of a large to moderate left varicocele with a small right varicocele, it is uncertain how much additional benefit derives from repairing the right varicocele. Of 65 patients with bilateral varicoceles who met the aforementioned criteria, there was no statistical difference between unilateral and bilateral varicocele ligation.[8] However, Doppler flow sonography was used to grade varicocele size and a grade I varicocele was, in fact, a subclinical varicocele by physical examination criteria. In this case a statistically significant improvement in semen parameters may not be expected. We hypothesized that most of the benefit of varicocelectomy would derive from repair of the larger, left varicocele. To test this hypothesis we prospectively compared the effect of unilateral versus bilateral microsurgical varicocelectomy in men with large (grade III) or moderate (II) left varicocele associated with small but palpable (I) right varicocele.

MATERIALS AND METHODS

Between 1986 to 1996, 912 men underwent microsurgical varicocelectomy by the same surgeon. Of these men 91 had a moderate (grade II) or large (III) left varicocele associated with a small but palpable (I) right varicocele, and met criteria for inclusion in the study. All patients with azoospermia, those without postoperative semen analysis and those lost to followup were excluded from the study. Preoperatively all patients were told that benefits of unilateral versus bilateral varicocelectomy were uncertain. Of the 91 patients who met

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inclusion criteria 65 elected to undergo bilateral and 26 opted for only left varicocelectomy.

All 91 patients presented for infertility evaluation. Semen analysis was performed preoperatively and no sooner than 3 months postoperatively. Semen was collected by masturbation after a 3-day abstinence period.[12] All specimens were analyzed within 1 hour of collection. Semen analysis included volume of ejaculate, sperm concentration (million sperm per ml.), percent motility, grade of motility and percent morphologically normal sperm. A Makler† chamber was used to assess sperm concentration. If azoospermia was detected on initial examination, the specimen was centrifuged down to a pellet and reexamined (2 bilateral group patients). Patients with persistent azoospermia on a pellet examination were excluded from study. Video micrography was used to analyze sperm motility. Motility was graded 0—none, 1—poor, 2—fair, 3—good and 4—excellent. A Papanicolaou stain was used to evaluate sperm morphology. The comparison of preoperative and postoperative semen analysis was based on mean values for each semen parameter for a particular patient. Mean plus or minus standard error of preoperative semen analyses was 2 ± 0.1 with a range of 1 to 8. Mean plus or minus standard error of postoperative semen analyses was also 2 ± 0.2 with a range of 1 to 9.

Varicoceles were graded by physical examination in a warm room with the patient standing. Sonography was not used for diagnosis. Varicoceles were graded according to guidelines of the World Health Organization.[18] A grade I varicocele was defined as an impulse with Valsalva's maneuver but not venous tortuosity and a venous diameter less than 1 cm., grade II as a palpable tortuosity through the skin with impulse on Valsalva's maneuver during examination, and grade III as palpable without Valsalva's maneuver and was observed as the classic "bag of worms" appearance through the scrotal skin.

The same surgeon performed all varicocelectomies using a microsurgical technique previously described.[6] Briefly, a 2 to 3 cm. incision is made over the external inguinal ring. The testicle is delivered into the operative field, and all external and gubernacular veins are ligated. Using the operating microscope at 6X to 25X magnifications, the internal spermatic artery and lymphatics are identified and preserved. All external and internal spermatic veins are clipped or ligated and divided. The vas deferens and its vessels are preserved.

Statistical analysis of the data was performed using the Student t test, which was considered significant at $p < 0.05$. In addition, the preoperative data for each group were compared using linear regression scales. Statistically significant r values were assigned for $p < 0.05$.

RESULTS

Of 91 patients 65 (71.5%) underwent bilateral and 26 (28.5%) underwent unilateral left repair. Mean age, which was not significantly different within the 2 groups, was 35.25 years (range 23 to 54) for the bilateral group, 34.12 (range 21 to 45) for the unilateral group and 35 (range 21 to 54) for the entire population. Varicocele grades were statistically similar between the groups preoperatively. Of the left varicoceles 53% were grade III in the bilateral and 61% were grade III in the unilateral group, and 47% were grade II in the bilateral and 39% were grade II in the unilateral group. Mean left testis volume was 16 cc and mean right testis volume was 18 cc for both groups. Mean followup for postoperative semen analyses was 8 months (range 3 to 24).

Mean sperm concentration increased from 23.86 ± 29.52 million sperm per ml. preoperatively to 48.6 ± 61.3 postoperatively in the bilateral ($p = 0.00016$) and from 41.1 ± 40.9 to 59.5 ± 66.7 in the unilateral ($p=0.052$) group. Mean total sperm count increased from 69.64 ± 90.08 million sperm preoperatively to 136.9 ± 157.2 postoperatively in the bilateral ($p = 0.00003$) and from 98.5 ± 94.8 to 167.6 ± 200.3 in the unilateral ($p = 0.052$) group. Percent motile sperm increased from 29.3 ± 28.5% to 39.5 ± 19.2% in the bilateral ($p = 0.11$), and from 35.7 ± 21% to 47.0 ± 14.2% in the unilateral ($p = 0.03$) group. Percent normal sperm increased from 23.9 ± 24.7 to 30.8 ± 24.5 in the bilateral ($p = 0.31$) and from 36.2 ± 23.1 to 36.3 ± 20.6 in the unilateral ($p = 0.43$) group. Finally, the concentration of motile sperm increased from 12.1 ± 17.7 to 23.7 ± 31.8 in the bilateral ($p < 0.0001$) and from 19.5 ± 21.4 to 27.8 ± 34.8 in the unilateral ($p = 0.07$) group. The effect of varicocele ligation within each group was evaluated using the Student t test (table 1 and figure)

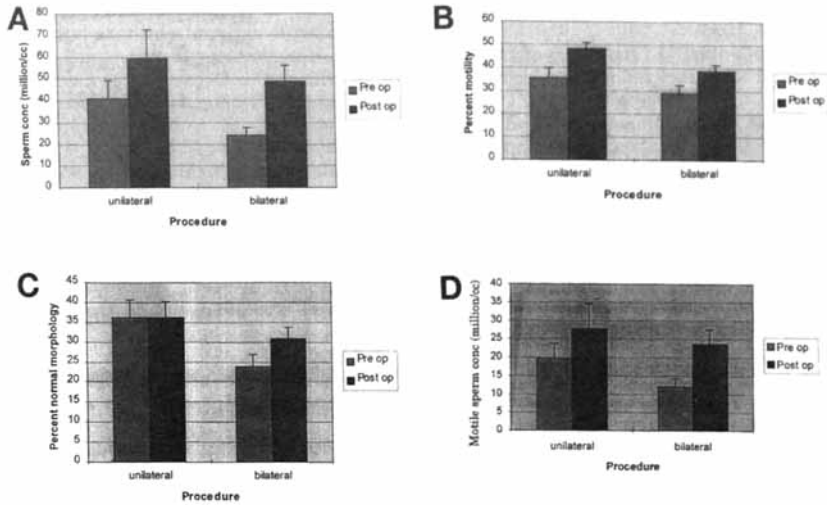
Mean percent change after varicocele ligation in individual semen parameters was compared between groups. A mean plus or minus standard deviation percent change in sperm concentration of 0.73 ± 1.84 was demonstrated in the unilateral ($p < 0.05$) versus 23.78 ± 165.59 in the bilateral ($p < 0.05$) group. Mean percent change in motile sperm concentration (percent motile sperm multiplied by the sperm concentration) was 1.13 ± 2.40 for the unilateral ($p < 0.05$) versus 166.95 ± 1,135 for the bilateral ($p < 0.05$) group. Mean percent change for total sperm count was 23.63 ± 161.05 for the bilateral and 0.99 ± 1.91 for the unilateral group. In terms of percent motility, mean percent change for the bilateral and unilateral group was 17.14 ± 69.25 and 0.44 ± 1.27, respectively. Mean percent change in grade of motility was 0.98 ± 2.91 for bilateral and 0.17 ± 0.51 for unilateral repair. Mean percent change in percent normal sperm was 23.61 ± 79.14 for the bilateral and 0.29 ± 1.00 for the unilateral group. Although all semen parameters revealed greater mean percent changes in the bilateral group, sperm concentration, count and motile sperm concentration achieved a statistically significant larger mean percent change in the bilateral versus unilateral group. Interestingly, the degree of change seen in each index was significantly greater for the bilateral group (table 2).

It was necessary to determine whether the preoperative differences in semen parameters between the groups had an impact on postoperative improvement for valid comparison between the 2 groups of data. Linear regression scales were developed for each preoperative semen parameter and compared with the postoperative percent change for that parameter. Due to complex statistical considerations the improvement seen in morphology (percent normal sperm) of the bilateral versus unilateral group may not be valid since the preoperative values between the groups differed for these 2 parameters. Nonetheless, morphology improved to a greater degree after bilateral varicocelectomy. However, all other semen parameters are statistically valid points of comparison between the 2 groups.

TABLE 1. *Mean pretreatment and posttreatment semen parameters*

	Mean ± SE		p Value
	Preop.	Postop.	
Bilat. group:			
Concentration	23.8 ± 29.5	48.6 ± 61.3	0.00016
Count	69.6 ± 90.0	136.9 ± 157.2	0.00003
% Motility	29.3 ± 28.5	39.5 ± 19.2	0.03
% Normal	23.9 ± 24.7	30.8 ± 24.5	0.31
Motile sperm concentration	12.1 ± 17.7	23.7 ± 31.8	0.000046
Unilat. group:			
Concentration	41.1 ± 40.9	59.5 ± 66.7	0.0515
Count	98.5 ± 94.8	167.6 ± 200.3	0.0519
% Motile	35.7 ± 21.0	47.0 ± 14.2	0.1115
% Normal	36.2 ± 23.1	36.3 ± 20.3	0.4342
Motile sperm concentration	19.5 ± 21.4	27.8 ± 34.8	0.0670

† Sefi Medical Industries, Ltd., Haifa, Israel.



A, changes in sperm concentration. *B*, changes in sperm motility. *C*, changes in sperm morphology. *D*, motile sperm concentration

TABLE 2. *Mean percent change*

	Mean ± SD		p Value
	Unilat. Group	Bilat. Group	
Sperm concentration	0.73 ± 1.84	23.78 ± 165.59	0.04
Total sperm count	0.99 ± 1.91	23.63 ± 161.05	0.01
% Motility	0.44 ± 1.27	17.14 ± 69.25	0.22
Grade motility	0.17 ± 0.51	0.98 ± 2.91	0.55
% Normal sperm	0.29 ± 1.00	23.61 ± 79.14	0.05
Motile sperm concentration	1.13 ± 2.40	166.95 ± 1135	0.02

DISCUSSION

Recent studies suggest that response to varicocele surgery is related to varicocele size, with greater improvement in semen parameters resulting from the repair of larger versus small varicoceles.[12,13] The significance of sonographically detected, or subclinical, varicoceles is controversial.[13,15,16] Current reports suggest that repair of subclinical varicoceles does not seem to improve semen parameters significantly.[19] Varicoceles detected by physical examination are associated with a greater postoperative improvement in semen parameters than those detected sonographically.[20] Varicoceles detected by a thorough physical examination are more predictive of a good clinical outcome than venous diameter on ultrasound.[21] However, an important controversy that remains is whether a small but clinically palpable right varicocele associated with a large or moderate left varicocele should be repaired.

There has been no consensus in the infertility literature as to the management of bilateral varicoceles, especially when 1 side is a grade I varicocele. Grasso et al have argued that due to the potential added morbidity and additional operating time the benefit obtained from repairing a small, right varicocele associated with a large left varicocele is minimal.[8] However, they categorized cases according to sonographic criteria rather than by physical examination. As Jarow et al indicated, varicoceles detected solely by sonography are different from those detected by physical examination in terms of the impact on postoperative seminal improvement.[13] There is greater potential for an improvement in sperm motility, concentration and morphology when varicocelectomy is performed on clinically palpable varicoceles.[13] Additionally, Grasso et al performed retroperitoneal varicocele ligation using the Palomo technique rather than microsurgical artery sparing varicocelectomy.[8] There is a statistically significant decrease in postoperative hydrocele formation and iatrogenic spermatic artery injury using the microsurgical technique of varicocelectomy compared to nonmicrosurgical techniques.[6,22]

Our data suggest that maximal improvement in semen parameters is achieved by a bilateral repair in patients with a grade I, palpable right varicocele associated with a grade II to III left varicocele. The postoperative changes in semen parameters consistently demonstrated more significant improvement in our bilateral group. Varicocele ligation has already been shown to improve postoperative semen parameters in the subfertile population.[6,23–25] There was a statistically significant improvement postoperatively for every semen parameter in the bilateral group. However, in the unilateral group statistical significance was not quite achieved but was only approached for the improvements in sperm concentration and count, and just barely in motility. Since all surgery in this population was performed using the same procedure and by the same operating surgeon, technical differences cannot explain the significance of these findings. The failure of all semen parameters to improve significantly after unilateral repair while statistically significant improvement was seen after bilateral repair should not discount the unilateral repair but should underscore the importance of a small right varicocele. In addition, it suggests that there is a bilateral effect of unilateral varicocele. In conclusion, a palpable right varicocele associated with a large or moderate left varicocele should be repaired for maximal improvement in semen parameters.

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Reassessing the value of varicocelectomy as a treatment for male subfertility with a new meta-analysis

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Objective: To determine the efficacy of varicocelectomy as a treatment for male factor infertility by improving the chance of spontaneous pregnancy.
Design: Meta-analysis.
Setting: Cleveland Clinic's Glickman Urological Institute.
Patient(s): Infertile men with abnormal results on semen analyses and a palpable varicocele.
Intervention(s): Surgical varicocelectomy.
Main Outcome Measure(s): Spontaneous pregnancy outcome.
Result(s): The odds of spontaneous pregnancy after surgical varicocelectomy, compared with no or medical treatment for palpable varicocele, were 2.87 (95% confidence interval [CI], 1.33–6.20) with use of a random-effects model or 2.63 (95% CI, 1.60–4.33) with use of a fixed-effects model. The number needed to treat was 5.7 (95% CI, 4.4–9.5).
Conclusion(s): Surgical varicocelectomy in infertile men with palpable lesions and at least one abnormal semen parameter improves the odds of spontaneous pregnancy in their female partners. Five studies were included (two randomized, three observational). All were scored for bias. Our study suggests that varicocelectomy in selected patients does indeed have beneficial effects on fertility status. (Fertil Steril® 2007;88:639–48. ©2007 by American Society for Reproductive Medicine.)

Key Words: Varicocelectomy, pregnancy, meta-analysis, random effect

Is a varicocelectomy an effective treatment for male factor subfertility? It is a seemingly simple question that has been the focus of intense debate for nearly 50 years. Many studies report improvement after surgery (1–9), but other studies show no benefit (10–17). Clearly, there are conflicting opinions whether a varicocelectomy improves fertility.

These differences of opinion are most obvious in the clinical guidelines for male factor infertility that have been published by various professional groups. For example, the Best Policies Practice Groups of both the American Urological Association and the American Society for Reproductive Medicine (18, 19) have stated jointly that correction of varicoceles is indicated for infertile men with palpable lesions and one or more abnormal semen parameters. However, they specifically noted that treatment of the varicocele is not indicated in patients with normal results of semen analyses or subclinical, nonpalpable varicoceles. In contrast, the National Collaborating Centre for Women's and Children's Health, 2005 (11) stated, "Men should not be offered surgery for varicoceles as a form of fertility treatment because it does not improve pregnancy rates." The European Urological Association Guidelines on Male Infertility simply concluded that treatment of varicoceles to achieve pregnancies remains controversial (20). Thus, the fundamental question remains whether the existing literature on varicoceles is reliable enough to resolve these differences of opinion and serves as the basis of a new meta-analysis.

Although randomized controlled trials remain the "gold standard" or level I evidence, the current group of randomized

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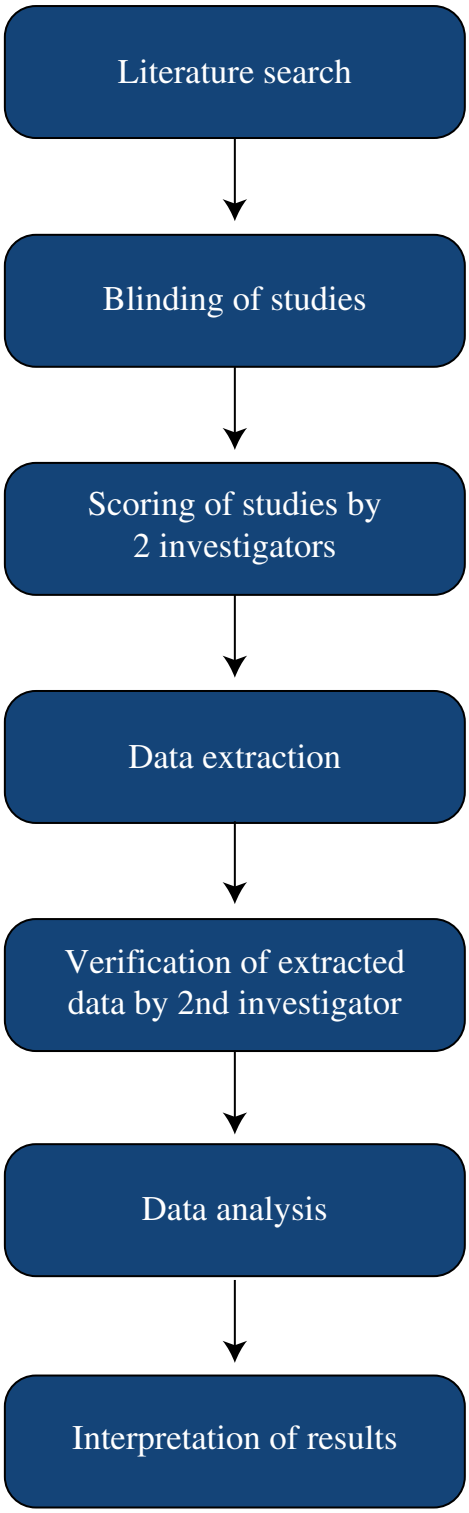
controlled trials on the subject of varicocelectomy and pregnancy outcome has been criticized for several reasons. The critics state that some randomized controlled trials included men with subclinical varicoceles or normal semen analyses and others had significant dropouts after randomization (11, 21–23). A recent critique concluded that analysis of the randomized controlled trial data in the current literature does not allow us to draw any favorable or adverse conclusions to the treatment of varicoceles in infertile couples (24).

Despite these criticisms, our group still believed that it might be possible to develop a new and reliable meta-analysis from the existing literature; however, such a meta-analysis would require several considerations that were fundamentally different. First, we would select only articles that included infertile men with palpable varicoceles who had at least one low semen parameter on three samples. Second, we would limit this study only to surgical repairs because there has been a difference of opinion regarding the outcomes with surgery compared with embolization (25, 26). Third, we would include only articles that reported data on the relationship of "surgical" varicocelectomies and "spontaneous or natural" pregnancy rates.

Furthermore, we would blind the articles for the reviewers and score them with our new scoring system to evaluate four types of study bias. Still further we would follow the lead of some investigators who have suggested that it is reasonable to include level II evidence from observational or case-controlled studies in a meta-analysis so long as the observational studies have considered carefully the potential for bias (21, 27). In various clinical situations, the existing evidence from randomized controlled trials addressing the effectiveness of specific interventions may be quite limited; therefore, it may not be inappropriate for systematic reviews to include carefully considered nonrandomized studies to provide a detailed picture of our current knowledge and limitations (28). Therefore, in the present meta-analysis on surgical varicocelectomy and spontaneous pregnancy, we intended to include both randomized controlled trials and observational studies (Fig. 1).

FIGURE 1

Flow diagram on selection of studies for the meta-analysis.



Marmar. Varicocelectomy—a new meta-analysis. Fertil Steril 2007.

MATERIALS AND METHODS

Types of Patients

Studies of infertile men with a diagnosis of unilateral or bilateral palpable varicoceles and at least one abnormal semen parameter were included. Control groups were composed of infertile men with varicoceles who declined to undergo surgical repair and who were randomly assigned either to no treatment or to medical treatment.

Types of Intervention

Surgical varicocelectomy (high ligation, inguinal, or microsurgery) was reviewed.

Types of Outcome Measure

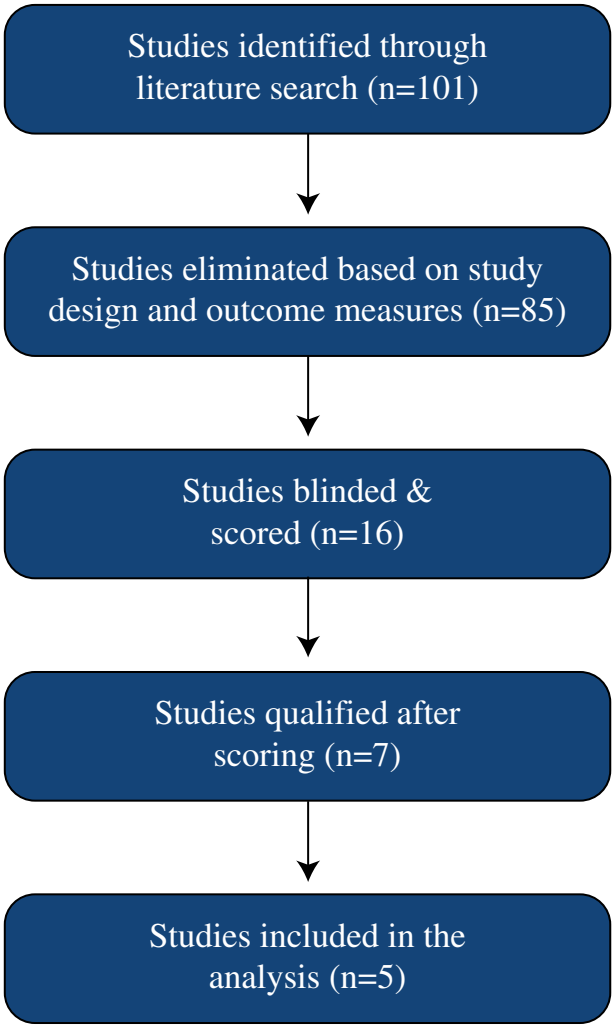
The outcome measure was the effect of surgical varicocelectomy on natural or spontaneous pregnancy outcome during follow-up of up to 24 months.

Search Strategy for Identification of Studies

Studies were identified by performing an extensive search with BIOSIS, EMBASE, and Medline (from 1985 to present) with the help of a professional librarian, as well as by hand-searching review articles and cross-references. The overall strategy for study identification and data extraction is outlined in Figure 2. The following key words were used to search the databases: varicocelectomy, microsurgery, high ligation, infertility, semen parameters, and pregnancy rate or outcome. No exclusions were made on the basis of language. Articles were evaluated for relevance by examining titles and abstracts. Studies were excluded if there were patients with subclinical varicoceles only or subclinical varicoceles combined with clinical varicocele and if the effect of treatment was examined only in an adolescent population.

FIGURE 2

Flow diagram on selection of studies evaluating the effect of varicocelectomy on the pregnancy outcome.



Marmar. Varicocelectomy—a new meta-analysis. Fertil Steril 2007.

Evaluation of Relevant Studies by Blinding and Scoring of Studies

All articles and reviewers were blinded during the evaluation period. The methods, results, tables, and figures from each study were extracted, and each article was assigned an identification number by an individual other than the two scorers. Actual quantitative or qualitative report of results was blacked out in each article to enable unbiased scoring of study quality. Data points or graphs were blacked out of figures, whereas axes and captions were still included for evaluation. Summary statistics, *P* values, or descriptions were blacked out of tables and texts, whereas labels such as comparison groups and parameters measured were left viewable. Two evaluators blinded to the concluding results, authors, journal, and year of the articles evaluated each study on its methodologic merits.

Articles with both preoperative and postoperative repeated measures of semen parameters were evaluated for methodologic quality by our initial scoring system (Appendix). The questions and scores were developed to evaluate four categories of bias: selection or follow-up bias, confounding bias, information or detection bias, and other sources of bias such as misclassification. Each study was scored by using the same set of questions for each type of bias (29, 30). Specific answers for different questions were given more weight than others as evidenced in the point system used to total the scores for each category of bias.

A higher score indicated that the study met most of the criteria required to avoid introducing bias in the study. If the point total for more than one category of bias was below an acceptable range, the study automatically was excluded from the final analysis. If the points for only one category totaled below the acceptable range, the study was reexamined to determine whether, indeed, the overall study was likely to be biased and, if not, whether it could be included in the meta-analysis.

The point ranges for exclusion or inclusion were determined by the epidemiologic importance of each study, its scientific quality, and the possibility of the article reaching a biased conclusion. For example, in the case of selection or follow-up biases, if a large proportion of subjects were lost to follow-up, then it becomes difficult to determine whether those who selectively dropped out may have been the ones with least improvement or whether the losses were simply too few in numbers to have biased the results. Thus, to deal with this potential quandary, a positive answer (no loss to follow-up over 10%) was given 2 points and a negative answer (loss to follow-up in more than 10% of participants) was given 1 point (Appendix). The same rationale was

carried out for all other sources of bias: confounding bias, information or detection biases, and other sources of bias such as misclassification. If information for a particular question was not stated, the study was given only 1 point for that question. Furthermore, the category of confounding was designed to include studies that made a comparison between the same subjects but not over more than a 2-year period. If the follow-up time was more than 2 years after the surgery, or with no follow-up within this time period, or if the study did not account for time-varying confounders, then it was likely that the study would be excluded.

This method of scoring studies was used rather than a simple checklist because the latter may produce bias (29). As an alternative, our scoring plan was intended to identify and quantify potential sources of bias. Two reviewers scored each study independently, and the final decision on whether a study was to be included was determined by discussion between the two reviewers.

Data Extraction

Data were extracted by one of the authors on a preformatted data extraction sheet. Population information (i.e., primary versus secondary infertility) and study characteristics such as the specific intervention (high ligation, microsurgery, and laparoscopy) were listed. These data were available for subsequent subgroup analyses.

The data were then entered in the RevMan software (version 4.2.8) developed by the Cochrane Collaborative for the purpose of meta-analysis (http://www.cochrane.org).

Effect of Varicocelectomy on Pregnancy Outcome

To examine the effect of varicocelectomy on "spontaneous or natural" pregnancy, we studied cohorts within a 2-year follow-up after varicocelectomy was performed in one male cohort and no, delayed, or medical treatment in the other cohort. Studies were excluded if they had men with subclinical varicoceles. Also, patients who had undergone assisted reproductive techniques (ART) such as IVF or IUI were not included in the analysis. Studies that used embolization or sclerosis techniques for varicocele corrections were excluded. Pregnancy data were recorded for the 24-month interval after surgery, and the overall odds were calculated by random-effects and fixed-effects models. The number needed to treat was calculated and evaluated by 95% confidence intervals (CI) (31). The number needed to treat was recalculated after removal of the most favorable study (1). All data were verified by a second investigator.

RESULTS

Of the 101 articles retrieved from the search containing pregnancy data, further elimination because of the study designs and relevance of outcomes measured was conducted, yielding 16 studies to be blinded. These 16 studies were then scored and assessed for quality. Two of these studies (15, 32) were excluded because they had both patients with surgical ligation and patients who had sclerosis or radiologic embolization. Patients whose partners achieved pregnancy with ART (IVF and/or IUI) were excluded from our analysis, but one of the included studies followed patients for spontaneous pregnancy after ART (4). The remainder of these studies were excluded on the basis of their scores for bias (Appendix). Therefore, our meta-analysis was limited to five surgical studies that included data on spontaneous pregnancy rates.

The mean age of the male cohorts was 31.2 years (range 20–46 years). Laterality was reported in four of the five studies. Left varicoceles were noted in 67.4% to 81.5% of the patients, bilateral varicoceles in 14.0% to 30.4%, and right varicoceles in 2.1% to 5.5%. The varicoceles were all palpable, but the specific sizes were recorded in only two of the five studies. Grade III (large) varicoceles were recorded in 9.5% and 34.3% of the patients, grade II (moderate) in 54.4% and 21.8%, and grade I (small) in 36.2% and 43.7%. The controls in four of the studies had no treatment, whereas in one study the controls used clomiphene citrate (Clomid).

The odds of spontaneous pregnancy after varicocelectomy compared with no or medical treatment for clinical varicocele were 2.87 (95% CI, 1.33–6.20, P=.007) with use of the inverse variance random-effects model (Table 1). A fixed-effects model also yielded a significant odds ratio of 2.63 (95% CI, 1.60–4.33], P=.00001). Results of the test for the presence of heterogeneity between study measures was not significant (P=.17).

Pregnancy outcome was also evaluated on the basis of the number needed to treat. Within the five studies there were 396 patients who underwent operation and who had 131 pregnancies (33.0%) versus 174 controls with 27 pregnancies (15.5%). The number needed to treat was 5.7 (95% CI, 4.1–9.5). When the data were recalculated after removal of the figures from the most favorable study (1), the number needed to treat was 6.6 (95% CI, 4.4–13.3), which represents comparable results following surgery.

DISCUSSION

A group of 20 scientists from nine countries, known as the Potsdam Consultation, convened to develop guidelines for the conduct and interpretation of meta-analyses. They added to the experience of earlier investigators and defined a meta-analysis as a systematic review that uses statistical methods to combine and summarize the results of several studies (29), and they listed 13 specific methodologic principles for the performance of these studies. In a separate study, Thacker et al. noted the benefits of a meta-analysis and stated that "decisions about clinical practice should be based on the combined weight of the evidence from available reports" (33). However, they warned that there are systematic rules for conducting a meta-analysis that include an explicit description of methodology so that results can be interpreted in light of any biases or limitations.

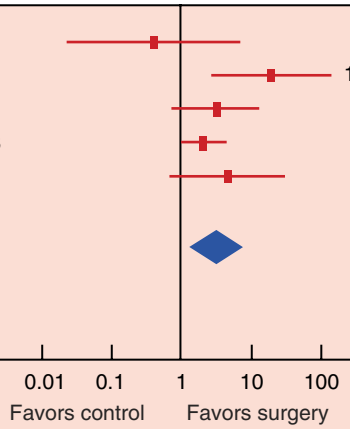
In the present meta-analysis, we examined the effect of surgical varicocelectomy on spontaneous pregnancy

TABLE 1

Confidence intervals and odds ratio for pregnancy after varicocelectomy among men with palpable lesions and at least one abnormal semen parameter.

Study	Varicocelectomy n/N	Control n/N	OR (random) 95% CI	OR (random) 95% CI
Grasso et al 2000	1 / 34	2 / 34		0.48 [0.04, 5.61]
Madgar et al 1995	16 / 25	2 / 20		13.50 [2.55, 71.40]
Marmar et al 1994	66 / 186	3 / 19		2.93 [0.82, 10.44]
Okuyama et al 1988	43 / 141	15 / 83		1.99 [1.02, 3.86]
Onozawa et al 2002	6 / 10	5 / 18		3.90 [0.76, 19.95]
Total (95% CI)	396	174		2.87 [1.33, 6.20]

Total events: 131 (Varicocelectomy), 27 (Control)
Test for heterogeneity: $Chi^2 = 8.47$, df = 4 (P= 0.17), r = 38.1%
Test for overall effect Z = 2.68 (P < 0.00001)



Note: OR = odds ratio; n = number of couples achieving pregnancy with male partners diagnosed with clinical varicoceles; N = total number of cases.

Marmar. Varicocelectomy—a new meta-analysis. Fertil Steril 2007.

outcome. We developed a different methodology than in previous meta-analyses: we adhered to the principles of the Potsdam guidelines, we "blinded" the reviewers during the evaluation process, and we developed a scoring system to quantify bias that was used to evaluate the literature on infertile men who had "surgical" correction of varicoceles. With this approach, the data from our meta-analysis led us to conclude that a surgical varicocelectomy improved the spontaneous pregnancy rates for infertile men with low semen parameters and palpable varicoceles. However, we believe that a critical discussion of our methods is necessary to understand the process.

A primary cause of bias in a meta-analysis can come from the reviewers. It is feasible that a reviewer may be influenced by the knowledge of institutions, investigators. and the concluding results associated with other aspects of the study (34). This has been termed inclusion bias (35). The mechanisms for inclusion bias have been reported (36), but they may be minimized by "blinding" the examiners and the documents during the evaluation process. Historically, the majority of meta-analyses have not been blinded. However, in the present meta-analysis we chose to make the effort and take particular precautions to proceed with blinded evaluations. In addition, we used other strategies to evaluate bias.

To evaluate the literature for bias, we developed a scoring system rather than a checklist (29). It is possible that a well-designed study with a traditionally acceptable checklist for inclusion (statement of randomization procedure, stated assessment of confounding, etc.) still may be biased because of unequal weighting. Some items on the checklist may value individual studies inappropriately over the others. Our scoring plan was intended to adjust for this type of bias. In some instances, specialty groups have developed and used standardized protocols for scoring literature in their fields (37, 38). In the absence of standard methods in the present field, we developed our own scoring system to evaluate several types of bias. Although the scoring system was not validated statistically, during several meetings before the initiation of this meta-analysis we discussed and adopted a set of specific questions and point scores to limit quantitatively against potential bias in the literature under consideration. The new system was applied to the blinded manuscripts to determine their inclusion into the meta-analysis. Two reviewers scored each study, independently, and the final decision on inclusion or exclusion was determined during a discussion between the two reviewers. This approach has been considered and accepted in other fields for the development of other meta-analyses (38, 39).

Some investigators have been critical of the fact that most varicocele studies have been uncontrolled and not randomized controlled trials. In an attempt to address these matters, two recent meta-analyses have been published on varicoceles (10, 12) with only level I evidence from a group of randomized controlled trials. Essentially, these two meta-analyses included the same group of randomized controlled trials, and both reviews came to the conclusion that varicocele repairs do not improve subfertility. However, these meta-analyses, themselves, have been the subject of several critiques that have cited methodologic flaws that may have biased the results. Specifically, the National Collaborating Centre for Women's and Children's Health, 2005 report (11) was critical for several reasons: these meta-analyses

had clinical heterogeneity in the subjects selected, and there were differences in the mean age of the male partners, differences in the duration of infertility, and high dropout rates after randomization. In another critique, Templeton (22) commented that Evers and Collins (12) elected to exclude a large, hitherto-unpublished World Health Organization (WHO) study that appeared in abstract form. These WHO data suggested that varicocelectomy appeared to improve pregnancy, and, according to Templeton, "exclusion of the multi-centre data is important and could have made a difference" (22), which raises concerns for publication bias. In still other critiques, some investigators pointed out that four of the eight randomized controlled trials included in these meta-analyses had men with subclinical varicoceles, and two had men with normal semen parameters (23). For example, Ficarra et al. (24) reevaluated data from a prior meta-analysis (12) by removing studies that included men with subclinical varicoceles and normal semen parameters. When they recalculated the data for the "as-treated" groups, the pregnancy rates were 36.4% for the surgically treated group and 20% for controls (P=.009). Therefore, these past meta-analyses have not resolved the issues surrounding varicocelectomy and subfertility. Nevertheless, our group believed that it was still possible to develop a new and more inclusive meta-analysis from the existing literature that may lead to valid conclusions.

In the present meta-analysis, we included both randomized controlled trials and observational studies. Although this approach may be controversial to some, we believe that it is sound for the current subject matter primarily because of the lack of reliable randomized controlled trial data. Several studies suggest that randomized controlled trials provide the highest level of evidence for causation, but they are known to be costly and difficult to complete, particularly without experiencing a significant number of dropouts after randomization (21, 27, 28). Furthermore, in some instances, the ethics of the randomized controlled trials may be viewed as borderline because the randomization and informed consent may not reach international standards, and in most cases they are done without peer review (40). Still further, some randomized controlled trials may be particularly unfair to infertile couples who are offered no treatment in one arm of the trial, when alternative treatment is available such as IVF (22). In these instances, treatment delays may expose these couples to the negative influence of advancing age on pregnancy outcome.

Because of these realities, we chose to include observational studies in addition to randomized controlled trials in the present meta-analysis. The Potsdam Consultation noted that observational studies should not be abandoned, but they may be included after critical appraisal, empirical study, and methodologic evaluation (29). Oftentimes, combining data from several smaller observational studies may be an efficient, effective, and perhaps the only means of reaching a conclusion (41). The challenge lies in developing a methodology for evaluating these observational studies and deciding whether to include a particular study. During the evaluation period, the observational studies were scrutinized with the same scoring system for bias as randomized controlled trials. Further, we analyzed the data with a random-effects analysis to accommodate for heterogeneity. One other approach to reduce heterogeneity is to remove primary studies selectively from consideration, but this method opens the door for other bias. If removal of studies from the analysis is not based on biological and clinical differences of study design or specific interventions, removal may shift the weight of the evidence inappropriately on the measured outcome.

Although our approach was not totally free of problems, it contained other safeguards against methodologic bias that plagued earlier meta-analyses. Our scoring system excluded studies during the evaluation phase with large numbers of individual dropouts after randomization, which was different from other meta-analyses that included these types of studies (42). The individuals who dropped out may differ systematically from those who stayed in, and, if studies with excessive dropouts are included, then the meta-analysis may be influenced by confounding bias. Not all the studies included in prior meta-analyses (even randomized trials) examined the distribution of age even though it is known to be a confounder, and some studies demonstrated detection bias because they included individuals with subclinical varicoceles. The five studies in the present meta-analysis all had men with palpable varicoceles only, including Grasso et al. (14), who studied men with ultrasound and a scoring system that included small, palpable, grade I lesions. Although it takes careful planning and a greater work effort, it seems important to evaluate for all of these types of bias during the evaluation phase to include the most reliable data in the meta-analysis.

With regard to spontaneous pregnancy outcome, some studies found that there is no difference in the odds of pregnancy for men who underwent varicocelectomy in comparison with those who did not. However, this lack of difference may be due to the fact that the researcher was not seeking to record pregnancy as a main outcome variable. If large studies are included in a meta-analysis with only partial pregnancy data, they may be given more weight, despite that the study did not aim to measure the odds of pregnancy. This would cause the overall conclusion to be weighted toward no effect. If the patients' cases had been followed up thoroughly, there might have been a different observed effect of treatment on the outcome.

In our meta-analysis, we used an approach that was consistent with the guidelines for meta-analyses of the Potsdam Collaboration (29). We included only studies that had spontaneous pregnancy data as an intended outcome. We evaluated five studies that led us to conclude that a surgical varicocelectomy improved spontaneous pregnancy outcome on the basis of the odds ratio and the number needed to treat. Furthermore, even after removal of the figures of the most favorable study (1), the number needed to treat results from the remaining four studies seemed comparable to those of the original five.

In a side study, we found that the pregnancy results after varicocelectomy were usually associated with the improvement in sperm density. The four studies with improved pregnancy rates all reported statistically significant increases in postoperative sperm density, whereas the one study that reported no improved pregnancy rates had no improvement in the postoperative sperm density. Presently, these findings may have increased clinical relevance, because recent reports have linked sperm density to fertility in other situations. For example, a study of fertile and infertile populations reported that the mean sperm densities for these groups were 19.5 versus 8.5 10^6/mL, respectively ($P<.001$) (43). Another study reported that doubling the sperm concentration, for example, from 4 to 8 $\times 10^6$/mL, increased the monthly conception rate by a factor of 2.8, and doubling the concentration from 8 to 16 $\times 10^6$/mL or from 16 to 32 $\times 10^6$/mL increased fecundability by factors of 1.34 and 1.32, respectively (44). Still other studies showed that the odds ratio for subfertility was 5.6 (3.3–8.3) for those men with sperm densities $<13.5 \times 10^6$/mL, compared with an odds ratio of 1.3 (1.2–2.2) for men with sperm densities between 13.5 and 48 $\times 10^6$/mL (45). Thus, the measurement of sperm density continues to be important in the evaluation of male factor infertility. However, there is usually great variability in the parameters from consecutive semen studies, and a panel of at least three preoperative and three postoperative semen analyses is needed to avoid the statistical phenomenon of regression toward the mean (3). Although semen data were not included in the present manuscript, future varicocele studies probably should include this type of panel to evaluate both patients and controls.

Recently, other new molecular and genetic markers have been used to stratify patients with varicocele (46, 47). For example, some studies have documented increased DNA damage to the sperm in the semen of infertile men with varicoceles; others demonstrate the presence of oxidative stress (48, 49). In still other studies, there was no improvement in semen parameters after varicocelectomy among men with Y-chromosome microdeletions or abnormal karyotypes (50), and reduced pregnancy outcomes after varicocelectomy among men with increased testis tissue cadmium, and microdeletions in the sequence of the L-type, voltage-dependent calcium channel (51). Thus, the presence or absence of these markers may explain why some men with varicoceles are fertile and others do not improve after varicocelectomy. Furthermore, future studies in men with varicoceles may be more selective by stratification with these markers. This approach may identify those patients with a realistic opportunity to benefit from these procedures versus those in whom varicocelectomy is likely to fail on a molecular/genetic basis.

CONCLUSION

On the basis of the data from current literature, we conclude from this meta-analysis that a surgical varicocelectomy is an effective treatment for improving the spontaneous pregnancy rate for couples with an infertile male partner who has low semen parameters and a palpable varicocele. In the future, randomized controlled trials should include stratification with a panel of semen analyses and molecular/genetic markers. Furthermore, the control groups should be offered some meaningful treatment such as IVF to avoid unfair conditions for participation in a research study.

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APPENDIX

Initial scoring sheet used for evaluating studies that included men with palpable varicoceles, at least one low semen parameter, and pregnancy data after varicocelectomies

Study number _____ **Reviewer Initials** _____

Selection/Follow-up **Total** _____

From what, if any, underlying cohort is the study population derived?
- 3 From a geographical cohort
- 3 From a community
- 2 From a clinic population
- 1 Unable to answer

How were subjects recruited?
- 3 All cases in the population were included
- 2 Cases were recruited consecutively over a period of time
- 3 Cases were randomly selected
- 1 Unable to answer

Was there loss of follow-up or lack of participation greater than 10% of those sampled initially?
1 Yes
2 No
1 Unable to answer

Did the investigators restrict against participants based on infection, previous treatment, and female factor infertility or conditions related to ART outcome and sperm parameters?
3 Yes
2 No
1 Unable to answer

Confounding **Total** _____

Was the time between the two follow-up periods short enough to allow for no confounding by age within subjects (under 2 years)?
3 Yes
1 No
1 Unable to answer

Did they evaluate and account for potential confounders that may vary over time?
ie, amount of follow-up time, season, smoking, alcohol consumption, original sperm count, time-varying exposures, etc.
1 No
2 Yes, but they do not adjust
3 Yes, and they adjust for them when necessary
1 Unable to answer

Did the investigators pre-specify the same procedures for analysis for before and after the intervention?
2 Yes
2 Not applicable
1 No
1 Unable to answer

Information/Detection Bias **Total** _____

Was the method of follow-up the same before and after treatment?
3 Yes
2 No
1 Unable to answer

If blinding was possible, were those evaluating outcomes blinded to the patient's intervention/disease status?
2 Blinding was not possible
1 Blinding was possible but not done for all/some investigators
3 Blinding was performed
1 Unable to answer

Was the measurement of outcome(s) objective?
Objective meaning medical records or diagnostic test, not objective/subjective meaning recall, etc.
3 Yes
2 No
1 Unable to answer

Was ascertainment of outcome performed at the same location both before and after treatment?
4 Yes
2 No
1 Unable to answer

Other **Total** _____

Does the study combine outcomes across groups with very heterogeneous histories/durations of infertility and across different interventions?
2 Yes, together

3 No
1 Unable to answer

Was severity/grade of varicocele evaluated both before and after the intervention?
3 Yes
2 No
1 Unable to answer

Did investigators use an established set of guidelines for semen analysis?
4 Yes
1 No
1 Unable to answer

Exclusion Criteria

Category	Maximum Score	Minimum Score	Include Score	Exclude Score
Selection	11	4	11–7	6–4
Confounding	8	3	8–5	4–3
Information	13	4	13–12	11–4
Other	10	3	10–8	7–3

- Any study will be excluded if 2 or more categories score in the "exclude range".
- Any study will be re-reviewed if only 1 category scores in the "exclude range".

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INVITED REVIEW

Male Fertility

Outcome of assisted reproductive technology in men with treated and untreated varicocele: systematic review and meta-analysis

Sandro C Esteves[1], Matheus Roque[2], Ashok Agarwal[3]

Varicocele affects approximately 35%–40% of men presenting for an infertility evaluation. There is fair evidence indicating that surgical repair of clinical varicocele improves semen parameters, decreases seminal oxidative stress and sperm DNA fragmentation, and increases the chances of natural conception. However, it is unclear whether performing varicocelectomy in men with clinical varicocele prior to assisted reproductive technology (ART) improve treatment outcomes. The objective of this study was to evaluate the role of varicocelectomy on ART pregnancy outcomes in nonazoospermic infertile men with clinical varicocele. An electronic search was performed to collect all evidence that fitted our eligibility criteria using the MEDLINE and EMBASE databases until April 2015. Four retrospective studies were included, all of which involved intracytoplasmic sperm injection (ICSI), and accounted for 870 cycles (438 subjected to ICSI with prior varicocelectomy, and 432 without prior varicocelectomy). There was a significant increase in the clinical pregnancy rates (OR = 1.59, 95% CI: 1.19–2.12, I^2 = 25%) and live birth rates (OR = 2.17, 95% CI: 1.55–3.06, I^2 = 0%) in the varicocelectomy group compared to the group subjected to ICSI without previous varicocelectomy. Our results indicate that performing varicocelectomy in patients with clinical varicocele prior to ICSI is associated with improved pregnancy outcomes.

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Keywords: assisted reproductive techniques; meta-analysis; pregnancy outcome; systematic review; varicocele; varicocelectomy

INTRODUCTION

Varicocele is defined as a dilatation of the pampiniform plexus veins. It is the most common cause of male infertility affecting about 15%–20% of the general population and 35%–40% of men presenting for an infertility evaluation.[1–3] Until now, the exact mechanisms that ultimately lead to infertility are not fully understood despite the fact that varicocele pathophysiology has been discussed for close to five decades. The main theories postulate that venous reflux leading to elevated testicular temperature and oxidative stress are the key elements.[4,5] Equally debatable is the actual benefit of interventions although recent evidence indicates that treatment may improve the chance of pregnancy in subfertile couples in whom varicocele is the only abnormal finding.[6,7]

Oxidative stress and elevated sperm DNA fragmentation have been associated with varicocele-mediated infertility.[4,6–11] Although sperm with fragmented DNA can fertilize oocytes with apparently similar efficiency to sperm without DNA fragmentation, it has been found that high DNA fragmentation negatively impacts embryo development and may jeopardize pregnancy outcomes in assisted reproductive technology (ART).[12,13] There is fair evidence indicating that surgical repair of clinical varicocele improves sperm parameters, decreases seminal oxidative stress and sperm DNA fragmentation, and increases seminal antioxidants.[6,7,14,15] However, it is unclear whether performing varicocelectomy in infertile males with clinical varicocele prior to ART improves treatment outcomes.[16]

The objective of this study was to collect and summarize all evidence that evaluated the benefit of varicocelectomy on ART outcomes in nonazoospermic infertile men with clinical varicocele.

MATERIALS AND METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement to report the results of this review.[17] The study was exempted from Institutional Review Board approval as it did not involve any interventions in humans.

Search strategy

An exhaustive electronic search was performed using the MEDLINE and EMBASE databases up to April 2015. There were no limits placed on the year of publication, but we restricted the search to articles published in English. We also searched among the references of the identified articles. The search combined relevant terms and descriptors related to varicocele, varicocelectomy, varicocele repair, IVF, ICSI, and ART.

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Eligibility criteria and data extraction

This systematic review and meta-analysis included studies comparing ART outcomes of nonazoospermic patients with clinical varicocele who underwent varicocelectomy prior to ART to those without prior varicocele repair. Clinical varicoceles were considered as those diagnosed based on the finding of varicose veins in the spermatic cord either by visual inspection or palpation with or without the aid of the Valsalva maneuver during physical examination with the patient standing.[18] ART was defined as all treatments or procedures that include the *in vitro* handling of both human oocytes and sperm or of embryos for the purpose of establishing a pregnancy. This included *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) and embryo transfer.[19] For the purpose of this review, ART did not include assisted insemination (artificial insemination) using sperm from either a woman's partner or a donor.

The selection criteria are described in **Table 1**. In the first screening, two independent authors (M.R. and S.C.E.) assessed all of the abstracts retrieved from the search and then obtained the full manuscripts of the citations that met the inclusion criteria. These authors evaluated the studies' eligibility and quality, and they subsequently extracted the data. Any discrepancies were solved by agreement and, if needed, they reached a consensus with the third author (A.A.).

Table 1: Selection criteria of included studies (PICOS)

	Included	*Excluded*
Population	Couples undergoing IVF/ICSI and the male partner diagnosed with clinical varicocele	Azoospermic/cryptozoospermic patients
Intervention	Varicocelectomy prior to IVF/ICSI	Varicocele embolization
Comparison	IVF/ICSI without previous varicocelectomy	
Outcomes	Live birth rate	
	Clinical pregnancy rate	
	Implantation rate	
	Miscarriage rate	
	Fertilization rate	
Study type	Any type	

IVF: *in vitro* fertilization; ICSI: intracytoplasmic sperm injection

Table 2: Quality assessment of included trials

Study	*Sequence generation*	*Allocation concealed*	*Blinding*	*Incomplete outcome data*
Esteves *et al.*[24]	No	Yes	No	No
Pasqualotto *et al.*[25]	No	Yes	No	No
Shiraishi *et al.*[2]	No	No	No	No
Gokce *et al.*[26]	No	Yes	No	No

Outcome measures

The pregnancy rates, both clinical pregnancy and live birth, were the primary outcomes of interest. Secondary outcomes included fertilization rate, implantation rate, and miscarriage rate. Clinical pregnancy was defined as a pregnancy observed sonographically by the visualization of a fetal heartbeat by 7 weeks of gestation. The clinical pregnancy rate was the number of clinical pregnancies expressed per 100 embryo transfers. The live birth rate was defined as the ratio between the number of deliveries resulting in at least one live birth and the number of embryo transfers. Miscarriage was defined as a nonviable clinical pregnancy on ultrasound follow-up until gestational week 20. The implantation rate was defined as the number of gestational sacs observed sonographically divided by the number of transferred embryos. The fertilization rate was defined by the number of two pronuclei zygotes divided by the number of metaphase II oocytes subjected to sperm injections.

Risk of bias assessment

We followed the guidance recommended by the Cochrane Collaboration to assess the risk of bias from the included studies.[20] We evaluated sequence generation, allocation concealment, blinding, and incomplete outcome data for each trial included in the review. A low risk of bias was considered when a judgment of "yes" for all domains was obtained, whereas a high risk of bias was considered when a judgment of "no" for one or more domains was obtained. An unclear risk of bias was defined when an "unclear" judgment in any domain was considered. The quality assessment of the included trials is shown in **Table 2**.

Analysis

We pooled the data of the dichotomous outcomes from the original studies to obtain the odds ratio (OR) for the occurrence of an outcome event and presented their corresponding 95% confidence intervals (CIs). Statistical significance was set at $P < 0.05$. To quantify statistical heterogeneity, we used the I^2 statistic in order to describe the variations across trials that were due to heterogeneity and not to sampling error. We pooled the outcome data from each study using a Mantel–Haenszel model and applied the fixed-effects model. When the heterogeneity was >50% ($I^2 > 50\%$), we applied the random-effects model.[21] We used the Review Manager 5 software (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to conduct the meta-analysis. It was not possible to perform a meta-analysis for implantation, miscarriage, and fertilization rates due the nature of the studies evaluating these outcomes.

RESULTS

Our electronic search retrieved 114 articles. After screening the titles and abstracts, we determined that six articles were eligible for inclusion. Among these, two articles were excluded. One of them was a review article,[22] and the other study did not fulfill the inclusion criteria[23] as the primary comparison was between patients submitted to varicocelectomy and observation. Although the authors of this aforementioned study evaluated ART outcomes in patients who did not achieve natural pregnancy after varicocele repair, they have included intrauterine insemination as an ART treatment modality. As stated in the eligibility criteria, the objective of our study was to compare only patients submitted to ART as per the ICMART definition. The complete selection process is depicted in **Figure 1**.

Description of the included studies

Four retrospective studies were included, all of which involved ICSI as the ART method.[2,24–26] The four included studies accounted for 870 ICSI cycles (438 with prior varicocelectomy, and 432 without prior varicocelectomy). In three of the included studies, the patients subjected to varicocelectomy had undergone microsurgical subinguinal varicocele repair.[24–26] The characteristics of the studies included in this review are presented in **Table 3**. Only two of the studies provided information about the interval between varicocelectomy and ICSI.[24,26] In the study by Esteves *et al.*, the mean interval between the operation and ART was 6.2 months (range 4 to 13) while it was 7.2 ± 2.8 months in the study by Gokce *et al.*[24,26] Two of the studies stated that only patients without varicocele recurrence were enrolled in the analysis.[24,25] As far as the varicocele grade is concerned, none of the included studies analyzed the association between varicocele grade and ART outcomes.

Outcomes

Clinical pregnancy rate

All four included studies reported data on clinical pregnancy (**Table 4**).[2,24–26] There was a statistically significant increase in the pregnancy rate in three of the studies, favoring the group with prior varicocelectomy.[2,24,26] In one of the studies, the authors did not find a statistically significant difference between the groups with and without previous varicocele repair.[25] Overall, there was a significant increase in the clinical pregnancy rate by ICSI with prior varicocelectomy compared with nonvaricocelectomy (OR = 1.59, 95% CI: 1.19–2.12, I^2 = 25%) (**Figure 2**).

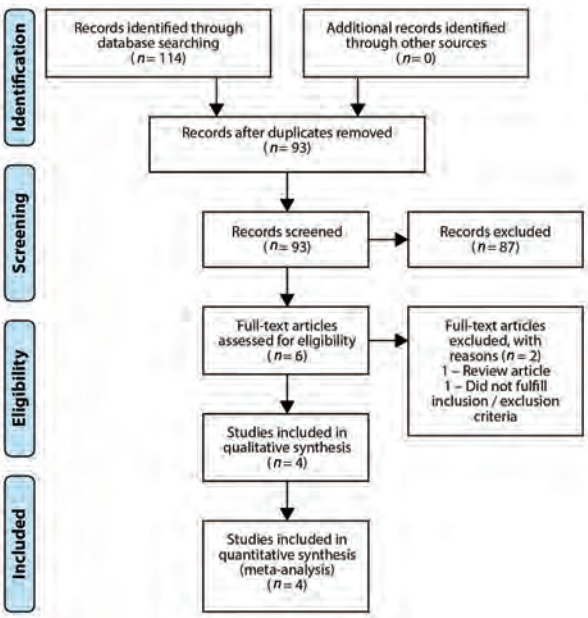

Figure 1: Flowchart showing the identification and selection process of studies included in the meta-analysis.

Live birth rate

Three of the included studies reported data on live birth.[2,24,26] All of them reported statistically increased live birth rates in the group of patients that have undergone varicocelectomy prior to the ICSI procedure (**Table 4**). A significant benefit on live birth rates was found for varicocelectomy plus ICSI compared to ICSI without previous varicocelectomy (OR = 2.17, 95% CI: 1.55–3.06, I^2 = 0%) (**Figure 3**).

Implantation rate

Only one of the included studies evaluated implantation.[25] It was observed that the implantation rate was not statistically different in the group subjected to varicocelectomy (17.3%) compared to the one without varicocelectomy (22.1%) (**Table 4**).

Miscarriage rate

There were three studies evaluating miscarriage.[24–26] One of them found that the chance of miscarriage was decreased (OR: 0.433; 95% CI: 0.22-0.84) after varicocele was treated.[24] Two of them did not find statistically significant differences between the two groups (**Table 4**).[25,26]

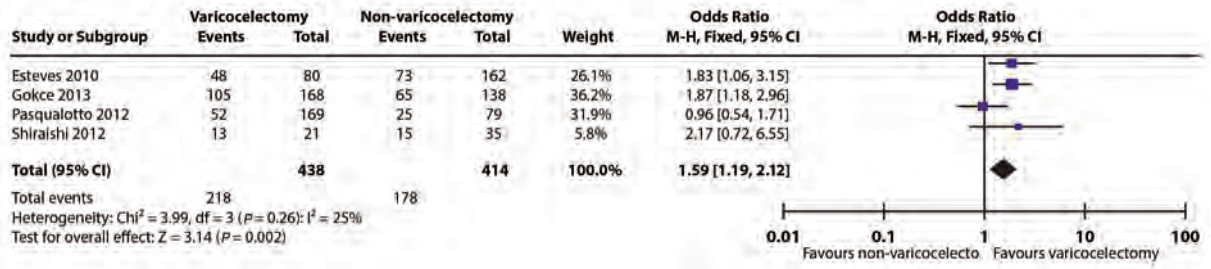

Figure 2: Forest plot of comparison: 1 Varicocelectomy + ICSI versus ICSI without varicocelectomy, outcome: Clinical pregnancy.

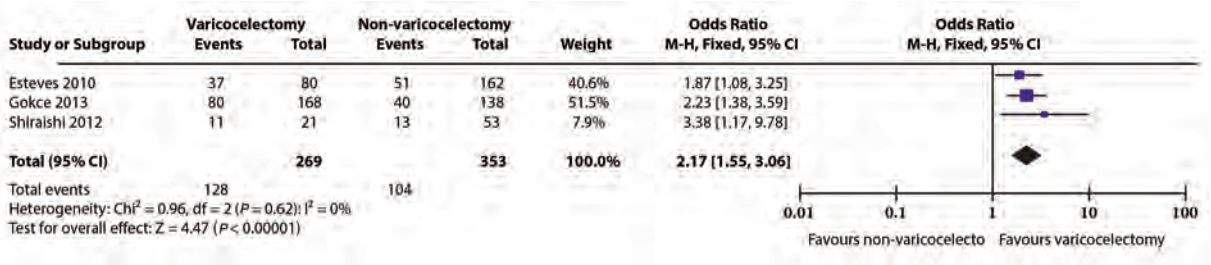

Figure 3: Forest plot of comparison: Varicocelectomy + ICSI versus ICSI without varicocelectomy, outcome: Live birth.

Table 3: Characteristics of the included studies

Study	*Design*	*ICSI cycles with prior varicocelectomy (n)*	*ICSI cycles without prior varicocelectomy (n)*	*Outcomes included in the review*
Esteves *et al.*[24]	Retrospective	80	162	Live birth, clinical pregnancy, miscarriage, and fertilization rates
Pasqualotto *et al.*[25]	Retrospective	169	79	Clinical pregnancy, implantation, miscarriage, and fertilization rates
Shiraishi *et al.*[2]	Retrospective	21	53	Live birth, clinical pregnancy, and fertilization rates
Gokce *et al.*[26]	Retrospective	168	138	Live birth, clinical pregnancy, and miscarriage rates

ICSI: intracytoplasmic sperm injection

Table 4: ICSI outcome in infertile men with treated and untreated clinical varicocele

Study	*Outcome*	*ICSI after varicocelectomy*	*ICSI and untreated varicocele*	*P*
Esteves *et al.*[24]	Live birth rate (%)	46.3	31.5	0.03
	Clinical pregnancy rate (%)	60.0	45.1	0.04
	Miscarriage rate (%)[§]	22.9	30.1	0.46
Pasqualotto *et al.*[25]	Live birth rate (%)	NR	NR	NR
	Clinical pregnancy rate (%)	30.9	31.1	0.98
	Miscarriage rate (%)	23.9	21.7	0.84
Shiraishi *et al.*[2]	Live birth rate (%)	52.3	24.5	0.02
	Clinical pregnancy rate (%)	61.9	28.3	0.02
	Miscarriage rate (%)	-	-	-
Gokce *et al.*[26]	Live birth rate (%)	47.6	29.0	0.0002
	Clinical pregnancy rate (%)	62.5	47.1	0.001
	Miscarriage rate (%)	14.9	18.1	0.057

ICSI: intracytoplasmic sperm injection; NR: not reported; [§]The chance of miscarriage was decreased (OR: 0.433; 95% CI: 0.22-0.84) after varicocele was treated

Fertilization rate

Three of the included studies evaluated fertilization after sperm injections. Esteves *et al*. found statistically significant differences between the two groups (78% *vs* 66%, $P = 0.04$), favoring the group with prior varicocelectomy.[24] In contrast, Pasqualotto *et al*.[25] found statistically significant differences between the two groups (64.9% *vs* 73.2%, $P = 0.03$), favoring the group without varicocele repair. Finally, Shiraishi *et al*.[2] did not find statistically significant differences between the two groups (70.3% *vs* 68.6%).

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis addressing the potential benefits of varicocelectomy on ART outcomes in nonazoospermic infertile men with clinical varicocele. Our study included only nonazoospermic patients with clinical varicocele who either underwent or did not undergo varicocelectomy prior to ICSI. Our electronic search did not retrieve any study that evaluated conventional IVF as the ART treatment method. Our findings, which included 870 ICSI cycles, indicated that varicocelectomy prior to ICSI resulted in significantly higher pregnancy rates compared to ICSI without varicocele repair. All included studies reported data on clinical pregnancy, and there was a significant increase in the clinical pregnancy rate with varicocelectomy compared with nonvaricocelectomy (OR = 1.59, 95% CI: 1.19–2.12, $I^2 = 25\%$). Three of the four included studies evaluated live birth rates, and a statistically significant increase in live birth rates was also observed in patients with clinical varicocele subjected to microsurgical varicocelectomy prior to ICSI (OR = 2.17, 95% CI: 1.55–3.06, $I^2 = 0\%$).

Although ICSI is an efficient treatment modality for severe male factor infertility, including varicocele as the underlying cause, the procedure does not take into account for the possibility that the selected spermatozoa have damaged DNA.[12] Sperm DNA fragmentation has been associated with poorer results in ART treatment[27–32] though this association is not conclusive.[33–35] The results of a recent meta-analysis showed a significant decrease in pregnancy using sperm with high DNA damage in IVF cycles, whereas there was no difference in pregnancy rates in ICSI cycles.[36] These differences might be explained by inherent distinction in the population treated and sperm handling techniques used by IVF and ICSI methods,[37] and reinforce the importance of performing further investigation to evaluate the correlation between sperm DNA damage and IVF/ICSI outcomes.

Despite the fact that none of the included studies had evaluated sperm functional factors, an improvement in sperm function would be a plausible explanation for the observed beneficial effect of prior varicocelectomy on ICSI outcomes. Of note, three of the included studies reported semen analysis results, and in two of them, a significant improvement in sperm count and motility was observed after varicocelectomy.[24,26] It has been shown that patients with a postoperatively improved semen quality are more likely to achieve natural conception after varicocelectomy.[6] In addition, varicocele repair may allow a couple with severely impaired semen parameters to improve and eventually pursue less invasive treatment modalities.[5] Finally, the surgical repair is associated with improvements in functional factors, such as seminal oxidative stress and sperm DNA integrity, which are not routinely assessed in the standard semen analysis.[38,39]

There is increasing evidence suggesting that sperm DNA fragmentation is associated with miscarriage in ART.[13,36,40] In a meta-analysis involving 2969 couples, the risk of miscarriage was increased by 2.16-fold when semen specimens with an abnormally high proportion of DNA damage were used for ICSI (95% CI: 1.54–3.03, $P < 0.00001$).[13] This increased risk of miscarriage would be related to a "late paternal effect" during the activation of male gene expression.[41] This means that despite nonapparent peri-fertilization, the influence of a damaged paternal chromatin could be observed after zygotic transcriptional activation.[42] In our study, three of the four included series had evaluated miscarriage rates. One of them had found lower chance of miscarriage in the group with prior varicocelectomy when compared to the group without varicocelectomy.[24] Two of the studies did not find statistically significant differences between the two groups. However, one of these studies[26] had included young female patients in whom the negative effect of sperm DNA damage on embryo development might have been modulated by the ability of the oocyte to repair sperm DNA damage before the first cleavage.[42–44] In the other, a group of patients with large palpable varicoceles was studied, but surprisingly enough, semen parameters in these patients were very well preserved before varicocele repair, which might have limited the beneficial effect of varicocelectomy.[25]

There are some limitations in our study as there are no randomized clinical trials concerning the research question. All of the included studies were retrospective. Therefore, the quality of this evidence is considered low to moderate. In addition, there is limited objective evidence related to the potential benefits of performing prior varicocelectomy as none of the included studies evaluated functional semen analysis, such as sperm DNA fragmentation. Despite that, a postoperative improvement in conventional semen parameters was noted in two of the included[24,26] In addition, the literature is scarce in studies evaluating the cost-effectiveness of performing microsurgical varicocelectomy prior to ART in nonazoospermic infertile men with clinical varicocele.[45] Thus, it is not possible to conclude whether the increased cost of performing varicocelectomy would be cost-effective for achieving a live birth in this category of infertile men requiring ART.

CONCLUSION

The findings of this systematic review and meta-analysis indicate that performing varicocelectomy in patients with clinical varicocele prior to ICSI is associated with improved pregnancy outcomes. The results of our study provide a rationale for conducting further prospective research to evaluate varicocelectomy in infertile men with clinical varicocele before performing ART treatment.

AUTHOR CONTRIBUTIONS

SCE designed the study, participated in the acquisition of data, and helped to draft and revise the manuscript. MR participated in the acquisition of data, performed data analysis and prepared the manuscript. AA revised the manuscript and helped in coordination. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declared no competing interests.

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Varicocelectomy to "upgrade" semen quality to allow couples to use less invasive forms of assisted reproductive technology

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Objective: To determine the magnitude of improvement in semen parameters after a varicocelectomy and the fraction that have improvements such that couples needing IVF or IUI are "upgraded" to needing less invasive assisted reproductive technology (ART).
Design: Retrospective review of prospectively collected data.
Setting: Academic medical centers.
Patient(s): Men presenting for a fertility evaluation with a clinical varicocele.
Intervention(s): Varicocele repair (surgical or embolization).
Main Outcome Measure(s): Total motile sperm count (TMSC) before and after repair, and the proportion of men considered candidates for: natural pregnancy (NP) >9 million, IUI 5–9 million, or IVF < 5 million.
Result(s): A total of 373 men underwent varicocele repair. The TMSC increased from 18.22 ± 38.32 to 46.72 ± 210.92 (P=.007). The most pronounced increase was with baseline TMSC <5 million, from 2.32 ± 1.50 to 15.97 ± 32.92 (P=.0000002); 58.8% of men were upgraded from IVF candidacy to IUI or NP. For baseline TMSC 5–9 million, the mean TMSC increased from 6.96 ± 1.16 to 24.29 ± 37.17 (P=.0004), allowing 64.9% of men to become candidates for NP. For baseline TMSC of >9 million, TMSC increased from 36.26 ± 52.08 to 81.80 ± 310.83 (P=.05).
Conclusion(s): Varicocele repair has an important role in the treatment of infertility. Even for low TMSCs, a varicocelectomy may reduce the need for IVF. Varicocele repair (by embolization or microsurgery) potentially reduces the need for IVF and IUI. (Fertil Steril® 2017;108:609–12. ©2017 by American Society for Reproductive Medicine.)
Key Words: Varicocele, semen, assisted reproductive technology, intrauterine insemination, in vitro fertilization

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Varicoceles are the most commonly seen and correctable male infertility factor (1). Varicoceles have an incidence of 4.4%–22.6% in the general population, 21%–41% in men with primary infertility, and 75%–81% in men with secondary infertility (2, 3). Although many men with varicoceles are able to father children, in some men varicoceles will negatively impact their fertility. This may manifest with impaired semen parameters (4), reduced natural pregnancy (NP) rates (5), lower IUI pregnancy rates (PRs) (6), lower IVF PRs (7), and/or higher rates of sperm DNA damage (8).

In some men, repair of varicoceles will result in an improvement in semen parameters or sperm DNA health. As such, it is the practice guideline of the American Urological Association and American Society of Reproductive Medicine that varicocele repair be offered to subfertile men with a palpable varicocele and one or more abnormal semen parameters (9, 10). Varicocele repair may result in improvements in semen parameters (4), sperm DNA fragmentation (8), NP rates (5), IUI PRs (6), and IVF PRs (7).

Although varicocele repair results in improved semen quality in most infertile men, the degree of improvement in

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semen parameters is less well studied. One study of 530 infertile men with a clinical varicocele found that varicocele repair may also allow for less invasive modalities of assisted reproductive technology (ART) to be used by couples (11). We sought to determine the magnitude of improvement in semen parameters after a varicocelectomy and what fraction of the men might have improvements such that couples needing IVF or IUI might be "upgraded" to needing less invasive ART.

MATERIALS AND METHODS

Men presenting for evaluation at a Male Infertility specialty clinic from 2008 to 2012 who underwent repair (microsurgical subinguinal or embolization) of a clinical varicocele were identified by a prospectively collected database. The data were reviewed in a retrospective manner. A varicocele was palpable in all cases, as performed by a fellowship-trained specialist in male infertility (A.Z., E.G., K.L., or K.J.). Physical examination for varicocele was performed according to the Dubin grading system with the patient upright in a heated examination room (12). The collection and the analysis of this data were approved by the Research Ethics Board of the Mount Sinai Hospital.

In brief, the microscopic subinguinal approach involved the following surgical technique. A 3- to 5-cm incision was made over the inguinal canal. The spermatic cord was elevated and the spermatic cord fascia opened. The testicle was not routinely delivered. Under the operative microscope, each component of the spermatic cord was identified. A microscopic Doppler was used to identify these as either arteries or veins. The veins were ligated using either sutures or surgical clips. The vas deferens, testicular arteries, and any lymphatic channels were preserved. For the percutaneous varicocele embolization, under venogram guidance, 0.018 coils were placed in the dilated main channel of the gonadal vein and back-filled, followed by 1-mL aliquots of sotradecol foam.

Semen analysis was performed using a standard protocol with a computer-assisted semen analysis technique (World Health Organization [WHO] 2010) (13). Semen parameters were analyzed for volume, sperm count, sperm motility, sperm morphology, and total motile sperm count (TMSC) before and after varicocele repair. Semen samples were collected at least 48 hours, but not >7 days, after the time of last ejaculation. After varicocele repair, semen analyses were performed at 3 months and for some men again at 6 months. The principal parameter used was the TMSC as this is often used as a means of deciding whether couples will require IVF or IUI. The TMSC was calculated before and after varicocele repair by the formula, TMSC = ejaculate volume × concentration × motile fraction, in all semen analyses.

For the purposes of this study, men were divided into three groups, as stratified by their baseline TMSC. These groups were representative of the type of ART that may have been recommended if varicocele repair was not performed to minimize the male factor infertility. Men with TMSC <5 million were considered candidates for IVF, 5–9 million for IUI, and >9 million for NP. Men were then regrouped after varicocele repair into the same three groups to determine changes in ART candidacy after varicocele repair. Student's *t*-test was used to compare changes in the semen parameters, with $P < .05$ considered indicative of significant differences.

There is known variability in semen parameters. To determine whether the improvements in semen parameters after varicocelectomy were due to the natural variability in the semen parameters or due to the varicocelectomy itself, we compared the changes in the first and second semen parameters before varicocelectomy to the changes in the semen parameters before and after varicocelectomy. We performed a χ^2 test on these groups comparing the fraction of men within each group who were "upgraded."

RESULTS

We identified 373 men who underwent varicocele repair. The mean age was 35 years (range, 23–62 years). Varicocelectomy was bilateral in 174 (46.6%), left side only in 198 (53.1%), and right side only in 1 (0.2%). Sixty-eight (18.2%) of the repairs were performed by radiographic embolization and 305 (81.8%) were performed by microsurgical subinguinal varicocelectomy. A total of 186 (49.9%) men had unilateral varicoceles and 187 (50.1%) had bilateral varicoceles. With respect to maximum varicocele grade, 38 of 166 men had a grade 1 varicocele, 66 of 166 had a grade 2 varicocele, and 62 of 166 had a grade 3 varicocele; 205 men did not have the grade of their varicocele noted. A total of 84 of the men had 2 semen analyses before repair and 97 men had 2 semen analyses after repair. The mean of these values was calculated and used for analysis.

The results are presented in Tables 1 and 2. Before varicocele repair, 168 of 373 men (45%) had TMSC >9 × 10^6 and were considered to have high enough TMSCs to be

TABLE 1

Total motile sperm count before and after varicocele repair.

Characteristic	Before varicocele repair TMSC (million sperm/mL)	After varicocele repair TMSC (million sperm/mL)	*P* value
IVF (<5 million)	2.32 ± 1.50	15.97 ± 32.92	.0000002
IUI (5–9 million)	6.96 ± 1.16	24.29 ± 37.17	.0004
Natural pregnancy (>9 million)	36.26 ± 52.08	81.80 ± 310.83	.05
All men	18.22 ± 38.32	46.72 ± 210.92	.007

Note: Data presented as mean ± standard deviation, unless noted otherwise. TMSC = total motile sperm count.

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TABLE 2

Changes in assisted reproductive technology candidacy after varicocele repair.

		Patients after varicocele repair TMSC		
Characteristic	**Patients, n**	**IVF (< 5 million)**	**IUI (5–9 million)**	**Natural pregnancy (> 9 million)**
IVF (<5 million)	139	65 (46.8)	30 (21.6)	44 (31.7)
IUI (5–9 million)	66	18 (27.3)	10 (15)	38 (57.6)
Natural pregnancy (>9 million)	168	12 (7.1)	17 (10.1)	139 (82.7)

Note: Data presented n (%), unless noted otherwise. TMSC = total motile sperm count.

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candidates for NP, 66 of 373 men (17.7%) had TMSCs 5–9 × 10^6 and were candidates for IUI, and 139 of 373 men (37.3%) had TMSCs <5 × 10^6 and were candidates for IVF. After varicocele repair, 221 of 373 men (59.2%) were candidates for NP, 57 of 373 men (15.3%) were candidates for IUI, and 95 of 373 men (25.5%) were candidates for IVF. A total of 38 of 66 men (57.6%) who would have initially been candidates for IUI were "upgraded" to NP candidacy. A total of 30 + 44/139 (53.2%) of men who would have initially been candidates for IVF were "upgraded" to IUI or NP candidacy.

For the entire cohort, the TMSC increased from 18.22 ± 38.32 million to 46.72 ± 210.92 million (P=.007). The most pronounced increase was seen in men with baseline sperm TMSC of <5 million, increasing from 2.32 ± 1.50 million to 15.97 ± 32.92 million (P=.0000002). Of these men 58.8% were then upgraded from candidates for IVF to IUI or NP. For men with a baseline sperm TMSC of 5–9 million, the mean TMSC increased from 6.96 ± 1.16 million to 24.29 ± 37.17 million after repair (P=.0004), allowing 64.9% to become candidates for NP. For men with a baseline TMSC of >9 million, the mean TMSC increased from 36.26 ± 52.08 million to 81.80 ± 310.83 million (P=.05) after varicocele repair.

There were also some men who had a "downgrade" of their classification after varicocelectomy (16/66 men with initial TMSC 5–9 million had post varicocelectomy TMSCs <5 million, and 24/168 men with initial TMSC >9 million had post varicocelctomy TMSC <9 million). To determine whether this "downgrading" was related to the varicocelectomy or simply reflected the natural variability of the semen parameters, we compared the rates of both "upgrading" and "downgrading" in the men having varicocelectomies versus men who had not had a varicocelectomy. There was a significantly lower rate of "downgrading" and a higher rate of "upgrading" in men after varicocelectomy compared with the matched group of men who had not undergone a varicocelectomy (χ^2: P<.001) indicating that varicocelectomy does not result in a significantly higher risk of "downgrading."

DISCUSSION

We found that varicocele repair may allow couples to use less invasive modalities of ART. Our results corroborate those from a 2002 series (11). In that series, 31% of IVF or intracytoplasmic sperm injection (ICSI) candidates were upgraded to being candidates for IUI or NP, and 42% of IUI candidates became NP candidates. These investigators saw an overall improvement in TMSC from 19.04 to 27.12 million. We sought to confirm these findings, using a cohort of men treated by four microsurgeons and including men undergoing varicocele embolization. We have shown that for unilateral varicoceles, embolization and a microsurgical approach have similar outcomes (14). This is the first study to include men undergoing both embolization and microsurgical approach.

We grouped men by TMSC, where those with a TMSC <5 million were considered candidates for IVF, those with 5–9 million for IUI, and those with >9 million for NP. We chose these threshold values based on the following. According to the 2010 WHO semen testing manual, the lower fifth centile for ejaculate volume is 1.5 mL, sperm concentration is 15 million/mL, and motility is 40%; therefore, the lower limit for a "normal" TMSC is 9 million/mL (13). This is why we chose 9 million/mL as our lower limit for potential candidates for NP. A study of 2,473 IUI cycles showed that a TMSC >5 million was associated with higher clinical PRs and live birth rates (15). In addition, a recent study of men with unexplained infertility found that men with TMSC >5 million are indicated for treatment with IUI (16). This is why we chose 5 million as our threshold for IUI. Men with a TMSC <5 million are generally considered not candidates for IUI, and are therefore candidates for IVF.

Although ART will continue to play a major role in helping couples achieve their family planning goals, the utilization of the least possible invasive modality offers several advantages for couples. One of the most obvious of these is from a cost perspective. Varicocele repair has been found to be a more cost effective strategy than ART (17, 18). Schlegel (18) estimated that the cost per live birth after varicocele repair to be $26,268, compared with $89,091 after ICSI. Although our study did not include a cost analysis, as "invasiveness" of reproductive assistance increases, so does the cost. According to Resolve, the National Infertility Association, the average cost for an IUI cycle in the United States is $865 and the average cost of an IVF cycle with fresh embryo transfer is $8,158 (19). In addition, many couples have concerns about the safety of IVF or hormonal stimulated IUI. In general, most couples would prefer the least invasive form of ART possible (20). Finally, there is a growing body of literature that suggests that varicocele repair has a positive effect on overall testicular health and preservation of T production (21).

We saw an improvement in semen parameters after varicocele repair. For the entire cohort, the TMSC increased from 18.22 ± 38.32 million to 46.72 ± 210.92 million (P=.007). The most pronounced increase was seen in men with baseline sperm TMSC of <5 million, increasing from 2.32 ± 1.50 million to 15.97 ± 32.92 million (P=.0000002). This is in contrast to the findings of several other small series finding that lower baseline sperm density was correlated with less dramatic improvements after varicocele repair (22). Specifically, one study (23) found that men with baseline sperm concentration of <5 million/mL were less likely to see improvements in semen parameters after varicocele repair. In contrast, a recent publication (24) of 83 men with nonobstructive azoospermia and left-sided varicoceles found that sperm recovery was found in 24% of patients after varicocele repair. The reason for these discrepancies is unclear. However, a recent meta-analysis (25) looking at the role of varicocele repair in men with nonobstructive azoospermia found that in 43.9% of patients, sperm were found in the postoperative ejaculates; 44% of men undergoing varicocelectomy would have enough sperm in the ejaculate to avoid surgical sperm retrieval. However, our data would suggest a role for varicocele repair even in men with low TMSCs. We found that a varicocelectomy may be of benefit in this group of men as 58.8% of men with TMSC <5 million improved to a point where IUI was possible, reducing the need for IVF.

Limitations of our study include the retrospective nature. Second, whereas TMSC of 9 million sperm/mL and 5 million sperm/mL are commonly used cutoff values for IUI and IVF, respectively, we acknowledge that these are not perfect predictors of conception success. In addition, as these data were obtained only from the male partner of couples and therefore do not factor in any female factors, these results may need to be interpreted with caution when applying them to individual couples.

Overall, our data support the premise that varicocele repair has an important role in overall treatment of couples struggling with infertility. Even for men with low TMSCs, a varicocelectomy may be of benefit as 58.8% of men with TMSC <5 million improved to a point where IUI was possible, potentially reducing the need for IVF. We should consider varicocelectomies an important therapy to reduce the need for IVF and IUIs.

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Grade 3 Varicocele in Fertile Men: A Different Entity

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Purpose: Although varicocele size has an inverse relationship with baseline semen parameters and a direct relationship with seminal reactive oxygen species in infertile patients, to our knowledge the effect of varicocele grade in fertile men is unknown. We evaluated the impact of varicocele grade on seminal parameters, testicular size and seminal reactive oxygen species in fertile men.

Materials and Methods: We prospectively evaluated 194 men from July 2004 to April 2010. Of the men 156 were fertile and classified by presence of varicocele. A total of 38 infertile patients with varicocele as the only identifiable cause of infertility comprised the control group. Physical examination, semen parameters and seminal reactive oxygen species were compared between the groups.

Results: Of 156 fertile men 43 (24.3%) had clinical varicocele, which was grade 1 to 3 in 22, 11 and 10, respectively. The remaining 113 men (72.7%) had no varicocele. Infertile men had smaller testes, decreased semen parameters and higher seminal reactive oxygen species than the fertile groups. Testicular size, reactive oxygen species and semen parameters did not differ between fertile men with vs without varicocele. Fertile men with varicocele grade 3 had higher seminal reactive oxygen species than those with lower grade varicocele. As varicocele grade increased, seminal reactive oxygen species increased and sperm concentration decreased.

Conclusions: Although fertile men have more efficient defense mechanisms to protect against the consequences of varicocele on testicular function, these mechanisms may not be sufficient in those with varicocele grade 3. Further research is needed to clarify whether they are at increased risk for future infertility.

Key Words: testis; infertility, male; varicocele; reactive oxygen species; spermatozoa

Abbreviations and Acronyms

ROS = reactive oxygen species

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Study received institutional review board approval.

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In 1965 MacLeod described the characteristic alterations in semen quality produced by varicocele, namely a variable depression in sperm count, a marked depression in motility and an alteration in morphology.[1] As a consequence, a high percent of immature sperm appear in ejaculate. In 1969 Dubin and Hotchkiss reported that seminal alterations result in infertility through the sloughing of immature sperm usually seen in testicular biopsies of patients with varicocele.[2] It is now known that immature spermatozoa containing a high concentration of residual cytoplasmic droplets in the sperm mid region are one of the major sources of ROS production in sperm.[3] Immature spermatozoa negatively correlate with sperm quality.[3] Also, data suggest that as the concentration of immature sperm in human ejaculate increases, the concentration of mature spermatozoa with damaged DNA also increases.[4]

Current data support the assertion that varicocele repair is successful in reversing the harmful effects of vari-

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cocele on testicular function.[5] A topic of considerable debate in the last decades is whether varicocele size affects the outcome of varicocelectomy since early studies suggested that varicocele grade did not affect semen parameters or the pregnancy rate.[6,7] However, other studies showed that varicocele size has a direct impact on the probability and amount of seminal improvement after varicocelectomy, suggesting that varicocele grade matters and not all sizes should be ligated.[8–10] Other series suggested that seminal ROS are significantly increased in infertile men with grades 2 and 3 vs grade 1 varicocele.[11,12]

Although many studies demonstrated an association between increased seminal ROS and varicocele in infertile patients, few groups have addressed this issue in fertile populations.[13–15] Furthermore, the impact of varicocele grade 2 or 3 on the oxidative stress status of the testis is not well described.[11,12,16] We evaluated the impact of varicocele grade on seminal parameters, testicular size and seminal ROS in fertile men.

MATERIALS AND METHODS

Study Population

The institutional review board approved this study. Written informed consent was obtained from all participants. This prospective study enrolled 156 men who underwent voluntary sterilization by vasectomy between July 2004 and April 2010. The study inclusion criterion for the fertile group consisted of having fathered at least 2 children. All semen analyses were done within 1 month before vasectomy. Of the 156 men 43 had a diagnosis of clinical varicocele and 113 had no varicocele.

The control group comprised 38 patients with clinical varicocele as the only identifiable cause of infertility after considering all exclusion criteria listed. They had failed to conceive after at least 1 year of regular unprotected intercourse. Female partners underwent complete gynecological evaluation, including history, physical examination, hormonal profile, transvaginal ultrasound and hysterosalpingography but no abnormalities were found. One male infertility specialist (MC) evaluated all participants.

Varicocele was clinically classified as grade 1—palpable during the Valsalva maneuver, grade 2—palpable without the Valsalva maneuver or grade 3—visible through the scrotal skin. When bilateral varicocele was present, grade was classified according to the higher grade. Testicular volume was measured with a Prader orchidometer.[17] Patients were excluded from the study population if there was any history of illicit drug use, exposure to any occupational toxin, use of medication with a proven adverse effect on fertility, radiation exposure, mumps with orchitis, cryptorchidism regardless of treatment, testicular torsion, genitourinary anomalies, or previous scrotal or inguinal surgery. To decrease the heterogeneity of the groups the same exclusion criteria were applied to all male participants. The variables compared in all groups were age, smoking and bilateral varicocele.

Semen Analysis

Semen was collected by masturbation after 48 to 72 hours of sexual abstinence. Each subject contributed 1 semen sample. The leukocytospermia (Endtz) test was performed in all samples. Men with semen samples containing 1×10^6 leukocytes or greater per ml semen were excluded from analysis. To avoid interobserver variability all analysis was done by a single experienced technician, who rigorously followed WHO guidelines.[18] However, we analyzed only semen parameters defined in the 2010 WHO manual.[19] Progressive and nonprogressive motility was defined as 1999 WHO grades a and b, and grade c, respectively.

Leukocytospermia Test

The leukocyte concentration in semen was measured by a myeloperoxidase staining test.[20] A 20 μl volume of liquefied specimen was placed in a 1.8 ml microtube and 20 μl phosphate buffered saline (pH 7.0) with 40 μl benzidine solution was added. The mixture was examined for cells that stained brown, indicating that they contained peroxidase and, thus, were granulocytes.

Reactive Oxygen Species

Seminal ROS production in neat semen was measured in all samples by a chemiluminescence assay using luminol (Sigma®) as a probe. Ten μl 5 mM luminol prepared in dimethyl sulfoxide (Sigma) were added to 400 μl of neat semen. ROS levels were determined by measuring chemiluminescence with a MicroBeta® Trilux luminometer, software version 4.7 for 15 minutes. Results are shown as 10^4 cpm)/20×10^6 sperm.

Statistical Analysis

Numerical data are shown as the median and IQR (25%–75%). They were compared by the Kruskal-Wallis nonparametric test. When a difference was found, the Mann-Whitney rank sum test with the Bonferroni correction was used for multiple comparisons. The chi-square and Fisher exact tests were used to compare categorical variables. Correlations between variables and the 95% CI were calculated using the Spearman nonparametric method.

To evaluate possible consequences of the small sample size for detecting differences between groups we performed post hoc power analysis. Statistical power (probability that the test will reject the null hypothesis when the null hypothesis is false) was calculated for the null hypothesis of equality of seminal ROS levels. All analysis was done with SPSS® for Windows®, version 16.0. All statistical tests were 2 tailed with $p < 0.05$ considered statistically significant.

RESULTS

Although there was a statistically significant difference in age among the groups, we noted a difference between fertile men with vs without varicocele ($p = 0.689$, table 1). The infertile group was significantly younger than the other groups ($p = 0.015$). There was no statistically significant difference in smoking frequency among the groups or in the frequency of bilateral varicocele between fertile and

Table 1. *Characteristics of fertile men with and without varicocele, and infertile men with varicocele*

	Median Fertile, No Varicocele (IQR)	Median Fertile, Varicocele (IQR)	Median Infertile (IQR)	p Value (Kruskal-Wallis test)
Age	35.0 (31.5–39.0)	34.5 (31.6–38.2)	31.1 (26.0–37.0)	0.012
Sperm concentration ($\times 10^6$/ml)	91 (52–143)	90 (47–145)	25 (15–41)	<0.001
Total sperm count ($\times 10^6$/ejaculate)	240 (152–388)	247 (171–436)	69 (40–120)	<0.001
% Motility:				
Total (progressive + nonprogressive)	66 (57–73)	69 (61–74)	49 (32–55)	<0.001
Progressive	40 (31–52)	45 (26–54)	23 (9–31)	<0.001
% Normal forms	5 (2–7)	4 (2–9)	1 (0–3)	<0.001
Testicular vol (ml):				
Rt	20 (18–25)	20 (20–20)	18 (15–20)	0.002
Lt	20 (15–25)	20 (18–20)	15 (12–20)	<0.001
Neat semen ROS ($\times 10^4$ cpm/20 $\times 10^6$)	0.16 (0.06–0.31)	0.18 (0.04–0.61)	0.99 (0.40–2.16)	<0.001

infertile men with varicocele (p = 0.426 and 0.315, respectively).

Of the fertile men 43 (24.3%) had clinical varicocele, which was grade 1 to 3 in 22 (51.2%), 11 (25.6%) and 10 (23.2%), respectively. Of the infertile men varicocele was grade 1 to 3 in 26.3%, 34.2% and 39.5%, respectively. There was no statistically significant difference in the grade distribution between fertile and infertile men (p = 0.068).

Although there was a significant difference among all variables analyzed among the 3 groups, after multiple comparison there was no significant difference in any variable between fertile men with vs without varicocele (table 1). However, all seminal parameters and testicular volume were lower in the infertile population while seminal ROS were higher than in the fertile populations (fig. 1). The power of the test in the seminal ROS comparison between the groups was 99.7%.

Seminal ROS levels in fertile men with varicocele negatively correlated with all seminal parameters and with left testicular volume. A positive correlation was also found between seminal ROS and varicocele grade (table 2). Varicocele grade in fertile men negatively correlated with the sperm concentration (r=−0.373, 95% CI −0.606, −0.082, p = 0.014).

There was no difference in the frequency of smoking or bilateral varicocele in fertile men according to any varicocele grade (p = 0.952 and 0.333, respectively). There was no significant difference in age, total sperm count, total or progressive motility, normal forms or testicular volume among fertile men with varicocele grade 1 to 3. However, there was a significant difference in sperm concentration and seminal ROS among the varicocele grades. Multiple comparison revealed a significantly lower sperm concentration and higher seminal ROS in fertile men with varicocele grade 3 vs grade 1 or 2 (fig. 2). There was no significant difference between these 2 variables when comparing fertile men with grade 1 and 2 varicocele (table 3). The power of the test calculated to compare seminal ROS between grades was 81.8%.

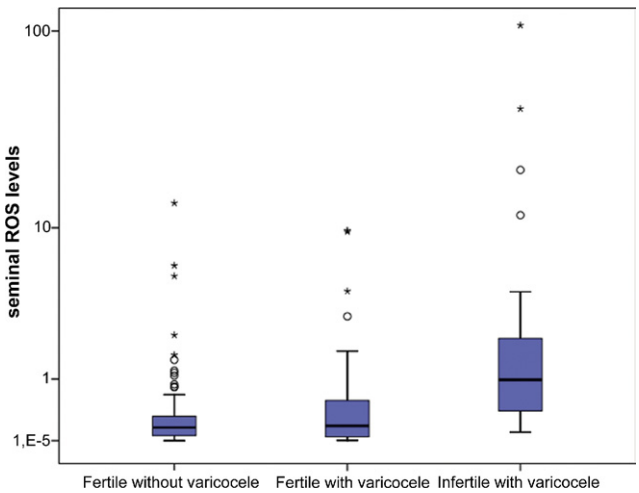

Figure 1. Infertile men with varicocele had significantly higher seminal ROS than fertile men with or without varicocele (p <0.001).

Table 2. *Seminal ROS according to seminal parameters, testicular volume and varicocele grade in fertile men*

	r (95% CI)	p Value (Spearman ρ test)
Sperm concentration	−0.769 (−0870, −0.614)	<0.001
Total sperm count	−0.721 (−0.830, −0.513)	<0.001
Motility:		
Total (progressive + nonprogressive)	−0.366 (−0.600, −0.074)	0.016
Progressive	−0.429 (−0.646, −0.148)	0.004
Normal forms	−0.461 (−0.697, −0.238)	0.002
Testicular vol:		
Rt	−0.142 (−0.424, 0.166)	0.365
Lt	−0.320 (−0.566, −0.021)	0.037
Varicocele grade	0.344 (0.049, 0.584)	0.024

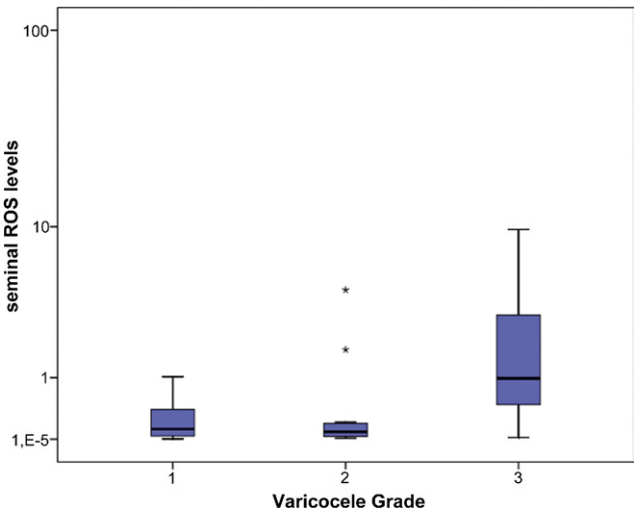

Figure 2. Fertile men with varicocele grade 3 had significantly higher ROS than fertile men with varicocele grade 1 or 2 ($p = 0.015$).

DISCUSSION

It is still a mystery why in some patients varicocele can produce a devastating effect leading to azoospermia while 75% of men who present with varicocele have a normal semen analysis.[21,22] The enormous range of influence that varicocele exerts on testicular function suggests that semen analysis is not an ideal diagnostic method to evaluate men presenting with clinical varicocele. Also, it is not yet clear in the literature whether fertile men who present with incidental varicocele tend to present with lower grade varicocele than infertile men who present for varicocele treatment. Perhaps there is a higher incidence of high grade varicocele in the infertile population, which could explain why these patients have testicular dysfunction with time.

Semen analysis is the most widespread method used to evaluate fertility potential in men. However, threshold values for sperm concentration, motility or morphology are not adequate to discriminate fertile from infertile men.[23] A recent meta-analysis identified high ROS as an independent marker of male factor infertility regardless of whether the patients had normal or abnormal semen parameters.[24] These findings suggest that ROS measurements could be used as a diagnostic tool during male fertility evaluation, especially for men with idiopathic infertility or those presenting with normal seminal parameters. Recent research in fertile populations focused on the impact of varicocele on seminal ROS to earlier identify men who are at increased risk for future infertility.[12,14,15]

Varicocele is associated with increased seminal ROS even in fertile men.[13–15,25] However, studies addressing varicocele effects in fertile men have 2 main limitations. 1) It is unclear whether the men truly represented a fertile population since some had never initiated pregnancy.[13] 2) No study mentioned the varicocele grade distribution in the population.[14,15] Since recently a group reported that seminal oxidative stress is associated with increased varicocele grade in infertile men, it would also be of interest to understand this relationship, if any, in a fertile population.[12]

Pasqualotto et al found no statistical difference in follicle-stimulating hormone, testicular size or seminal parameters between fertile men with vs without varicocele.[26] In a previous study our group found similar results regarding seminal parameters and testicular size but we further evaluated seminal ROS.[16] Although we did not identify any difference in seminal ROS between fertile men with vs without varicocele, we compared varicocele grade 1 with grades 2 and 3 together. At that time we did not have a sufficient number of men with varicocele grade 3 to compare them as an independent group. However, in the current study varicocele grade 3 exerted a different impact even in a fertile population. We also found that as varicocele grade in fertile men increased, seminal ROS increased and the sperm concentration decreased. To our knowledge

Table 3. *Seminal parameters, testicular volume and seminal ROS in fertile men by varicocele grade*

	Median Varicocele Grade (IQR)			
	1	2	3	p Value
Age	34.2 (32.7–37.4)	33.0 (30.0–35.8)	38.9 (30.7–40.4)	0.298
Sperm concentration ($\times 10^6$/ml)	110 (60–158)	97 (56–142)	47 (32–52)	0.017
Total sperm count ($\times 10^6$/ejaculate)	189 (111–330)	187 (108–347)	134 (63–164)	0.203
% Motility:				
Total (progressive + nonprogressive)	70 (59–75)	69 (64–75)	68 (57–73)	0.804
Progressive	44 (30–56)	50 (21–51)	38 (25–49)	0.671
Normal forms (%)	6 (3–10)	4 (2–9)	2 (1–7)	0.202
Testicular vol (ml):				
Rt	20 (20–20)	20 (15–20)	20 (20-20)	0.287
Lt	20 (20–20)	20 (15–20)	20 (15–20)	0.583
Neat semen ROS ($\times 10^4$ cpm/20 $\times 10^6$)	0.12 (0.03–0.40)	0.08 (0.02–0.21)	1.02 (0.47–3.05)	0.015

the association of increased seminal ROS in fertile men with higher varicocele grade has not previously been described in the literature.

Current diagnostic modalities, such as routine semen analysis and physical examination, are not enough to indicate which patients with varicocele should be treated when fertility potential has not been tested. Although we found no difference in most seminal parameters or in testicular volume among fertile men by varicocele grade, those with varicocele grade 3 had a lower sperm concentration and higher seminal ROS than those with grade 1 or 2 varicocele. However, there was no difference in the total sperm count according to varicocele grade. Considering the most recent WHO publication, none of our fertile groups would be considered abnormal with respect to any seminal parameter analyzed except morphology in men with varicocele grade 3.[19] As a consequence, seminal ROS would be useful to differentiate the groups.

The use of testicular volume as a fertility predictor in patients with varicocele is still controversial. Although Pinto et al noted that testicular size was not a predictor of fertility potential in patients with varicocele,[27] testicular hypotrophy is still the most widely accepted indication for correcting adolescent varicocele. However, our data on fertile men revealed a significant negative correlation between seminal ROS and left testicular size but no correlation with varicocele grade. These findings suggest that fertile men with testicular hypotrophy may be at higher risk for decreased fertility potential regardless of varicocele grade.

The limited number of patients and the cross-sectional design are potential drawbacks of this study. However, the power of the test was more than 80% for all ROS comparisons, data were collected prospectively and all patients underwent a preestablished protocol, which strengthen our results.

Currently there is no consensus on the inclusion of ROS measurements in the routine evaluation of fertility potential in men with varicocele and the WHO manual describes ROS measurement as a research procedure.[19] Perhaps in the near future seminal ROS measurement could help to better evaluate men with varicocele and no current attempt to conceive, especially those who present with normal semen parameters. Since recent reports showed that varicocelectomy is effective for decreasing seminal ROS as well as DNA integrity, men with palpable varicocele and normal seminal parameters may have the same benefit from varicocelectomy if high ROS levels are found in semen.[28,29]

Based on our research seminal ROS tests could be offered to young men who present with normal seminal parameters and varicocele grade 3. We must keep in mind that interpreting the new reference ranges for semen parameters recently proposed by WHO requires an understanding that seminal parameters within the 95% reference interval do not guarantee fertility while values outside those limits do not necessarily indicate male infertility.[19] However, since the new lower reference limits are even lower than the previous reference values, clinicians will likely be faced with an increased number of men presenting with varicocele who have semen parameters within the normal reference limits. This may illustrate an urgent need for new diagnostic tools to evaluate these men.

CONCLUSIONS

Our study confirms prior reports documenting intact seminal parameters and testicular size in most fertile men who present with clinical incidental varicocele. The fertile population may have more efficient defense mechanisms to protect against the consequences of varicocele on testicular function since they may better neutralize excessive ROS caused by varicocele. However, we found in the same population that seminal ROS increased and the sperm concentration decreased as varicocele grade increased. More importantly men with varicocele grade 3 have significantly increased seminal ROS. Thus, perhaps the diagnosis of incidental varicocele in these men is not truly benign in regard to testicular function.

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Decreased Sperm DNA Fragmentation After Surgical Varicocelectomy is Associated With Increased Pregnancy Rate

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Abbreviations and Acronyms

ART = assisted reproductive technique

DFI = DNA fragmentation index

FSH = follicle-stimulating hormone

IVF = in vitro fertilization

LH = luteinizing hormone

ROS = reactive oxygen species

SCSA = sperm chromatin structure assay

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Purpose: We prospectively evaluated changes in sperm chromatin structure in infertile patients before and after surgical repair of varicocele, and the impact on the pregnancy rate.

Materials and Methods: Included in the study were 49 men with at least a 1-year history of infertility, a palpable varicocele and oligospermia. World Health Organization semen analysis and sperm DNA damage expressed as the DNA fragmentation index using the sperm chromatin structure assay were assessed preoperatively and postoperatively. Pregnancy (spontaneous and after assisted reproductive technique) was recorded 2 years after surgery.

Results: Mean sperm count, sperm concentration and sperm progressive motility improved significantly after varicocelectomy from 18.3×10^6 to 44.4×10^6, 4.8×10^6/ml to 14.3×10^6/ml and 16.7% to 26.6%, respectively ($p < 0.001$). The DNA fragmentation index decreased significantly after surgery from 35.2% to 30.2% ($p = 0.019$). When the definition of greater than 50% improvement in sperm concentration after varicocelectomy was applied, 31 of 49 patients (63%) responded to varicocelectomy. After varicocelectomy 37% of the couples conceived spontaneously and 24% achieved pregnancy with assisted reproductive technique. The mean postoperative DNA fragmentation index was significantly higher in couples who did not conceive spontaneously or with assisted reproductive technique ($p = 0.033$).

Conclusions: After varicocelectomy sperm parameters significantly improved and sperm DNA fragmentation was significantly decreased. Low DNA fragmentation index values are associated with a higher pregnancy rate (spontaneous and with assisted reproductive technique). We suggest that varicocelectomy should be considered in infertile men with palpable varicocele, abnormal semen analysis and no major female factors.

Key Words: testis; fertility, male; varicocele; spermatozoa; DNA damage

VARICOCELE is a common abnormality, found in 12% of the adult male population and in 25% of men in infertile couples.[1] The exact pathophysiology of male infertility due to varicocele is still not clear and varicocele treatment remains controversial in clinical andrology. Although WHO data clearly indicate that varicocele is associated with semen abnormalities, and decreased testicular volume and Leydig cell function,[1] it remains to be proved whether varicocele repair also restores male fertility potential.[2]

Two recent meta-analyses showed that surgical varicocelectomy signifi-

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cantly improves sperm concentration and motility in infertile men with palpable varicocele and abnormal preoperative semen parameters,[3,4] and increases the odds ratio of spontaneous pregnancy.[4]

A large body of evidence has accumulated to indicate that sperm DNA damage is increased in infertile men and high levels of damage are associated with a decreased pregnancy rate, including spontaneous pregnancy[5,6] and pregnancy after ART.[7] Several groups reported that varicocele is associated with increased sperm DNA damage.[8,9] Since varicocelectomy may improve sperm DNA damage in infertile men,[10,11] we evaluated repair induced changes in sperm chromatin structure and correlated postoperative DNA damage with the pregnancy rate (spontaneous and after ART).

MATERIALS AND METHODS

Patients

A total of 52 men with at least a 1-year history of infertility, a palpable varicocele, oligospermia and normal or correctable female fertility were eligible for this pilot study from November 2003 to June 2006. Andrological examination included medical history, physical examination, testicular volume measurement with a Prader orchidometer, scrotal ultrasound, endocrine analysis of serum LH (normal 1.5 to 8.0 IU/l), FSH (normal 2.0 to 7.0 IU/l), testosterone (normal 10.0 to 30.0 nmol/l) and inhibin B (normal 150 to 400 ng/l), and semen analysis according to WHO guidelines.[12] Sperm DFI was assessed by SCSA.

A palpable varicocele was confirmed by scrotal ultrasound done using a Nemio™ 20 with a 12 Hz transducer equipped with color flow imaging when at least 1 scrotal vein had a maximum diameter of at least 3 mm and retrograde flow was observed at rest or after the Valsalva maneuver. Grade 1 varicocele was diagnosed when reflux was measured at less than 2 seconds, grade II when reflux lasted for more than 2 seconds and grade III when reflux was noted at spontaneous respiration.

Postoperative followup at 3 months to assess the effect of varicocelectomy comprised WHO semen analysis, SCSA, scrotal ultrasound and endocrine evaluation. Patients served as their own controls since we compared the effect of varicocele repair on sperm quality with time. In 2 patients no preoperative semen sample was collected and 1 was lost to followup. A total of 49 couples were available for analysis. Since SCSA is incorporated in the standard evaluation of semen at our laboratory, medical ethical and institutional review board approval was not separately issued. In 2008 pregnancies ART, the pregnancy outcome and time to pregnancy were evaluated from patient records.

Sperm DNA Fragmentation Measurement

The SCSA was performed essentially as described by Evenson and Jost[13] using a FACScan™ flow cytometer. Briefly, frozen samples were quickly thawed, diluted to a concentration of 1 to 2 $\times$ 10^6 sperm cells per ml, exposed to acid detergent solution and stained with acridine orange. A similarly treated reference sample run before actual sample measurements was used to adjust the voltage gains of the flow cytometer FL3 and FL1 photomultipliers, which analyze red and green fluorescence, respectively. An aliquot of reference sample was run after every 5 to 10 samples. Voltage gains were readjusted when the fluorescent signal of the reference sample drifted. Data collection of the fluorescent pattern in 5,000 cells was done 3 minutes after acid treatment. Debris, bacteria and leukocytes were gated out during acquisition, as recommended by Evenson and Jost. The extent of DNA damage is expressed as the DFI, reflecting the ratio of red to total fluorescence. CellQuest™ Pro and WinList™ software were used to calculate the DFI of each sample. Each sperm sample was measured in duplicate and the mean of the results were used for analysis.

Statistical Analysis

Statistical analysis was performed using SPSS® 15.0. All results are expressed as the mean $\pm$ SD. The 1-sample Kolmogorov-Smirnov test was used to test for normality. Nonnormal distributed parameters (paired t test, total sperm count and sperm concentration) were logarithmically transformed to obtain normally distributed data. Differences between preoperative and postoperative semen variables were analyzed with the paired samples Student t test. Correlations were calculated using Spearman's rank correlation coefficient.

All patients were divided into 2 groups based on the spermatogenic response to varicocele repair. Responders were defined as patients in whom the sperm concentration increased by 50% or more after varicocelectomy.[14,15] Preoperative differences in continuous variables between the 2 consequent data sets were analyzed with the t test and the chi-square test was used for dichotomous variables to identify possible predictors of the response to surgery. All variables at a maximum of $p = 0.2$ were used in a backward multivariate logistic regression analysis model to evaluate determinants of surgical response. Univariate analysis using ANOVA and the t test was done to evaluate possible predictors of spontaneous and ART assisted pregnancies.

RESULTS

The mean age of male patients was 34 $\pm$ 6.9 years and mean partner age at varicocele repair was 30 $\pm$ 4.9 years. Included in analysis were 41 men diagnosed with primary infertility and 8 with secondary infertility. The mean duration of infertility was 2.7 $\pm$ 1.6 years.

Six female partners were diagnosed with irregular cycles, of whom 3 were successfully treated with clomiphene citrate and 2 couples were eventually treated with IVF. In 1 female who remained anovular despite treatment endometriosis was diagnosed during diagnostic laparoscopy.

Medical history revealed that 10 of 49 patients were smokers, 1 was a farmer who was periodically exposed to pesticides, 4 were treated for cryptorchidism at childhood, which was unilateral and bilateral

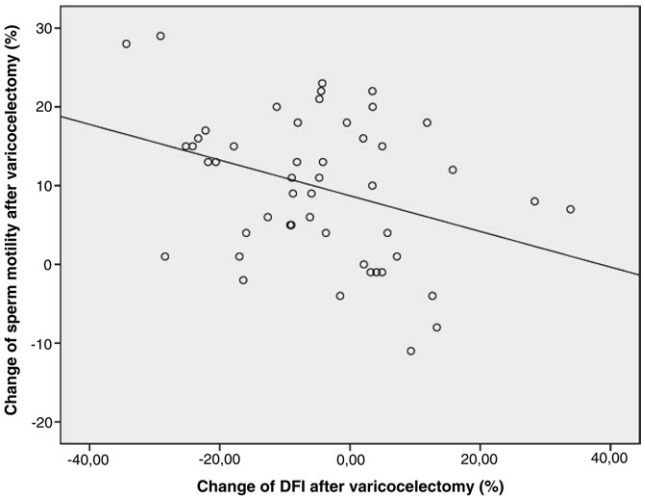
in 2 each, 5 had a history of urogenital infection, 4 underwent hernia repair in childhood and 1 was treated with urethrotomy for a urethral stricture.

A left grade I varicocele was found in 16 patients, grades II and III varicoceles were present in 15 and 13, respectively, and 5 had bilateral varicocele. Left high inguinal spermatic vein ligation[16] was performed in 36 men and microsurgical varicocelectomy[17] was done in 8. All bilateral varicoceles were treated with bilateral high inguinal ligation. Because only 1 urologist (GRD) at our clinic had mastered microsurgical varicocelectomy, this technique was not exclusively performed in 2003 to 2006. In 4 of 49 patients (8%) recurrent varicocele diagnosed during followup was treated with high inguinal ligation for bilateral (2), and grades I (1) and III (1) varicocele.

Mean sperm count, concentration and progressive motility improved significantly after varicocelectomy but DFI significantly decreased after surgery (table 1). A significant negative relationship was detected between the change in DFI and the change in sperm motility after varicocele surgery (see figure).

When defining a positive response as greater than a 50% improvement in sperm concentration after varicocelectomy, 31 of 49 patients (63%) were responders. Analysis of SCSA results in the responder group showed a significant decrease in DFI after surgery (table 2). Preoperative reproductive hormones were not significantly different in the responder and nonresponder groups. However, LH and FSH increased significantly after varicocele treatment in the nonresponder group.

On univariate analysis only the log preoperative sperm concentration was associated with a positive surgical outcome ($p = 0.039$). Also, when continuous and dichotomous preoperative variables at a maximum of $p = 0.2$ were reviewed, log preoperative sperm count ($p = 0.097$) and preoperative LH ($p = 0.085$) applied and were entered in a backward multivariate logistic regression analysis model. Only log preoperative sperm concentration predicted a positive surgical outcome (OR 0.229, $p = 0.044$). This means that a lower preoperative sperm concentration was associated with a positive response to surgery.



DFI change after varicocelectomy and subsequent sperm motility change (Spearman correlation r −0.312, p = 0.029).

After varicocelectomy 18 of the 49 couples (37%) conceived spontaneously within a mean of 7.2 ± 6.7 months. In 12 of the 49 couples (24%) spontaneous pregnancy was not achieved and they decided not to proceed with ART. A pregnancy rate of 22% (11 of 49 couples) was achieved after ART within a mean of 14.6 ± 7.7 months after varicocele repair. Intrauterine insemination, IVF and intracytoplasmic sperm injection were performed in 8, 4 and 7 couples, respectively. Nine of the 19 couples (42%) in whom ART was used failed to conceive after 3 intracytoplasmic sperm injection cycles in 5, a poor response after IVF in 1 and 6 intrauterine insemination cycles in 2. The mean postoperative DFI was significantly different in couples who could not conceive spontaneously or with ART ($p = 0.033$, table 3). The mean DFI was significantly increased in couples

Table 1. *Sperm parameters and DFI before and after varicocelectomy*

Parameter	Mean ± SD Preop	Mean ± SD Postop	p Value
Total sperm count (× 10^6)	18.3 ± 23.3	44.4 ± 48.0	<0.001
Sperm concentration (× 10^6/ml)	4.8 ± 4.7	14.3 ± 14.3	<0.001
% Progressive motility	16.7 ± 12.5	26.6 ± 15.7	<0.001
% Normal morphology	2.5 ± 2.1	2.8 ± 1.9	0.188
% DFI	35.2 ± 13.1	30.2 ± 14.7	0.019

Table 2. *DFI and endocrine parameters in responders and nonresponders*

	Mean ± SD Preop	Mean ± SD Postop	p Value
31 Responders:			
% DFI	35.3 ± 14.3	28.6 ± 14.7	0.009
LH (IU/l)	3.9 ± 1.8	4.3 ± 1.8	0.436
FSH (IU/l)	8.0 ± 6.2	9.2 ± 5.6	0.508
Testosterone (nmol/l)	14.9 ± 4.8	15.0 ± 4.3	0.084
Inhibin B (ng/l)	126.7 ± 48.5	126.2 ± 65.3	0.102
18 Nonresponders:			
% DFI	35.0 ± 11.2	33.0 ± 14.8	0.602
LH (IU/l)	3.0 ± 1.3	4.0 ± 1.6	0.018
FSH (IU/l)	6.6 ± 2.8	7.6 ± 3.6	0.006
Testosterone (nmol/l)	14.7 ± 5.2	15.3 ± 4.5	0.390
Inhibin B (ng/l)	140.7 ± 60.1	133.8 ± 63.8	0.224

Table 3. *Postoperative DFI in 4 pregnancy groups*

	Mean ± SD % DFI
Spontaneous pregnancy	30.1 ± 12.2
Failure to conceive spontaneously	37.5 ± 13.3
Pregnancy after ART	21.3 ± 14.7
Failure to conceive after ART	36.9 ± 15.6

with failure to conceive after ART compared to couples that achieved pregnancy with ART ($p = 0.041$). DFI was also increased in couples who failed to conceive spontaneously vs couples who conceived after ART ($p = 0.014$). Overall the mean DFI was significantly lower in couples who conceived spontaneously or with ART compared to that in couples with failure (26.6% ± 13.7 vs 37.3% ± 13.9, $p = 0.013$).

DISCUSSION

In accordance with previous studies we found a significant increase in postoperative sperm count, concentration and progressive motility after surgical repair of palpable varicoceles in patients with abnormal semen parameters.[3,4] Since sperm quality expressed as WHO semen parameters is subject to large biological variation and semen analysis is hampered by high interobserver and intra-observer variation,[18] it was suggested that this variability may explain the apparent differences between preoperative and postoperative semen samples after varicocele repair. Sperm DNA fragmentation provides additional information about sperm quality and the ability of a couple to conceive.[5] SCSA is a validated method for studying sperm chromatin integrity.[19] We previously reported that DFI biological variation is much lower than that of conventional semen parameters and DFI variability is not increased by varicocele.[20]

Not all men with a varicocele have improved sperm parameters after varicocelectomy and a 50% to 70% success rate was reported.[15] We applied a strict definition of greater than 50% improvement in sperm concentration to identify clinically relevant responders to surgery[14,15] and found that 63% of our patients responded to varicocele repair. In this pilot study DFI decreased significantly after varicocelectomy in the whole study population and in the responder group, suggesting that varicocele repair is effective for decreasing DFI in most patients. In the nonresponder group no clear effect on sperm DNA damage was observed but the lower number of patients in that group may explain this. A limitation of our pilot study is that for practical reasons only 1 postoperative semen sample was used.

Although lower postoperative DFI was associated with a higher pregnancy rate, postoperative mean DFI was relatively high in the spontaneous pregnancy group at 30.2% when considering that fertility is reported to be limited when DFI exceeds 30%.[19] Our preliminary results require validation in a larger study of sperm DNA damage in multiple postoperative semen samples.

In the search for molecular mechanisms associated with varicocele related infertility recent research has focused on ROS and apoptosis markers in testicular tissue, and semen in varicocele cases.[21] Oxidative stress and testicular apoptosis are well documented causes of increased sperm DNA fragmentation. Varicocele is associated with increased ROS production in spermatozoa and decreased antioxidant capacity in semen.[22] ROS was decreased after varicocele repair[11] even in patients in whom semen quality did not improve after varicocelectomy.[23] Sperm DNA damage may be a late effect of excessive ROS, which may explain why not all infertile patients in our study showed a decrease in sperm DNA damage after varicocele repair.

Germ cell apoptosis is an inherent process in spermatogenesis but it is clearly up-regulated in a number of stress conditions, such as varicocele.[24] Patients who responded to varicocelectomy had significant lower apoptosis levels in testicular biopsies.[14]

Because idiopathic male infertility and varicocele are linked to increased ROS, increased apoptosis and increased sperm DNA damage, one could also hypothesize that these phenomena are merely hypospermatogenesis symptoms. Abnormalities associated with hypospermatogenesis, such as improper protamination, aberrant apoptosis and the release of abnormal spermatozoa with immature chromatin status, may contribute to the generation of high ROS levels.[25] Most likely a combination of mechanisms is involved in the etiology of defective spermatogenesis in patients with a varicocele. This may be an explanation of the heterogeneous clinical presentation in men with a varicocele and the variable response to varicocelectomy.

Perhaps our population of treated patients was too heterogeneous to attribute postoperative effects only to varicocele repair. However, our patient population reflects real life practice, in which many infertility patients and their partners have multiple defects that may explain the failure to conceive. According to the second hit hypothesis introduced by Marmar, "Varicocele is a secondary opportunistic lesion that contributes to infertility, the underlying cause being genetic or epigenetic factors, expressed in both testes."[21] Our finding that LH and FSH were significantly increased after surgery in the nonresponder group may indicate that in these patients more predominant, ongoing causes of hyposper-

matogenesis and sperm DNA damage other than varicocele led to infertility.

Recently Cayan et al reported a 38% spontaneous pregnancy rate in a meta-analysis of the best surgical technique in a Palomo series and a 42% rate in a microsurgical varicocelectomy series.[26] Agarwal et al previously noted no differences in sperm quality improvement after microsurgical varicocelectomy or high inguinal ligation.[3] Although in our study the number of patients treated with microsurgical varicocele repair was small, the spontaneous pregnancy outcome was not related to surgical technique. Microsurgical varicocele treatment seems to be the best technique with a higher spontaneous pregnancy rate and lower postoperative recurrence. Also, it is recommended by the American Urological Association best practice policy group.[27]

Ficarra et al reviewed randomized, controlled trials of varicocele repair and found a significant increase in the pregnancy rate in patients who did vs did not undergo varicocele treatment (36% vs 20%).[28] Marmar et al reported a 33% pregnancy rate in patients treated with surgical varicocelectomy and a 16% rate in controls with no surgery.[4] These reported pregnancy rates are comparable to the 37% spontaneous pregnancy rate after varicocelectomy in our series. Couples with lower sperm DNA damage who do not achieve natural pregnancy after varicocele treatment have better results with ART.

CONCLUSIONS

Varicocelectomy can restore spermatogenesis, as reflected by improved sperm parameters and a significant decrease in sperm DNA fragmentation. Since lower DFI was associated with a higher pregnancy rate (spontaneous and after ART), we suggest that varicocelectomy should be considered in infertile men with a palpable varicocele, abnormal semen analysis and no major female factors.

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Varicocele as a risk factor for androgen deficiency and effect of repair

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Study Type – Therapy (case control)
Level of Evidence 2b

OBJECTIVE

- To determine whether men with varicoceles have lower testosterone levels than those without and to ascertain if testosterone levels increase after varicocelectomy.

PATIENTS AND METHODS

- We measured preoperative testosterone levels in 325 men with palpable varicoceles and in 510 men with vasectomy reversal without varicoceles who served as a comparison group.
- The testosterone levels between groups were compared by age. Of the men with varicoceles, 200 had data on both pre- and postoperative testosterone levels, which were compared to assess postoperative changes.

RESULTS

- Men with varicocele had significantly lower testosterone levels than the comparison group, with mean (SD) levels of 416 (156) vs 469 (192) ng/dL ($P < 0.001$). This difference persisted when analysed by age.
- The testosterone levels significantly increased after repair from 358 (126) to 454 (168) ng/dL ($P < 0.001$).
- Of the 70% of patients with postoperative improvement in testosterone levels, the mean (SD) increase in testosterone was 178 (142) ng/dL. The percentage change in testosterone levels was: 30% had no increase, 41% increased by ≤50%, 19% increased between by 51–100%, and 10% increased by >100%.
- There was no association between change in testosterone level and age, laterality of varicocele, or varicocele grade.

CONCLUSIONS

- Men with varicoceles had significantly lower testosterone levels than the comparison group of men with vasectomy reversal.
- Microsurgical varicocele ligation resulted in a significant increase in serum testosterone levels in more than two-thirds of men.
- These findings suggest that varicocele is a significant risk factor for androgen deficiency and that repair may increase testosterone levels in men with varicocele and low testosterone levels.

KEYWORDS

varicocele, testosterone, hypogonadism, androgen deficiency

INTRODUCTION

Varicocele is an abnormal dilatation of the pampiniform plexus of veins draining the testis. Varicocele causes a well-established negative effect on spermatogenesis [1,2] and is the most common cause of male infertility. The association between varicocele and male factor infertility was first noted in the late 1800s when Bennet [3] reported an improvement in semen quality after correcting bilateral varicoceles in a patient. Thirty years later, Macomber and Sanders [4] described an infertile man with low sperm counts who became normospermic and fertile after undergoing varicocele repair. Many larger-scale studies have since shown an improvement in semen parameters and fertility status after varicocele repair [5,6].

Multiple cross-sectional and longitudinal studies have established that, as men age, serum testosterone levels decrease [7–11]. Androgen insufficiency predisposes men to sexual dysfunction, loss of bone mineral density, sarcopenia, reduced strength and endurance, decreased energy levels, increased fatigability, and depression, as well as impaired memory, concentration and cognitive dysfunction. A growing body of evidence suggests that in addition to effects on spermatogenesis, varicocele also impairs testicular Leydig cell function with a consequential decrease in testosterone production [12,13]; correction of the varicocele may result in improved serum testosterone levels [14]. Recent studies have also identified a higher prevalence of varicocele in men as they age [15,16]. Men with varicocele may, therefore, be at risk for premature androgen deficiency.

The present study tested two hypotheses regarding the impact of varicocele on serum testosterone:

i) that men with varicocele have lower testosterone levels than those without varicoceles.
ii) that surgical repair of clinically palpable varicoceles increases testosterone levels.

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FIG. 1. Serum testosterone in patients with varicocele (416 mg/dL) vs comparison group (469 ng/dL), P < *0.001.*

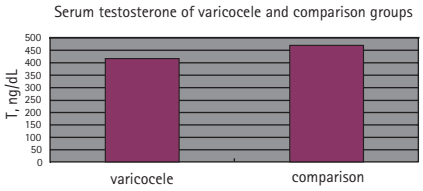

FIG. 2. Comparison of serum testosterone before (358 ng/dL) and after (454 ng/dL) varicocelectomy, P < *0·001.*

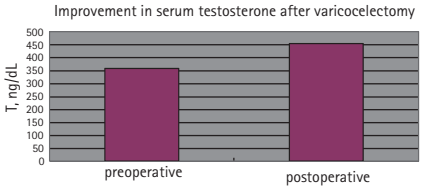

TABLE 1 Proportion of patients with unchanged or improved testosterone levels after varicocelectomy

Testosterone level response	%
No increase	30
Increase of 0–50%	41
Increase of 51–100%	19
Increase of >100%	10

PATIENTS AND METHODS

PATIENT POPULATION

This research protocol was approved by the Institutional Review Board at Weill Cornell Medical College of Cornell University. Men aged 18–70 years with clinically palpable varicoceles as determined by physical examination constituted the population group to be studied; most had primarily been referred for infertility evaluation. Surgical correction was performed via subinguinal microsurgical varicocelectomy [17]. Men presenting for vasectomy reversal surgery, with proven fertility as defined by prior conception and without varicocele on physical examination, served as the comparison group. Additional documented variables recorded included varicocele laterality, varicocele grade, and testicular volume as ascertained by physical examination using a Prader orchidometer. Most patients with varicocele did undergo scrotal ultrasonography; however, varicocele grading was based on physical examination findings. All patients were examined by a board-certified urologist with a practice limited to andrology.

TESTOSTERONE LEVEL DETERMINATION

All men had testosterone levels measured preoperatively as assessed by a peripheral venous serum sample taken between 0800 hours and 1030 hours. If more than one preoperative serum testosterone sample had been drawn, the mean of values was used as the preoperative baseline for statistical analysis. For patients who underwent varicocelectomy, serum testosterone level was assessed at 3–12 months postoperatively for most patients. Although most men only had one postoperative blood sample drawn, if more than one serum testosterone level was drawn, the mean of values was used as the postoperative value for analysis purposes.

STATISTICAL ANALYSES

An independent measures *t*-test was used to compare testosterone levels of the comparison group to the varicocele group. An independent measures analysis of covariance (ANCOVA) was then used to control for age. In the varicocelectomy group, a repeated measure *t*-test was used to compare the preoperative serum testosterone levels to postoperative testosterone levels. Multiple regression analysis was used to identify potential predictors of the change in testosterone levels before and after surgery. The variables tested as predictors were age, mean testicular volume, testicular volume group (<16 mL on either side vs other), or varicocele grade (grade 3 on either side vs other).

RESULTS

PATIENT POPULATION

In all, 325 men with varicocele were compared with 510 men in the comparison group. As a group, the patients with varicoceles were significantly younger than the comparison group, with a mean (SD) age of 35 (8) years vs 43 (8) years ($P < 0.001$). In the patients with varicocele, 225 (70%) had bilateral varicoceles, 92 (28%) had unilateral, while eight (2%) had no designation. For left varicocele grade, 20 (7%) had a grade I, 73 (25%) had a grade II, and 203 (68%) had a grade III. When focusing on right varicocele grade, 69 (29%) had a grade I, 110 (46%) had a grade II, 42 (17%) had a grade III.

COMPARISON OF TESTOSTERONE LEVELS BETWEEN GROUPS

Men with varicocele had significantly lower mean (SD) serum testosteronelevels than the comparison group, at 416 (156) ng/dL vs 469 (192) ng/dL ($P < 0.001$; Fig. 1). As it is well established that age is associated with testosterone levels, age was used as a covariate in an ANCOVA analysis. When including age as a covariate, the significant difference in testosterone levels remained between the groups ($F = 29.01$, $P < 0.001$). When controlling for age, the testosterone level of the varicocele group remained significantly lower (testosterone level 402 ng/dL) compared with the comparison group (testosterone level 478 ng/dL).

CHANGES IN TESTOSTERONE LEVELS AFTER VARICOCELECTOMY

Of the patients who had undergone varicocelectomy, 200 had documented postoperative serum testosterone values. The mean (SD) age of this group was 36 (8) years. After microsurgical varicocelectomy, patients' postoperative serum testosterone levels were significantly higher than their preoperative levels, at a mean (SD) of 454 (168) ng/dL vs 358 (126) ng/dL ($P < 0.001$; Fig. 2). Most patients exhibited an increase in serum testosterone levels postoperatively (Table 1). For patients with postoperative testosteronelevel improvement (142 men), the mean (SD) increase in testosterone level was 178 (142) ng/dL. Of those patients with testosterone levels of <300 ng/dL preoperatively (58 men), 79% had their testosterone levels increase to >300 ng/dL postoperatively. Conversely, of those patients with testosterone levels of >300 ng/dL preoperatively (142 men), only 12% had a testosterone level declineto <300 ng/dL. Multiple regression analysis was used to identify potential predictors of the change in testosterone levels before and after surgery. Variables tested as predictors were age, mean testicular volume, testicular volume group (<16 mL on either side vs other), or varicocele grade (grade 3 on either side vs other). There were no predictors of change in testosterone levels.

The preoperative endocrine data accumulated for the patients with varicocele also included serum levels of FSH, luteinizing hormone (LH), and oestradiol. The mean values were within the normal range for each hormone. Too few patients had postoperative levels drawn for a meaningful preoperative/postoperative comparison.

DISCUSSION

The negative impact of varicocele on spermatogenesis has long been recognized. For clinically significant varicoceles, varicocele ligation is performed with the goal of improving semen parameters in the setting of subfertility. The association between clinically significant varicocele and impaired testosterone production is less well-established. Furthermore, the utility of varicocelectomy for optimizing Leydig cell function and testosterone production has not yet been studied.

Varicoceles are diagnosed in up to 15% of the general population [18], in about one-third of men who present for evaluation of primary infertility [5,6] and in as many as 80% of patients with secondary infertility [2,19]. The vast majority of varicoceles are left-sided or bilateral with left generally larger than right. For impact on semen parameters, varicoceles are associated with lower sperm concentration, reduced motility and/or abnormal morphology on semen analysis [1,3,20]. Larger varicoceles cause more severe impairment of testis function [19]. These and other studies suggest that varicocele induces progressive, duration-dependent damage to the testes [19,21]. Semen parameters and fertility status improve after varicocele repair [4–6,22]

Several hypotheses have been suggested to explain how varicocele has a deleterious effect on testis function. The most widely accepted of these theories relates to alterations in the testicular thermal environment. Under normal scrotal conditions, a counter-current heat-exchange mechanism between the outflow of the pampiniform plexus and testicular arterial inflow supports the cooler temperature required for optimal sperm production [23]. Multiple studies indicate disruption of this cooling mechanism in patients with varicocele, leading to elevated scrotal and testicular temperatures [24,25]. Further, a reduction in testicular temperature has been shown to occur after varicocele repair. The heat impact on spermatogenic function may be independent of local effects on testicular testosterone production [26].

For varicocele repair, subinguinal microsurgical varicocelectomy is the repair technique with the lowest reported rates of failure and morbidity [17]. A small incision is made overlying the external inguinal ring and the spermatic cord is mobilized and spermatic veins are ligated with preservation of the vasal complex, testicular arteries and lymphatics.

In addition to the negative effects on semen parameters, varicocele has also been associated with diminished serum testosterone levels in infertile men; correction of the varicocele may result in improved serum testosterone levels [14]. Additional reports indicate that varicocele-related impairment of testicular Leydig cell function, as evidenced by decreased serum testosterone levels, also occurs in men without infertility [12,13]. It has been well-established that serum testosterone levels decrease as men age [7–11,26]. Recent studies have also identified a higher prevalence of varicocele in men with increasing age [15,16]. Given consideration of these separate findings, taken together it is reasonable to propose that men with varicocele may be at risk for premature androgen deficiency and that varicocele repair may reduce this risk.

The mechanism by which varicocele impairs testosterone production has not yet been clearly identified. Studies have shown abnormalities in the hypothalamic-pituitary-testis axis of infertile men with varicoceles [28,29]. An *in vitro* study of testicular tissue obtained from oligospermic men with varicoceles showed suppressed testosterone production [30]. Similar to the hypothesis regarding varicocele and its pathophysiological impact on spermatogenesis, thermal alterations may also negatively affect testosterone synthesis [14,27]. Varicocele has been implicated in altered function of 17 α-hydroxyprogesteronealdolase, which converts 17-hydroxyprogesterone to testosterone. Heat effects related to varicocele could have a negative effect on the enzyme's action, thus resulting in decreased testosterone production [31]. The documented temperature decrease reported after correction of varicocele may improve the Leydig cell environment for enzyme activity, thus resulting in postoperative improvement in serum testosterone levels as in the present study.

An interesting rat model of varicocele and varicocelectomy recently implicated varicocele as causing deterioration in intratesticular testosterone production, and showed that artery-preserving varicocele repair resulted in correction of the intratesticular testosterone to normal levels [32]. Further experimental and clinical studies are appropriate to substantiate or refute the suggestion that thermal effects are associated with decreases in testosterone production in men.

The present study confirms that men with varicoceles have lower testosterone levels compared with a comparison group without varicocele across age categories. Although there were statistically significant differences between the ages of the varicocele group and the comparison group, in each case the varicocele group had a lower mean age than that of those in the comparison group; this indicates that the 'true' difference in testosterone levels is, perhaps, even *more* significant than that identified in the present study. Based on the present findings, it appears that men with varicoceles have an accelerated deterioration in testosterone levels as compared with the normal age-related decline.

The present findings also indicate microsurgical varicocelectomy as a means to improve serum testosterone levels. The nearly 100 ng/dL increase in serum testosterone levels after surgery, from 358 ng/dL preoperatively to 454 ng/dL postoperatively, in the varicocelectomy population as a whole corroborates similar results reported in a previous study in a smaller cohort of patients [14]. In addition, the mean improvement in testosterone of >150 ng/dL in those patients who did exhibit postoperative testosterone increases would be expected to be clinically significant.

Sample sizes for the two groups evaluated were large, with convincing statistical findings related to testosterone level differences between the two groups and the postoperative changes in testosterone levels within the varicocelectomy group. However, given that this was a retrospective study,

selection bias may exist. Most, but not all, patients with varicocele had been referred for fertility evaluation, so the referral population was not entirely homogeneous. Further, longer scheduled follow-up to assess durability of improvements in testosterone levels would help ascertain the long-term benefits of varicocele repair on men's health.

For the comparison group, men seeking vasectomy reversal were used. However, men seeking vasectomy reversal may represent a population of men with intrinsically higher-than-average serum testosterone levels for age. A better comparison would be recruitment of randomly selected men without fertility issues, not seeking vasectomy reversal, to serve as a true control group. In addition, it would be interesting to include a third group comprised of men with varicocele and without infertility to assess how their serum testosterone levels compare with these two groups.

These data strongly suggest that varicocele is a significant risk factor for androgen deficiency and that microsurgical repair of clinically palpable varicoceles significantly increases testosterone levels in men with varicocele and low serum testosterone levels. At the very least, repair is likely to restore men to the normal slope of age-related decline in testosterone.

In conclusion, varicocele is a risk factor for androgen deficiency. Microsurgical repair significantly increases testosterone levels. The identification of varicocele as a treatable cause of androgen deficiency has broad implications for maintenance of general male health and well-being.

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CONFLICT OF INTEREST

None declared.

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Abbreviation: **ANCOVA**, analysis of covariance.

Cost-effectiveness analysis reveals microsurgical varicocele repair is superior to percutaneous embolization in the treatment of male infertility

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Abstract

Introduction: Varicoceles are a common cause of male infertility; repair can be accomplished using either surgical or radiological means. We compare the cost-effectiveness of the gold standard, the microsurgical varicocele repair (MV), to the options of a non-microsurgical approach (NMV) and percutaneous embolization (PE) to manage varicocele-associated infertility.
Methods: A Markov decision-analysis model was developed to estimate costs and pregnancy rates. Within the model, recurrences following MV and NMV were re-treated with PE and recurrences following PE were treated with repeat PE, MV or NMV. Pregnancy and recurrence rates were based on the literature, while costs were obtained from institutional and government supplied data. Univariate and probabilistic sensitivity-analyses were performed to determine the effects of the various parameters on model outcomes.
Results: Primary treatment with MV was the most cost-effective strategy at $5402 CAD (Canadian)/pregnancy. Primary treatment with NMV was the least costly approach, but it also yielded the fewest pregnancies. Primary treatment with PE was the least cost-effective strategy costing about $7300 CAD/pregnancy. Probabilistic sensitivity analysis reinforced MV as the most cost-effective strategy at a willingness-to-pay threshold of >$4100 CAD/pregnancy.
Conclusions: MV yielded the most pregnancies at acceptable levels of incremental costs. As such, it is the preferred primary treatment strategy for varicocele-associated infertility. Treatment with PE was the least cost-effective approach and, as such, is best used only in cases of surgical failure.

Introduction

Infertility affects about 15% of couples in the United States, with approximately 50% due to a male factor.[1] Consisting of a dilated and tortuous conglomeration of refluxing pampiniform plexus veins, varicoceles are present in 15% of the general population, about 35% of men with primary infertility and 80% of those with secondary infertility.[2-4] While varicoceles are the most easily treatable cause of male infertility, these vascular malformations are associated with a progressive worsening of testicular function if left untreated.[5-7] Varicocele repair improves semen quality and sperm DNA integrity,[8] increases clinical pregnancy and live birth rates during in-vitro fertilization (IVF) via intra-cytoplasmic sperm injection (ICSI)[9] and potentially recovers semen parameters in men with nonobstructive azoospermia.[10,11] While the effects of varicocele repair are well-established, the method of correction that is most cost-effective, is controversial.

Numerous surgical techniques exist to correct varicocele-induced infertility. The current gold standard is the open microsurgical varicocele repair (MV) via either an inguinal or sub-inguinal incision. Both approaches allow for the spermatic cord to be delivered into the incision, making it easy to identify the artery, veins and lymphatics.[2] In a recent review, the microsurgical subinguinal technique was found to yield the highest pregnancy rates, fewest recurrences and lowest complication rates.[4] Another surgical option, the non-microsurgical varicocele repair (NMV), is still currently practiced, but is not considered to be standard of care.[2]

Another, non-surgical treatment option for varicocele repair is percutaneous embolization (PE). Typically performed by an interventional radiologist, PE is the selective embolization of gonadal veins. Using coils, PE has the suggested advantages of faster recovery time and protection of the testicular artery without the requirement for anesthesia. PE is unfortunately accompanied by higher failure rates (4%-11%) and increased rates of recurrences.[2] Studies have identified similar improvements in semen parameters and pregnancy rates compared to surgical correction.[12-14] Interestingly, a recent retrospective review of 158 patients post-PE noted very low failure rates for unilateral, left-sided

embolization prompting the authors to suggest that men with unilateral left-sided varicoceles could be offered either MV or a PE with good expectant outcomes.[15]

When considering varicocele repair in the modern era, the rise of assisted reproductive technology (ART) needs to be considered. The widespread expansion of IVF has resulted in patients with a correctible varicocele offered immediate IVF instead of male factor treatment.[1] While IVF is effective, this ART approach is still very expensive and has implications for both the offspring and mother, including multiple gestations, low birth weights and possibly increased birth defects.[1] Moreover, in a recent decision analysis by Meng and colleagues,[1] varicocele repair was more cost effective than ART while, at the same time, providing comparable live birth rates.[1] Moreover, in cases of varicocele-associated infertility, immediate IVF should rarely be considered as the favoured treatment strategy.[16] Indeed, the results of these previously cited studies have almost uniformly demonstrated that initial correction of the underlying cause is the more cost-effective strategy.[16,17]

To date, there are very few studies comparing different methods of surgical correction to themselves and/or to PE. There is a further paucity in the literature with respect to decision analysis and cost-effectiveness regarding these different approaches. As such, the purpose of our current study was to comprehensively analyze the cost-effectiveness of various surgical approaches available to correct varicocele-associated male infertility. Specifically, we employed a decision-analysis model to determine whether MV, MNV or PE would yield the best treatment strategy with respect to costs, complications, fertilization and live birth rates.

Methods

Model design

Classification of treatment arms was determined based on currently accepted techniques and a review of recent literature.[15,18-20] The various strategies include NMV, MV and PE (Table 1). The treatment strategies were organized with decision arms progressing from primary to secondary treatment approaches over time (Fig. 1). Exclusion of the retroperitoneal, scrotal and laparoscopic options was made given the relative infrequency with which these surgeries were performed and the associated lack of comprehensive costing and outcomes.[21,22]

A decision tree was constructed (Fig. 1) using decision analysis software (TreeAge Pro Healthcare 2009, TreeAge Software Inc., Williamstown, MA.). Each treatment strategy

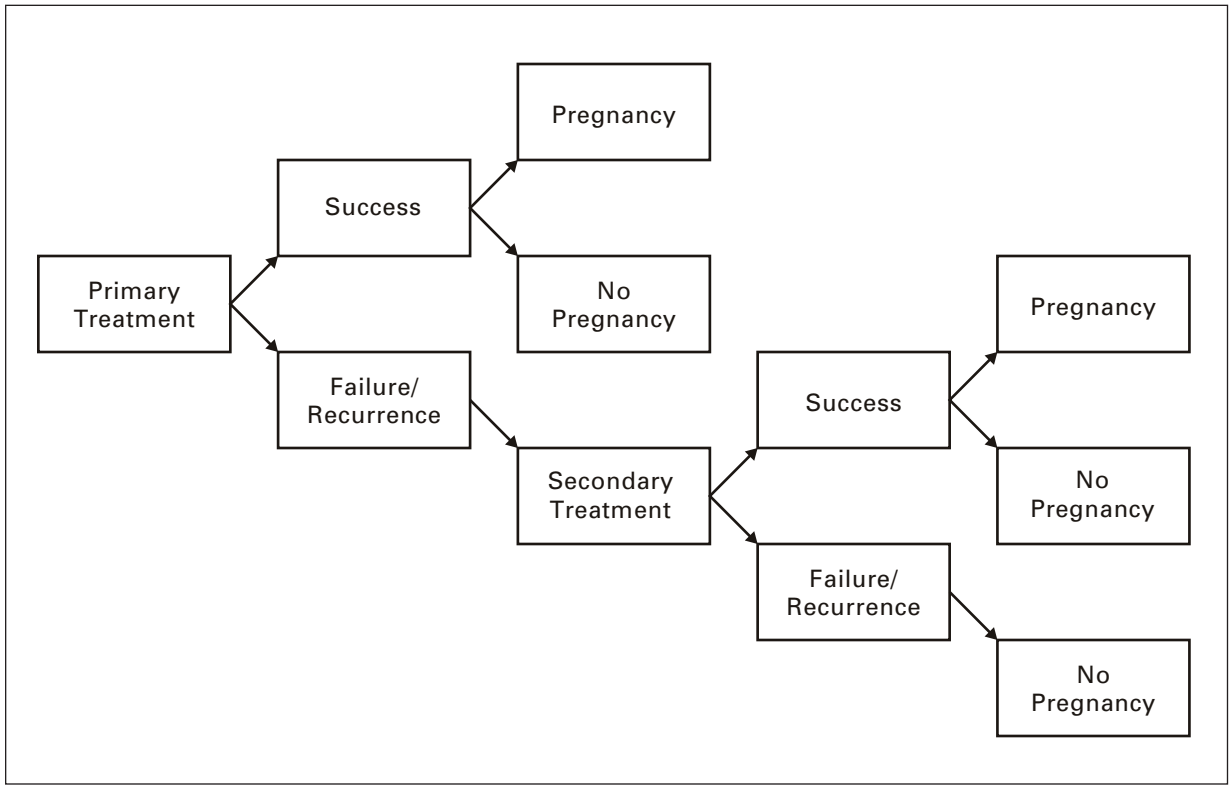

Fig. 1. Decision tree.

Table 1. Treatment arms

Treatment strategy	Primary treatment	Secondary treatment
1	NMV	PE
2	MV	PE
3	PE	NMV
4	PE	MV
5	PE	PE

NMV: non-microsurgical approach; PE: percutaneous embolization; MV: microsurgical varicocele repair.

consisted of a primary treatment followed by a secondary treatment for recurrences or treatment failures (Table 1, Fig. 1). The decision to exclude surgical approaches (NMV, MV) as secondary treatments for primary treatment surgical failures (Table 1) was made given the lack of literature available for this treatment condition. A Markov simulation cycle was then developed to estimate costs and pregnancy rates, as well as to evaluate each type of procedure (NMV, NMV and PE). Within the model, recurrences following MV and NMV were re-treated with PE and recurrences following PE were treated with repeat PE, MV or NMV (Fig. 1). Primary or secondary treatments complicated by a hydrocele could then proceed to hydrocele repair. Other complications of varicocele repair were excluded from the model. The time to progress from the start of the decision tree to the Markov cycle was considered immediate and no time was accrued during this period. Costs, pregnancy rates and recurrence-free rates were computed for each treatment strategy by performing 10 000 Monte Carlo micro-simulations.

Model data sources

Probability estimates

Varicocele recurrence rates (Table 2a), pregnancy rates (Table 2b) and hydrocele formation rates (Table 2c) following MV, NMV and PE were obtained from a pooled analysis of 33 studies evaluating varicocele repair outcomes by Diegidio and colleagues.[4] Reported recurrence rates were assumed to represent both recurrences and treatment failures.

Estimated recurrence rates following NMV, MV and PE as primary treatments were 15.7%, 2.1% and 4.3%, respectively (Table 2a). Recurrence rates following each procedure as a secondary treatment was estimated as 110% of their respective primary recurrence rate. This was done to reflect a possible decreased success rate in patients already demonstrating a predilection to recurrence as previously described.[23,24]

Table 2a. Recurrence rates

Technique	Mean (%)	Range (%)
NMV	15.7	3.6–17.5
MV	2.1	0.7–15.2
PE	4.3	3.6–17.5

NMV: non-microsurgical approach; PE: percutaneous embolization; MV: microsurgical varicocele repair.

Estimated pregnancy rates following NMV, MV and PE were 30.1%, 44.8% and 31.9%, respectively (Table 2b). In simulations where a secondary treatment was required for recurrence, the pregnancy rate was estimated as the lesser of the primary and secondary procedure types.

Estimated hydrocele formation rates following NMV, MV and PE were 7.5%, 0.7% and 0%, respectively (Table 2c). Reports describing the frequency that patients with post-varicocele repair hydroceles pursued repair was not available; however, we estimated this frequency as 25% based on expert opinion. All hydrocele repairs were assumed to be successful and the complications of the hydrocele repair were not considered.

Cost estimates

Costs were estimated from a payer perspective. Detailed cost derivations in Canadian and US (United States) dollars were determined and summarized (Table 3a, Table 3b). US dollar costs were based on current (2013) conversion rates. The direct costs of NMV, MV and PE were estimated from a retrospective review of institutional cost data at a Canadian Hospital.

Hospital costs included the use of operating room, operating room personnel, surgical equipment, disposables, use of post-anesthetic recovery room and medications used in hospital (Table 3a, Table 3b). The surgeon, radiologist and anesthesia fees were based on the 2012 Ontario Health Insurance Plan (OHIP) fee schedule (Table 3a, Table 3b).[25] All procedures were assumed to be outpatient procedures requiring no hospital admission. The capital cost and depreciation of the operative microscope was not considered since it is typically available at most institutions with costs

Table 2b. Pregnancy rates

Technique	Mean (%)	Range (%)
NMV	30.1	20.0–31.5
MV	44.8	33.8–51.5
PE	31.9	12.2–40.0

NMV: non-microsurgical approach; PE: percutaneous embolization; MV: microsurgical varicocele repair.

Table 2c. Hydrocele rates

Technique	Mean (%)	Range (%)
NMV	7.5	4.3–17.5
MV	0.7	0.0–1.6
PE	0.0	0.0

NMV: non-microsurgical approach; PE: percutaneous embolization; MV: microsurgical varicocele repair.

Table 3a. Cost estimates for NMV and MV*

	NMV	MV
Hospital costs	$1175 (range: $702–1619) ($1184 USD)	$1711.13 (range: $1224.56–3304.56) ($1723.80 USD)
Surgeon fee	$205.35 ($206.87 USD)	$205.35 ($206.87 USD)
Anesthesia fee	$225.15 ($226.82 USD)	$315.21 ($317.54 USD)
Total cost	$1605.50 ($1617.39 USD)	$2231.69 ($2248.21 USD)

*Cost $ CAD ($US). NMV: non-microsurgical approach; MV: microsurgical varicocele repair.

shared among several surgical services.

Indirect patient costs included costs of outpatient analgesia routinely prescribed and health-related productivity loss (HRPL) or societal costs (Table 4a, Table 4b). HRPL was calculated by incorporating the mean time off work (Table 4a) multiplied by the mean Canadian hourly wage for males (Table 4b). The mean time off work and the average wages were obtained from Canadian Government source documents. The costs of the operative hydrocele repair were calculated using similar methodologies.

Univariate and probabilistic sensitivity analysis

The robustness of our model to variations in key parameters was first analyzed by performing a univariate sensitivity analysis. Each parameter was individually varied across a clinically plausible range of values and the outcome of the model was recalculated throughout this range. Although univariate sensitivity analysis can identify the relative influence of individual parameters on model outcome, it inadequately reproduces real-world variability where multiple parameters may change simultaneously.

We thus addressed these limitations by performing a probabilistic sensitivity analysis, which realistically reflects real world uncertainty by varying each model parameter simultaneously. This analysis was done by substituting each parameter estimate with a probability distribution and by performing a Monte Carlo simulation. In these simulations, we estimated a theoretical patient's progress through the decision analysis model with parameter values randomly drawn from each probability distribution. Thus, probability distributions were created around each parameter using the variance reported in the literature.[26]

Table 4a. Societal costs

Technique	Mean (days)	Range (days)
NMV	6.6	3–9
MV	4.8	1–8
PE	1.0	NA

NMV: non-microsurgical approach; PE: percutaneous embolization; MV: microsurgical varicocele repair; NA: not available.

Table 3b. Cost estimates for PE*

Hospital costs	$1907.94 (range: $1840.65–2477.45) ($1922.07 USD)
Radiologist fee	$317.40 ($319.75 USD)
Anesthesia fee	$0 ($0 USD)
Total cost	$2225.34 ($2241.82 USD)

*Cost $ CAD ($US). PE: percutaneous embolization.

Clinically plausible estimates of variance were used when no published variance data were available.[26] Following standard conventions, costs were modelled with gamma distributions and transition probabilities were modelled with beta distributions. The results of 1000 Monte Carlo simulations were plotted on a cost-effectiveness axis. A cost-effectiveness acceptability curve (CEAC) was then generated by determining the percentage of simulations that remained cost-effective over a range of willingness-to-pay (WTP) thresholds. Reported WTP thresholds, which reflect the highest additional cost infertile couples are willing to pay for one additional pregnancy, ranged from $15 000 to $65 000 USD.[4,16,26] There is currently no consensus on society's WTP threshold for providing an infertile couple with one additional pregnancy.

Results

The results of the index case cost-utility analysis are summarized in Table 5. PE followed by PE was the least costly strategy at $2538 CAD, but had the second lowest pregnancy rate at 0.319 pregnancies. MV followed by PE was the strategy that achieved the highest pregnancy rate (0.444), although it did so at a higher cost ($3271 CAD). Adjusting the cost per pregnancy, MV-PE was superior at a cost of $7363 CAD per pregnancy. The incremental cost-effectiveness ratio (ICER) of MV-PE was $5569 CAD per pregnancy. Given a WTP range from $15 000 to $65 000 CAD, this highlights MV-PE as the preferred strategy with a higher effectiveness versus cost ratio (Fig. 2).

The remaining strategies: PE-NVM, PE-MV and NMV-PE all failed to show any increase in pregnancy rate compared to MV-PE (0.316, 0.319, 0.299, respectively). The higher associated costs of PE-NVM, PE-MV and NMV-PE compared to PE-PE resulted in higher costs per pregnancy.

Recurrence, pregnancy and hydrocele rates following NVM, MV, and PE were described above in Table 2a, Table 2b and Table 2c. Using a WTP of $15 000 to $60 000 CAD, MV-PE was the preferred strategy at all ranges of sam-

Table 4b. Lost wages

Average wage (per hour)	Work hours (per day)	Average wage (per day)
$25.58 CAD ($25.77 US)	8	$204.64 CAD ($206.16 US)

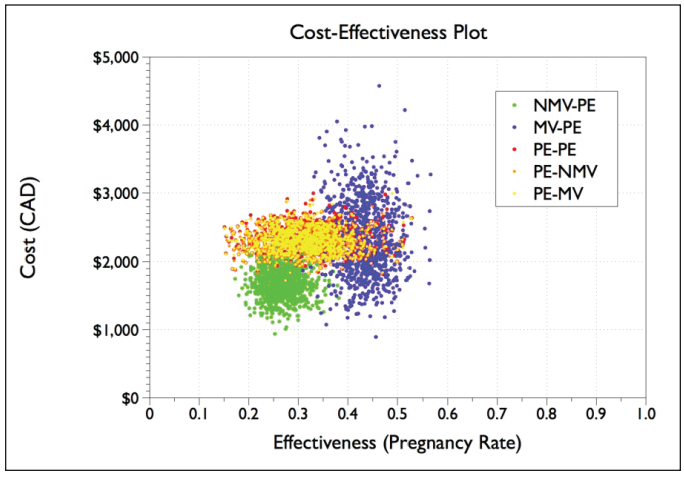

Fig. 2. A cost-effectiveness plot demonstrating the superiority of microsurgical varicocele repair-percutaneous embolization (MV-PE) as the most cost-effective treatment approach.

pled parameters. The cost-effectiveness acceptability curve (CEAC) (Fig. 3) shows a change from PE-PE at $5790 USD to MV-PE. Using a WTP of $15 000 to $60 000 CAD, it can be concluded that MV-PE is the most cost-effective strategy.

Discussion

Our study demonstrates that in varicocele-associated causes for male infertility, MV resulted in higher pregnancy rates than any of the other treatment strategies. In addition, it did so with an acceptable ICER ($5569/pregnancy), making it the most cost-effective strategy in our decision-analysis. PE was not as cost-effective and should therefore be saved for varicoceles that have previously failed surgical management. Both strategies are within the WTP threshold of $15 000 to $60 000 CAD with MV-PE still preferred. MV-PE is still preferred in part because of the higher success rates and ultimately, the lower achievable costs per pregnancy. Both PE and MV were far superior to NVM given the increased cost per pregnancy and highest complication rates.

To our knowledge, no randomized, controlled clinical studies comparing the outcomes of the different treatment methods for varicocele repair currently exist. In a recently performed prospective, randomized clinical trial, subinguinal MV resulted in improved semen analysis parameters, as well as enhanced rates of spontaneous pregnancies when compared to observation (13.9% vs. 32.9%) with a number needed to treat of 5.27.[27] A meta-analysis performed by Cayan and colleagues in 2009[28] is currently the benchmark for comparison. The authors analyzed 36 studies from 1980 to 2008 and showed that spontaneous pregnancy rates using MV were 41.97%. This was significantly greater than the 33.2% using PE[28] and similar to the results that we have obtained using our model. Moreover, Cayan and colleagues[28] also demonstrated that NMV had a spontaneous pregnancy rate of 36%, a recurrence rate 2.63%, and a hydrocele formation rate of 7.3%. The laparoscopic technique, which was not included in the current study, has a less successful 30.07% spontaneous pregnancy rate with a recurrence rate of 4.3%. Given the significantly inferior pregnancy rates obtained using a laparoscopic approach, it was excluded from our study.[28]

With regards to cost-effectiveness, several studies have been performed looking at male infertility secondary to the presence of a varicocele. An early study by Schlegal and colleagues in 1997[17] evaluated whether using ART as the primary method of treatment for varicocele-associated male infertility was more cost-effective compared to surgical correction. When male factor infertility was bypassed via direct treatment using ART, men with varicoceles had an average cost per successful delivery of $89 091 USD.[17] This was significantly more than the $26 268 USD cost per delivery for men who had their varicoceles surgically repaired prior to ART.[17] The authors concluded that specific treatment for varicocele-associated infertility with surgical repair was more cost-effective than primary treatment with ART. More recently, Penson and colleagues[16] noted similar findings: immediate IVF was not as cost-effective as varicocele repair followed by IVF. Specifically, immediate IVF accrued average costs of $20 394 USD, with a live birth effectiveness probability of 0.61.[16] This was more expensive and less effective than initial varicocele repair followed by IVF ($15 980 USD, effectiveness probability = 0.72).[16] Interestingly, when the couples were 'treated' with observation (assumed to be at a cost of $0), the cost per live pregnancy was, as would be expected, substantially less than varicocele repair followed by IVF. Given that observation alone was effective 14% of the time, the cost-savings occurred at the expense

Table 5. Index case cost-utility analysis

Treatment strategy	Cost $CDN ($USD)	Pregnancy rate	Cost per pregnancy, cost $CDN ($USD)	ICER, cost $CDN ($USD)
PE–PE	$2538 ($2557 USD)	0.319	$7964 ($8023 USD)	—
PE–NMV	$2565 ($2584 USD)	0.316	$7964 ($8023 USD)	Dominated
PE–MV	$2574 ($2593 USD)	0.319	$8068 ($8128 USD)	$122 775/pregnancy ($123684 USD)
MV–PE	$3271 ($3295 US)	0.444	$7363 ($7418 USD)	$5569/pregnancy ($5610 USD)
NMV–PE	$3412 ($3437 USD)	0.299	$11 429 ($11 514 USD)	Dominated

NMV: non-microsurgical approach; PE: percutaneous embolization; MV: microsurgical varicocele repair; NA: not available; ICER: incremental cost-effectiveness ratio.

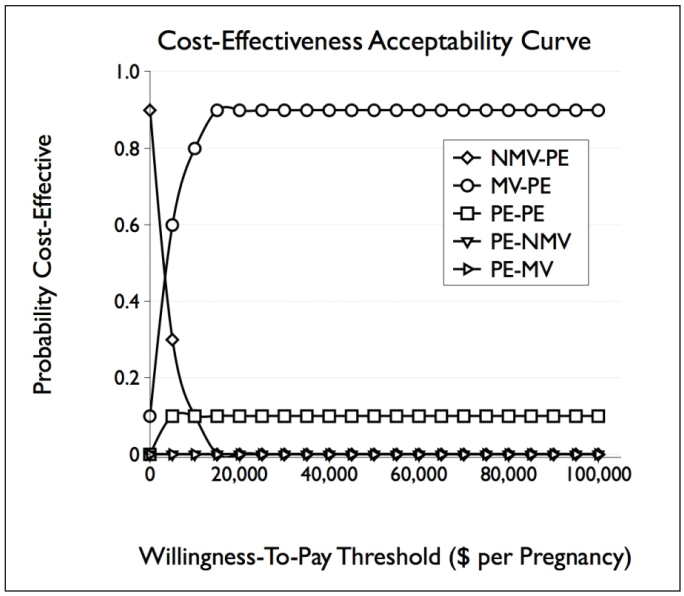

Fig. 3. The cost-effectiveness acceptability curve concluding that microsurgical varicocele repair-percutaneous embolization (MV-PE) is the most cost-effective strategy.

of success.[16] When multiple pregnancies were considered, varicocele repair followed by IVF dominated immediate IVF without surgical repair.[16]

While we did not consider multiple pregnancies within our decision analysis model, the current study has other limitations. Similar to all models of decision analysis, the quality of data is highly reliant on the information used to populate the model. Since there is a limited amount of literature comparing PE to MV, most of our data came from a single pooled analysis of 33 studies.[4] Thus, to strengthen our limited data, we used a comprehensive sensitivity analysis to minimize the uncertainty. Ideally, a multicentre randomized control trial comparing the cost of MV and PE, along with their respective spontaneous pregnancy rates, could be used to resolve the controversy. Further limitations include the fact that the costing was done based on the data from a single Canadian centre. As such, variability would be expected both regionally and internationally.

Conclusion

In the current study, the cost-effectiveness of surgical varicocele repair was compared to PE. MV yielded the greatest number of pregnancies at an acceptable level of incremental cost. Based on these findings, MV should be the first-line treatment for varicocele-related infertility. Conversely, we found that PE is best reserved to treat varicoceles refractory to surgical management.

Competing interests: Dr. Kovac, Dr. Fantus. Dr. Lipshultz, Dr. Fischer and Dr. Klinghoffer all declare no competing financial or personal interests.

This paper has been peer-reviewed.

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Loss of fertility in men with varicocele*

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Objective: To test the hypothesis that men with varicocele who have already fathered children are immune to the detrimental effect of varicocele on their fertility and will continue to be fertile. If this were the case, one would expect a very low incidence of varicocele in currently infertile men who were able to father a child in the past (secondary infertility) compared with men who have never been fertile (primary infertility).

Design: Survey of men with male factor infertility.

Setting: Tertiary care university medical center.

Patients: One thousand ninety-nine infertile men of whom 98 (9%) met our criteria for secondary infertility. Men with prior vasectomy and men whose partners were over age 40 were excluded.

Main Outcome Measure: Difference in the incidence of varicocele in men with secondary infertility versus primary infertility.

Results: A varicocele was palpable in 35% (352/1,001) of men with primary infertility and 81% (79/98) of men with secondary infertility. This difference in the incidence of varicocele was highly significant. Men with secondary infertility and varicocele were slightly older (37.9 versus 33.5 years), had a lower mean sperm concentration (30.2 versus 46.1×10^6/mL), more abnormally shaped sperm (72% versus 40%,), and higher mean serum follicle-stimulating hormone levels (17.6 versus 7.9 mIU/mL,) compared with men with primary infertility and varicocele.

Conclusions: The incidence of varicocele is much higher in male factor secondary infertility compared with primary infertility. These findings suggest that varicocele causes a progressive decline in fertility and that prior fertility in men with varicocele does not predict resistance to varicocele induced impairment of spermatogenesis. Men with a varicocele may benefit from early evaluation and prophylactic varicocelectomy to prevent future infertility. Fertil Steril 1993;59:613–6

Key Words: Varicocele, infertility, secondary infertility, loss of fertility

The incidence of palpable varicocele is higher among infertile men (21% to 41%) compared with the general population (4.4% to 22.6%) (1). Studies in animals (2–4) and humans (5, 6) suggest that varicocele causes progressive duration dependent testicular damage. Although varicocele is associated with infertility, many men with varicoceles father children. It is possible that those men with varicoceles who are of proven fertility are resistant to the detrimental effects of varicocele on spermatogenesis. If this were true, one would expect a lower incidence of varicocele in men who are currently infertile but who were able to father a child in the past (secondary infertility) compared with men who have never been fertile (primary infertility). If, however, the detrimental effect of varicocele on spermatogenesis is a progressive phenomenon and it is simply a matter of time before testicular injury becomes clinically evident, one would then expect a higher incidence of varicocele in men with secondary infertility compared with men with primary infertility.

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In the present study, we determined the incidence of varicocele in men presenting with primary versus secondary infertility. We then compared the semen analyses as well as the serum testosterone (T) and follicle-stimulating hormone (FSH) levels in men with primary infertility and varicocele versus men with secondary infertility and varicocele.

MATERIALS AND METHODS

Patients

The records of 1,300 consecutive men presenting with suspected male factor infertility were reviewed. Male factor infertility was defined as: [1] failure to achieve pregnancy with current partner after unprotected coitus for at least 1 year and [2] present female partner having been previously pregnant and/or having undergone complete gynecological infertility examination to rule out any identifiable female factors. Men whose partners were over 40 years of age were excluded. Men presenting for reversal of vasectomy were excluded from this study.

A complete medical and reproductive history was obtained from all men. This included age, age of partner, duration of infertility, previous pregnancies and pregnancy outcomes, and history of any prior systemic or genitourinary disorders. All patients underwent a complete physical examination by the same physician in a warm room. Varicoceles were graded as follows: *small:* distinct dilation of the internal spermatic veins palpable during a Valsalva maneuver in the upright position; *moderate:* palpable in the upright position without the aid of a Valsalva maneuver; *large:* both palpable and visible through the scrotal skin, without the aid of a Valsalva maneuver in the upright position. The diagnosis of varicocele was independently confirmed by another examiner. Men with only subclinical varicoceles diagnosed by Doppler, sonography, or venography were excluded from the study.

Semen was obtained by masturbation after between 2 and 5 days of abstinence and examined within 30 minutes of ejaculation. Semen volume, sperm concentration, percent and progression of motility, and morphology were recorded as per World Health Organization (WHO) recommendations (7). The mean number of ejaculates collected was 2.3 per patient (range, 1 to 4). Serum T and FSH levels were determined by standard radioimmunoassay.

Statistical analysis of differences between groups was performed using Student's t-test. To ensure validity of these t-tests, data were evaluated for normality of distribution via normal probability plots and for equality of group variances via the variance ratio F-test. Abnormal sperm motility and morphology comparisons were carried out by means of the χ^2 test.

RESULTS

Review of 1,300 consecutive infertility visit records identified 1,099 men who met our criteria for male factor infertility. One thousand one (91%) of these men presented with primary (1°) infertility and 98 (9%) men met our criteria for secondary (2°) infertility defined as previously demonstrated paternity on at least one occasion with either present or former partners. A varicocele was palpable in 35% (352/1,001) of men with 1° infertility and 81% (79/98) of men with 2° infertility. This difference in incidence of varicocele was significant ($P < 0.001$).

The mean age of men with 1° infertility and varicocele was 33.5 years (range, 22 to 49 years), and the mean age of their female partners was 31.7 years (range, 19 to 40 years). The mean age of men with 2° infertility and varicocele was 37.9 years (range, 25 to 56), and the mean age of their female partners was 33.8 years (range, 18 to 40 years). The mean duration of unprotected intercourse for these couples was 28 months in the 1° infertility and varicocele group and 21 months in the 2° infertility and varicocele group. The 79 men with 2° infertility and varicocele had been responsible for a total of 134 known pregnancies for a mean of 1.7 paternities per patient (range, 1 to 5). Fifty-one (65%) had impregnated their present partner, and 15 of these men had achieved pregnancies with former partners as well. The remaining 28 (35%) men had achieved pregnancies with prior partners only. The mean duration since last known paternity was 8.8 years (range, 1 to 24). Two thirds of the partners of men with 2° infertility and varicocele had been pregnant in the past and also had a recent gynecological exam revealing no identifiable female infertility factor. The remainder fulfilled at least one of these criteria.

Varicocele size and laterality data are depicted in Table 1. The differences between men with 1° versus 2° infertility were not significant.

Semen analysis data are presented in Table 2. Two thirds of men with 2° infertility and varicocele had sperm concentrations under 40×10^6/mL and nearly 40% had counts $< 20 \times 10^6$ sperm/mL. The mean sperm concentration for these men was 30.2 million sperm/mL compared with 46.1 for men with 1° in-

Table 1 Varicocele: Location and Size

	1° infertility	2° infertility
Location		
Left	195 (55)*	46 (58)
Right	10 (3)	3 (4)
Bilateral	147 (42)	30 (38)
Total	352	79
Size		
Small	188 (43)	39 (36)
Moderate	179 (32)	47 (43)
Large	129 (25)	23 (21)
Total	499	109

* Values in parentheses are percents.

fertility and varicocele ($P < 0.01$). Subnormal sperm motility (i.e., <40% motile sperm) was noted in 43% of men with 2° infertility and varicocele compared with 40% of men with 1° infertility and varicocele (P = not significant). Abnormal sperm morphology (i.e., >60% abnormal forms) was observed in 72% of men with 2° infertility and varicocele compared with only 40% of men with 1° infertility and varicocele.

The mean values for serum T and FSH were within normal limits for both groups (Table 2). The mean T level was lower for men with 2° infertility and varicocele (507 versus 585) ($P < 0.05$). These men also exhibited a significantly higher mean FSH level (17.6 mIU/mL) than men with 1° infertility and varicocele (7.9 mIU/mL), ($P < 0.001$).

DISCUSSION

Varicocele is a common finding on the physical examination of young men. Although the incidence of varicocele in infertile men is increased compared with the incidence in the general population, many men with varicocele father children. We hypothesized that men with varicocele who are of proven fertility are resistant to varicocele-induced impairment of testicular function. If this hypothesis were correct, one would expect that those men with varicocele who already fathered children have demonstrated their immunity to the detrimental effect of varicocele on their fertility and will continue to be fertile. If this were true, the incidence of varicocele in men with secondary infertility should be very low. Our data, however, refute this hypothesis.

We found that varicocele was the most common abnormality associated with nonvasectomy related male factor secondary infertility. It is present in a significantly higher percentage of men with secondary (81%) as compared with primary (35%) infertility. In addition, although of prior proven fertility, men with 2° infertility and varicocele had a significantly lower mean sperm concentration and poorer sperm morphology than did men with varicocele and primary infertility. The significantly higher mean serum FSH level in men with 2° infertility and varicocele suggests a greater degree of seminiferous tubular injury. Although the men with 2° infertility were slightly older (37.9 years) than men with primary infertility (33.5 years), age alone would not account for their loss of fertility (8). The difference in the age of the female partners (31.7 for primary versus 33.8 for secondary) is too small to explain a significant decline in fertility. It is likely that the detrimental effect of varicocele on the testicular function of these men since last known paternity (mean, 8.8 years) is responsible for the observed loss of fertility in these men. An alternative explanation for the higher prevalence of varicoceles in the secondary infertile population is that other causes of male factor infertility may decrease rather than varicoceles increase. This seems unlikely, however, because the cumulative effects of other common infertility etiologies such as infection with resultant obstruction, exposure to the gonadotoxic effects of drug or alcohol abuse, or the effect of chronic diseases such as diabetes, would be expected to increase rather than decrease over time.

Table 2 Semen Analysis and Endocrine Data of Men With Varicocele

	1° inferility (n = 352)	2° infertility (n = 79)	Probability
Sperm concentration ($\times 10/^6$mL)	46.1 ± 1.21 (0 to 96.0)*	30.2 ± 1.46 (0 to 107)	<0.01
Abnormal motility (<40% motile)	141 [40]†	34 [43]	NS‡
Abnormal morphology (<40% abnormal forms)	140 [40]	57 [72]	<0.001
Serum T (ng/dL) (normal = 300 to 1,000)	585 ± 0.88 (88 to 1,808)	507 ± 0.51 (70 to 1,288)	<0.05
Serum FSH (mIU/mL) (normal = 4.2 to 19)	7.9 ± 0.03 (2 to 75)	17.6 ± 0.54 (2 to 87)	<0.001

* Values are means ± SEM with ranges in parentheses.
† Values in brackets are percents.
‡ NS, not significant.

Our explanation of the increased incidence of varicocele in secondary infertility is supported by studies in animals suggesting that varicocele produces a progressive, duration dependent deterioration of seminiferous tubular function. Harrison et al. (4) surgically created varicoceles in monkeys and noted a progressive decline in sperm concentration, percent normal morphology, and motility over time. Saypol and colleagues (2) showed histologic changes to be worse at 3 months compared with 1 month after surgical creation of varicoceles in rats and dogs. Nagler et al. (3) reported identical findings in rats.

Several studies in humans support the concept of duration-dependent testicular injury with varicocele. Russell (5) observed that of 48 men with varicoceles, 82% of those older than 30 years had sperm concentrations $< 20 \times 10^6$ compared with 30% of those younger than 30 years old. Lipshultz and Corriere (6) compared subfertile patients with varicoceles, fertile patients with varicoceles, and normal controls. Although the fertile patients with varicoceles had normal semen analyses, they had a significant diminution in testicular volume compared with controls, as did the subfertile varicocele group. The subfertile group was significantly older than the fertile men with varicoceles. Nagao and colleagues (9) studied fertile men with varicoceles (n = 42), subfertile men with varicoceles (n = 24), and a control group (n = 55). The fertile men with varicoceles had significantly higher sperm concentrations than their subfertile counterparts, but both groups had elevated baseline luteinizing hormone (LH) values and had significantly higher LH responses to administration of LH-releasing hormone than the control group. Their study identified a subgroup of men with varicoceles who, despite proven fertility, exhibited evidence of subclinical testicular dysfunction. This dysfunction may precede gross deterioration in semen quality. Cheval and Purcell (10) followed a cohort of men with normal semen parameters and varicoceles over time and clearly demonstrated a significant decline in sperm count and motility. A WHO study of 9,034 men found that the incidence of varicocele in men with abnormal semen was more than twice that of men with normal semen and that varicocele was accompanied by decreased testicular volume (11).

Our current observations as well as prior studies in animals and humans suggest that varicocele causes a progressive decline in fertility and that prior fertility in men with varicocele does not assure future fertility. In adolescents and young men with varicoceles, age at the time of marriage and attempt at conception is unpredictable. Those who marry early are likely to be more successful in impregnating their partners than those who delay. Encouraging early marriage and attempts at conception for young men with varicocele is one approach to this problem. Alternatively, young men with varicocele may benefit from early evaluation to detect testicular atrophy or abnormal semen analysis. Varicoceles may now be repaired with minimal risk of morbidity (12). Prophylactic varicocele repair may prevent future infertility in men with varicocele (13).

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Microsurgical management of male infertility

Marc Goldstein* and Cigdem Tanrikut

SUMMARY

The introduction of microsurgical techniques has revolutionized the treatment of male infertility. As a result of technical advances and innovation over the past 10–15 years, previously infertile couples are now able to conceive naturally or to parent their own biological children with the aid of assisted reproductive technologies. This article reviews the indications, techniques, and outcomes of the various microsurgical procedures currently used to optimize male fertility. The most up-to-date methods of microsurgical vasal and epididymal reconstruction, sperm retrieval, and varicocele repair are discussed.

KEYWORDS male infertility, microsurgery, varicocele, vasoepididymostomy, vasovasostomy

REVIEW CRITERIA

Information presented in this review is based on the authors' extensive collection of research papers, textbooks, and Marc Goldstein's vast personal experience in the field of male infertility.

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INTRODUCTION

According to the Centers for Disease Control and Prevention 2003 Assisted Reproductive Technology (ART) Report, male factors play a significant role in 30–40% of couples dealing with infertility.[1] The more common causes of infertility in men include obstruction of the reproductive tract, which can be congenital, acquired or iatrogenic, and impairment of sperm production associated with karyotypic or Y-chromosomal abnormalities, testicular pathology or the presence of varicocele. Most causes of male infertility are treatable, and many treatments restore the ability to conceive naturally.

The dramatic recent improvements in the management of male infertility are largely attributable to improved microsurgical techniques for the repair of obstruction, microsurgical varicocelectomy for enhancement of spermatogenesis, new options for sperm retrieval, and refined microsurgical intracytoplasmic sperm injection (ICSI). These factors have made male infertility one of the fastest growing subspecialties of urology.[2–11]

VASAL AND EPIDIDYMAL OBSTRUCTION

The most common causes of vasal and epididymal obstructions are vasectomy and iatrogenic vasal injury (7% of cases) from previous scrotal/inguinal surgeries, particularly those performed in childhood.[12,13] Microsurgical reconstruction remains the safest and most cost-effective treatment option for these patients,[14–16] and also allows natural conception, which is preferred by couples.

The lumina of the vas deferens and epididymal tubule are only about 0.3 mm and 0.2 mm in diameter, respectively, and, therefore, a precise microsurgical technique is the most important factor in the success of reconstruction (as defined by return of sperm to the ejaculate). With recent improvements in microsurgical techniques, the success rate for vasovasostomy is between 70% and 99%,[2,3,17,18] and success rates between 40% and 90% have

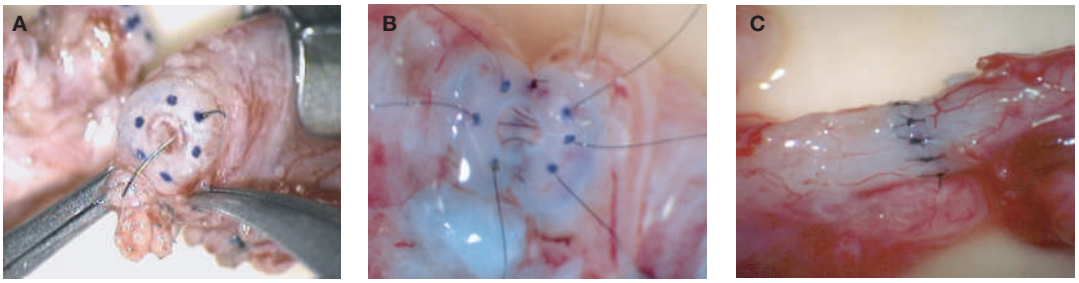

Figure 1 Microsurgical vasovasostomy with multilayer microdot method (×25). (**A**) Placement of 10-0 nylon suture inside the vasal lumen and through the microdot target. (**B**) The first three (of six) sutures of the anastomosis have been placed and tied down. The final three sutures have been placed and are ready to be tied. (**C**) Completed anastomosis. Reproduced with permission from reference 23 © (2002) Elsevier Inc.

been reported for microsurgical vasoepididymostomy.[2,6,19,20] Many patient-related factors, such as time interval from vasectomy, sperm granuloma at the site of anastomosis,[21] antisperm antibodies[22] and gross appearance of the vasal fluid,[23] can influence the outcome of the reconstruction. The age of the female partner should also be taken into account.[24] In addition, the surgeon's skill, reconstructive technique and experience all have a significant impact on surgical outcome.

MICROSURGICAL VASECTOMY REVERSAL

Vasectomy is the most common urologic operation in North America, where between 500,000 and 1 million men undergo the procedure each year. Before undergoing vasectomy, the patient should receive counseling regarding the permanency of the procedure and be offered the option of sperm banking. Despite preoperative counseling, surveys suggest that 2–6% of vasectomized men will ultimately seek vasectomy reversal because of unforeseen changes in lifestyle.[25]

Vasovasostomy

The microdot technique was developed at Cornell University as a means of improving the vasovasostomy procedure. It ensures precise suture placement by the exact mapping of each planned suture. When sperm are found in the fluid emanating from the testicular end of the vas, the patency rate of this technique for return of sperm to the ejaculate is 99.5%, and the 1-year cumulative pregnancy rate for partners of patients undergoing this procedure is 70%.[3] The microdot method separates the planning of suture position from the physical act of suture placement. Much as an architect prepares blueprints before the builder constructs the house, the perioperative planning of suture placement is critical to a successful surgical outcome. This painstaking planning allows the surgeon to focus on one task at the time of suture placement, 'hitting the bulls eye'. In addition, the discrepancy in diameter between the proximal (obstructed) vasal lumen and the distal (nonobstructed) vasal lumen is typically 2:1 to 3:1, sometimes more; careful, even spacing of the sutures minimizes luminal discrepancy and limits 'dogears' and leaks, thus decreasing the risk of postoperative stricture, granuloma formation, and reconstructive failure. The microdot method results in substantially improved accuracy of suture placement and minimizes the discrepancy between luminal diameters of the proximal and distal vasal ends, allowing for a watertight anastomosis.

A microtip skin-marking pen is used to map out planned needle exit points. Exactly six monofilament 10-0 double-arm nylon mucosal sutures (first layer) are used for every anastomosis, because they are easy to map out and always result in a leak-proof closure, even when the lumen diameters are markedly discrepant. After completion of the mucosal layer, six 9-0 deep muscularis sutures are placed exactly in between each mucosal suture, just above, but not penetrating, the mucosa (second layer). Six additional 9-0 nylon interrupted sutures are then placed between each muscular suture (third layer). These sutures only involve the adventitial layer that covers the underlying mucosal suture. The anastomosis is finished by approximating the vasal sheath with six interrupted sutures of 7-0 PDS, completely covering the anastomosis and relieving it of all tension (fourth layer). All anastomoses consist of four layers of

Table 1 Surgical recommendations based on gross appearance of vasal fluid and microscopic findings.

Appearance of vasal fluid	Most common findings on microscopic examination	Surgical procedure recommended
Copious, crystal clear, watery	No sperm	Vasovasostomy
Copious, cloudy thin, water soluble	Sperm with tails	Vasovasostomy
Copious, creamy yellow, water insoluble	Many sperm heads, occasional sperm with short tails	Vasovasostomy
Copious, thick white toothpaste-like, water insoluble	No sperm	Vasoepididymostomy
Scant white thin fluid	No sperm	Vasoepididymostomy
Scant fluid, no granuloma at vasectomy site	No sperm	Vasoepididymostomy
Scant fluid, granuloma present at vasectomy site	Barbotage fluid reveals sperm	Vasovasostomy

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six sutures, for a total of 24 sutures (Figure 1). The dartos layer is approximated with interrupted 4-0 absorbable sutures and the skin with subcuticular sutures of 5-0 Monocryl® (Johnson and Johnson, New Brunswick, NJ).

Vasoepididymostomy

Microsurgical vasoepididymostomy

Microsurgical vasoepididymostomy is considered the most technically challenging type of surgery for the male reproductive system. In virtually no other operation are results so dependent upon the surgeon's technical expertise. Surgeons who perform vasoepididymostomy, therefore, must have extensive experience in microsurgical techniques and carry out the procedure frequently. The indications for performing vasoepididymostomy at the time of vasectomy reversal, based on gross appearance of the vasal fluid,[23] are reviewed in Table 1. Although occasional discrepancies exist between gross and microscopic findings, they correlate approximately 80% of the time. It is, however, essential to view the vasal fluid under the microscope, in order to determine whether to proceed with vasovasostomy or with vasoepididymostomy. For obstructive azoospermia that is not due to vasectomy or absence of the vas deferens, vasoepididymostomy is indicated when the testis biopsy reveals complete spermatogenesis and scrotal exploration reveals the absence of sperm in the vasal lumen.

Microsurgical end-to-side two-suture intussusception vasoepididymostomy

The intussusception technique, originally known as the three-suture triangulation technique, was developed by Berger.[26] Marmar described a modified technique that consists of two sutures with transverse double-needle placement within the epididymal tubule.[27] At Cornell University, a longitudinal two-suture intussusception vasoepididymostomy approach (Figure 2A) was developed in order to further improve the procedure.[7] With this method, four microdots are marked on the cut surface of the vas deferens and two parallel double-arm sutures are placed in the distended epididymal tubule; however, the needles are not pulled through. After the epididymal fluid is tested for sperm and aspirated into micropipettes for cryopreservation, the two needles within the epididymal tubule are pulled through, and all four

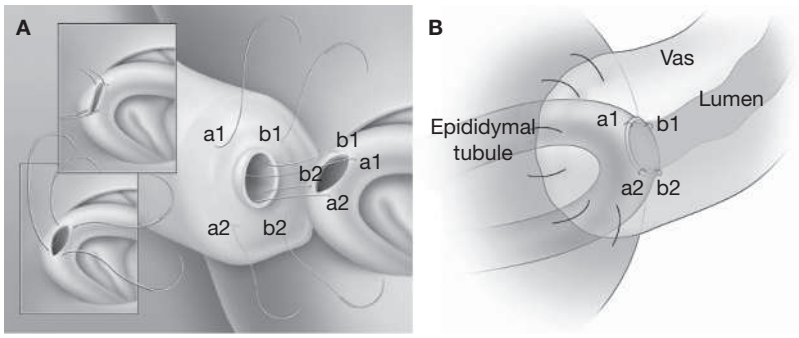

Figure 2 Microsurgical end-to-side two-suture intussusception vasoepididymostomy. (**A**) Two parallel sutures are placed in the selected epididymal tubule, oriented longitudinally, then the tubule is incised between the two needles (top inset). Once the epididymal tubule has been incised, the sutures are pulled through (bottom inset). The double-arm needles are placed in-to-out through the vasal lumen. The suture points are labeled to indicate where they run (a1 to a1, etc.). (**B**) Completed anastomosis. The suture points at the completed anastomosis are indicated by a1, a2, b1 and b2. Reproduced with permission from reference 7 © (2003) Elsevier Inc.

Table 2 Advantages and disadvantages of surgical techniques for sperm retrieval.

	Advantages	Disadvantages
Microsurgical epididymal sperm aspiration	Low complication rate if performed microsurgically Epididymal sperm have better motility than testicular sperm Large number of sperm can be harvested for cryopreservation of multiple vials in a single procedure	General anesthesia preferred Requires microsurgical skills Not indicated for nonobstructive azoospermia
Percutaneous epididymal sperm aspiration	No microsurgical skill required Local rather than general anesthesia Epididymal sperm have better motility than testicular sperm	Variable success in obtaining sperm Smaller quantity of sperm obtained than with microsurgical epididymal sperm aspiration Not indicated for nonobstructive azoospermia Complications include hematoma, pain and vascular injury to testes and epididymis
Testicular sperm aspiration	No microsurgical skill required Local rather than general anesthesia Can be used for obstructive azoospermia	Immature or immotile sperm Small quantity of sperm obtained Poor results in nonobstructive azoospermia Complications include hematoma, pain and vascular injury to testes and epididymis
Testicular sperm extraction	Low complication rate if performed microsurgically Preferred technique for nonobstructive azoospermia	Requires general anesthesia and microsurgical skills

needles are placed through the vas lumen at the marked locations. Tying down the sutures allows the epididymal tubule to be intussuscepted into the vasal lumen, completing the anastomosis (Figure 2B). The patency rate with the longitudinal intussusception vasoepididymostomy approach was over 90% in a recent clinical series, and intussusception is the preferred method for all vasoepididymostomies.[6]

All successful vasovasostomy and vasoepididymostomy techniques rely on adherence to surgical principles that are universally applicable to anastomoses of all tubular structures: an accurate mucosa-to-mucosa approximation; leakproof anastomosis; tension-free anastomosis; good blood supply; healthy mucosa and muscularis; and atraumatic anastomotic technique.

EPIDIDYMAL SPERM ASPIRATION

When to perform sperm extraction

Although most postvasectomy patients are candidates for microsurgical reconstruction, not all obstructive-azoospermic men can be managed surgically. In order that these men can become biological fathers, various sperm-retrieval techniques have been developed for use in conjunction with *in vitro* fertilization (IVF). Before the introduction of ICSI, sperm retrieval was performed with IVF and limited forms of micromanipulation, such as partial zona dissection. ICSI has now replaced all other types of assisted reproduction.

Congenital bilateral absence of the vas deferens (CBAVD) is an abnormality related to cystic fibrosis. In patients with mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, segments of the excurrent ductal system anywhere from the midportion of the epididymis to the seminal vesicles are missing.[28] Only a minority of patients with a CFTR gene mutation have enough healthy tissue for reconstruction to be feasible.[29] The majority of patients with CBAVD, therefore, will need epididymal sperm aspiration for IVF via ICSI.[30–32] Before IVF is performed, it should be determined whether both partners are carriers of the CFTR gene mutation.

There are various surgical techniques for sperm retrieval; their advantages and disadvantages are summarized in Table 2. These techniques are also useful for intraoperative retrieval of sperm during reconstructive procedures such as vasoepididymostomy, which have failure rates high enough that intraoperative cryopreservation of sperm for a future IVF cycle should be considered, in the event that the reconstructive surgery is unsuccessful.

Sperm obtained from patients with chronically obstructed reproductive systems usually have poor motility and decreased fertilization capacity. The use of ICSI is essential to achieve optimal results in most cases. One notable exception is chronic obstruction secondary to previous vasectomy. Female partners of

men who underwent vasovasostomy more than 15 years after their initial vasectomy still achieved a natural pregnancy rate of 44%.[20] The sperm of patients with chronic epididymal obstruction in this setting will take longer to regain motility; however, even if natural conception does not occur, ejaculated sperm could be used for intrauterine insemination or ICSI.

Open epididymal tubule sperm retrieval technique

Microsurgical epididymal sperm aspiration can be employed either for intraoperative sperm retrieval at the time of vasoepididymostomy or as an isolated procedure in men with congenital absence of the vas deferens or unreconstructable obstructions.[33] Under the operating microscope, the epididymal tunic is incised and a dilated epididymal tubule is selected, isolated and incised with a 15° microknife (Figure 3A). The fluid is touched to a slide, a drop of saline or Ringer's solution is added, a cover slip is placed over the slide, and the fluid is immediately examined under a bench microscope. As soon as motile sperm are found, a dry micropipette is placed adjacent to the effluxing epididymal tubule (Figure 3B). A standard hematocrit pipette is less satisfactory, but can be used if a micropipette is not available. Sperm are drawn into the micropipette by simple capillary action. Negative pressure, as is generated by the action of an in-line syringe, should not be applied during sperm retrieval as this can disrupt the delicate epididymal mucosa. Two micropipettes can be employed simultaneously in order to increase the speed of sperm retrieval. The highest rate of flow is observed immediately following incision of the tubule. Progressively better-quality sperm are often found following the initial washout. Gentle compression of the testis and epididymis enhances flow from the incised tubule. With patience, 25–50 µl of highly concentrated epididymal fluid, containing approximately 75 million sperm, can be recovered. This is diluted in multiple aliquots of 2–3 ml of human tubal-fluid medium, so that there are 5–10 million sperm per ml. Those specimens not used immediately for ART are cryopreserved for possible future use. If no sperm are obtained, the epididymal tubule and tunic are closed with 10-0 and 9-0 monofilament nylon sutures, respectively, and an incision is made more proximally in the epididymis, or even at the level of the efferent ductules, until motile sperm are obtained.

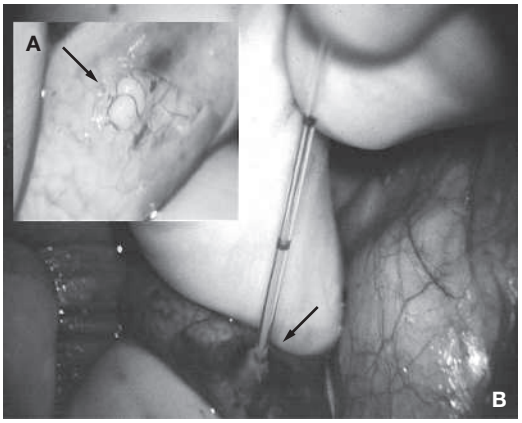

Figure 3 Microsurgical epididymal sperm aspiration (**A**) Selection and isolation of dilated tubule (×10). (**B**) Aspiration of sperm into micropipette by capillary action (×15). Reproduced with permission from reference 23 © (2002) Elsevier Inc.

Box 1 Causes of nonobstructive azoospermia.

Congenital and developmental

Genetic
- Karyotypic abnormalities
- Y-chromosomal microdeletions

Testicular
- Cryptorchidism
- Torsion
- Bilateral anorchia

Endocrinologic
- Deficiencies of gonadotropin-releasing hormone agonist, luteinizing hormone, and follicle-stimulating hormone
- Excess of androgen, estrogen, prolactin, glucocorticoid
- Thyroid abnormalities
- Receptor abnormalities

Varicocele

Acquired

Environmental hazards
- Radiation
- Heat or thermal injury

Iatrogenic
- Ischemic atrophy
- Radiotherapy
- Chemotherapy

Diseases
- Neoplastic diseases
- Infections or inflammatory causes
- Systemic illness

Drugs or gonadotoxins

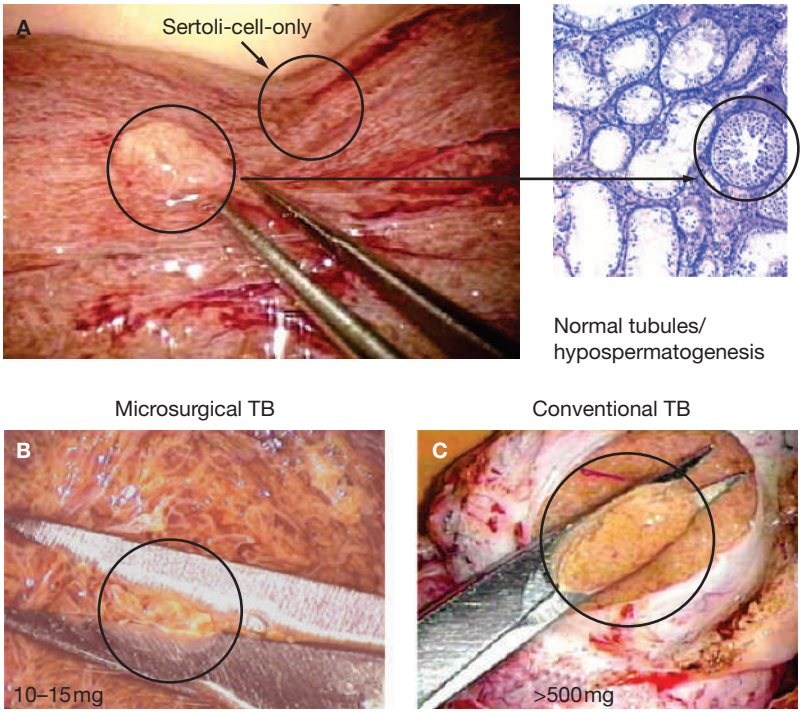

Figure 4 Microdissection testicular sperm extraction. (**A**) Comparison of full, white sperm-containing tubules (to left) with stringy-appearing, yellowish Sertoli-cell-only tubules (right) (×25). An example is provided of what a sample might look like under microscopic histologic examination. (**B**) Excision of full tubules under microscopic assistance (×25). (**C**) Conventional testis biopsy. Abbreviation: TB, testis biopsy. Reproduced with permission from reference 23 © (2002) Elsevier Inc.

Success of sperm extraction techniques

Sperm retrieval from the epididymides of men with obstructive azoospermia is possible in over 99% of patients when performed by experienced microsurgeons.[34,35] Success rates such as these are possible even if multiple prior procedures have been performed and extensive scarring is present in the scrotum. If the epididymis is obliterated because of previous procedures or infection, the most proximal efferent ductules of the testis can be exposed by reflection of the caput epididymis to uncover the 7 to 11 dilated tubules. One should be able to aspirate sperm from at least one of these tubules.

In a study of 76 attempts at sperm retrieval using MESA and ICSI in men with obstructive azoospermia, clinical pregnancies were detected by a fetal heartbeat after 75% of attempts, with ongoing pregnancy or delivery achieved for 64% of attempts.[36] For men with CBAVD, the success rate is even higher.[37] Optimal fertilization and pregnancy rates are obtained with a technique of agressive immobilization of spermatozoa prior to ICSI. It is possible that aggressive immobilization acts by enhancing sperm membrane permeability to improve the ability of immature spermatozoa to fertilize oocytes.[38] The teamwork and collaborative effort of reproductive endocrinologists, embryologists, and male reproductive surgeons is of paramount importance for successful results.

NONOBSTRUCTIVE AZOOSPERMIA

Nonobstructive azoospermia (NOA), or testicular failure, is the most challenging type of male-factor infertility to manage. Various conditions that can lead to NOA have been identified (Box 1). While some of the underlying causes of NOA might be reversible to a degree, advanced ART techniques are needed for the majority of patients with this condition. With the advent of ART, particularly ICSI in conjunction with sperm obtained via testicular sperm extraction (TESE), many of these men are now able to father their own biological children. However, there remain subgroups of 20–40% of patients with NOA who, despite the advent of ICSI and advances in microsurgical sperm extraction techniques, are not able to have sperm retrieved for assisted reproduction.[39] In these cases, the couples should consider donor-sperm fertilization or adoption as alternatives.

Testicular-sperm extraction

Testicular sperm can be found within the testicular tissue of many men with NOA. The optimal technique of sperm extraction would be minimally invasive and avoid destruction of testicular function, without compromising the chance of retrieving enough spermatozoa with which to perform ICSI.

Microdissection testicular sperm extraction

Microdissection TESE is an advanced version of TESE that applies microsurgical techniques to the retrieval of sperm from the seminiferous tubules. Although microdissection TESE is not a minimally invasive technique, it results in the removal of a minimal amount of testicular tissue with maximal sperm yield, and minimizes the negative impact on testicular function. This method was developed by Schlegel,[40] and is an effective method for the retrieval of sperm from men with NOA, for use in ICSI. The seminiferous tubules from different areas of the testis are often associated with different states

of maturation of spermatogenesis. In other words, in some areas of the testis, the Sertoli-cell-only pattern might be present, whereas other areas might show maturation arrest, hypospermatogenesis, or even normal spermatogenesis. Under the operating microscope (×25), an experienced surgeon can usually distinguish between 'more active' and 'less active' seminiferous tubules by their appearance; tubules that appear full, opaque, and are larger in comparison to other tubules are more likely to contain sperm (Figures 4A and 4B).

The conventional TESE technique requires multiple, blind testis biopsies with excision of large volumes (>500 mg) of testicular tissue, which can result in permanent damage to the testis (Figure 4C). The microdissection TESE technique of sequential excision of microdissected seminiferous tubules (10–15 mg, or 2 mm in length, of seminiferous tubule) has been shown to be more successful, compared with the results achieved by conventional TESE, or random biopsies of testicular tissue. In a sequential series of TESE attempts, Schlegel showed that sperm-retrieval rates improved from 45% (10 out of 22 patients) with conventional TESE to 63% (17 out of 27 patients) with microdissection TESE. Microdissection samples yielded an average of 160,000 spermatozoa per 9.4 mg sample, whereas only 64,000 spermatozoa were found in an average 720 mg conventional biopsy sample ($P<0.05$ for all comparisons).[41]

Outcomes of testicular sperm extraction

By using microdissection TESE in men with NOA, a sufficient number of spermatozoa can be retrieved with a minimal amount of testicular tissue being excised. In addition, optical magnification allows for the minimal disturbance of the testicular blood supply.[42] Microdissection TESE is a more efficient technique for sperm retrieval in men with NOA than conventional TESE, and results in less postoperative intratesticular scarring.[43]

The likelihood of sperm retrieval in patients with nonobstructive azoospermia can be estimated on the basis of the most advanced pattern of spermatogenesis (not the most predominant pattern) seen on histopathology, if a previous testis biopsy has been performed.[44] In men with at least one area of hypospermatogenesis, microdissection TESE resulted in successful sperm retrieval in 81% of patients. In men where the most advanced form of spermatogenesis was maturation arrest, the retrieval rate was 44%. Even those who exhibited a Sertoli-cell-only pattern had sperm retrieved in 41% of cases.[43]

In an extension of the 1999 study by Palermo *et al.*,[45] the team at Cornell University made 684 attempts at sperm retrieval, using microdissection TESE for men with NOA, with encouraging results. Sperm were retrieved from 59% of the men. The fertilization rate from subsequent ICSI procedures using the extracted sperm was 59% per injected oocyte, and clinical pregnancy, as defined by detection of a fetal heartbeat, was achieved in 48% of the cycles in which sperm were retrieved (PN Schlegel, unpublished data).

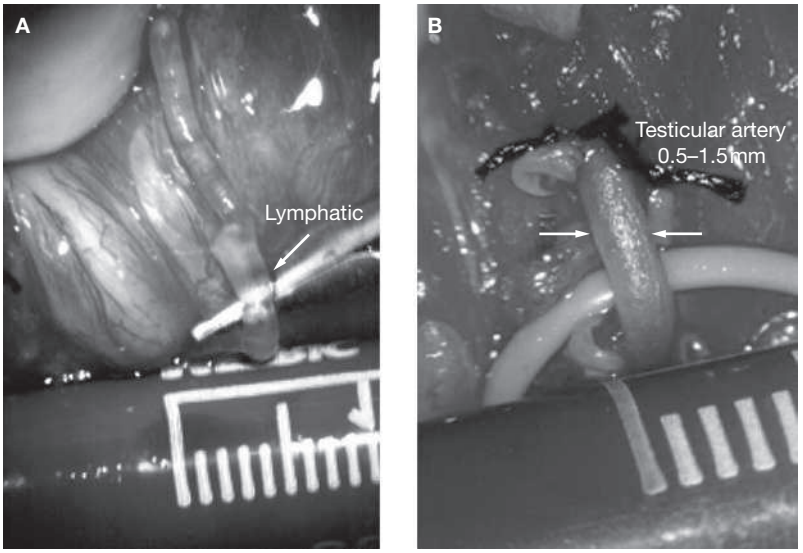

Figure 5 Microsurgical varicocelectomy (×25). (**A**) Lymphatic vessel. (**B**) Testicular artery. Reproduced with permission from reference 23 © (2002) Elsevier Inc.

Varicocelectomy

Varicocelectomy is the most common procedure for male infertility. Varicoceles are found in approximately 10–15% of unmarried, male military recruits,[46] in 35% of infertile men who have never fathered a child, and in 81% of men who were once fertile, as proven by previous conception, but who are now infertile (secondary infertility).[47] Repair of varicocele for treatment of male infertility is controversial;[48] however, any studies that have not shown an improved pregnancy rate after varicocele repair were small, were not stratified by grade of varicocele, and did not control for type of repair technique.[49]

Table 3 Techniques of varicocelectomy and potential complications.

Technique	Artery preserved	Incidence of hydrocele (%)	Failure rate (%)	Potential for serious morbidity
Microscopic inguinal	Yes	<1	<1	No
Conventional inguinal	No	3–30	5–15	No
Retroperitoneal	No	7	15–25	No
Laparoscopic	Yes	12	5–15	Yes

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It is possible that varicocelectomy can halt further damage to testicular function and improve spermatogenesis, as well as enhancing Leydig-cell function (as reflected by an increase in postoperative serum testosterone levels in infertile men).[50] Urologists might, therefore, have a valuable role in preventing future infertility and androgen deficiency[51,52] in aging men, and this underscores the importance of using a varicocelectomy technique that minimizes the risk of complications and varicocele recurrence.

Preferred approaches: microsurgical inguinal and subinguinal operations

The advantages of microsurgical techniques over other approaches to varicocele repair (e.g. open surgical, laparoscopic, and percutaneous techniques) are the reliable identification and preservation of the testicular artery or arteries, cremasteric artery or arteries, and lymphatic channels, as well as the reliable identification of all internal spermatic veins and gubernacular veins. Delivery of the testis through the subinguinal incision allows inspection of the gubernacular veins, assuring direct visual access to all possible routes of venous return, including external spermatic, cremasteric, and gubernacular veins.[53] Postoperatively, venous return is via the deferential (vasal) veins, which drain into the internal pudendal veins and usually have competent valves.

The application of microsurgical techniques[53,54] to varicocelectomy has resulted in a substantial reduction in the incidence of hydrocele formation. This is because the lymphatic vessels can be more easily identified and preserved (Figure 5A). Furthermore, the use of magnification enhances the surgeon's ability to identify and preserve the 0.5–1.5 mm testicular artery[55] (Figure 5B), thus avoiding the complications of atrophy or azoospermia.

Varicocelectomy outcomes

The goals of varicocele repair are to relieve pain in symptomatic cases and to improve semen parameters, testicular function, and pregnancy rates in couples with male-factor infertility associated with varicocele. Studies have shown that varicocele repair can improve all three of these in infertile men,[46,56] with a significant improvement in semen analysis seen in 60–80% of men.[57] Varicocele repair in young men might be able to prevent infertility and androgen deficiency later in life.[50]

The clinical outcomes of varicocelectomy are also related to the size of the varicocele. Repair of large varicoceles results in a significantly greater improvement in semen quality than repair of small varicoceles.[58,59] In addition, large varicoceles are associated with greater preoperative impairment in semen quality than small varicoceles; consequently, overall pregnancy rates are similar regardless of varicocele size. In the presence of small (grade I) varicoceles along with larger (grade II and III), contralateral varicoceles, greater improvement in semen parameters can be expected if repair is performed bilaterally, rather than only the larger side being repaired.[60] Some evidence suggests that the younger the patient is at the time of varicocele repair, the greater the improvement after repair and the more likely the testis is to recover from varicocele-induced injury.[61–63] Testicular artery ligation and post-varicocelectomy hydrocele formation may be associated with poor postoperative results.

In a controlled trial of varicocele repair in infertile men that compared surgery with no surgery, the surgery group had a pregnancy rate of 44% at 1 year, compared with 10% in the no-surgery group. Using the microsurgical technique in 1,500 men who underwent varicocelectomy, the pregnancy rate in couples was

43% after 1 year and 69% after 2 years, compared to 16% in couples with men who declined surgery and instead had hormone treatment or used ART. There have been only 14 recurrences (1%), no reports of hydrocele or testicular atrophy,[53] and only a 1% incidence of inadvertent unilateral testicular artery ligation.[64]

The most common complications of varicocelectomy are hydrocele formation, varicocele recurrence, and testicular artery injury (Table 3). Use of the operating microscope allows for reliable identification of spermatic cord lymphatics, internal spermatic veins and venous collaterals, and the testicular artery or arteries; the incidence of such complications can, therefore, be significantly reduced. Delivery of the testis through a small subinguinal incision provides direct visual access to all possible avenues of testicular drainage to ensure complete ligation. Failure to deliver the testis might result in varicocele recurrence in 7% of patients because of scrotal collaterals.[65] Additional benefits of delivery of the testis include the identification of otherwise-undetected small testicular tumors and previously undiagnosed epididymal or vasal obstructions (M Goldstein, unpublished data).

Advocates of nonmicrosurgical techniques contend that the deferential (vasal) artery and, if preserved, the cremasteric artery, will ensure blood supply to the testes that is adequate to prevent atrophy.[66,67] Anatomic studies, however, have shown that the diameter of the testicular artery is greater than the diameter of the deferential artery and cremasteric artery combined.[55] The testicular artery is the main blood supply to the testes. At the very least, it is inarguable that ligation of the testicular artery is unlikely to enhance testicular function. Microsurgical varicocelectomy is a safe and effective approach to varicocele repair, and preserves testicular function, improves semen quality and pregnancy rates in a significant number of couples. Ultimately, the ideal intervention for varicoceles can only be determined by a large, prospective, randomized and controlled study using a microsurgical, artery and lymphatic-sparing technique.

CONCLUSION

Very few medical fields have changed as dramatically over the past decade as reproductive medicine, particularly in terms of the diagnostic and treatment strategies for male infertility. These advances include ICSI, refined microsurgical reconstructive techniques (vasovasostomy and vasoepididymostomy), microsurgical techniques for surgical sperm retrieval from the epididymis and testis, and microsurgical varicocele repair. These techniques remain the safest and most cost-effective ways of treating infertile men, and, perhaps more importantly for the couples involved, many of these techniques enable couples to conceive naturally.

KEY POINTS

- Successful vasovasostomy is predicated on the basic surgical principles of a tension-free, watertight anastomosis with mucosa-to-mucosa apposition.
- Performing vasovasostomy or vasoepididymostomy is more cost-effective for achieving pregnancy than assisted reproductive technologies that use sperm aspiration
- Vasoepididymostomy is the most technically difficult of all microsurgical procedures, and should only be performed by experienced microsurgeons
- Varicocele is a risk factor for impaired spermatogenesis and Leydig-cell function, and varicocele repair can improve testicular function
- Ligation of the testicular artery during varicocele repair is not likely to improve testicular function
- Preservation of lymphatic drainage during varicocele repair decreases the risk of postoperative hydrocele

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INHERITANCE OF VARICOCELES

JAY D. RAMAN, KONSTANTIN WALMSLEY, AND MARC GOLDSTEIN

ABSTRACT

Objectives. To evaluate the inheritance of varicoceles through examination of first-degree relatives of patients with known varicoceles.

Methods. A total of 44 patients with a known varicocele had available first-degree relatives (n = 62) examined for the presence of a varicocele between October 1997 and November 2003. An additional cohort of 263 men presenting for vasectomy reversal without a history of subfertility or varicocele was used as the control group. Varicocele grade and the presence of bilateral varicoceles were examined as predictive factors for inheritance.

Results. Of the 62 first-degree relatives of patients with a known varicocele, 35 (56.5%) had a clinically palpable varicocele on physical examination. This was significantly greater than the 18 (6.8%) of 263 men in the control group ($P < 0.0001$). Of the first-degree relatives, 20 (74%) of 27 brothers, 13 (41%) of 32 fathers, and 2 (67%) of 3 sons had palpable varicoceles. Neither varicocele grade nor bilaterality was predictive of inheritance in these first-degree relatives.

Conclusions. The increase in varicocele prevalence is significant in the first-degree relatives (particularly brothers) of patients with known varicoceles. Given the detrimental effect of varicoceles on spermatogenesis and steroidogenesis, patients should be counseled about this increased risk in male family members. UROLOGY **65:** 1186–1189, 2005. © 2005 Elsevier Inc.

Varicoceles are detected in approximately 15% of the general male population, with the prevalence increasing to 35% of men presenting with primary infertility, and up to 80% of men with secondary infertility.[1,2] The etiology of varicoceles is likely multifactorial. Potential causes include the length of the gonadal vessels, the absence of valves within the gonadal veins, renal vein to inferior vena cava pressure gradients, and the angle of insertion of the left gonadal vein into the left renal vein.[3,4]

Animal and human studies have confirmed that varicoceles are associated with a progressive, duration-dependent decline in testicular function.[1,2,5,6] The most likely mechanism is an elevation of testicular temperature due to an impaired countercurrent heat exchange mechanism.[7,8] MacLeod[9] first described the triad of oligospermia, impaired motility, and an increased percentage of immature forms to be characteristic of semen analyses in men with a varicocele. Johnson *et al.*[10] further showed that 70% of healthy, asymptomatic military recruits with a palpable varicocele had an abnormal semen analysis. Varicocele repair halts further testicular damage, and in most men, results in an improvement in spermatogenesis, as well as enhanced Leydig cell function.[11–13]

Despite the relatively high prevalence of varicoceles in the general population, as well as its association with impaired spermatogenesis and steroidogenesis, a paucity of information is available regarding the potential inheritance patterns of this condition. In the present study, we identified and examined the first-degree relatives of men with known varicoceles to determine the potential for inheritance better. Varicocele grade and the presence of bilateral varicoceles were further examined as possible predictive factors for inheritance within first-degree relatives.

MATERIAL AND METHODS

Patient Selection

We retrospectively reviewed the charts of men presenting to a tertiary care university center between October 1997 and

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TABLE I. ***Varicocele characteristics in primary patients, first-degree relatives, and control population***

Cohort	Patients (n)	Varix (%)	Unilateral (L/R)	Bilateral	Grade I	Grade II	Grade III	Mean Grade
Primary	44	44/44 (100%)	16 (16/0)	28	16	18	38	2.3
First-degree relative	62	35/62 (56.5%)*	20 (19/1)	15	16	17	17	2.0
Control	263	18/263 (6.8%)	13 (12/1)	5	0	10	13	2.6

Key: L/R = left/right.
** P <0.0001 compared with control population.*

November 2003 and identified those patients diagnosed with a palpable varicocele during an evaluation of subfertility. Of the these men, 44 agreed to have their available first-degree relatives contacted for screening of varicoceles. Of the 106 first-degree relatives contacted, 62 (58.5%) elected to participate in this study. All first-degree relatives included in this study were asymptomatic and had neither a history of infertility nor a prior diagnosis of a varicocele. All participants provided informed consent per the Helsinki guidelines. The institutional review board of the New York Presbyterian Hospital–Weill Medical College of Cornell University approved this study.

A cohort of 263 consecutive men who presented to this same tertiary care university center between 1984 and 1998 for vasectomy reversal without a history of subfertility or a varicocele were used as a control population. All patients in the control group had undergone an identical rigorous physical examination by the same urologist as the study population.

Physical Examination

Physical examination of the scrotum and its contents was performed in all cases by a single urologist. The patients were examined in a warm room in the supine and standing positions, both with and without the Valsalva maneuver. Testicular volume, consistency, and the presence of varicoceles were assessed in each patient. The severity of the varicoceles was classified by a standard grading system. Grade I varicoceles were small and palpated only with the Valsalva maneuver, grade II were medium and palpable only in the standing position, and grade III were large and easily visualized through the scrotal skin without the Valsalva maneuver.

Statistical Analysis

Excel 2000 software (Microsoft, Redmond, Wash) and Statistical Analysis System, version 9.1, for Windows (SAS Institute, Cary, NC) were used to perform all statistical calculations, with $P < 0.05$ considered statistically significant. The chi-square test was used to compare the prevalence of varicoceles in our first-degree relative population and our control population. Multivariate logistic regression analysis was used to evaluate whether varicocele grade or the presence of bilaterality was predictive of inheritance. Finally, 95% confidence intervals were calculated to assess the precision of the obtained estimates.

RESULTS

The characteristics of the study participants are presented in Table I.

Primary Patients

The mean age of the 44 primary patients with a known palpable varicocele was 29.1 ± 11.6 years (range 14 to 77). Of the 44 men, 16 had a unilateral varicocele (all left), and 28 had bilateral palpable varicoceles. More than 50% of the palpable varicoceles were grade III, with left-sided varicoceles averaging a grade of 2.8 and right averaging a grade of 1.5.

First-Degree Relatives

The mean age for the 62 first-degree relatives was 42.7 ± 16.2 years (range 15 to 77). Of these 62 men, 35 (56.5%) had a palpable varicocele on physical examination. Among the first-degree relatives, 20 (74%) of 27 brothers, 13 (40.6%) of 32 fathers, and 2 (67%) of 3 sons had palpable varicoceles. Nineteen men had a unilateral left varicocele, 1 a unilateral right varicocele, and 15 bilaterally palpable varicoceles. One third of the palpable varicoceles were grade III, with left-sided varicoceles averaging a grade of 2.3 and the right averaging 1.4.

Control Patients

The mean age of the 263 men used as a control population for the prevalence of varicoceles was 50.3 ± 7.1 years (range 34 to 76). Of these 263 men who presented without a known history of varicoceles, 18 (6.8%) had a palpable varicocele on physical examination. Of the 18 patients, 12 had a unilateral left varicocele, 1 a unilateral right varicocele, and 5 bilaterally palpable varicoceles. No grade I varicoceles were identified in this group of patients; the distribution of grade II and III varicoceles (mean grade 2.6) was relatively equal.

Prevalence of Varicoceles

Compared with our control population (6.8%), the prevalence of palpable varicoceles in the first-degree relatives (56.5%) of patients with known varicoceles was eightfold greater ($P < 0.0001$).

Predictive Factors for Inheritance

Unilateral Versus Bilateral. Of 25 first-degree relatives of primary patients with a unilateral varicocele, 14 (56.0%) also had a varicocele, and 21 (56.8%) of 37 first-degree relatives of primary patients with bilateral varicoceles had palpable varicoceles ($P = 0.95$, chi-square test). After adjust-

ment for the varicocele grade status and age of the primary patient in a logistic regression model, this difference remained nonsignificant (odds ratio 1.1; 95% confidence interval 0.4 to 3.5; $P = 0.85$).

Varicocele Grade. In the consideration of varicocele grade, the greatest observed varicocele grade in the primary patients was used. Seven (63.6%) of 11 first-degree relatives of primary patients with a grade II varicocele had a palpable varicocele compared with 28 (54.9%) of 51 first-degree relatives of primary patients with a grade III varicocele ($P = 0.60$, chi-square test). After adjustment for bilateral status and age of the primary patient in the logistic regression model, this difference remained nonsignificant (odds ratio 0.8; 95% confidence interval 0.2 to 3.6; $P = 0.77$).

COMMENT

Varicoceles have been described in the medical literature since the first century. Most of the studies of varicoceles have focused on its pathophysiology, as well as on the methods and results of repair.[11–15] The heredity of varicoceles and the potential transmission to first-degree relatives has rarely been addressed.

To our knowledge, this study is the largest to date to evaluate the inheritance of varicoceles. We found that more than 50% of first-degree relatives of patients with a varicocele also had a palpable varicocele. This was eightfold greater than in our control population of patients, who had a 6.8% incidence, as well as substantially greater than the reported incidence of 10% to 15% in multiple other large series.[1,2,16] In general, the varicoceles were smaller in the first-degree relatives than in our primary patient population (mean 2.0 versus 2.3, respectively). In addition, fewer grade III varicoceles were noted in the first-degree relatives than in the primary patients (34% versus 53%, respectively). Neither of these two observations achieved statistical significance. We also found that neither the varicocele grade nor the presence of bilateral varicoceles in our primary patient population was predictive of inheritance in the first-degree relatives.

Because the numbers of the subgrouped relatives (father, brothers, sons) examined was relatively small, it was difficult to generalize trends of inheritance within each group. Of particular note, however, was the observation that more than 70% of brothers of men with varicoceles also had an asymptomatic, palpable varicocele.

The present study had a few limitations. First, we acknowledge that the 60% response rate of first-degree relatives, and the absence of grade I varicoceles in the control population contributed some component of a selection and screening bias to the study. A prospective, blinded study would limit some of these confounding variables and is being planned for the future. Second, we understand that our control group may have had a lower prevalence of varicoceles than the general population, because these men all had prior proven fertility. A comparison with the greatest reported incidence of 15% in other series, however, still revealed an almost fourfold increase within the first-degree relatives.

Currently, no recommendations are available regarding the counseling of brothers, sons, or fathers of men with a palpable varicocele. To date, no evidence has suggested that more aggressive counseling of these men is warranted. On the basis of our data, we recommend that patients with varicoceles be counseled regarding the increased risk of a similar lesion in their male relatives. This is particularly true of brothers, who appear to have the greatest probability of also having a varicocele. Men with undiagnosed varicoceles are at risk of impaired spermatogenesis and steroidogenesis, which may contribute to future infertility and premature androgen deficiency.

CONCLUSIONS

On the basis of the known estimates of the incidence of varicoceles in the general population, as well as the comparison with our control group, a significant increase in varicocele prevalence is present in the first-degree relatives (particularly brothers) of men with known varicoceles. Neither varicocele size nor bilaterality appeared to increase the risk of inheritance. Given the detrimental effect of varicoceles on spermatogenesis and steroidogenesis, patients should be counseled about this increased risk in male family members.

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THE EFFECT OF VARICOCELECTOMY ON SERUM TESTOSTERONE LEVELS IN INFERTILE MEN WITH VARICOCELES

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ABSTRACT

Purpose: We evaluated the effect of varicocelectomy on serum testosterone.

Materials and Methods: We retrospectively reviewed the effect of varicocelectomy on serum testosterone levels in 53 infertile men with varicoceles.

Results: Mean serum testosterone increased from a preoperative level of 319 ± 12 to 409 ± 23 ng./dl. postoperatively ($p < 0.0004$). Men with at least 1 firm testis preoperatively had a greater increase in serum testosterone ($p < 0.005$). An inverse correlation was noted between preoperative testosterone levels and change in testosterone after varicocelectomy ($r = -0.34$, $p < 0.013$).

Conclusions: Varicocelectomy can increase serum testosterone for infertile men with varicoceles. Although improvement in serum testosterone does not necessarily cause a direct improvement in semen quality, varicocelectomy may improve hormonal and spermatogenic function.

KEY WORDS: varicocele, testosterone, infertility, testis

In the last 2 decades there has been growing evidence that the pathophysiology of varicoceles may partially involve dysfunction of the hypothalamic-pituitary-gonadal axis. The literature strongly supports the hypothesis that hormonal dysfunction occurs at the level of the Leydig cell. Weiss et al demonstrated the suppression of in vitro testosterone synthesis by the testicular tissue of men with varicoceles and severe oligospermia compared to normal men.[1] This apparent disruption of androgen biosynthesis was later supported by Ando et al, who demonstrated an increase in the 17-hydroxyprogesterone-to-testosterone ratio after intramuscular human chorionic gonadotropin stimulation, suggesting enzymatic impairment of the final steps of testosterone biosynthesis in men with varicoceles.[2] Sirvent et al used histological and immunohistochemical techniques to study testicular biopsies from men with varicoceles and noted a decreased number of Leydig cells staining positive with the testosterone peroxidase-antiperoxidase method.[3] Taken together these studies suggest that varicoceles cause a disturbance of Leydig cell function with decreased testosterone biosynthesis. Despite the apparent lower production of testosterone by Leydig cells in men with varicoceles several studies have demonstrated no significant difference in peripheral blood levels of testosterone compared to levels in men without varicoceles.[1,4,5] It is possible that the decreased testosterone synthesis per Leydig cell is compensated for by an increase in Leydig cell number. This hypothesis is supported by Sirvent et al, who documented Leydig cell hyperplasia in men with varicoceles.[3]

Although the detrimental effect of varicoceles on Leydig cell function appears well established, the reversibility of the hormonal dysfunction with varicocelectomy remains controversial. Hudson et al have demonstrated at 6 to 12 months after retroperitoneal varicocelectomy that in 14 men with varicoceles and oligospermia there was a trend toward increased serum testosterone, which was not significantly different from the preoperative levels.[6] Segenriech et al also noted an insignificant rise in serum testosterone in 24 varicocele patients who underwent high ligation of the internal spermatic vein.[7] On the other hand, Comhaire and Vermeulen evaluated 10 patients with varicoceles and sexual inadequacy (mean testosterone 346.2 ng./dl.) who had low preoperative testosterone levels and noted that plasma testosterone concentration returned to normal after surgery.[8] It is important to remember that serum testosterone levels are highly variable for an individual. Given the inability of limited studies to detect smaller but clinically important changes in serum testosterone larger studies may be needed to provide the statistical power necessary to demonstrate the increase in serum testosterone after varicocelectomy. To clarify the effect of varicocelectomy on serum testosterone levels we retrospectively studied 53 infertile men with varicoceles who underwent microsurgical inguinal varicocelectomy.

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MATERIALS AND METHODS

Patients. We retrospectively reviewed the records of 53 patients who underwent varicocelectomy with documented preoperative and postoperative serum testosterone levels. These patients presented to 1 of 2 male infertility specialists at our institution. Duration of infertility ranged from 0 to 156 months (mean 21). Patient age ranged from 22 to 57 years (mean 35). Preoperative evaluation included a complete history, physical examination, at least 2 semen analyses and measurement of serum hormone levels. A total of 52 patients presented because of presumed male factor infertility and 1 had testicular pain ipsilateral to a varicocele. Varicoceles were graded as I to III and recorded as unilateral or bilateral based on physical examination.[9] The consistency of the testes was firm or soft. Varicocelectomy was performed only on palpable varicoceles using a microsurgical inguinal or subinguinal technique.[10] Semen analyses were obtained at 3-month intervals postoperatively. Those who had undergone previous surgical interventions (for example orchiopexy) or were concurrently receiving medical treatment (for example clomiphene citrate) were excluded from the study.

Semen analysis. Semen specimens were obtained by masturbation after a minimum of 3 days of abstinence. The samples were examined within 1 hour of collection and semen parameters, including sperm concentration, semen volume, percent motility of sperm and sperm morphology, were assessed according to criteria defined by the World Health Organization.[11] Preoperative and postoperative semen analysis parameters were separately averaged and used as the mean values for concentration, motility and morphology of all semen analyses (preoperatively and postoperatively) for each patient. Only semen analyses obtained 6 months or longer after varicocelectomy were considered evaluable.

Measurement of plasma hormone levels. Total circulating testosterone levels were measured using a commercial ^{125}iodine testosterone technique. Intra-assay and interassay coefficients of variation were 9.57% and 6.97%, respectively. Serum follicle-stimulating hormone and luteinizing hormone concentrations were determined using commercial radioimmunoassay kits. Preoperative and postoperative serum hormone levels were separately averaged and used as the mean values of testosterone, follicle-stimulating hormone and luteinizing hormone for each patient. Postoperative testosterone levels were measured at least 1 month after varicocelectomy. Preoperative and postoperative testosterone determinations were performed between 8 and 10 a.m. The normal range for each hormonal determination at our laboratory is 300 to 1,100 ng./dl. testosterone, 1.6 to 17.2 IU/l. follicle-stimulating hormone and 4.9 to 25.1 IU/l. luteinizing hormone.

Statistical analyses. Statistical analyses were performed using the 2-sample paired and unpaired t tests. Regression analyses were calculated using the method of least squares and analysis of variance. Statistics for 2-sample comparisons were reported as the mean plus or minus standard error of mean.

RESULTS

Change in serum testosterone. Serum testosterone levels in our study population ranged from 122 to 585 ng./dl. preoperatively and 111 to 1,020 ng./dl. postoperatively. Mean serum testosterone concentration for the study population increased from a preoperative level of 319 ± 12 to 409 ± 23 ng./dl. after varicocelectomy ($p < 0.0004$, fig. 1). Preoperative and postoperative mean testosterone concentrations were within the normal range (300 to 1,100 ng./dl.).

Size of varicocele and response to varicocelectomy. When stratifying the population according to size of varicocele, a trend was noted in that patients with grade I varicoceles achieved the greatest mean increase in serum testosterone and those with grade III varicoceles had the smallest increase after varicocelectomy (analysis of variance regression analysis, $r = -0.26$, $p = 0.06$, fig. 2). There was no significant difference between mean preoperative serum testosterone levels for different preoperative varicocele sizes (grade I—311 ± 21 ng./dl., grade II—324 ± 19 ng./dl. and grade III—321 ± 26 ng./dl., analysis of variance regression analysis, $r = 0.047$, $p = 0.74$).

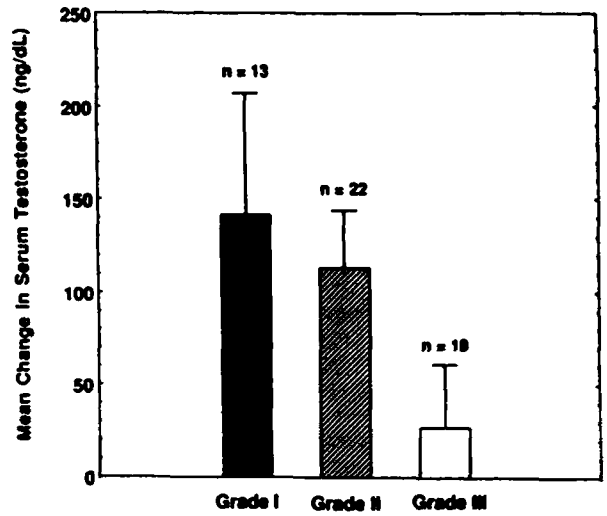

FIG. 2. Trend was noted between grade of varicocele and subsequent mean change in testosterone after varicocelectomy with $r = -0.26$ and $p = 0.06$ according to analysis of variance regression analysis.

Consistency of testis and response to varicocelectomy. The 32 patients with at least 1 firm testis preoperatively had a greater mean increase in serum testosterone postoperatively (144 ± 33 ng./dl.) than the 21 with bilaterally soft testes (10 ± 26 ng./dl.). This difference was highly significant ($p < 0.005$, fig. 3). There was no significant difference in mean preoperative testosterone levels for men with at least 1 firm testis (310 ± 16 ng./dl.) or bilaterally soft testes (332 ± 18 ng./dl., $p = 0.40$). Patients with firm testes also had significantly smaller varicoceles on average (grade 1.8 ± 0.13) than those with soft testes (grade 2.6 ± 0.11, $p < 0.0001$).

Patient age and response to varicocelectomy. There was no correlation between patient age and preoperative testosterone ($r = -0.028$, $p = 0.84$), subsequent change in serum testosterone postoperatively ($r = -0.031$, $p = 0.83$) or grade of varicocele ($r = 0.042$, $p = 0.77$). Men with bilaterally soft testes were older on average (38 ± 2 years) than those with

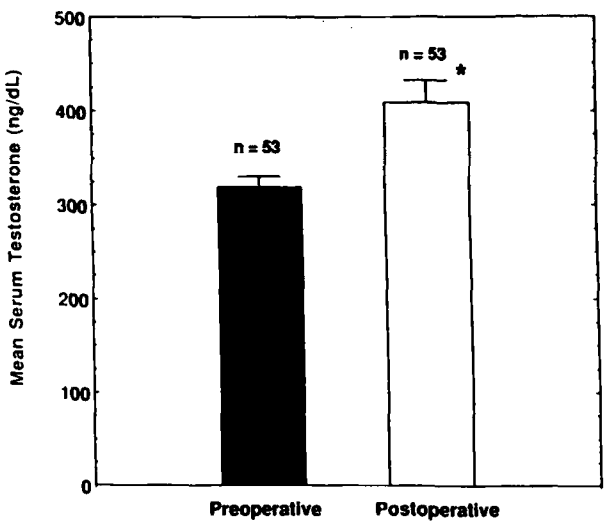

FIG. 1. Mean serum testosterone levels increased after varicocelectomy with $p < 0.0004$ (*).

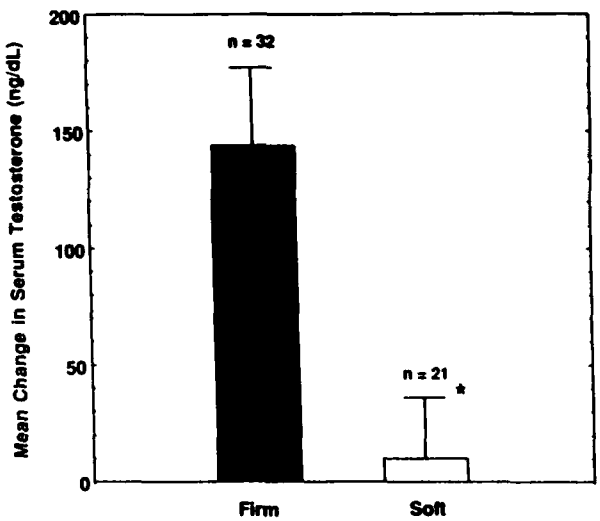

FIG. 3. Men with at least 1 firm testis had greater increase in serum testosterone after varicocelectomy compared to those with bilaterally soft testes with $p < 0.005$ (*).

at least 1 firm testis (35 ± 1 year) but the difference was not statistically significant (p = 0.15).

Preoperative testosterone and response to varicocelectomy. There was an inverse linear correlation between preoperative testosterone levels and subsequent change in testosterone after varicocelectomy (r = −0.34, p <0.013, fig. 4). Of 35 patients (66%) with testosterone levels in the normal range preoperatively testosterone increased in 20 (57%), decreased but remained within the normal range in 10 (29%) and decreased below normal in 5 (14%). Of the remaining 18 patients (34%) with subnormal testosterone levels preoperatively (less than 300 ng./dl.) testosterone increased into the normal range in 10 (56%) after varicocele correction, increased but remained subnormal in 2 (11%) and decreased in 6 (33%) after varicocelectomy.

There was no consistent preoperative historical or physical finding that distinguished the men with decreased serum testosterone after varicocelectomy from others undergoing varicocelectomy. In addition, there was no significant difference in improvement in semen parameters compared to the entire study group. Those with decreased testosterone levels were slightly more likely to have large (grade III) varicoceles. Of the patients with decreased testosterone levels 53% had grade III varicoceles versus 26% with stable or increased serum testosterone levels but this finding did not achieve statistical significance (p >0.2).

Changes in serum luteinizing hormone and follicle-stimulating hormone. No significant changes were noted in mean serum luteinizing hormone (10 ± 2 IU/l. preoperatively versus 9 ± 1 IU/l. postoperatively, p = 0.76) or follicle-stimulating hormone (20 ± 4 IU/l. preoperatively versus 19 ± 4 IU/l. postoperatively, p = 0.90) after varicocelectomy. Preoperative and postoperative mean luteinizing hormone concentrations were within the normal range, whereas mean follicle-stimulating hormone concentrations were slightly above normal before and after varicocelectomy.

Changes in semen analysis parameters. Sperm concentration and sperm motility increased postoperatively (fig. 5). Mean sperm concentration increased from 34 ± 6 to 45 ± 7 million per ml. postoperatively in 39 men (p <0.021) and mean sperm motility increased from 34 ± 2 to 39 ± 2% following the operation in 38 (p <0.018). No correlation was noted between change in testosterone and subsequent change in sperm concentration (r = −0.22, p = 0.18) or total motile sperm per ejaculate (r = −0.10, p = 0.54) although there was a negative correlation with subsequent change in sperm motility (r = −0.34, p <0.04).

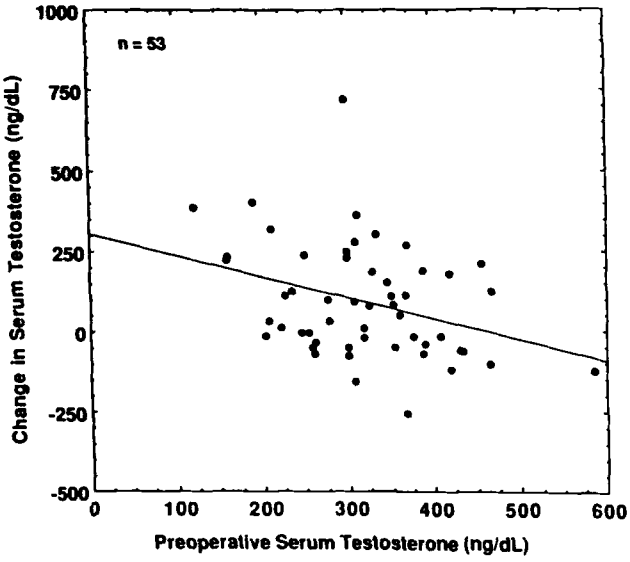

FIG. 4. Inverse correlation was noted between preoperative serum testosterone concentration and subsequent change in serum testosterone after varicocelectomy (r = −0.34, p <0.013).

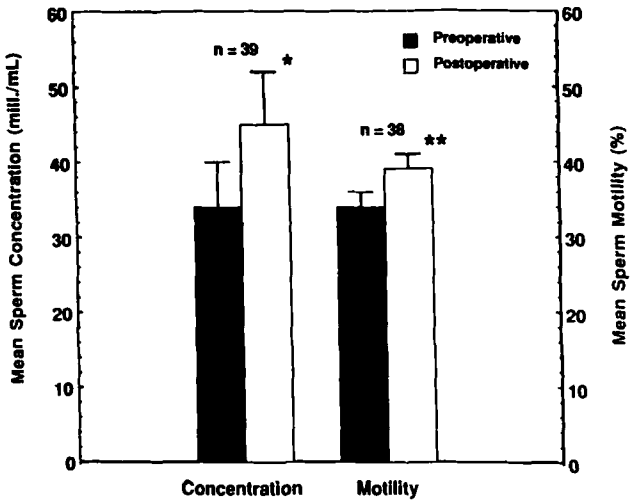

FIG. 5. Mean sperm concentration and motility increased after varicocelectomy with p <0.021 (*) and p <0.018 (**), respectively.

DISCUSSION

The exact mechanism by which a varicocele may affect hormonal function of the testis remains controversial. Studies demonstrating decreased testicular responsiveness to intramuscular injection of human chorionic gonadotropin suggest dysfunction at the Leydig cell level.[2,12] Other studies of men with varicoceles show an exaggerated gonadotropin (luteinizing hormone and follicle-stimulating hormone) response to intravenous gonadotropin-releasing hormone.[6] Blunted testosterone and exaggerated gonadotropin responses to human chorionic gonadotropin and gonadotropin-releasing hormone stimulation, respectively, that become normal after surgical correction of the varicocele support the hypothesis that the presence of a varicocele may induce testicular hormonal dysfunction that is reversed by varicocelectomy.

The effect of varicocelectomy on nonstimulated testosterone levels has not been extensively investigated. Hudson[6] and Segenriech[7] et al investigated only small populations (14 and 24 patients, respectively) with varicoceles and demonstrated no significant change in serum testosterone after varicocelectomy. Each group used a different surgical approach to varicocelectomy than in our study. Their techniques result in a higher percent of varicocele recurrence than the microsurgical approach that we use, which could contribute to the lack of significant change in serum testosterone in these 2 studies.[10] However, it is more likely that the small patient populations in these studies did not provide the statistical power necessary to demonstrate a small increase in the naturally highly variable parameter of serum testosterone after varicocelectomy. In 1975 Comhaire and Vermeulen demonstrated an improvement of plasma testosterone in a small group of men who underwent surgical repair of varicoceles.[8] However, this group was limited to 10 men of whom many had sexual inadequacy. The patients in this study were younger than 40 years with low preoperative plasma testosterone levels.

In our study of 53 patients (mean age 35 years) with preoperative testosterone levels ranging from 122 to 585 ng./dl. we demonstrated a statistically significant increase in mean serum testosterone following microsurgical inguinal varicocelectomy. This finding supports the concept that varicocelectomy can im-

prove Leydig cell function in men with varicoceles based on the measured increase in serum testosterone postoperatively. Others have shown that a varicocele is associated with impaired function of the terminal step of testosterone synthesis, that is conversion of 17-hydroxyprogesterone to testosterone by 17α-hydroxyprogesterone aldolase.[2,13] The activity of this enzyme, like other enzymes, is temperature-dependent and may be adversely affected by the high intratesticular temperature in patients with varicoceles.[14] It is possible that the physiological effect of varicocelectomy is to relieve the inhibition of the 17α-hydroxyprogesterone aldolase enzyme.

Varicocelectomy does not appear to increase serum testosterone for all patients with varicoceles. The small negative correlation between preoperative testosterone and subsequent change in testosterone in our study population suggests that the primary effect of varicocelectomy is to normalize serum testosterone levels. Therefore, the procedure appears to benefit especially patients in whom varicoceles have a more detrimental effect on hormonal function of the testis, resulting in lower serum testosterone concentrations, while having a lesser effect (for example smaller absolute change in testosterone) in those who preoperatively had normal or low normal testosterone levels.

Our findings that men with at least 1 firm testis have a more favorable hormonal response to varicocelectomy than those with bilaterally soft testes is not surprising since firm testes represent the normal healthy state. The ability of firm testes to manufacture testosterone is likely to exceed that of bilaterally soft testes, which may have end stage dysfunction. The results of our study also demonstrate that men with smaller varicoceles tend to have greater increases in serum testosterone after varicocelectomy than those with larger varicoceles. This finding is in contrast to the study by Steckel et al, which demonstrated that greater improvements in sperm concentration, motility and fertility index (motile sperm concentration) occur after the repair of larger varicoceles.[15] Furthermore, we noted no significant correlation between the magnitude of change in serum testosterone and improvements in sperm concentration or total motile sperm per ejaculate following varicocelectomy. Taken together these results suggest that, although improvements in Leydig cell function and spermatogenesis may occur simultaneously in patients postoperatively, the improvement in hormonal function may be independent of improvements in spermatogenesis. The effect of varicocelectomy on spermatogenesis may be related to changes in venous pressure, temperature or intratesticular interstitial fluid volume, not hormonal changes alone. In addition, germ cells are known to be more sensitive than Leydig cells to noxious stimuli. Therefore, it is expected that hormonal responses and changes in spermatogenesis after varicocelectomy may not occur simultaneously in all patients.

CONCLUSIONS

Our study demonstrates that varicocelectomy can increase serum testosterone, especially in patients with abnormally low serum testosterone levels. Although improvement in serum testosterone does not necessarily cause a direct improvement in semen quality, varicocelectomy may improve hormonal and spermatogenic function.

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RELATIONSHIP BETWEEN VARICOCELE SIZE AND RESPONSE TO VARICOCELECTOMY

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ABSTRACT

We studied the relationship between varicocele size and response to surgery in 86 men with a unilateral left varicocele who reported either infertility (83), pain (1) or pain and testicular atrophy (2). Varicoceles were graded according to size: grade 1—small (22 patients), grade 2—medium (44) and grade 3—large (20). Sperm count, per cent motility, per cent tapered forms and fertility index (sperm count times per cent motility) were measured preoperatively and postoperatively.

Preoperatively, men with grade 3 varicocele had lower sperm counts and poorer fertility indexes compared to men with grades 1 and 2 varicocele. Sperm concentration improved significantly in men with grade 2 (33 ± 5 million per cc preoperatively to 41 ± 6 million postoperatively, $p < 0.04$) and grade 3 (18 ± 5 million preoperatively to 32 ± 7 million postoperatively) varicocele after microsurgical ligation of the varicocele. Motility improved significantly in men with grade 3 varicocele. Decrease in per cent tapered forms was significant in all groups. A comparison of per cent change in fertility index among the groups revealed that men with grade 3 varicocele improved to a greater degree (128%) than men with grade 1 (27%) or grade 2 (21%) varicocele. Pregnancy rates 2 years postoperatively were 40% for grade 1, 46% for grade 2 and 37% for grade 3 varicocele patients. The difference in pregnancy rates among the groups was not statistically significant.

In conclusion, infertile men with a large varicocele have poorer preoperative semen quality but repair of the large varicocele in those men results in greater improvement than repair of a small or medium sized varicocele.

KEY WORDS: varicocele, infertility, semen

Varicoceles were recognized in the first century when the Greeks accurately observed that "the veins are swollen and twisted over the testicle, which becomes smaller than its fellow."[1] Varicoceles are the most frequently encountered, surgically correctable cause of male infertility.[2] The incidence in the unscreened, healthy male population is 15%. However, approximately 35% of all men evaluated for infertility have a varicocele.[3] The exact pathophysiology of varicocele is incompletely understood. Most recent studies on the mechanism of varicocele-induced infertility note an increase in testicular temperature due to impairment of the countercurrent heat exchange mechanism.[4-6]

MacLeod first described the triad of oligospermia, decreased motility, and increased percentage of immature and tapered forms characteristic of infertile men with varicocele.[7] Following varicocele ligation many investigators report an improvement in semen quality in 60 to 70% of the patients and pregnancy rates of 20 to 40%.[3] Although several studies indicate that larger varicoceles are associated with greater impairment of spermatogenesis,[6-11] others suggest that response to surgery is independent of varicocele size.[3,5,10,12] We correlated semen analyses before and after microsurgical varicocelectomy with varicocele size in an attempt to determine how varicocele size influences response to an operation.

METHODS

Patients. A total of 86 men with a unilateral left varicocele presented for surgery because of either infertility at least 1 year in duration (83), pain (1) or testicular atrophy and pain (2). Men with bilateral varicocele were excluded. Patient age ranged from 16 to 57 years (mean 34). The patients were examined while standing in a warm room. Varicocele size was classified as grade 1 (small)—distinct impulse palpated with Valsalva's maneuver, no tortuosity and less than 1 cm. in diameter; grade 2 (medium)—palpable dilation greater than 1 cm. and with tortuosity detected with Valsalva's maneuver, and grade 3 (large)—easily visualized through the scrotal skin and palpable without Valsalva's maneuver. All gradings were performed by the same examiner.

Semen analysis. Semen was obtained by masturbation after a minimum of 3 days of abstinence. An average of 2.97 semen analyses were done preoperatively. In 2 patients less than 20 years old undergoing surgery for pain and atrophy only 1 semen analysis was done preoperatively and postoperatively. In infertile men semen analyses were obtained at 3 and 6 months postoperatively, and every 6 months thereafter or until pregnancy occurred. The mean number of postoperative analyses was 2.72. Specimens were examined within 1 hour of collection and assessed for sperm concentration, per cent motility and morphology. Sperm counts were performed with a Makler chamber.† Motility was evaluated by video micrography. Morphology was assessed after preparation with the Papanicolaou stain. Mean values of all preoperative and postoperative specimens were used as the preoperative and postoperative values for each patient. Normal values for our semen analysis laboratory are sperm concentration 25 to 200 × 10^6/ml., sperm motility more than 40% and tapered forms less than 4%.

Surgical technique. All men underwent ambulatory unilateral varicocelectomy with a microsurgical inguinal technique with delivery of the testes.[13] Briefly, the testis is delivered through a 2 to 3 cm. inguinal incision, and all external spermatic and gubernacular veins are ligated. The testis is returned to the scrotum and the spermatic cord is dissected under the operating

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† Selfi-Medical Instruments, Haifa, Israel.

microscope. The testicular artery and lymphatics are identified and preserved. All internal spermatic veins are doubly ligated with metal clips or 4-zero silk sutures and divided. The vas deferens and its vessels are preserved.

Statistical analyses. Statistical analyses were performed with the paired t test (Wilcoxon signed rank test) or the 2-sample t test (Mann-Whitney test).

RESULTS

Of 86 patients studied 22 had grade 1, 44 grade 2 and 20 grade 3 varicoceles (table 1). Therefore, in this population of predominantly infertile men grade 2 varicoceles were twice as common as grade 1 or 3. Mean sperm concentrations increased significantly after repair of grades 2 and 3 varicoceles. Sperm counts increased from 33 ± 5 million per cc preoperatively to 41 ± 6 million per cc postoperatively in the grade 2 group ($p < 0.04$) and from 18 ± 5 million per cc preoperatively to 32 ± 7 million per cc postoperatively in the grade 3 group ($p < 0.02$, fig. 1). Sperm counts after repair of grade 1 varicoceles increased from 38 ± 7 to 46 ± 9 million per cc but this difference was not statistically significant. Improvements in per cent motility were significant in grade 3 varicocele patients, in whom varicocele ligation increased motility from 30 ± 4 to 41 ± 4% ($p < 0.01$, fig. 2). All groups showed a significant decrease in per cent tapered forms (fig. 3).

A fertility index (motile sperm concentration) was calculated by multiplying sperm concentration by per cent motility.[9] Fertility index increased marginally in men with grade 2 varicocele ($p < 0.10$) and significantly in men with grade 3 varicocele ($p < 0.01$, fig. 4). Preoperatively, men with a large varicocele had lower sperm concentrations compared to those with a medium sized ($p < 0.05$) and small ($p < 0.01$) varicocele. Similarly, men with a large varicocele had poorer fertility indexes compared to those with a medium sized ($p < 0.05$) and small ($p < 0.01$) varicocele.

The per cent change in fertility index, sperm concentration and per cent motility among groups of patients was compared (table 2). In men with a grade 3 varicocele the fertility index improved to a greater degree compared to those with a grade 1 ($p < 0.03$) or grade 2 ($p < 0.03$) varicocele. A 27% improvement was noted in the grade 1 group, 21% for grade 2 and 128% for grade 3 ($p < 0.03$). There was no significant per cent change in fertility index when comparing grades 1 and 2 ($p < 0.10$). Similarly, a marginally significant difference in per cent improvement in sperm concentration was detected between grades 1 (21%) and 3 (94%, $p < 0.06$). Differences in improvements in per cent motility were significant between grades 2 and 3 groups ($p < 0.03$). There was no significant difference when comparing grades 1 and 2 ($p < 0.63$). The pregnancy rates 2 years after surgery for male factor infertility in men available for followup were 40% (8 of 20) for grade 1, 46% (19 of 41) for grade 2 and 37% (7 of 19) for grade 3. The differences in pregnancy rates

TABLE 1. *Results after surgical ligation of left varicoceles*

Grade	No. Pts.	Sperm concentration (million/cc)*		% Motility*	
		Preop.	Postop.	Preop.	Postop.
1	22	38 ± 7	46 ± 9	39 ± 2	45 ± 3
2	44	33 ± 5	41 ± 6	39 ± 3	40 ± 3
3	20	18 ± 5	32 ± 7	30 ± 4	41 ± 4

* Values are given as mean plus or minus standard error.

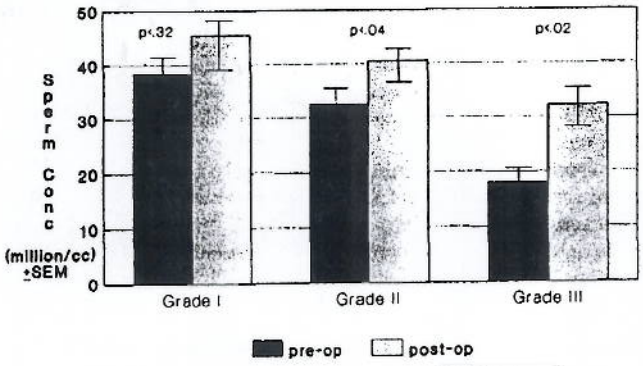

FIG. 1. Left varicocele: sperm concentration

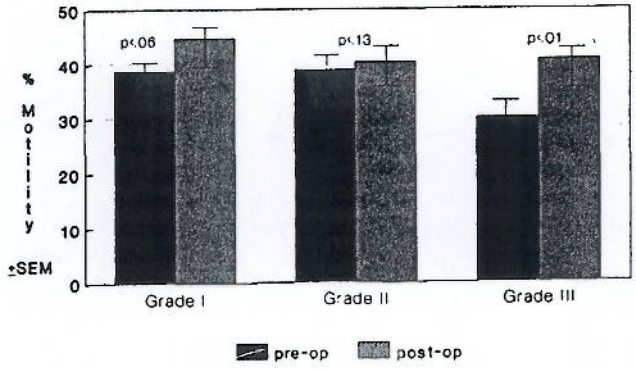

FIG. 2. Left varicocele: % motility

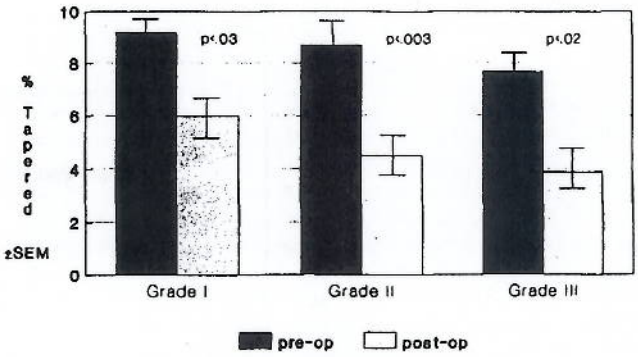

FIG. 3. Left varicocele: % tapered forms

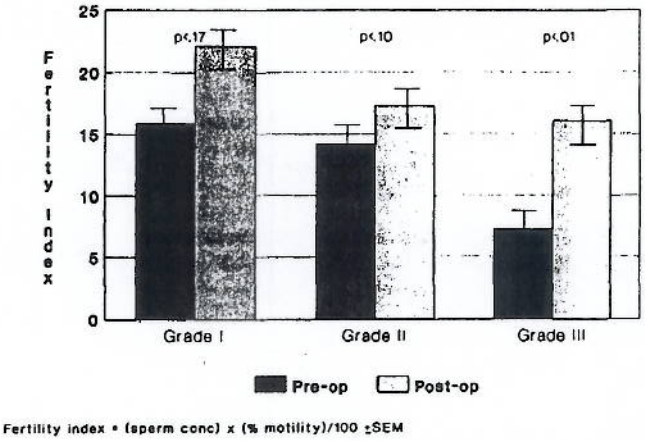

FIG. 4. Left varicocele: fertility index

TABLE 2. *Postoperative changes*

Grade	Fertility Index (%)	Sperm Concentration (%)	Motility (%)
1	27	21	15
2	21	24	3
3	128	94	37

among the groups were not statistically significant. The overall pregnancy rate was 42.5% (34 of 80 patients).

DISCUSSION

It has been shown previously that spermatogenesis and fertility in infertile men with a varicocele improve after varicocele ligation.[8,13-16] In our study varicoceles were graded by size and response to surgery was compared. Postoperative sperm concentration, per cent motility, per cent of tapered forms, and fertility index all improved more significantly in the group with large versus small varicoceles. Our results confirm the findings of Tinga et al,[11] and Scott and Young,[14] who also demonstrated greater improvement after repair of a large varicocele.

Our data clearly show that semen parameters are poorer preoperatively in men with a large varicocele and their response to an operation is more dramatic. Our results also confirm those of Dubin and Amelar showing no difference in pregnancy rates after repair of small versus large varicoceles.[10] A possible explanation is our finding that although men with a large varicocele begin with significantly poorer semen quality than men with a small varicocele, surgery results in a more dramatic improvement in those with a large varicocele so that postoperatively there is no significant difference in either semen parameters or pregnancy rates.

These findings clearly indicate that repair of a large varicocele results in a greater improvement in semen quality than repair of a small varicocele. This information is of value when counseling infertile couples regarding the expected outcome of varicocele surgery.

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THE PULSE
Progress comes in small packages. The percentage of adults engaging in leisure-time physical activity rose from 29.8% in 1998 to 30.2% in 1999 and 31.9% in 2000.
SOURCE: NATIONAL CENTER FOR HEALTH STATISTICS

Infertility: A Guy Thing

Sparse or sluggish sperm can make parenthood inconceivable. But there's help.

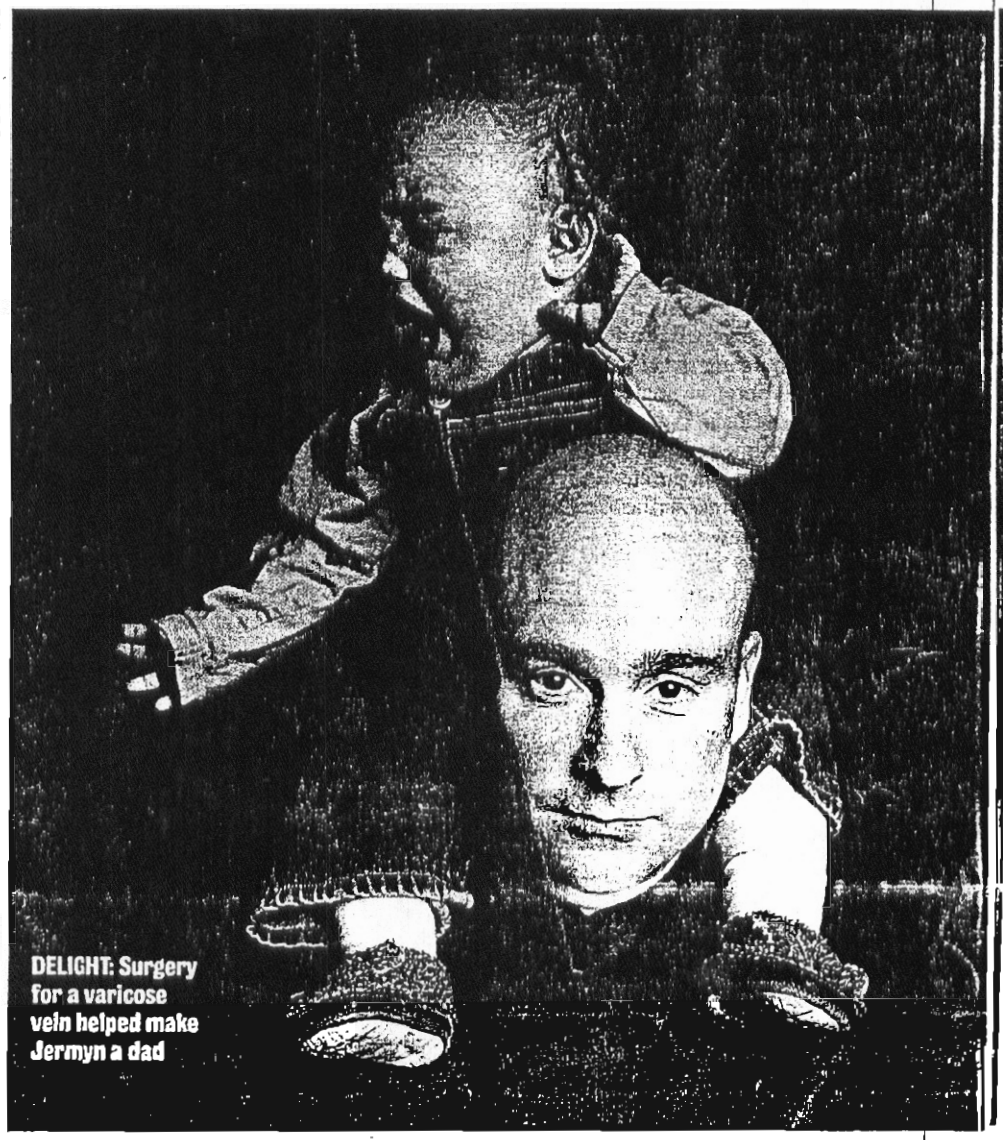
BY TEMMA EHRENFELD

PATRICK JERMYN WILL NEVER forget his first experience with a urologist. He and his wife, Jennifer, had been trying unsuccessfully for a year and a half to get pregnant. He was a 34-year-old lawyer, she a 30-year-old schoolteacher, and they were both in fine health. But after looking at two semen samples and conducting a routine exam, the urologist offered a harsh verdict. Patrick's sperm quality was so poor that he might never father a child naturally.

Women have been blamed for barren marriages from the Bible on. In truth, a fifth of all infertility stems exclusively from male factors, and an additional third involves both partners. Gynecological problems account for only 40 percent of infertility, yet doctors still tend to view it as a female condition. The good news, as Patrick Jermyn discovered, is that the most common male problems can be fixed.

The top enemies can be described in two words: heat and blockage. In order to produce healthy sperm, the testicles need to be four degrees cooler than the rest of the body. That's why they're mounted outside the torso. Sperm cells spend three months growing within the testicles, then travel through an ultrathin coiled tube (the epididymis), where they learn how to swim. Finally they move into the vas deferens—two tubes, one from each testicle—which contract to make ejaculation possible.

The most common cause of male infertility is a varicocele, a cluster of enlarged veins in the scrotum. These varicose veins may cause no symptoms (some men experience a slight ache when lifting heavy objects), but the heat they generate may wreak havoc on sperm production. Men with varicoceles can be fertile, but the condition is associated with low sperm counts, sperm that swim poorly and sperm so misshapen they can't enter an egg. Jermyn's local urologist checked him for varicoceles but didn't see any—probably because the patient was sitting on a cold examining table and experiencing the "Seinfeld" shrinkage effect. Later, at Jennifer's insistence, Patrick visited New York's Weill Cornell Medical Center. This time he got to sit on a heating pad during the exam—and the urologist, Dr. Marc Goldstein, noticed the telltale tiny, thick spot on his scrotum. Goldstein was able to repair it with a minimally invasive surgical procedure. The operation improves sperm counts, and studies suggest that it more than doubles a couple's odds of achieving pregnancy within a year—from 17 percent to 43 percent. Three months after the procedure, Patrick's sperm looked normal.



DELIGHT: Surgery for a varicose vein helped make Jermyn a dad

Besides checking for varicoceles, a good urologist also looks for swelling in the epididymis and vas deferens. Common venereal infections, such as chlamydia and gonorrhea, can leave behind scar tissue that blocks the epididymis. And urologists often discover that a man's vas deferens has been injured in a past hernia operation—with the same results as an intentional vasectomy. Roughly a fifth of all male infertility involves these mechanical blockages. Fortunately, most of them can be corrected with microsurgery, restoring typical sperm counts in men who would otherwise produce none.

For a normal, healthy male, staying fertile doesn't require surgery, but it does take some care. Any form of substance abuse, from smoking cigarettes to snorting cocaine, can hamper sperm production. If you're concerned about fertility, stick to two drinks twice a week. Even a single drinking binge can temporarily disrupt the process, resulting in sperm with deformed heads and curled tails. You should also ask your doctors if any of your prescriptions can hamper fertility. The danger zone surprisingly includes popular items like the ulcer drug Tagamet (cimetidine), the heart drug Crystodigin (digitalis), the alpha blockers and calcium blockers used to treat high blood pressure and standard antibiotics. Sperm quality usually rebounds once the drug is discontinued.

If you're getting clean, lose the Mick Jagger underwear, too. Anything that heats the testicles—steam rooms, a fever, long drives—can reduce your odds of fatherhood. (Three thousand years ago, Japanese men took daily hot baths as a form of contraception.) Finally, look into occupational hazards. "I've seen truckdrivers impregnate their wives after they switched to dispatching," says Goldstein. "And I had a pizza-parlor owner whose wife got pregnant when he stayed away from the oven."

Finally, couples who discover that the man has a fertility problem shouldn't assume they will never be parents. A year to the day after Patrick Jermyn left the hospital without his varicocele, Jennifer left another hospital with their son, Ryan Patrick. Last month Ryan had his first birthday. ■

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Marc Goldstein, MD, DSc (hon), FACS is the Matthew P. Hardy Distinguished Professor of Reproductive Medicine, and Urology at Weill Cornell Medical College of Cornell University; Surgeon-in-Chief, Male Reproductive Medicine and Surgery; and Director of the Center for Male Reproductive Medicine and Microsurgery at the New York Presbyterian Hospital Weill Cornell Medical Center. He is Senior Scientist with the Population Council's Center for Biomedical Research, located on the campus of Rockefeller University.

Dr. Goldstein is the only male infertility specialist cited in the American Health Magazine special issue on ***The Best Doctors in America.*** He is listed in New York Magazine's ***Best Doctors in New York*** (2011). He is listed in the books ***Best Doctors in America*** (2011), The Castle Connolly Guide ***America's Top Doctors*** (2011) and ***How to Find the Best Doctors***, New York Metro Area (2011), as well as ***Who's Who in America*** (2011). He is a board certified urologic surgeon and member of a dozen national and international medical societies dealing with male infertility and reproduction. He is Past-President of the Society for Male Reproduction and Urology of the American Society for Reproductive Medicine, and recipient of the 1997 ***Master Teacher in Urology Award*** and the 2002 ***Distinguished Alumni Achievement Award*** from his alma mater. He has been honored by RESOLVE and the American Infertility Association for his "***Outstanding Dedication and Commitment to Family Building"***. He received the 2002 ***John Kingsley Lattimer Award in Urology*** from the Kidney and Urology Foundation of America and is the recipient of the 2007 ***Lifetime Achievement Award*** of The American Fertility Association. He received an ***honorary Doctor of Science*** in 2008 from the State University of New York, Downstate Medical Center. In 2009, he received the ***John Coleman, M.D. Teaching Award*** from the Department of Urology at Weill Cornell Medical College.

Dr. Goldstein is internationally renowned for his pioneering work in vasectomy reversals and microsurgical repair of varicoceles and blockages. He has performed over 1,000 microsurgical vaso-vasostomies and vaso-epididymostomies. His technique of microsurgical vasectomy reversal, as published in a peer-reviewed journal, yields the highest reported sperm return and pregnancy rates. He developed a microsurgical technique of varicocelectomy in 1984 and has performed over 3000 cases with the lowest reported failure and complication rates. He was the first American surgeon to be trained in, and perform, the Chinese method of No-Scalpel Vasectomy.

Dr. Goldstein has authored or co-authored over 250 journal articles and book chapters. He is the author of ***Surgery of Male Infertility,*** the first textbook on the subject. He is co-author of **The Couple's Guide to Fertility** (Broadway/Random House 2001, 3rd edition), **The Vasectomy Book** (Houghton Mifflin), **Reproductive Medicine Secrets** (Hanley & Belfus, 2004), **A Baby at Last** (Simon & Schuster 2010), and the upcoming **Male Infertility** (Cambridge University Press). He is on the editorial board of the medical journals ***Microsurgery*** and ***Fertility and Sterility***. He has also been featured in interviews on numerous major media outlets including NBC's ***The Today Show***, ABC's ***Good Morning America***, ABC's ***Eyewitness News, Newsweek***, ***The Wall Street Journal*** and ***The New York Times.***

A ***summa cum laude*** graduate of the College of Medicine, State University of New York – Downstate Medical Center in Brooklyn, New York, Dr. Goldstein worked as a resident in general surgery at Columbia Presbyterian Hospital in New York. After three years overseas in the U.S. Air Force, attaining the rank of Major and flying in F4 Phantom aircraft as a Flight Surgeon, Dr. Goldstein was trained in urology at Downstate Medical Center. He continued his post-graduate training in reproductive physiology at the Population Council, Center for Biomedical Research, located on the campus of Rockefeller University, and at the Rockefeller University Hospital.

Dr. Goldstein is a long distance runner and triathlete who races regularly and has completed 20 New York City Marathons.

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