and liver function test were minor outcome measures. Results: Pioglitazone significantly improved major outcome measures compared with placebo. The decrease from baseline of total cholesterol level was more in pioglitazone than in placebo-treated groups. In 84% (32 out of 38) of the sildenafil poor-responders, at least one of the associated risk factors of ED was found. There was undiagnosed hypercholesterolemia in 34% of the subjects. Serum levels of T, DHEAS, glucose and other parameters remained unchanged in both groups. The intervention was well tolerated. Conclusions: Pioglitazone increased sildenafil response to improve ED of men with prior sildenafil failure and seems to be safe based on the present preliminary study. This improvement is likely regardless of fasting glucose and sex hormones levels.

**Editorial Comment:** This seems to be a worthwhile treatment opportunity—to salvage sildenafil failures with pioglitazone (Actos®). Pioglitazone is used for the treatment of diabetes mellitus type 2 (also known as noninsulin dependent diabetes mellitus or NIDDM) in monotherapy but usually in combination with sulfonylurea, metformin or insulin. Perhaps pioglitazone helps with glycemic control, which may help treat ED.

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**Male Infertility**

**A Decision Analysis of Treatments for Obstructive Azoospermia**

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Background: Treatments for post-vasectomy obstructive azoospermia include vasectomy reversal, microsurgical epididymal sperm aspiration (MESA) or percutaneous testicular sperm extraction (TESE) with IVF/ICSI. We examined the cost-effectiveness of these treatments. Methods: A decision analytic model was created to simulate treatment. Outcome probabilities were derived from peer-reviewed literature and the Society for Assisted Reproductive Technologies database. Procedural costs were derived from a sampling of high-volume IVF centers and the Medicare Resource Based Relative Value Scale. Indirect costs of complications, lost productivity and multiple gestation pregnancies were considered. Sensitivity analyses were performed. Results: Vasectomy reversal was more cost-effective than either MESA or TESE under all probability conditions. In 1999, vasectomy reversal demonstrated superior cost-effectiveness to TESE and MESA ($19,633 versus $45,637 and $48,055, respectively, equivalent to $25,321 versus $58,858 and $61,977 in 2005 dollars). In 2005, vasectomy reversal ($20,903) remained the most cost-effective treatment over TESE ($54,797) and MESA ($56,861). The cost-effectiveness of all treatments improved over projections by inflation. The relative cost-effectiveness of the therapies was unchanged over time. Conclusions: Vasectomy reversal appears more cost-effective than percutaneous TESE and MESA for treatment of obstructive azoospermia when the impact of indirect costs is considered. The absolute cost-effectiveness of all therapies improved over time. These results may be tailored with institution-specific data to allow more individualized results.

**Editorial Comment:** Men who have undergone vasectomy and their partners have a choice when it comes to having children—reverse the vasectomy, or obtain sperm from the testis or epididymis for in vitro fertilization (IVF). Aside from the obvious advantages of restoring the male anatomy and having as many children as desired the natural way, it is worth considering the cost of vasectomy reversal compared to IVF with surgically obtained sperm. Goldstein and Schlegel previously conducted a number of well performed analyses demonstrating a relative cost advantage to vasectomy reversal. In the most broad based analysis of its kind the authors include data for 1999 and 2005 from the Society for
Assisted Reproductive Technologies registry of the American Society for Reproductive Medicine, and costs from the 5 highest volume IVF facilities in the United States and for high volume andrology centers. Using a robust decision tree probability model, and considering direct and indirect costs, the authors conclude that surgical reconstruction is generally less than half the cost of IVF with surgically obtained sperm. While there may be instances where reconstruction is impossible, it seems surgical reversal is the most logical and inexpensive first-line therapy for those who have undergone vasectomy and subsequently want children.

Craig Niederberger, M.D.

Impact of Clinical Varicocele and Testis Size on Seminal Reactive Oxygen Species Levels in a Fertile Population: A Prospective Controlled Study


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Objective: To investigate: 1) the impact of clinical varicocele on reactive oxygen species (ROS) levels in neat and washed semen in a proven fertile population; and 2) the correlation between ROS levels, testicular volume, and varicocele grade in the same population of fertile men. Design: Prospective controlled clinical study. Setting: Andrology laboratory at tertiary-care hospital. Patient(s): One hundred fourteen healthy fertile men (81 normal fertile and 33 fertile with clinical varicocele) and 30 infertile patients (control subjects). Intervention(s): Standard semen analysis and measurement of sperm ROS production. Main Outcome Measure(s): Seminal parameters, seminal ROS levels, seminal leukocyte levels, clinical varicocele, and testis size. Result(s): Thirty-three of the 114 (29%) fertile men had clinical varicocele (grade 1, n = 14; grade 2, n = 11; and grade 3, n = 8), and the remaining 81 (71%) had a normal physical examination. Levels of ROS and semen quality did not differ significantly between the fertile men with or without varicocele. No significant differences in ROS levels in neat and washed semen were observed compared with fertile men with grades 2 and 3 varicocele and with fertile men with varicocele grade 1. The ROS levels in neat and washed semen were not significantly correlated with varicocele grade in fertile men. No significant correlations between ROS levels and testis volume were observed between the fertile groups. Conclusion(s): The presence of clinical varicocele in fertile men is not associated with higher seminal ROS levels or abnormal semen parameters. Levels of ROS are not correlated with varicocele grade or testis volume in the same population of fertile men.

Editorial Comment: Prior studies have indicated a relationship between varicocele and seminal ROS, suggesting a mechanism by which a varicocele renders a man infertile. An interesting question is whether ROS is correlated to varicocele in fertile men as well. Cocuzza et al measured ROS levels and sperm quality in 33 fertile men with and 81 fertile men without varicocele, and 30 infertile men with varicocele. The study included only men with clinically significant varicocele—here “grade I” refers to a palpable varicocele with Valsalva, not to a nonpalpable varicocele that can only be identified by imaging. As in previous studies, ROS levels were significantly greater and semen parameters were poorer in infertile men with varicocele compared to fertile men. However, no correlation was found in fertile men between ROS levels and the presence of a varicocele or its size. Thus, the authors suggest that ROS levels may serve as a marker indicating which men with varicocele are destined to suffer infertility.

Craig Niederberger, M.D.
Sperm Nuclear DNA Fragmentation and Mitochondrial Activity in Men With Varicocele


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Objective: To verify the impact of varicocele on semen quality and sperm function (DNA integrity and mitochondrial activity). Design: Prospective study. Setting: Patients in an academic research environment. Patient(s): Seventeen patients with a clinical diagnosed varicocele of grade II or III and 20 men without a varicocele. Main Outcome Measure(s): Rate of sperm DNA fragmentation as assessed by the Comet assay and categorized as classes I (no DNA fragmentation), II (little DNA fragmentation), III (meaningful DNA fragmentation), and IV (high DNA fragmentation). Rate of mitochondrial activity as assessed by the diaminobenzidine (DAB) assay and categorized as grades I (all mitochondria active), II (most mitochondria active), III (most mitochondria inactive), and IV (all mitochondria inactive). Result(s): No statistically significant differences were found between the study and control groups with respect to age, ejaculatory abstinence, and round cell count. Men with varicocele had significantly higher ejaculate volume, concentration of immotile sperm, and neutrophil count and lower mean percentage of sperm concentration, progressive motility, and morphology than men in the control group. The study group presented a lower percentage of sperm with little DNA fragmentation (class II) and a higher percentage of sperm with DNA fragmentation (class IV). In addition, the study group presented a greater percentage of sperm with inactive mitochondria (class III). Conclusion(s): Compared with men without varicocele, men with varicocele had a higher percentage of cells with DNA fragmentation and sperm with inactive mitochondria. Indeed, varicocele causes a decrease in motility, concentration, and morphology and an increase in volume and concentration of immotile sperm and neutrophils. The sperm functional evaluation (DNA fragmentation and mitochondrial activity) could be important factors in deciding treatment options for men with varicocele.

Editorial Comment: The compendium of the literature supports that palpable or visible varicocele causes male infertility but the mechanism for the ill effect remains unclear. Blumer et al assessed sperm DNA integrity using the well established molecular biological comet assay and mitochondrial activity with the DAB assay in 20 men without and 17 men with clinically evident varicoceles. In men with varicoceles the investigators observed a significantly lower percentage of sperm with intact DNA, a higher percentage of DNA fragmentation and a higher percentage of sperm with inactive mitochondria. Thus, this study presents evidence of 2 possible mechanisms by which varicocele impairs fertility—sperm mitochondrial dysfunction and DNA damage.

Craig Niederberger, M.D.

Significant Decrease in Sperm Deoxyribonucleic Acid Fragmentation After Varicocelectomy

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Objective: To measure sperm DNA integrity values before and after varicocelectomy in patients with elevated preoperative levels of sperm DNA fragmentation. Design: Retrospective. Setting: Private urology clinic. Patient(s): Eleven patients with grade 1, 2, or 3 varicocele. Intervention(s): Varicocelectomy. Main Outcome Measure(s): Sperm DNA fragmentation values were assessed before and after varicocelectomy. Results(s): Ninety percent of the patients showed a significant decrease in
sperm DNA fragmentation levels. Conclusions(s): Although this study was small, 10 of the 11 patients with varicocele showed a significant decrease in sperm DNA fragmentation after varicocele repair. Elevated sperm DNA fragmentation has been shown to have a significant negative effect on pregnancy outcome with use of in vivo, IUI, routine IVF, and to a lesser extent intracytoplasmic sperm injection fertilization; therefore pregnancy outcome may improve after varicocelectomy.

**Editorial Comment:** Although the clinical significance is unclear regarding the degree of sperm DNA denaturation in acidic conditions as measured by the sperm chromatin structure assay (SCSA), the assay presents one way of assessing sperm nuclear integrity. Werthman et al studied SCSA results before and after varicocelectomy in 11 infertile men with an abnormal semen analysis and DNA fragmentation index greater than 27%. SCSA levels decreased in 90% of men 3 to 6 months after varicocelectomy with an average change of 24% in the DNA fragmentation index. Although the number of subjects was small and the effect of regression to the mean cannot be excluded as a reason for the decline in SCSA levels in an uncontrolled study, these observations suggest a possible avenue for investigation into a mechanism by which varicocele impairs male fertility.

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**Prevalence of Psychiatric Disorders in Infertile Women and Men Undergoing In Vitro Fertilization Treatment**

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**Background:** This study was undertaken to determine the prevalence of psychiatric disorders in infertile women and men undergoing in vitro fertilization (IVF) treatment. Methods: Participants were 1090 consecutive women and men, 545 couples, attending a fertility clinic in Sweden during a two-year period. The Primary Care Evaluation of Mental Disorders (PRIME-MD), based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edn (DSM-IV), was used as the diagnostic tool for evaluating mood and anxiety disorders. Results: Overall, 862 (79.1%) subjects filled in the PRIME-MD patient questionnaire. Any psychiatric diagnosis was present in 30.8% of females and in 10.2% of males in the study sample. Any mood disorder was present in 26.2% of females and 9.2% of males. Major depression was the most common mood disorder, prevalent in 10.9% of females and 5.1% of males. Any anxiety disorder was encountered in 14.8% of females and 4.9% males. Only 21% of the subjects with a psychiatric disorder according to DSM-IV received some form of treatment. Conclusions: Mood disorders are common in both women and men undergoing IVF treatment. The majority of subjects with a psychiatric disorder were undiagnosed and untreated.

**Editorial Comment:** Identification of psychiatric disorders in prospective mothers and fathers undergoing IVF is important not only for the health of the parent, but also for the milieu of the offspring. Using the Primary Care Evaluation of Mental Disorders psychometric, Volgsten et al assessed the prevalence of psychiatric disorders in a large group of Swedish men and women undergoing IVF. Approximately 1 in 10 men suffered from any psychiatric disorder, and 1 in 11 from a mood disorder. While this study bears repeating in other populations such as the United States, urologists are well advised to consider teaming with mental health care professionals when treating the infertile male.

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Craig Niederberger, M.D.