Varicocele Repair in Patients With Nonobstructive Azoospermia: A Meta-Analysis

John W. Weedin,*,† Mohit Khera‡ and Larry I. Lipshultz§

From the Scott Department of Urology, Baylor College of Medicine, Houston, Texas

Purpose: Multiple small case series have reported sperm in the ejaculate and spontaneous pregnancies in patients with nonobstructive azoospermia after varicocele repair. We hypothesized that men with favorable testicular histopathology on testis biopsy such as maturation arrest or hypospermatogenesis would have a higher probability of success than those with more ablative pathology, eg Sertoli-cell-only.

Materials and Methods: A review of the literature on varicocele repair in patients with nonobstructive azoospermia was performed and 11 publications from the previous 20 years were evaluated. Histopathological data were presented in 8 publications, and were categorized as Sertoli-cell-only, maturation arrest and hypospermatogenesis. Maturation arrest was further differentiated by 4 publications. Early maturation arrest was defined as maturation ending at the secondary spermatocyte and late maturation arrest was defined as maturation ending at the spermatid without spermatozoa present. Success after repair was defined as having sperm in the ejaculate or spontaneous pregnancy.

Results: A total of 233 patients were analyzed. After varicocele repair 91 (39.1%) patients had motile sperm in the ejaculate and 14 spontaneous pregnancies were reported. Success rates in patients with maturation arrest (42.1%) or hypospermatogenesis (54.5%) were significantly higher than in those with Sertoli-cell-only (11.3%, $p < 0.001$ in both groups). Patients with late maturation arrest had a higher probability of success (45.8%) than those with early maturation arrest (0%, $p = 0.007$).

Conclusions: Infertile men with nonobstructive azoospermia can have improvement in semen analysis and achieve spontaneous pregnancy after repair of clinical varicoceles. This meta-analysis demonstrates that men with late maturation arrest and hypospermatogenesis have a higher probability of success and, therefore, histopathology should be considered before varicocele repair in men with nonobstructive azoospermia.

Key Words: infertility, male; azoospermia; varicocele; testis; pathology

Abbreviations and Acronyms

FSH = follicle-stimulating hormone

HS = hypospermatogenesis

ICSI = intracytoplasmic sperm injection

ISV = internal spermatic vein

IVF = in vitro fertilization

MA = maturation arrest

NOA = nonobstructive azoospermia

SCO = Sertoli-cell-only

TESE = testicular sperm extraction

Submitted for publication October 1, 2009.

* Correspondence: Baylor Clinic, 6620 Main St., Suite 1325, MS BCM380, Houston, Texas 77005 (telephone: 713-798-4001; FAX: 713-798-5553; e-mail: weedin@bcm.edu).

† Nothing to disclose.

‡ Financial interest and/or other relationship with Allergan, Auxilium, Coloplast and Slate Pharmaceuticals.

§ Financial interest and/or other relationship with Allergan, Auxilium, Pfizer, Lilly, AMS and Vivus.

Editor's Note: This article is the fifth of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 2474 and 2475.

INFERTILITY is a common problem, affecting approximately 15% of couples. A male factor is solely responsible in 20% of couples and contributes to infertility in another 30% to 40%.[1] The prevalence of azoospermia is 1% in all men and 10% to 15% in subfertile men. For a male with NOA to initiate his own biological pregnancy TESE coupled with in vitro fertilization and intracytoplasmic sperm injection is typically required.[2]

A varicocele is identified in approximately 35% of men with primary infertility and in 81% of those with secondary infertility.[3] Varicoceles are believed to cause male infertility by impaired drainage or pooling of blood around the testis leading to increased scrotal temperature. Hypoxia, increased testicular pressure, and reflux of noxious renal and adrenal metabolites have also been hypothesized to cause de-

0022-5347/10/1836-2309/0
THE JOURNAL OF UROLOGY®

Vol. 183, 2309-2315, June 2010
Printed in U.S.A.
DOI:10.1016/j.juro.2010.02.012

structive effects on spermatogenesis. Varicocele repair by occlusion of the affected spermatic vein(s) is the treatment of choice for most physicians, and can result in improvements in scrotal discomfort, serum testosterone, semen parameters and spontaneous pregnancy.[4] Repair is performed surgically or by ISV embolization. Approaches to surgical varicocelectomy include retroperitoneal, inguinal, subinguinal or laparoscopy.[5]

Varicoceles are found in 4.3% to 13.3% of men with azoospermia or severe oligospermia.[6] It remains to be proven whether varicoceles can cause or contribute to azoospermia. In 1952 Tulloch reported the first spontaneous pregnancy after surgical varicocelectomy in an azoospermic male which was paralleled by improvement in semen parameters.[7] For the next 2 decades several groups reported varying success after varicocele repair with semen parameters improving 0% to 57%.[6] During the last 15 years there has been a renewed interest in varicocele repair in azoospermic men resulting from the introduction of ICSI in 1993.[8] Success rates have varied and no predictors of success have been definitively identified because of the small numbers in the case series. We used a meta-analysis to examine the ability of varicocele repair to result in improved semen parameters and pregnancy in patients with NOA, focusing on factors that might predict success.

MATERIALS AND METHODS

A PubMed® and Ovid MEDLINE® search was performed for articles published between January 1990 and August 2008, querying the key words varicocele, varicocele repair, varicocelectomy, male infertility and azoospermia. We collected 20 articles reporting varicocele repair in men with azoospermia. We included in the review only articles published in English reporting on the treatment of men with NOA with surgical varicocelectomy or ISV embolization. We excluded from study patients with obstructive azoospermia, severe oligospermia and cryptoozospermia. Furthermore, we excluded articles that included patients with subclinical varicoceles, individual case reports and followup of less than 4 months. Each article needed to have confirmation of azoospermia by 2 separate semen analysis with centrifugation and pellet analysis, and to exclude patients with obstructive azoospermia.

Successful varicocele repair was defined as the discovery of motile sperm in any semen analysis performed at least 3 months postoperatively or spontaneous pregnancy. Relapse into azoospermia was defined as azoospermia found on postoperative semen analysis performed after demonstration of motile sperm in a previous sample. Varicoceles were graded on a scale of 1 to 3 as previously described.[3] A testis was classified as hypotrophic if volume on physical examination was less than 15 ml or was 25% less than that of the contralateral testicle.[9] Normal FSH ranges varied per article and generally ranged from 2 to 10 mIU/ml. Unilateral or bilateral varicocele repair was performed based on clinical findings.

Open testicular biopsy was performed unilaterally or bilaterally according to author preference before or at the time of varicocele repair. All articles presenting histopathology used the same pathological diagnoses. Diagnoses were SCO/germ cell aplasia based on the absence of germ cells, MA when mature spermatozoa were absent and germ cells were present but spermatogenesis halted at a particular stage, and hypospermatogenesis when mature spermatozoa were present in decreased numbers. MA was further classified as early or late in 4 articles. Early MA was defined as arrest at the level of the spermatocyte and late MA as arrest at the level of the spermatid. Statistical analysis using SPSS® software included 2-tailed Fisher's exact test, the Fisher-Freeman-Halton test and the chi-square test to analyze categorical variables with $p < 0.05$ considered statistically significant.

RESULTS

Of 20 articles published on varicocele repair in men with NOA 11 publications from 7 countries met the inclusion criteria of our meta-analysis. All articles were retrospective and excluded men with known genetic abnormalities. To our knowledge no prospective or randomized trials have been published. Overall 233 patients were analyzed with a mean age of 30.1 years and a mean postoperative followup of 13.3 months (table 1).[9–19] The average number of semen samples analyzed postoperatively could not be analyzed because few articles included this information. Of the articles 5 reported varicocele repairs performed microscopically through an inguinal approach, 4 reported procedures performed microscopically through a subinguinal approach and 2 described percutaneous embolization of the ISV. Bilateral repair was performed in 64.8% of patients. Motile sperm was found on postoperative semen analysis in 91 of 233 (39.1%) men, resulting in 14 (6%) spontaneous pregnancies and 10 pregnancies with the assistance of IVF. Mean ± SD postoperative sperm density was $1.6 \times 10^6 \pm 1.2 \times 10^6$ and mean sperm motility was 20.1% ± 18.5%. After postoperative semen analysis demonstrated motile sperm in the ejaculate 11 (4.6%) patients had relapse into azoospermia within 2 to 6 months. No surgical complications were reported.

The outcome of varicocele repair related to histopathology was reported in 8 articles (table 2)[9–12,14,16,17,19] with 4 distinguishing between patients having early vs late MA (table 3).[10–12,16] Of 44 patients with a diagnosis of SCO 5 (11%) had sperm in semen postoperatively. None of these repairs resulted in pregnancy and 80% of patients experienced relapse into azoospermia. Of 55 patients with HS 30 (55%) had motile sperm in the postoperative ejaculate. In terms of maturation arrest 24 of 57 patients (42%) had motile sperm in postoperative ejaculate. The probability of successful varicocele repair was significantly greater for patients with HS or MA than for those with SCO (OR 9.4; 95% CI 3.2,