Active Surveillance of the Adolescent with Varicocele: Predicting Semen Outcomes from Ultrasound

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Purpose: We hypothesized that active surveillance of the adolescent varicocele is not associated with a high prevalence of suboptimal semen analysis and that patients with abnormal semen analysis have smaller testicular volumes and larger volume differentials.

Materials and Methods: We conducted an institutional review board approved retrospective cohort study of adolescents with a clinically detected varicocele. Patients were initially observed by serial scrotal ultrasound evaluating testicular size and differential. Semen analysis was routinely collected in Tanner V cases, around age 18 years. Prevalence of normal semen analysis parameters was calculated, and logistic regression was used to model the ability of age at presentation and testicular volume parameters to predict a normal semen analysis.

Results: A cohort of 73 patients underwent surveillance with a mean ± SD age at presentation of 15.5 ± 2.3 years. Median followup was 2.7 years, during which time subjects underwent a median of 3 scrotal ultrasounds. A low total motile count was found in 48 patients (66%). Neither age at presentation nor testicular volume differential could predict normal semen volume, density, sperm motility or total motile count. Total testicular volume from the final ultrasound predicted total motile count ($p = 0.008$). However, the collective observations of volume during the entire period of surveillance could not predict total motile count ($p = 0.847$).

Conclusions: There is a high prevalence of suboptimal semen analysis in adolescents with a varicocele who are followed with active surveillance. Total testicular volume can predict total motile count at the end of adolescence but not throughout.

Key Words: adolescent, scrotum, semen analysis, ultrasound, varicocele

Abbreviations and Acronyms

ASurv = active surveillance
LTV = left testicular volume
RTV = right testicular volume
SA = semen analysis
ScrUS = scrotal ultrasound
TMC = total motile count
TTV = total testicular volume
TVDiff = testicular volume differential
Vx = varicocele/s

Accepted for publication November 7, 2013.
Study received institutional review board approval.

Varicoceles are present in 15% of the male population and in approximately 40% with infertility.[1] While clearly not all men with varicoceles have infertility, there appears to be a link between the 2 conditions. Adolescents with varicoceles comprise an interesting conundrum, since the diagnosis is made years in advance of issues arising from potential infertility. As a result of this lead time, the optimum management of adolescents with varicoceles is unknown and debated. Treatment options include surgical varicocelectomy, embolization and observation.

We sought to determine the prevalence of suboptimal semen analysis in a cohort of adolescents with a Vx undergoing active surveillance (nonsurgical followup of testicular volumes through time). We also planned to use

0022-5347/14/1915-1401/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2013.11.020
Vol. 191, 1401-1406, May 2014
Printed in U.S.A.

scrotal ultrasound obtained during active surveillance to develop a model to predict SA outcomes. We hypothesized that 1) active surveillance of adolescent Vx is not associated with a high prevalence of suboptimal SA and 2) those with suboptimal SA identified during active surveillance would have smaller testicular volumes and larger testicular volume differentials.

MATERIALS AND METHODS

Following local institutional review board approval, a retrospective cohort study was conducted in male adolescents with a unilateral (left) clinical Vx who were referred to the urology clinic. Patients needed to undergo at least 1 ScrUS and SA to be included. Postoperative SAs were not included. Practitioners in our department have adopted an algorithm for management of adolescents with a Vx, with SA being routinely collected around age 18, once a patient has reached the final stage of sexual development (Tanner V). We did not control for the specific laboratories processing the SA. Patients were excluded if they had a potential confounding abnormality of the hypothalamic-pituitary-testicular axis (such as hypospadias/cryptorchidism), if they underwent varicocelectomy before collection of the SA or if the abstinence period was less than 72 hours preceding the SA.

The cohort was initially followed with ASurv using ScrUS for measurement of testicular volumes. Surgical intervention was offered during the period of observation if patients had associated and characteristic pain, 2 abnormal SAs or TVDiff exceeding 20% on consecutive ultrasounds. Patients were censored at SA submission.

Age at initial presentation to the clinic and number of ultrasounds were determined. Length of followup was defined as the interval from initial presentation to collection of SA. ScrUS was used for calculation of left, right and total testicular volumes, using the Lambert formula, volume = length*width*height*0.71.[2] Similarly TVDiff was calculated from the ultrasound findings using the formula, [RTV − LTV]/TTV.[3] The SA was used to examine semen volume (ml), semen density (million sperm per ml) and sperm motility (percent motile sperm). Sperm morphology was not analyzed due to shifts in laboratory standards for interpretation of normal morphology that occurred during the study period. Total motile count was calculated for each subject according to the formula, TMC = volume*density*percent motility.

Descriptive statistics were calculated. World Health Organization 2010 standards were used to define abnormal SA, ie semen volume less than 1.5 ml, sperm concentration less than 15 million per ml and sperm motility less than 40%. Those with a TMC of less than 20 million per ejaculate were similarly defined as abnormal. This cut point has been used to counsel patients regarding the need for assisted reproductive technology vs the ability to achieve spontaneous pregnancy.[4] Logistic regression of disease on age at presentation, and on testicular volume and TVDiff (from the most recent scrotal ultrasound proximal to the SA) was performed. A panel analysis of the longitudinal data from the entire observation period was also performed using a mixed effects multiple regression model to predict TMC. This model was chosen based on the fact that there were multiple observations of testicular size in individuals through time but subjects did not always have the same number of observations. Logistic regression models were chosen because SA data are typically not normally distributed. Statistical analysis was conducted using STATA®, version 12.

RESULTS

A total of 97 patients met inclusion criteria. Of these patients 24 were excluded, leaving a cohort of 73 subjects. Exclusion criteria were failure to obtain SA before undergoing varicocelectomy (11 patients); lack of scrotal ultrasound before SA (2); presence of hypospadias (1), cryptorchidism (1) or viral illness (1) at SA; abstinence period less than 3 days (3); and incomplete SA (2) or scrotal ultrasound reports (3). Mean ± SD age at presentation was 15.5 ± 2.3 years. Mean ± SD length of followup was 3.1 ± 2.3 years. Median number of ScrUSs for each patient was 3 (IQR 2, 4). Last ScrUS and SA were performed at a median age of 18.0 (IQR 17.6, 18.7) and 18.3 (18.1, 19.3) years, respectively, with a median of 0.4 years between tests. Testicular volume and SA data for the cohort are outlined in table 1. Varicocelectomy was eventually elected after a period of ASurv in 13 patients (18%). Indications were pain in 3 patients, abnormal SA in 11 and increased TVDiff in 1 with an abnormal SA.

Semen volume and density, sperm motility and TMC were normal in 63 (86%), 23 (38%), 58 (79%) and 25 patients (34%), respectively. No variable (TTV, TVDiff, age at presentation) was able to predict a normal/abnormal outcome for volume, density or motility (table 2). TTV could predict TMC on univariate analysis (OR 1.08 [1.02, 1.15]), whereas TVDiff (OR 0.92 [0.01, 68.3]) and age at presentation (OR 0.85 [0.69, 1.06]) could not.

Mixed effects logistic regression modeling revealed no ability to predict TMC for the serial observations of total testicular volume throughout the period of ASurv. Evaluating all data (248 observations of TTV in 73 subjects), the overall model gives p = 0.973, with p = 0.980 for age at ultrasound and p = 0.847 for TTV. A sensitivity

Table 1. *Cohort characteristics*

Mean ± SD age at presentation (yrs)	15.5 ± 2.3
Mean ± SD LTV (cm^3)	17.6 ± 5.1
Mean ± SD TTV (cm^3)	37.6 ± 10.0
Mean ± SD testicular vol differential (%)	6.2 ± 11.3
Median million/ml semen density (IQR)	11 (3.6, 27)
Median ml semen vol (IQR)	2.7 (1.6, 4.0)
Median million sperm count (IQR)	28.6 (12, 47)
Median % sperm motility (IQR)	51 (40, 66)
Median million TMC (IQR)	13.5 (4.6, 29.1)