HHS Public Access

Author manuscript

J Pediatr Urol. Author manuscript; available in PMC 2017 June 01.

Published in final edited form as:

J Pediatr Urol. 2017 February ; 13(1): 77.e1–77.e5. doi:10.1016/j.jpurol.2016.09.008.

The natural history of semen parameters in untreated asymptomatic adolescent varicocele patients: A retrospective cohort study

David I. Chu, **Stephen A. Zderic**, **Aseem R. Shukla**, **Arun K. Srinivasan**, **Gregory E. Tasian**, **Dana A. Weiss**, **Christopher J. Long**, **Douglas A. Canning**, and **Thomas F. Kolon**

Division of Urology The Children's Hospital of Philadelphia, Philadelphia, PA, USA

Summary

Introduction—Adolescent males with varicoceles present a dilemma for surveillance and treatment. Testicular volumetrics have not been shown to predict SA outcomes. Serial SAs are thus recommended in asymptomatic adolescent males with varicoceles and normal testicular development, but the natural history of semen parameters is unknown.

Objective—To explore the natural history of semen parameters in adolescent boys with a left varicocele under active surveillance.

Study design—Adolescents with an asymptomatic unilateral left varicocele, Tanner V development, normal testicular volumes, and an initial SA were retrospectively reviewed in a single-institution prospectively followed cohort. Total motile count (TMC) was calculated. A cutoff of TMC Z 20 million was used to dichotomize SA results into "normal" or "poor." Those with poor SA were offered repeat SA. Cumulative probabilities of normal TMC over successive rounds of SA were calculated. Bivariate models were used to explore associations of a second consecutive poor TMC with age and varicocele grade.

Results—A total of 216 patients provided an initial SA between 1992 and 2015. We excluded 17 for a history of cryptorchidism or incomplete SA data for a final cohort of 199 patients with median follow-up of 3.3 years (interquartile range 1.5–5.6 years). The mean age at initial SA was 17.9 years (range 14.8–21.8 years). One hundred and nine out of 199 had an initial normal TMC. Of the 90 out of 199 with an initially poor TMC, 51 had repeat SA and 24 of the 51 patients improved to normal TMC. Of the 27 patients with two consecutive poor TMCs, 15 had a third SA and five out of 15 improved to normal TMC. Thus, cumulatively, 55%, 67%, and 69% of all patients had a normal TMC after an initial, second, and third SA, respectively. However, fewer patients in each round of SA normalized their TMC (Figure). Neither age nor varicocele grade was associated with a second consecutive poor TMC.

Discussion—Two-thirds of Tanner V boys with an uncorrected varicocele and normal testicular volumes achieve a normal TMC regardless of varicocele grade or age. Despite Tanner V

Correspondence to: T.F. Kolon, Division of Urology, The Children's Hospital of Philadelphia, 3401 Civic Center Boulevard, Philadelphia, PA 19104, USA, kolon@email.chop.edu (T.F. Kolon).

Conflict of interest

None.

development, 47% with an initial “poor” SA will improve to normal status without surgery. However, a small subgroup of patients will have persistently poor TMC and thus should be targeted in future research for timely intervention.

Conclusion—Semen parameters improve over time. SA should be followed and repeated at least once in symptomatic Tanner V boys with varicoceles.

Keywords

Adolescent varicocele; Semen analysis; Total motile count; Natural history

Introduction

Varicocele is one of the most common urologie abnormalities seen in adolescent males, with an incidence of 15% among 15–19 years old [1]. Although varicocele is the most common male factor in cases of infertility, 85% of adolescents with uncorrected varicoceles have been able to achieve paternity [2]. However, a small subset of adult males with varicocele may ultimately require surgical repair, which has been shown to improve not only semen parameters [3–5] but also spontaneous pregnancy rates [4,6].

Various surrogate markers for future infertility have been studied. Semen analysis (SA) is possibly the most accurate predictor of future fertility [7–9], although for some physicians ethics concerns have arisen for obtaining the sample [10]. Testicular volumetrics offer a non-invasive method of gauging future fertility potential [11–15], but it may not be an accurate predictor of SA results [12,14]. Testicular catch-up growth has also been proven to occur without surgery, thereby lessening the importance of testicular volumetrics [11,16,17].

Given the uncertainty of timing of intervention solely for abnormal testicular volumes, we sought to examine the natural history of semen parameters in untreated, asymptomatic, Tanner V adolescents with normal testicular development. We hypothesized that, similar to testicular catch-up growth exhibited on serial ultrasounds, abnormal SA could improve over time without surgical varicocele correction.

Materials and methods

Study design

Following local institutional review board approval, a retrospective cohort study was conducted of a prospectively followed registry of adolescent males referred to our institution for varicocele. This registry included patients enrolled from January 1992 to September 2015.

Our institutional varicocele clinical pathway has been previously described [12]. Briefly, a patient who initially presented with a clinical varicocele was offered surgical repair if he had pain or a >20% discrepancy in testicular sizes using total volume differential [11]. Testicular volumes were previously assessed using scrotal ultrasound, but this was changed to orchidometer-based measurements after previous work showed no association between ultrasound-based testicular volumetrics and SA outcomes [12]. If the patient was

asymptomatic with symmetric normal-sized testes, annual surveillance with orchidometer measurements was advised until the patient reached Tanner V stage of sexual development and age 15, at which point an initial SA was recommended. Each SA was obtained after 2 days' abstinence. We recommended a repeat SA if the initial one had poor results. If the second SA also had poor results, we recommended repair, although certain patients requested completion of a third SA. If the initial SA was normal, a repeat SA was not recommended. Repeat SAs, if performed, were collected at least 3 months apart. All SAs were analyzed according to standard WHO criteria [18].

Inclusion and exclusion criteria

For this study, inclusion criteria included patients with a unilateral left varicocele who remained asymptomatic, had symmetric normal-sized testicular volumes, were followed non-surgically through puberty, and who provided at least one SA when they became Tanner V.

Patients were excluded if they had a potential confounding abnormality of the hypothalamic–pituitary–testicular axis such as cryptorchidism or had incompletely reported SA data that prevented calculation of primary outcome.

Outcome variable and covariates

The primary outcome was total motile count (TMC) as calculated by total semen volume (milliliter [mL]) × percent normal motility × sperm density (million sperm/mL). TMC was dichotomized into "poor" if less than 20 million and "normal" if greater than or equal to 20 million, as this cutoff has been previously accepted as a measure of sperm quality in multiple studies [8,9,14,19,20].

Covariates included age at each SA and grade of varicocele (I, palpable standing with Valsalva; II, palpable standing; III, visible). Testicular volumes were not included since all patients in this study had normal volumes as per our inclusion criteria and since previous work showed no association between ultrasound-based testicular volumetrics and SA outcomes [12]. Our institution does not routinely check peak retrograde flow on scrotal ultrasonography so these data were unavailable.

Statistical analysis

Descriptive statistics were generated after each round of SA. Since not every patient with a poor SA repeated a SA, we assessed overall cumulative rate of normal TMC after each round of SA.

Among those patients with an initial poor TMC who provided a second SA, secondary exploratory analyses were performed to investigate the associations between our covariates of age and varicocele grade and a second consecutive poor TMC, as this subgroup of patients may constitute the higher-risk population who should undergo surgical repair. We used Student's *t*-test for age as a continuous variable and Fisher's exact test for varicocele grade as a categorical variable. All statistical tests were performed using STATA (version 14.1) with a two-tailed alpha of 0.05.

Results

Initial query of our prospectively accrued varicocele registry generated 216 patients who met our inclusion criteria. After exclusion of 17 (8%) patients for history of cryptorchidism, endocrinopathy, or missing SA data, our final study cohort consisted of 199 patients. The median follow-up for this cohort was 3.3 years (interquartile range (IQR) 1.5–5.6 years).

Cohort characteristics are described in Table 1. The mean age at first SA was 17.9 years (range 14.8–21.8 years). On the initial SA, median TMC was 25.3 million (IQR 5.9–55.5 million). Forty-nine percent of patients had grade III varicocele.

Of the 199 initial SA, 109 (55%) had normal TMC and 90 (45%) had poor TMC (Fig. 1). Of the 90 patients with an initial poor TMC, 51 (57%) provided a second SA at a median of 4 months after the first SA, seven underwent varicocele repair (per family request), and the remaining 32 refused repeat SA or were lost to follow-up. Of the 51 s SAs, 24 (47%) had normal TMC and 27 (53%) had poor TMC.

Of the 27 patients with two consecutive poor SA results, 15 (56%) provided a third SA at a median of 11 months after the second SA, 6 underwent varicocele repair, and six were lost to follow-up. Of the 15 third SAs, 5 (33%) had normal TMC and 10 (67%) had poor TMC. Two of these 10 patients with three consecutive poor TMC have undergone varicocele repair to date.

Cumulative overall probability of normal TMC was 55% (109/199) after one SA, 67% (133/199) after two SA, and 69% (138/199) after three SA. Had surgery been performed for an initial poor TMC, 29 of the 51 (57%) patients who provided additional SA would have undergone unnecessary surgery (by SA criteria).

Our secondary analyses showed no significant associations between a second consecutive poor TMC and our covariates of age and clinical grade of varicocele (Table 2).

Discussion

The natural history of semen parameters in the asymptomatic Tanner V adolescent varicocele patient shows a regression to the mean for previously poor SA results in subsequent SA. Nearly half those patients with an initial poor TMC normalized their semen parameters on a repeat SA. Thus, cumulatively, two-thirds of Tanner V adolescent males with an asymptomatic left varicocele and normal testicular development will ultimately have a normal TMC if the SAs are repeated. A subpopulation of high-risk patients, however, persistently had poor TMC and remains a target of future investigation. Our results support conservative management of adolescent varicoceles in the form of active surveillance with serial SA.

The role of early intervention for adolescent varicoceles remains controversial. Historically, studies suggest that early intervention may reverse testicular hypotrophy and abnormal semen parameters [21,22] and may especially be indicated in grade III varicoceles to prevent potential bilateral testicular hypotrophy [23]. However, not every adolescent varicocele

requires surgical correction, as reflected by guidelines from the American Urological Association and the European Association of Urology [24,25]. These best practice policies recommend serial observation, with timely intervention reserved for persistent differences in testicular size [24]. Additionally, they warn against the risk of overtreatment among adolescents [25].

More contemporary studies of varicocele patients on surveillance protocols suggest conservative management using testicular volumetrics may not be reliable. In adolescent males with left varicocele and without significant testicular size differences that met surgical criteria, one study demonstrated no changes in volumetrics over a median follow-up of two years [26]. However, we have previously shown that serial testicular volumes cannot predict SA outcomes and TMC [12]. Other studies showed evidence of catch-up growth in the affected smaller testicle. Over a mean follow-up of 79 months, 50% of conservatively managed males who began with a baseline testicular Atrophy Index of less than 20% demonstrated catch-up growth [16]. Similarly, in males who demonstrated significant testicular size differences but were monitored without surgical correction, spontaneous catch-up growth of the affected testicle was demonstrated on serial scrotal ultrasounds to occur in 50–70% of patients with follow-up periods ranging from 2.1 to 3.5 years [11,17]. Thus, the possibility of intervening too early for differences in testicular volumes, or too late for lack of such differences, raises the risks of overtreatment and undertreatment, respectively.

Our study and institutional protocol therefore relied on SA outcomes as a better surrogate endpoint for adolescent patients with varicoceles. Using serial SA as the surveillance tool rather than testicular volumetrics, we have demonstrated that repeat SA are necessary in the management of these patients as nearly half of those patients with an initially poor TMC normalized their semen parameters on the second SA. After three rounds of semen analyses, if a TMC of less than 20 million were an indication for surgery, up to 57% of patients would have avoided unnecessary surgery had it been performed for the first poor SA.

The findings from our study add to the limited published evidence on the natural history of semen parameters in varicocele patients. One study examined semen parameters in adolescent patients with no testicular size differences managed conservatively, with 59 of 60 patients demonstrating normal parameters on serial SA [16]. However, this study did not define “normal” semen parameters and it is not clear if TMC was used. Another report studied predictors of progressive deterioration of semen quality among slightly older patients (mean age 22 years) followed conservatively and noted that, at a mean follow-up of 63 months, 87% of patients with an initially poor SA, defined by multiple measures including TMC, had progressive deterioration compared with 20% of patients with an initially normal SA [7]. The higher deterioration rate after an initially poor SA in this study differs from ours possibly because of the older population, suggesting that after a certain age and therefore certain duration of exposure to an unrepaired varicocele, SA parameters will not rebound. Indeed, our results demonstrated that a certain subset of adolescent males never normalized their TMC over three serial SA. Bivariate analyses showed no associations between age and varicocele grade and a second consecutive poor TMC in our study, although the limited sample size may preclude adequate power to assess the association

between age and outcomes. Further research is therefore necessary to identify this at-risk group for appropriate early intervention, as conservative management may be more likely to fail. As such, our current institutional treatment algorithm advocates for adolescent varicocelectomy to be offered after two consecutive SA demonstrate poor TMC [1].

The results of our study must be interpreted in light of their limitations. As in all retrospective reviews, unmeasured confounders may be present. Additionally, other predictors of SA outcomes, such as peak retrograde flow [15], may not have been measured. However, since all patients had normal testicular sizes as part of the inclusion criteria for active surveillance, we do not believe significant differences in peak retrograde flow would have been noted. Selection bias was also present with the loss to follow-up or refusal to submit a repeat SA after a previous poor TMC. Our cumulative estimate of TMC outcomes, however, essentially assumes that those patients lost to follow-up or who refused repeat SA will have continued poor TMC. Despite this assumption, we still showed improvement in semen parameters over time without intervention. Furthermore, within-patient variation in TMC has been previously documented [27], potentially limiting reproducibility of this semen parameter, especially since our protocol of not repeating a second SA given a normal initial SA precludes investigation of fluctuations in TMC among patients with a normal initial SA. In the same study, however, two consecutive SA were shown to improve reliability considerably, thereby enhancing the ability to stratify risk among patients. Lastly, as in all varicocele studies that utilize TMC as a surrogate for future paternity, our primary outcome of TMC may not reflect true future rates of spontaneous pregnancy. Counseling adolescent patients about possible impaired fertility using an imprecise surrogate marker often may be difficult, and we therefore recommend follow-up with an adult infertility specialist if post-repair TMCs remain low. To measure pregnancy outcomes, however, would require very close follow-up over several years' duration, which may be impractical outside a prospective trial [4]. A recent study also supports TMC as the best surrogate of all semen parameters for spontaneous pregnancy rates [19].

In summary, we have shown that a substantial proportion of adolescent males with asymptomatic left varicoceles, Tanner V stage sexual development, and normal testicular volume will ultimately have normal semen parameters without intervention, despite an initially poor SA. Careful patient selection to avoid overtreatment must be balanced with stringent active surveillance to prevent undertreatment, particularly in the subset of patients who have persistently low TMC on serial SA.

Acknowledgments

Funding

Dr. Chu was supported by T32-DK007785 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The NIDDK had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The views expressed in this article are those of the authors and do not necessarily represent the official view of the NIDDK.

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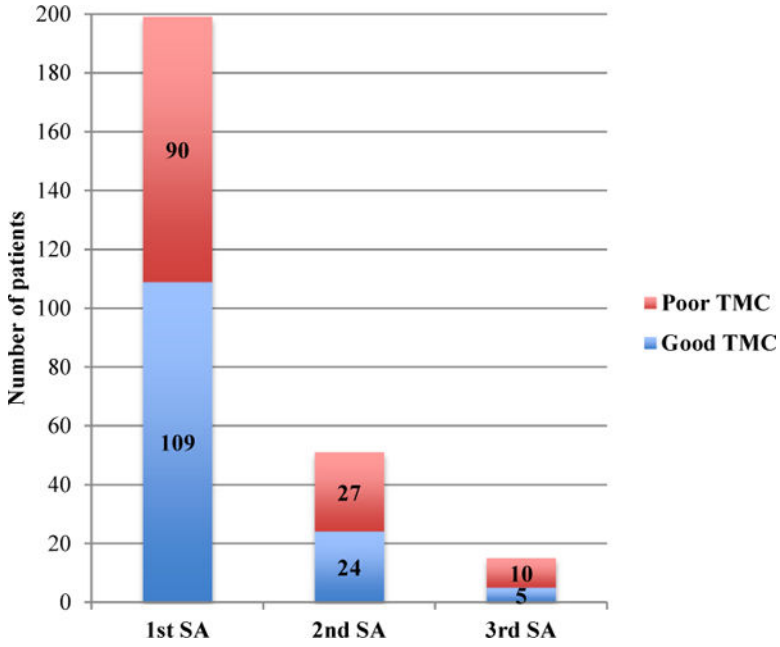

Figure.
Semen analysis outcomes.

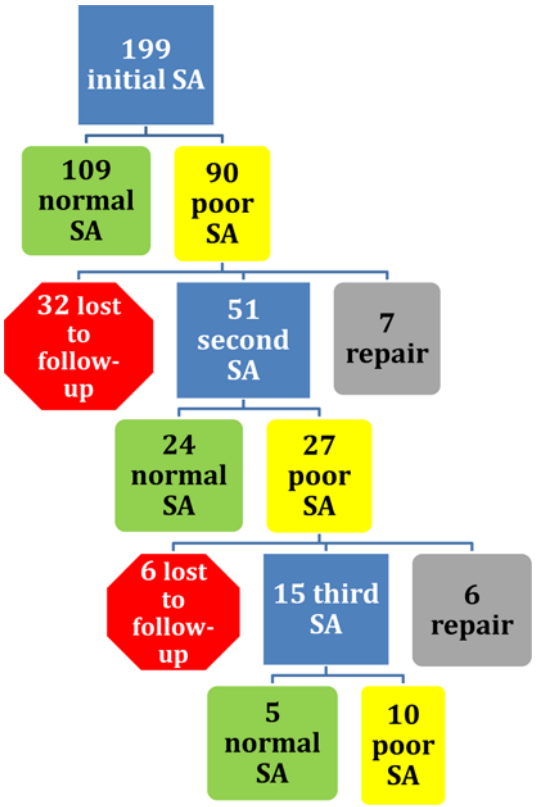

Figure 1.
Flow diagram of semen analysis results. SA = semen analysis.

Table 1

Cohort characteristics (n = 199).

Variable	Statistic	% (*n*)
Age at diagnosis, years		
Mean (range)	14.4 (7–19)	
Median (IQR)	15 (13–16)	
Age at initial SA, years		
Mean (range)	17.9 (14.8–21.8)	
Median (IQR)	18.1 (17–18.6)	
Varicocele grade		
I		13 (26)
II		26 (51)
III		49 (97)
Not recorded		13 (25)
Initial TMC		
Mean (range)	48.1 (0–486)	
Median (IQR)	25.3 (5.9–55.5)	
< 20 million (“poor”)		45 (90)
≥ 20 million (“normal”)		55 (109)

IQR = interquartile range; SA = semen analysis; TMC = total motile count.

Table 2

Bivariate analyses of varicocele grade and age with second semen analysis outcomes after initial “poor” semen analysis.

Variable	Poor TMC	Normal TMC	*P*
Varicocele grade, % (n)			0.75[a]
Grade I	22 (6)	17(4)	
Grade II	15(4)	25 (6)	
Grade III	56 (15)	46 (11)	
Not recorded	7 (2)	13 (3)	
Age at SA, y, mean (SD)	17.6 (1.2)	18.3 (1.3)	0.09[b]

SA = semen analysis; SD = standard deviation; TMC = total motile count.

[a] Fisher’s exact test.

[b] Student *t*-test with equal variances.