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Natural history of testicular size in boys with varicoceles

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Summary

Introduction
Testicular size is commonly used as a proxy for future fertility in adolescent boys diagnosed with varicoceles. Surgery is often performed based on a 15—20% reduction in volume of the ipsilateral testicle when compared to the unaffected side. Recent European Association of Urology guidelines, however, have highlighted the risk of overtreatment. Data on the natural progression of testicular size discrepancy are limited in this population. To evaluate the role of a non-surgical approach, the present study reports on testicular size progression in 35 boys with left-sided varicoceles managed with observation alone.

Methods
In the present study, 103 consecutive boys who were seen for varicocele were retrospectively evaluated; the 35 who were seen for at least three sequential visits by the same pediatric urologist for a unilateral left varicocele were selected. In the present practice, surgical management of varicoceles in teens is offered, but not recommended unless surgery is being performed for another reason (3/103). The Prader orchidometric testicular volumes that were documented for all visits were recorded and the volume of the left testicle as a percentage of the right was calculated. This analysis was performed for the entire population, and subgroup analysis was conducted for boys with a Grade 3 varicocele, with >10% asymmetry at diagnosis, and by dividing the population into prepubertal and pubertal age groups. Boys with bilateral varicoceles, concurrent testicular masses, or volumes recorded by a nurse practitioner were excluded from the study.

Results
The mean left testicular volume in the population was found to measure 96%, 95% and 96% of the right at the first, second and third visit (median interval was 2.0 years), respectively. Among the 26 boys seen for a fourth visit (median 3.3 years) and the 15 seen for a fifth visit (median 4.3 years), the mean left testicular volumes were 98% and 97% of the right at diagnosis and 97% at both the fourth and fifth visits (Figure). Likewise, no differences were seen after dividing the population into prepubertal (9—11 years, $n = 9$) and pubertal (12—14 years, $n = 26$) groups. Among the 13 (37%) boys with a Grade 3 varicocele at presentation, the left testicular volume was 95% (SD 11.4) of the right and remained unchanged by the third visit (96%, $P = 0.69$). In addition, among the 11 boys (31%) with greater than 10% size difference at the first visit, the left testicle measured 82% of the right (SD 5.3) at diagnosis and increased to 92% (SD 6.3) by the third visit ($P < 0.001$).

Discussion
In the 35 boys observed over a median of 2.0 years or three consecutive visits, there was no worsening of testicular asymmetry. This finding is consistent with some previous observational data on pediatric varicoceles, but carries the advantages of a narrower age range and longitudinal follow-up in all patients. At the same time, these results differ from other studies that show no improvement or worsening of asymmetry during follow-up. This difference is attributed to the inherent characteristics of the present study population and the choice of orchidometer for measurement. The present data have the advantage of excluding selection bias. Recognizing that this study is a retrospective, single-operator study with a small sample size, prospective, randomized trials are recommended to weigh surgery vs observation in adolescent varicocele patients.

Conclusions
No progression in atrophy/hypotrophy of the left testis was found in a series of 35 consecutive patients who were followed non-surgically for left-sided varicocele. Our data thus support observation as management for childhood varicocele in younger teens.

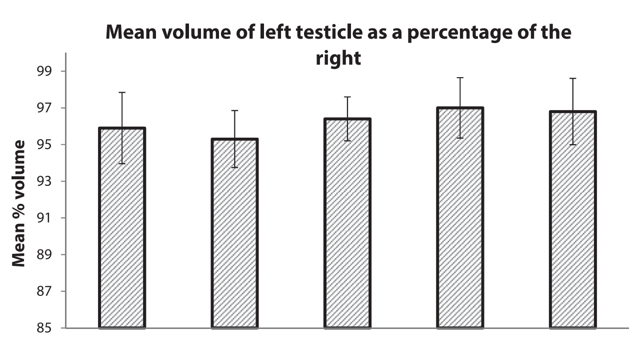

Figure No significant change noted in mean relative volume of the left testicle during follow-up. Errors bars represent Standard Error of Mean.

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Introduction

It is estimated that varicoceles occur in about 15% of adolescent boys [1]. The vast majority are asymptomatic, left sided and incidentally noted by a primary care provider. An associated finding is decreased volume of the ipsilateral testicle, which is reported in up to 70% of cases in some series, although most studies show a lower rate. The atrophy/hypotrophy of the left testis raises concerns regarding future fertility [2]. Whereas this can be addressed in adults by using semen analysis, the challenges of performing semen analysis in teenagers, especially those less than Tanner stage 5, as well as the limited data on normal semen parameters in this population, complicates their management.

In the absence of semen analysis, testicular size is a commonly used proxy for future fertility. A best-practice policy published by the AUA in 2001 recommended that all adolescents with reduced ipsilateral testicular growth should be offered varicocele repair. In subsequent years, investigators redefined criteria for surgical intervention, with the most commonly cited threshold being a 15–20% reduction in ipsilateral testicular volume compared to the unaffected side. Studies by Diamond and coworkers were instrumental in defining this criterion, as it was noted that up to 59% of Tanner stage-5 adolescents with a 20% difference in testicular volume showed abnormal total sperm counts [3]. Indeed, with 20% chosen as the marker for intervention, varicocelectomy improved testicular discrepancy to less than 20% in 85% of adolescents at 12 months post surgery [4]. Interestingly, despite these findings, the 2012 European Association of Urology guidelines on male fertility noted that 'in adolescents there is a significant risk of overtreatment' [5]. While numerous studies have sought to define the timing and necessity for intervention based on testicular size, few have reported on the natural progression of testicular growth associated with adolescent varicoceles. Furthermore, those few observational studies have several limitations, including a very wide age range, variable follow-up and variable approach towards surgical intervention, with some patients followed for as little as 6 months [4,6,7]. In order to fill this gap, a retrospective analysis of 35 boys with varicoceles, taken from a population that was non-surgically managed and seen regularly for a minimum of three visits, was performed.

Patients and methods

After Institutional Review Board approval, the records of all patients presenting with a diagnosis of varicocele between 2007 and 2013 were reviewed. The subset of patients who were seen during this period showed 103 consecutive boys who were first seen when younger than 18 years of age. All but three had been non-surgically followed; those three were operated on for their varicocele at the time of a concurrent anesthetic for a different surgical procedure. This was consistent with the practice standard, where although surgery is offered, it is not recommend prior to adulthood unless concomitant surgery is being performed for another reason.

Seventy boys were found with orchidometric measurement at the first encounter. Of these, 35 boys, who had documented follow-up for at least three annual visits by the same examiner (B.A.K.), were isolated. Thus, those with fewer than three visits were not included in the analysis. Other exclusion criteria were: having been examined by another attending examiner, an Nurse Practitioner/Physician Assistant, patients with right sided or bilateral varicoceles or those with scrotal masses. Consequently, all 35 boys had isolated left-sided varicoceles and had orchidometric measurements taken by the same pediatric urologist over at least three encounters. Furthermore, a subset of 26 and 15 boys were seen for fourth and fifth visits, respectively. None of the 35 boys underwent surgical intervention and one boy reported significant pain.

Varicocele grades were determined on a scale of 1–3: (1) palpable with valsalva; (2) palpable without valsalva; (3) visually evident without palpation. Testicular volumes were determined using a Prader orchidometer (Endocrine Society (Washington, DC)). A few boys had undergone an ultrasound, but for consistency these measurements were not used in this study. The same attending physician consistently assessed both volume and grade.

Testicular volumes and varicocele grades across all visits were recorded and then the size of the left testicle as a percentage of the right was calculated. Percent asymmetry was likewise calculated as $[(\text{Vol R}-\text{Vol L})/\text{Vol R}] \times 100$. Paired t-tests were used to compare the change in relative testicular size between visits. Data were further analyzed based on whether the boys presented between the ages of 9–11 (prepubertal) or 12–14 years (pubertal). The data were also scrutinized for boys with Grade 3 varicoceles and for those with a greater than 10% difference in testicular size at the initial visit. A difference of 10% was chosen to be inclusive, as there were concerns that orchidometric (vs ultrasound) measurements might decrease the sensitivity of the size discrepancies. All statistical analysis was conducted with GraphPad Prism 5 (GraphPad Software, Lajolla, CA) with $P < 0.05$ as the standard for significance.

Results

The study population comprised 35 boys presenting with left-sided varicoceles and at a median age of 12 years (range 9–14 years). At the initial visit, the median varicocele grade was 2 and the mean left testicular volume was 96% of the right. Eleven (31%) boys presented with a >10% difference between right and left testicles and, likewise, 13 (37%) demonstrated Grade 3 varicoceles at presentation. By definition, all 35 boys were followed for three visits, with the third visit at a median of 2.0 years. Data for fourth and fifth follow-up visits were available for a subset of 28 and 15 boys, at a median of 3.3 and 4.3 years, respectively.

Table 1 outlines the left testicular volume as a percentage of the right, across the entire study population. At visit 1, the boys demonstrated a mean left testicular volume that was 96% of the right; this remained unchanged at visit 3, with a volume of 96%. Similar findings were also seen in the boys who were followed for fourth and fifth visits, with a mean left volume of 97% of the right at each visit.

Table 1 Mean relative volume of the left testicle. The size of the left testicle remains well preserved, compared to the right, across five visits.

Visit	1	2	3	4	5
Median follow-up (years)	0	1	2	3.3	4.3
Number of boys remaining in follow-up	35	35	35	26	15
Left testicular volume as % of right (mean ± sd)	95.9 ± 11.5	95.3 ± 9.2	96.4 ± 7.1	97.0 ± 8.4	96.8 ± 7.0

Similar findings were noted after analyzing the population based on age. In the prepubertal group, left testicular volume was a mean 98% and 96% of right at first and third visits, respectively, while in the pubertal group, the values were 95% and 96%. To further corroborate this overall pattern, Fig. 1 illustrates the close match between mean left and right volumes across five visits and the steady growth in testicular size within the population during follow-up.

Boys with greater than 10% asymmetry on first encounter

Testicular volume changes in boys who presented with greater than 10% asymmetry at initial encounter were analyzed. A group of 11 (31%) met this criterion, with a mean left testicular volume at 82% of right at first visit, and only one boy demonstrated asymmetry greater than 20%. Because this was a highly selected population of boys, who were examined at three consecutive visits by a single practitioner, the rate of size discrepancy in the 70 boys who were not included was also looked at. It was found that 24 of the 70 (35%) demonstrated greater than 10% asymmetry at initial visit. This number is almost the same as the 31% in the present study group.

In the study population, by the second visit, the left testicular volume had increased to 92% (median 1.0 year) ($P < 0.001$) and at the third visit remained stable at 92% (median 2.2 years) ($P < 0.001$). Importantly, by the third visit, only five of the eleven boys continued to demonstrate asymmetry of greater than 10%. In the group of boys starting out with <10% asymmetry, two worsened to >10% difference by the third follow-up. Observation continued, as surgical intervention during puberty is not recommended. Therefore, by the third visit, the rate of asymmetry decreased from 11/35 (31%) to 7/35 (20%).

Data were available for six and three out of the 11 boys at the fourth and fifth visits, respectively. While small, the numbers show a continued increase in left testicular volume to 95% and 94% of the right at the fourth visit (3.2 years) ($P < 0.05$) and fifth visit (4.5 years), respectively. Fig. 2 depicts the findings in boys starting with >10% asymmetry.

Boys with Grade 3 varicoceles at first visit

Subgroup analysis was performed for 13 of the 35 boys presenting with Grade 3 varicoceles. Mean left testicular volume in this group was 95% of the right at the first visit and remained stable at 97% by the third visit (1.9 year). For the 10 boys who were followed to a fourth visit, the left volume was 97% of the right. Similarly, for the four boys seen at a fifth visit, the left volume was 95% of the right. Fig. 3 shows preservation of testicular symmetry, even in boys presenting with high-grade varicoceles.

Discussion and conclusion

The present study examined the natural history of testicular size in 35 boys aged 9–14 years (median 12 years) with left-sided varicoceles who were managed expectantly for a minimum of three annual visits (median 2 years). The data suggest that from a population perspective, there was no

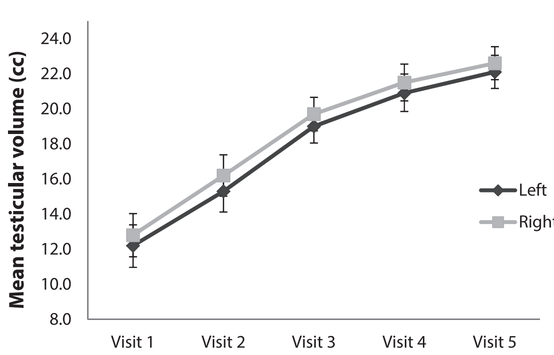

Figure 1 **Mean testicular volumes during follow-up.** Mean volumes steadily progress and remained closely matched in the study population over five visits. Error bars show Standard Error of Mean.

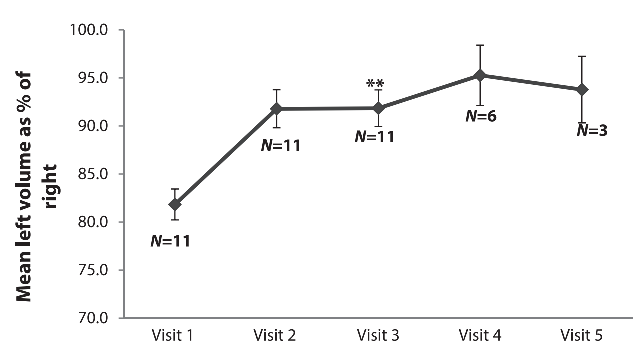

Figure 2 **Relative volume of the left testicle in boys with >10% asymmetry.** Improvement is seen in the mean relative left testicular volume in boys with >10% asymmetry on the first encounter. ** The change in mean volume from visit 1 to 3 was statistically significant with $P < 0.001$. Error bars show Standard Error of Mean.

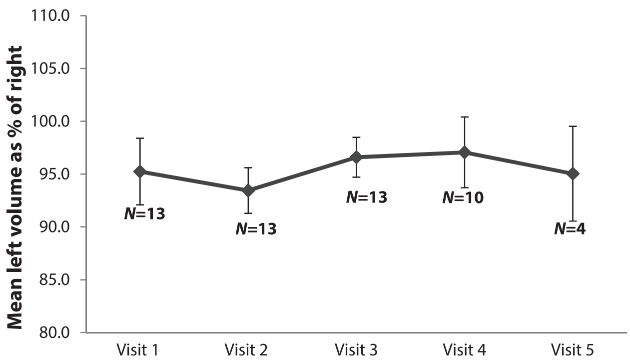

Figure 3 Relative left testicular volumes in boys with Grade 3 varicoceles. In boys with high-grade varicoceles, relative left testicular volume remains unchanged during follow-up. Error bars show Standard Error of Mean.

difference over time, as the left and right testicles remained closely matched throughout follow-up.

It was found that 11 of the 35 boys (31%) had a left testis >10% smaller than the right at presentation. Over the first two years of follow-up, five (55%) improved to less than 10% discrepancy and only two of the remaining 24 (8%) worsened. This work is consistent with prior studies that reported on expectantly managed varicoceles. Kolon et al. followed 71 patients over a mean of 3.5 years and noted at onset, using ultrasound, >15% asymmetry in 38 patients (53%) [6]; at follow-up, asymmetry decreased to below 15% in 71% of the patients. Preston et al. also reported on 25 varicocele patients with a smaller left testicle who were followed with ultrasound [7]. Asymmetry of >10% was found in 21 patients (84%) at presentation and eight (38%) had improvement to <10% at a median of 2.2 years. Both studies had some limitations such as a wide age distribution, wide follow-up time periods, and lack of longitudinal time points. The population studied by Kolon et al., for instance, included boys aged 6–17 years with follow-ups ranging between 2–9.5 years. Similarly, Preston et al. recruited boys aged 9–16 years and reported on follow-ups of 0.5–5 years. In contrast, the present study reported on boys aged between 9–14 years and with longitudinal follow-up in each patient.

In contrast to the present study, others have demonstrated both progression and worsening of testicular asymmetry in the presence of unilateral varicoceles. Batavia et al. described 115 boys of age 9.5–20 years (again a large age range), who were followed over a mean of 11.7 months (relatively short follow-up) via ultrasound [8]. They observed that up to 63 boys (55%) presented with >15% asymmetry from the start. They did find that 21 (33%) boys had resolution of testicular asymmetry, but 22 (49%) of the 45 boys without asymmetry worsened to >15%. Along the same lines, Korets et al. identified, with ultrasound, 37/89 (42%) adolescent varicocele patients with more than 10% asymmetry on initial encounter (no age range reported) [9]. At a median of 27 months, they observed that nearly 61 of the 89 (69%) showed >10% asymmetry.

The present study's contrasting results may relate to the study population, length of follow-up or measurement technique. A study by Poon et al. illustrates these possibilities [10]. The authors reviewed asymmetry data, compiled using both ultrasound and orchidometer, of 181 patients followed for a median of 12 months. Nearly 71% of the population demonstrated 10% or more asymmetry from onset and 67% eventually underwent surgical repair. This prompts the question as to whether selection of a population undergoing early surgery may skew the likelihood of resolution. Indeed, the Poon study noted that for adolescents presenting with >20% asymmetry, greater resolution was seen in the group observed for >12 months than in the group followed <12 months. This seems to support the notion that longer follow-up is needed before recommending surgical intervention.

The measurement technique also differentiates the present data from prior studies. The majority of studies used ultrasound to determine testicular volumes, while the present study used an orchidometer. The focus on ultrasound has stemmed from work by Diamond et al., who reported that the orchidometer is less sensitive than ultrasound in detecting small volume differences [11]. It is understood that orchidometers have limited ability to differentiate between testicular tissue and surrounding soft tissue. Moreover, they constrain the observer to specific size choices ranging from 1 cc to 25 cc, and the effect of pairing a testicle with a particular size (such as picking 10 cc vs 8 cc) can lead to an error of up to 20%. To this end, Mabieri et al., when comparing orchidometer values with volumes of dissected testicles, showed that an orchidometer consistently overestimates testicular volume by 25%, but there still remains significant correlation between the two measurements [12]. In theory, any error in the orchidometric measurements should distribute itself across both testicles and only influence the absolute volume, not the volume difference. This would be particularly true when the same urologist, as in the present study, consistently examines each patient.

While it is recognized that ultrasound is more objective than an orchidometer, caution against the routine use of ultrasound should be exercised, based on its higher cost, and for the philosophy that for a testicular size difference to be clinically relevant, the difference should be palpable. It is also likely that ultrasound, similar to orchidometer, is subject to operator bias. Those sonographers with an interest in ultrasound of patients with varicoceles may be looking for a smaller left testis. Moreover, because ultrasound volumes depend on multiplying three separate measurements, a small difference in each of the three dimensions can have a significant effect on volume, particularly in smaller testes (as was true in most of the present group). For example, a testis that is 3.5 mm $\times$ 2.2 mm $\times$ 2.2 mm would be 12 ml in volume, but one that is 3.4 mm $\times$ 2.1 mm $\times$ 2.1 mm would be 10.6 ml; which is a difference of >10% simply due to a 1 mm difference in each direction.

A major limitation of the present study was the small size. Because the study was limited to longitudinal patients examined by the same physician, the numbers were small. Yet this weakness is also strength, as it provides consistency of measurement over a longitudinal study in a largely consecutive series. Moreover, by counseling a non-operative approach in virtually all cases, this study provides the best information on the natural history of untreated adolescent varicoceles.

Finally, when viewing the present findings alongside prior studies, it is wondered whether short-term testicular asymmetry remains the best proxy for future fertility and the need for more reliable markers in young patients is highlighted. Nonetheless, in the absence of a better proxy, it is suggested that testicular volume be measured over several years of follow-up before recommending surgical correction in patients under the age of 18. In addition, recognizing that this is a small, single-operator, retrospective study, there is strong support of a prospective, multi-center trial with patients randomized to observation vs surgery.

Conflict of interest statement

The study authors acknowledge that they have no affiliation or involvement in any organization or entity with any financial or non-financial interest in the completion of this work.

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Nil.

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