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Clinical outcome of pediatric and young adult subclinical varicoceles: a single-institution experience

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Subclinical varicocele represents an abnormality of veins of the pampiniform plexus on scrotal ultrasound (US) without a clinically palpable varicocele. Its significance remains unclear. While guidelines do not recommend surgical intervention, clinical management is variable. As there is limited information on long-term outcome of subclinical varicoceles due to challenges in diagnosis and management, we performed a single-institution, retrospective review of patients from October 1999 to October 2014 with subclinical varicocele and with available US studies reviewed by a single radiologist. Subclinical varicocele was defined as dilation of the pampiniform venous plexus on US involving ≥ 2 vessels with diameter > 2.5 mm, without clinical varicocele on physical examination or prior inguinal surgery. Thirty-six of 98 patients identified were confirmed as having a subclinical varicocele and analyzed. The mean age at initial visit was 15.5 years, with a mean follow-up of 26.5 months. The majority were right-sided (69.4%, $n = 25$), usually with a contralateral clinical varicocele. Testicular asymmetry ($> 20\%$ volume difference of the affected side by testicular atrophy index formula) was assessed in 9 patients with unilateral subclinical varicocele without contralateral clinical or subclinical varicocele and observed in 1 patient. Of 17 patients with follow-up, 3 (17.6%) progressed to clinical varicocele without asymmetric testicular volume, as most remained subclinical or resolved without surgery. In our experience, subclinical varicoceles appeared unlikely to progress to clinical varicoceles, to affect testicular volume, or to lead to surgery. Although our study is limited in numbers and follow-up, this information may aid clinical management strategies and guide future prospective studies.

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INTRODUCTION

A varicocele is an abnormal dilation of the pampiniform venous plexus which envelops the spermatic cord structures. Approximately 15% of the normal adult male population has a varicocele.^{1,2} However, in a population of men who present with infertility, the incidence of varicocele can be as high as 40%.³ Based on clinical and animal research data, varicoceles can have a deleterious effect on spermatogenesis. The exact mechanism by which abnormally dilated spermatic veins affect testicular function and sperm production is not clear. Nevertheless, repair of palpable varicoceles in adult patients with male factor infertility associated with abnormal semen parameters can improve spermatogenesis and fertility rates, and it is a procedure recommended by the American Urological Association (AUA) and the American Society of Reproductive Medicine (ASRM).^{3,4}

Subclinical varicocele represents an abnormality of the pampiniform plexus detected during scrotal ultrasound (US). The diagnosis is based on the presence of venous dilation and/or retrograde venous blood flow in the absence of a clinically palpable varicocele on the ipsilateral side.^{5–7} A precise definition for subclinical varicocele has not been agreed upon, and the significance of this ultrasonographic finding is unclear. This lack of a precise definition has led to variability in diagnosis of this condition. Previously published reports have utilized the Dubin and

Amelar classification as well as the Hirsch Doppler classification.^{6,8} In addition to the presence of venous dilation, some authors have included specific measurement ranges of dilated veins as a means of better characterization.^{9–11} The use of objective venous measurements alone without analysis of Doppler flow to assess for subclinical varicoceles can be performed, but with less sensitivity and specificity.¹²

For the adult patient, varicocele repair typically occurs in the immediate setting of male factor infertility, clinically evident varicocele, and abnormal semen parameters. In comparison, indications prompting repair of left-sided clinical varicoceles in adolescents have varied, but have included persistent testicular size discrepancy, abnormal semen parameters, and testicular discomfort or pain.^{13–15} Varicocele repair during the adolescent period represents a preemptive attempt to enhance peripubertal testicular growth and potentially function in the hope of improving future fertility potential.

While repair of clinically apparent varicoceles is regarded as physiologically beneficial, the benefit of repairing subclinical varicoceles in the infertile adult male population is unclear and controversial.^{16,17} Although some studies in adults have reported improved semen parameters and pregnancy rates after right-sided subclinical varicocele repair in the presence or absence of a contralateral left-sided clinical varicocele, others have indicated the contrary.^{16,18–25} Unlike clinical

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varicoceles, best practice statements and guidelines from the ASRM/AUA and European Association of Urology (EUA) do not recommend surgical correction of a subclinical varicocele, and there is a lack of guidance on management and practice, particularly the role and need of surveillance or observation.^{4,26–28} Deciding how to manage subclinical varicoceles in the peripubertal adolescent is even more challenging, as there is little or no similar evidence to provide guidance.^{29,30} The complexities in management are further compounded by other factors: testicular volume changes normally occur during pubertal development; semen analyses are only meaningful in Tanner V patients and can be difficult to obtain; and long-term fertility outcomes are not available.

Given the paucity of data on subclinical varicoceles in the pediatric and young adult population, we systematically reviewed our experience with this population to gain a greater understanding of this entity. The objective of this study was to examine the natural history of pediatric and young adult subclinical varicoceles diagnosed in a tertiary pediatric care center, focusing on US-based determination of resolution or progression to a clinically palpable varicocele. We hypothesized that subclinical varicoceles might lead to a clinical varicocele requiring surgical intervention.

PATIENTS AND METHODS

Study population

A single-institution, retrospective review was performed of all patients referred to the Department of Urology at Boston Children's Hospital (Boston, MA, USA) with the diagnosis of "subclinical varicocele" initially evaluated between October 1999 and July 2013 and subsequently followed up to October 2014. Patients were identified from the outpatient urologic consultation database at Boston Children's Hospital from primary care or emergency room providers for reason of "varicocele" based on prior clinical examination or US studies ($n = 1008$). Institutional review board (IRB) approval for the study (P00010714) was obtained from the Committee on Clinical Investigation at Boston Children's Hospital. The IRB deemed this retrospective data review as minimal risk, and therefore a waiver of consent was also obtained and approved. All patients were evaluated with both a physical examination by one of nine urologists and an ultrasound study. Clinical examinations were performed by the same urologist at the initial and at the subsequent follow-up visits. A scrotal US with Doppler was performed by the Department of Radiology in addition to the clinical visit with a urologist. The protocol for US studies included imaging of both kidneys with escalation to a full and formal abdominal study if an abnormality was identified.

Demographic and clinical data were obtained for all patients. Information reviewed and collected included age at diagnosis and age at subsequent evaluations, number of follow-up visits and examinations, US studies (number of studies and reported findings including testicular volume measurements), and clinical evaluation (physical examination reports, surgical findings, and semen analyses). Individuals whose diagnosis of subclinical varicocele could be confirmed based on review of available records and US images, absence of clinical varicocele on physical examination, and lack of prior varicocele or inguinal surgery were included in the analysis. Patients whose US images were unavailable or insufficient for review and assessment were excluded, as were those who did not meet US criteria as defined below.

Ultrasound criteria for identification and assessment of subclinical varicocele

US studies utilized a high frequency ultrasound transducer with low-flow Doppler settings to optimize slow-flow detection within

varicoceles in all patients. A linear array transducer on the order of 5–10 MHz was used in older children and adolescents, while a smaller footprint, higher frequency transducer on the order of 6–15 MHz was used for evaluation of very small testes in infants and young children. Studies were performed using a number of different ultrasound machines, including an Acuson 128XP model (Acuson, Mountain View, CA, USA), GE Logiq 700 and Logiq E9 models (GE Medical Systems, Milwaukee, WI, USA), and Philips HDI 5000 and IU22 models (Philips Medical Systems, Bothell, WA, USA). Augmentation of venous flow was achieved by having patients perform a Valsalva maneuver which was more practicable and reliable in this pediatric population than by performing studies with patients upright.

Subclinical varicocele was defined as follows: (1) absence of a palpable varicocele on physical examination performed with the Valsalva maneuver; and (2) dilation of the pampiniform venous plexus observed on scrotal US with Doppler, involving 2 or more vessels with a diameter ≥ 2.5 mm (with or without Valsalva maneuver).¹² All US studies with available images and which were reported as suggestive of the development or resolution of subclinical varicocele were retrospectively reviewed by a single radiologist. While Doppler imaging was performed in all patients to demonstrate vascular flow, Doppler-determined velocity measurements were not consistently performed and could not be included in the dataset.

Ultrasound measurements for testicular volume and asymmetry

Testicular measurements of length (L), width (W), and thickness (T) were recorded in centimeters (cm). Volume was calculated utilizing the formula of $L \times W \times T \times 0.71 \text{ cm}^3$.^{3,31} Differences in testicular volumes between the affected, subclinical side and the contralateral unaffected or larger side were determined for each patient utilizing the testicular atrophy index formula: $(\text{contralateral [or larger] testis volume} - \text{affected testis volume}) / \text{contralateral (or larger) testis volume} \times 100\%$.³² Testicular asymmetry, defined as $>20\%$ difference in volume of the affected side compared to the contralateral unaffected side,³³ was determined for patients with a unilateral subclinical varicocele without a clinical contralateral varicocele or without bilateral subclinical varicoceles.

Identification of and assessment of progression to clinical varicocele

Clinical varicocele and grade were determined on physical examination according to the Dubin and Amelar classification system. Varicoceles were defined as follows: grade I = palpable venous dilation only during a Valsalva maneuver, not visible; grade II = palpable venous dilation without a Valsalva maneuver, not visible; and grade III = visible venous dilation without a Valsalva maneuver.³⁴

RESULTS

Patient demographics

We identified 98 patients (9.7%) in the varicocele database ($n = 1008$) with a diagnosis of "subclinical varicocele." Thirty-four patients were excluded due to misclassification as they were determined to have clinical varicoceles based on chart review. Another 3 were excluded for prior inguinal surgery. Four patients did not have US images available for review, and 19 had insufficient information on US studies. An additional two patients did not meet US criteria for varicocele on review. Thirty-six patients were confirmed to have subclinical varicocele suitable for further analysis (**Figure 1**). Twenty-five of these patients (69.4%) had a subclinical varicocele on the right, 8 (22.2%) on the left, and 3 (8.3%) were bilateral. Twenty-four patients (66.7%) had a contralateral clinical varicocele: in every case, there was a right-sided subclinical varicocele and a left-sided clinical varicocele. The mean age

at initial visit was 15.5 (range: 8.8–21.5) years with a mean follow-up of 26.5 (range: 1–86) months. The majority of patients (55.6%) had at least one follow-up US that included sufficient information with regard to testicular volume, venous diameter measurements, and assessment of flow reversal, as well as at least one follow-up visit with physical examination (75.0%), as shown in **Figure 2**. Seventeen patients (47.2%) had both follow-up examinations and US with sufficient data to assess for clinical progression. For this subgroup, the mean age at initial visit was 14.9 (range: 10.8–18.1) years with a mean follow-up of 32 (range: 4–86) months. Only two patients had a semen analysis recorded during the follow-up period.

Development of clinical varicocele

Of the 17 patients who had at least one follow-up clinical examination and US, only 3 patients (17.6%) – two with left-sided and one with

right-sided subclinical varicoceles – progressed to a clinical ipsilateral varicocele. None of these 3 patients underwent surgery, demonstrated asymmetric testicular volume, or were assessed with a semen analysis over the duration of recorded follow-up. Nine patients (52.9%) – 8 with right-sided and 1 with left-sided subclinical varicoceles – demonstrated persistence of a subclinical varicocele without progression. Five patients (29.4%), all with a right-sided subclinical varicocele, had subsequent resolution by physical examination and by US.

Testicular volume differences and testicular asymmetry

Differences in testicular volume were calculated in 35 of 36 patients (1 patient did not have recorded measurements included in the initial US). The majority of patients (75.0%, $n = 27$) did not have a volume difference of $>20\%$ between sides on the initial US. Nine patients had a unilateral subclinical varicocele without contralateral varicocele, either

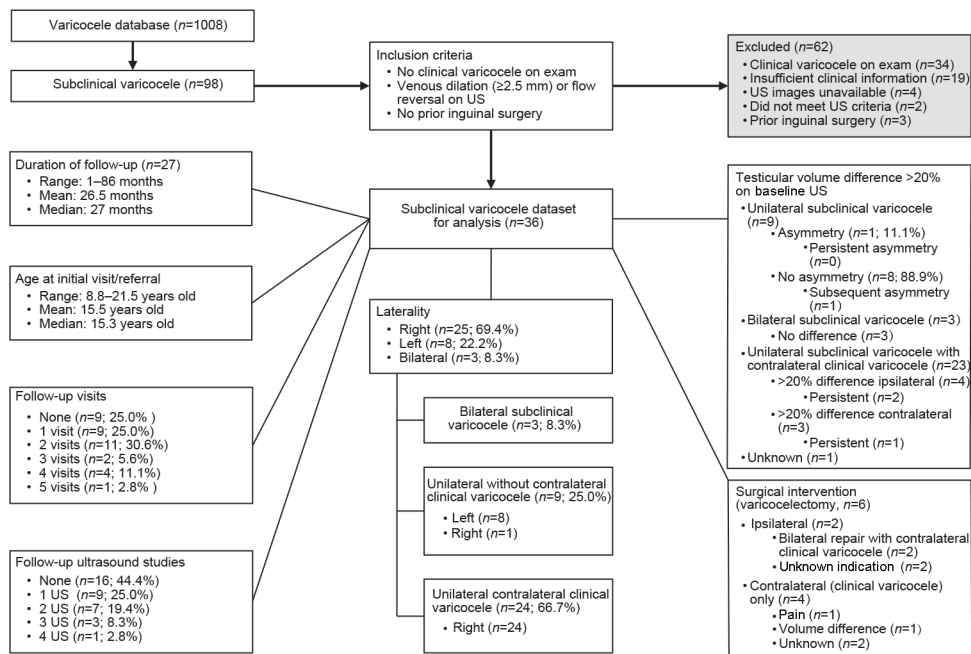


Figure 1: Subclinical varicocele patients. US: ultrasound.

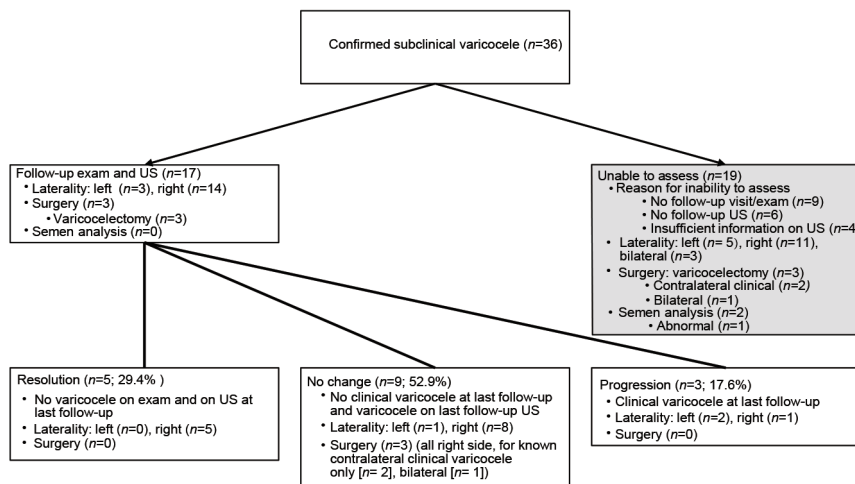


Figure 2: Subclinical varicocele patients with follow-up assessment. US: ultrasound.

clinical or subclinical. Testicular asymmetry attributed to subclinical varicocele was determined in these patients. Only one (11.1%) patient had asymmetry on the initial US, which did not persist at follow-up. Another patient demonstrated asymmetry on a subsequent study but did not undergo intervention during the follow-up period.

Three patients with bilateral subclinical varicoceles did not have a >20% volume difference between testes. The remaining twenty-three patients had right-sided subclinical varicoceles and clinical left-sided varicoceles. Four of these patients had a >20% testicular volume discrepancy. This was present on follow-up in 2 patients but did not lead to surgery during the timeframe of this study. Three patients had decreased left testicular volume that persisted in 1 patient who eventually underwent ipsilateral varicocelectomy.

Surgical intervention

Six patients (16.7%) underwent varicocelectomy during the period of follow-up. All of these patients were assessed at their initial visit and again in follow-up at least once before surgery. All six had a subclinical right varicocele and a clinical left varicocele. Of these patients undergoing surgery, 4 had surgical correction of the clinical varicocele alone, while 2 patients had repair of both the subclinical and clinical varicoceles. The indications for surgery for these latter 2 patients were unclear, as one had no evidence of progression from subclinical to clinical ipsilateral varicocele and the other had insufficient available information to assess for progression.

DISCUSSION

Current guidelines for male infertility associated with abnormal semen parameters recommend correcting only clinically palpable varicoceles, not subclinical varicoceles. This philosophy extends to the pediatric age group, where clinically palpable varicoceles associated with persistent testicular hypotrophy or with pain are repaired. However, management of subclinical varicoceles in the pediatric and adolescent population is not standardized, primarily because the significance of this finding as a predictor for subsequent clinical varicocele development and abnormal testicular maturation is unknown.

In our experience, we found that subclinical varicoceles occurred in only a small percentage of patients referred for evaluation. However, when present, they were likely to occur on the right side in the majority of patients, and most of these patients also had a contralateral left clinical varicocele. Of note, we observed one case of an isolated subclinical right varicocele that was not associated with intra-abdominal pathology but might reflect normal physiologic changes during adolescent development. While detection of subclinical varicoceles may be the result of improved US technology or its more widespread use,⁷ it is also possible that there may be underlying hormonally driven effects on the circulatory regulation of both testes, with differences in anatomy leading to a clinical varicocele on the left side and a lesser degree of dilation on the right side resulting in a subclinical varicocele. Most cases we observed did not appear to be associated with ipsilateral testicular hypotrophy or lead to surgical correction, although prophylactic intervention may be undertaken by some urologists at the time of repair of a contralateral clinical varicocele. The absence of an association between the presence of subclinical varicocele and testicular hypotrophy is in keeping with prior work showing no association between grade of clinical varicocele and testicular hypotrophy in adolescents as measured by scrotal US.³⁵

Regarding progression to clinical varicocele, Cervellione *et al.*⁶ previously reported that left subclinical varicoceles in children have been associated with progression in 28% of patients. In our study,

subsequent development of a clinical varicocele occurred in a minority of patients (17.6%) and was observed in cases of both left-sided ($n = 2$) and right-sided ($n = 1$) subclinical varicoceles. In our study, right-sided subclinical varicoceles were more likely to remain stable or to resolve (13 of 14 patients, 92.8%). This suggests that subclinical varicocele may represent a benign physiologic finding. In comparison, left-sided subclinical varicoceles seemed to progress to clinically evident varicoceles (2 of 3 patients, 66.7%). However, none of these patients had evidence of hypotrophy on follow-up imaging or underwent surgical intervention. Based on these data, it is uncertain whether patients who later develop a clinical varicocele will experience pain or impaired testicular growth requiring intervention. The only patients in our series who underwent varicocelectomy were those who had a contralateral clinical varicocele.

While this study contributes insights into the entity of subclinical varicocele, there are several limitations we wish to acknowledge. Specifically, the retrospective approach and available data led to the small number of patients who could be compared, and to selection bias of the database, thereby limiting our ability for more detailed analyses and generalizability. The paucity of available data was due in part to the variability in both the clinical examinations and US studies. Venous diameter measurements, documentation of flow reversal, and use of the Valsalva maneuver were not always performed. In our experience, there was variability in the timing of follow-up and imaging studies, with a short mean follow-up for many patients of only 2–3 years that limits a fuller assessment of progression and outcomes. Semen analyses were not routinely obtained as part of clinical management, and we were unable to assess impact on fertility in our patient population. While it would be ideal to calculate numbers needed to screen and to treat, this was not possible due to the small sample size and lack of long-term functional data. Consequently, conclusions involving function and development of infertility later in life cannot be made. These shortcomings, however, highlight areas requiring future study and will serve as the foundation for a rigorous prospective analysis.

Since some right- and left-sided subclinical varicoceles were observed to progress, and the long-term implications of this progression are currently unknown, it would be reasonable to monitor cases during pubertal maturation. Laterality may potentially influence how clinicians counsel patients and recommend interval follow-up. Our experience highlights the absence of standardized recommendations for serial monitoring of patients diagnosed with a subclinical varicocele. Prospective studies with longer follow-up to assess the correlation of left subclinical varicocele with standardization in scoring or classification, testicular size discrepancy, semen parameters, and fertility outcomes are clearly indicated.

CONCLUSIONS

Subclinical varicocele is a relatively uncommon finding with limited information available on long-term outcome, owing in part to challenges in both diagnosis and management. Most subclinical varicoceles identified in our cohort were right-sided and occurred in association with a left-sided clinical varicocele, suggesting their potentially incidental or benign nature. Although the majority of subclinical varicoceles in our patients did not progress to clinical varicoceles, impair testicular growth, or require surgery, a small percentage eventually become clinically evident, particularly those occurring on the left side. Although their long-term clinical significance remains unclear, it might be prudent to follow these patients as they could benefit from routine physical examination and US imaging, particularly if there are concerns for testicular size discrepancy, to

evaluate for the development of palpable varicoceles or to better assess testicular volume, and to obtain a semen analysis, if clinically indicated.

AUTHOR CONTRIBUTIONS

PSC, RNY, HJP, MAM, and DAD participated in the design of the study. RNY, MAM, XRL, and AV performed the chart review and data collection. HJP reviewed all available US studies. PSC performed the data analysis. PSC drafted and revised the manuscript, with RNY, HJP, and DAD providing editorial corrections only. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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