# Varicoceles in the pediatric population: Diagnosis, treatment, and outcomes

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Cite as: *Can Urol Assoc J* 2017;11(1-2Suppl1):S34-9. http://dx.doi.org/10.5489/cuaj.4340

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## Abstract

Varicocele is commonly encountered in adolescents. There are still many controversies regarding pathophysiology, health effects, clinical significance, and optimum treatment of this condition. This article reviews the current evidence pertaining to children and adolescents with varicocele. This group present a unique and somehow challenging situation, since they are still going through pubertal changes that may confound the effects of the disease and its treatment on the developing testes.

## Introduction

Pediatric varicoceles are common, affecting up to 15% of male children and adolescents.[1] There is controversy surrounding the urological management of varicoceles in the pediatric population.[1,2] Historically, surgical management of pediatric varicoceles was offered in higher grades or those associated with a discrepancy in testicular volume (size is >2 mL or >20% difference on the non-affected side) in order to prevent testicular function decline and infertility.[3,4] More recently, the use of surgical repair of varicoceles has been questioned with regard to whether or not it truly leads to improved clinical outcomes. Additionally, advances in surgical and radiological procedures, such as laparoscopic, microsurgical, and sclerotherapy techniques, have altered the landscape of management options for this condition.

## Etiology and pathophysiology

A varicocele is the result of an abnormal enlargement of the pampiniform venous plexus, the structure responsible for venous drainage of testicles to the gonadal vein trunci, pudendal and cremasteric veins. Varicoceles are predominantly seen on the left side. Experts believe that anatomical differences in venous drainage of the testicles could be a reason for this discrepancy.[5] The left testicular vein enters the renal vein while the right testicular vein enters the inferior vena cava. It was initially postulated there is a difference in hydrostatic pressure between the left and right side accounting for the differences in varicocele formation.[6] In particular, the differences in length of the left and right veins and the potential compression of the left testicular vein by the superior mesenteric artery and aorta in what is known as the "nutcracker effect" may lead to increased venous pressure on the left side.[7] Varicoceles are significantly more common in adolescents than in children; it is also postulated that the increased arterial blood flow to the testes at puberty exceeds the venous capacity, resulting in pampiniform venous plexus dilatation.[8,9]

Spermatogenesis is the testicular function most affected by the presence of a varicocele.[10] In adolescents with varicoceles, decreased sperm density, increased number of pathological forms, and decreased mobility have been observed, thus, suggesting varicocele-associated reduced fertility.[11] There are several postulated mechanisms by which a varicocele alters testicular function and fertility. These are outlined in Table 1. In brief, a combination of hyperthermia, hypoxia, renal and adrenal venous reflux, and increased hydrostatic pressure from the varicocele leads to increased free radicals and endocrine imbalance, and induces autoimmunity mediators that are disruptive to normal testicular function and fertility.[12]

## Epidemiology

Varicoceles are uncommon in boys under 10 years of age.[1] In adolescence, the prevalence of varicoceles typically ranges from of 10–15%.[1] In a retrospective review by Raman et al, increased varicocele prevalence was observed in first-degree relatives (particularly brothers) of patients with known varicoceles.[13] Up to 40% of adult men with primary infertility have a varicocele and prevalence rises to 81% in men with secondary infertility.[14]

## Diagnosis and evaluation

### Varicocele grading

A varicocele can be detected clinically on physical examination with the patient in a standing position. The clinical grading system proposed by Dubin and Amelar is commonly used and consists of the following:[15]

- Grade I: Only palpable on Valsalva maneuver.
- Grade II: Palpable with no Valsalva maneuver.
- Grade III: Visible with no need for palpation.

With widespread availability and use of ultrasound, the World Health Organization (WHO) has expanded the current grading system to include "subclinical" or Grade 0 (not palpable including during Valsalva) varicocele, which is only detectable by ultrasonography.

The relationship between varicocele grade and ipsilateral testicular hypotrophy is not clear. In a case series published by Kass et al involving 434 boys (age range 6–21 years) with palpable varicoceles, patients with Grade II and III varicoceles had a significantly smaller ipsilateral testicle compared to controls.[16] However, other studies have not shown the same correlation.[17] Thus, varicocele grade alone should not be used as an indication for surgical repair.

There is currently a paucity of available data on the effects of subclinical varicoceles on testicular size or long-term fertility. In a study by Cervellione et al involving 36 children (mean age 12.8 years) with subclinical varicoceles, 10 children (28%) had progressed to a clinically detectable varicocele at four-year followup while 24 (67%) remained unchanged.[18] Regular follow may be considered in these patients.

### Testicular asymmetry

Testicular asymmetry has generally been accepted as a potential indicator for long-term subfertility and, thus, an indication for treatment of adolescent varicoceles. Testicular size and volume can be estimated in the office with an orchidometer. Some studies have shown accurate correlation between testicular volume measurements from a Prader orchidometer and ultrasonography.[19,20] Others, however, support the use of ultrasonography as a more accurate modality to measure testicular volume and follow changes longitudinally.[21,22] Testicular volume is often calculated using the Lambert formula (volume=0.71 x length x width x height).[21] The accuracy of both the orchidometer and ultrasonography can be influenced by clinician experience and inter-examiner variability. Thus, a decision for surgery should be from several measurements in a consistent manner taken over a period of time.

**Table 1. Pathophysiology of varicocele**

| Proposed mechanism | Details |
| --- | --- |
| Hyperthermia | The scrotal position of the testicle allows for heat exchange between the pampiniform venous plexus and testicular artery regulating optimal temperature for spermatogenesis.[37] In humans, the presence of a varicocele leads to elevated temperature of the testicle and impaired spermatogenesis.[38,39] |
| Hypoxia | In rats, the expression of hypoxia inducible factor is elevated in the presence of a varicocele and subsequently decreases with repair.[40,41] It is postulated that stasis of blood could affect partial oxygen pressure and metabolism in the testis.[42] |
| Renal and adrenal reflux | In rats, it has been demonstrated that adrenal and renal metabolites are refluxed down the testicular vein and contribute to testicular damage.[43] Reflux of blood down the testicular vein has been demonstrated in patients with varicoceles.[44,45] |
| Abnormal blood flow | It is postulated that increased blood flow to the testicle may lead to increased hydrostatic pressure and change in the composition of the interstitial fluid.[46,47] This, in turn, can alter the paracrine communication between Leydig cells, myoid cells and Sertoli cells, altering spermatogenesis.[48] |
| Free radicals | It has been shown that increased concentration of free radicals, generated by conditions of hypoxia, hyperthermia, and endocrine imbalance in testes associated with varicoceles, leads to germ cell harm and testicular function impairment in humans.[49] |
| Autoimmunity | The presence of a varicocele can disrupt the blood-testis barrier and lead to increased antisperm antibody and altered spermatogenesis. This has been demonstrated in rats, but not humans.[12,50] |
| Endocrine imbalance | The hypothalamic-pituitary-testicular axis is central to testicular development and function. It is postulated that altered endocrine hormones as the result of the varicocele can lead to decreased testicular function. Increased luteinizing hormone (LH) results in Leydig cell hyperplasia, which is a known histological finding on varicocele testicular biopsy in humans.[51,52] Furthermore, Sertoli cell responsiveness to follicular stimulating hormone (FSH) is decreased in patients with varicoceles compared to those without varicoceles. Lastly, in adults, varicoceles have been shown to reduce testosterone.[53] Alterations in the hypothalamic-pituitary-testicular axis by the presence of a varicocele likely alter testicular function and fertility. |

Abnormal semen parameters have been correlated with testicular volume differentials as low as 10%.[23] Currently, threshold values for clinically significant asymmetry range from 10–20% relative difference in volume or an absolute differential of 2–3 mL.[23,24] On the other hand, Kolon et al observed that the degree of testicular asymmetry was reduced in up to 80% of adolescents with varicoceles due to catch-up growth of the smaller testicle without any intervention.[25] Thus, the challenge lies in selecting patients with testicular asymmetry who are unlikely to have spontaneous catch-up growth of the affected testicle.

### Sonographic parameters

Measurement of the peak retrograde venous flow (PRF) in the spermatic cord using Doppler colour flow imaging has emerged as a predictor for progressive testicular asymmetry.[26] PRF is measured with the patient performing the Valsalva maneuver in the supine position.[26] A retrospective review by Kozakowski et al assessing the PRF in 77 patients (age range 9–20 years) showed that catch-up growth is rare in patients with greater than 20% asymmetry and a PRF of greater than 38 cm/second (mean followup 13 months).[27] Poon et al had similar findings in a retrospective review involving 181 patients.[28] In patients with a PRF between 30 cm/second and 38 cm/second, data from various series show increased risk for developing progressive testicular asymmetry even when initial testicular asymmetry was less than 15%.[27,29,30]

Measurement of the maximum vein diameter (MVD) of the pampiniform plexus during Valsalva in adults is a prognosticator for semen parameters following varicocele repair, with an MVD greater than 3 mm preoperatively associated with favourable outcomes.[31] However, there is a paucity of evidence with regards to the diagnostic value of MVD in adolescents. MVD does not appear to be a reliable predictor of progression of testicular asymmetry.[27]

### Semen analysis

In a study involving 57 Tanner stage V adolescent males with varicoceles and testicular asymmetry (age range 14–20 years), Diamond et al performed semen analysis that showed decreased sperm concentration and total motile sperm count.[23] In a study by Moursy et al, 59 of 60 patients with a varicocele and less than 20% asymmetry managed conservatively were found to have normal semen analysis at age 18 (mean followup 79 months).[32] Others have also described normalization of total motile sperm count in two-thirds of Tanner V boys with uncorrected varicocele.[33] On the other hand, randomized trials have shown improvement in semen parameters following varicocelectomy (see *Treatment and outcomes*). There are no standard norms for adolescent semen analysis. Currently, the WHO adult standards are extrapolated to this group. In evaluating the data available thus far, the current role of semen analysis in the evaluation of adolescent varicocele remains unclear.

### Endocrine evaluation

The presence of varicocele has been postulated to affect testosterone production and, in turn, the hypothalamic-pituitary-gonadal axis. Multiple studies involving adult men have shown an improvement in testosterone levels post-varicocele repair.[34] Although testosterone measurements are affected by multiple factors, such as the assay technique itself, lifestyle factors and age, most recent evidence in adults suggest a positive relationship between varicocele repair and improvement in testosterone levels.[34,35] In a recent cross-sectional study by Daamsgard et al involving 7035 men (median age 19 years), 1102 (15.7%) men had a palpable varicocele.[36] The presence of a varicocele was associated with higher baseline serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels, and lower serum inhibin B levels, with a trend towards greater deviation from controls as varicocele grade increased.[36] There was no difference in baseline serum testosterone levels in those with varicoceles compared to those without.[36]

There are, however, practical considerations to bear in mind with regards to endocrine evaluation in adolescents. This includes defining standard norms for adolescents with varying tanner stages and the cost of testing and multiple blood draws, especially if done pre- and post-procedure. Taken together, the utility of obtaining baseline hormonal evaluation in identifying adolescents at risk for infertility has not yet been demonstrated and the significance of testosterone change pre- and post-intervention remains unclear.

## Treatment and outcomes

### Indications for treatment

The diagnostic evaluation of adolescents with varicoceles continues to evolve. Patients should be followed regularly with serial physical examination and assessment of testicular size as the bare minimum.

There continues to be a lack of consensus on the threshold for testicular asymmetry (10%, 15%, or 20%) that warrants varicocele intervention. The decision for surgery should be from several measurements taken over a period of time and in a consistent manner. The effect of ongoing pubertal changes and the possibility of spontaneous catch-up growth should be taken into account.

| Study or subgroup | Experimental Mean | Experimental SD | Experimental Total | Control Mean | Control SD | Control Total | Weight | Mean difference IV, fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Laven 1992 | 24.2 | 4.9 | 27 | 20.3 | 3.7 | 26 | 28.3% | 3.90 (1.57, 6.23) |
| Paduch 1997 | 16.9 | 5.1 | 88 | 14.5 | 4.7 | 36 | 44.1% | 2.40 (0.53, 4.27) |
| Yamamoto 1995 | 25.2 | 4.8 | 29 | 21.5 | 3.8 | 22 | 27.6% | 3.70 (1.34, 6.06) |
| Total (95% CI) | | | 144 | | | 84 | 100.0% | 3.18 (1.94, 4.47) |

Heterogeneity $Chi^2$=1.22, df=2 (p=0.54), $I^2$=0%
Test for overall effect Z=5.03 (p<0.00001)

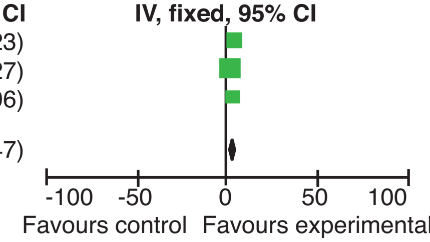


***Fig. 1.*** Forest plot of comparison between surgical or radiological intervention to conservative management, outcome: Changes in testicular volume. CI: confidence interval; SD: standard deviation.

Ultrasonography is an accurate modality for following testicular size, as it enables clinicians to compare previous images and measurements more precisely. In patients with testicular asymmetry, measurement of the PRF may be helpful in selecting which patients are likely to demonstrate catch-up growth vs. those who may benefit from early intervention. Based on the data available, surgical intervention should be considered in patients with a PRF of greater than 38 cm/second and concurrent testicular asymmetry greater than 20%.

In Tanner V adolescents, semen analysis can be considered as an additional way to assess testicular function. The semen analysis may help the patient and clinician in reaching a decision as to whether an intervention should be performed.

A plethora of different types of interventions to treat varicocele exist in the literature. These range from monitoring to open surgery. The procedural interventions may be divided into open, laparoscopic, and endovascular procedures. All the procedures involve occlusion of the testicular veins or pampiniform plexus. The anatomical site of occlusion varies from distal spermatic cord (low inguinal) to proximal testicular vein (retroperitoneal). Multiple variations in techniques have been reported, primarily to reduce postoperative failures and complications. Examples are arterial- and lymphatic-sparing approaches to reduce the risk of testicular atrophy and hydrocele, respectively.

Our group recently conducted a systematic review of randomized, controlled trials to assess the outcomes of radiological and surgical interventions for varicocele in children and adolescents. We did not include cases series and uncontrolled studies since they tend to overestimate the effect of intervention. In our meta-analysis of nine eligible studies at six months' followup, we demonstrated an improvement in testicular volume (mean difference 3.18 mL [95% confidence interval (CI) 1.94–4.42]) and in sperm count (mean difference 25.54 x $10^6$/mL [95% CI 12.84–38.25]) in patients who underwent radiological or surgical treatment as compared to conservative management (Figs. 1 and 2, respectively). Morphology and motility parameters were not changed significantly following intervention. Paternity rates following adolescent varicocele repair have not been evaluated in randomized, controlled trials. Nevertheless, Bogaert et al were not able to show any significant difference in paternity in an observational study that followed the participants for over 15 years.[54]

Lastly, there was no statistically significant difference in other variables, including operating time and length of stay, observed. Varicocele recurrence and hydrocele have

| Study or subgroup | Experimental Mean | Experimental SD | Experimental Total | Control Mean | Control SD | Control Total | Weight | Mean difference IV, fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Laven 1992 | 68.9 | 46.2 | 27 | 46.5 | 26.6 | 26 | 39.5% | 22.40 (2.20, 42.60) |
| Yamamoto 1995 | 73.9 | 31.2 | 29 | 46.3 | 28.1 | 22 | 60.5% | 27.60 (11.27, 43.93) |
| Total (95% CI) | | | 56 | | | 48 | 100.0% | 25.54 (12.84, 38.25) |

Heterogeneity $Chi^2$=0.15, df=1 (p=0.69), $I^2$ = 0%
Test for overall effect Z=3.94 (p<0.00001)

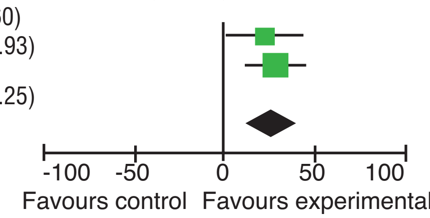


***Fig. 2.*** Forest plot of comparison between surgical or radiological intervention to conservative management, outcome: Sperm concentration. CI: confidence interval; SD: standard deviation.

been reported with a prevalence of 0–31% and 0–13%, respectively. The quality of the studies is moderate to low.

In conclusion, currently there is a moderate level of evidence that treatment of varicocele in adolescents may improve testicular growth and sperm density.

**Competing interests:** The authors report no competing personal or financial interests.

This paper has been peer-reviewed.

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