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The dilemma of adolescent varicoceles: Do they really have to be repaired?

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Abstract

The primary indication for varicocele repair in adults, that of failed paternity, must be substituted in the adolescent population with surrogate parameters of testicular size differential and semen analysis. Making recommendations based on these two parameters is incredibly difficult because studies often have contradictory findings, different patient populations, and lack of long term follow up of the key endpoint, paternity. Therefore, it is not a surprise that recommendations for adolescent varicocele repair are general (with some exceptions) and necessarily so because of limitations in quality of evidence. Apart from pain, all indications for varicocele repair in adolescence remain controversial. This highlights the most important task for future studies: to prevent pediatric urologists from allowing a potentially damaging process to go untreated, while at the same time avoiding unnecessary intervention on a highly prevalent condition.

A Historic Introduction

Although varicoceles have been operated on since antiquity - Celsus reported cauterizing varicoceles on the scrotum with thin, sharp hot-irons in the first century AD¹ - early thoughts on etiology and pathophysiology remained simple. The famous French surgeon Paré (1510–1590) who saw in varicoceles “a bundle of vessels filled with melancholic blood” where “the flow of thickened, dark venous blood stagnates in dilated, elongated convolutions”², was probably the first to understand the deleterious effect of blood stasis in varicoceles. The Ottoman surgeon Serefeddin Sabuncuoglu believed that the cause of this disease was “filthy blood”³, a theory that with a small amount of imagination can be seen as a nascent idea of toxic metabolites being involved in the pathophysiology of varicoceles.

Until the 19th century, pain or the inability to ride horseback was the primary indication for surgical treatment.² However, until the refinement of hygienic and aseptic standards, varicocele surgery (such as ligation or cauterization) remained dangerous with gangrene,

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sepsis and bleeding as common complications². In spite of the tremendous progress made in surgery around 1900, especially in Central Europe (which introduced inguinal approaches to varicocele surgery)², conservative treatment like scrotal support or changes in lifestyle remained the most widespread principle of varicocele therapy.

The association of varicocele and fertility disorders was not discovered until the 1950s⁴. This, together with the development of more sophisticated inguinal and retroperitoneal ligation methods led to marked increase and success of varicocele surgery.

However, procedural success with a low complication rate alone and the assumption of improved fertility in the adolescent population may not have enough evidence to support surgical intervention. Therefore it is not a surprise that recommendations for adolescent varicocele repair are general (with some exceptions) and with limited evidence⁵. This review will try to bring all of the scientific and not so scientific literature together and reach conclusions regarding the appropriateness of correcting varicoceles in this population. This attempts to provide an understanding of the basic pathophysiology for each of the four relatively accepted, but debatable, indications for varicocele repair and their application in adolescents: abnormal semen analysis (SA), pain, testicular size asymmetry and infertility.

Epidemiology

The prevalence of varicoceles in prepubertal children is low (<1 % in boys under 10 years)⁶ and increases during puberty to a prevalence of 15%⁷, which is similar to that seen in adults. Although most adolescents are without symptoms and identified by routine screening or self-examination, approximately 5% can present with a dull, aching or sharp scrotal pain⁸. Those that do present with pain are more likely to have a higher grade varicocele⁹. The vast majority of varicoceles in adolescents are left-sided; isolated right-sided varicoceles are exceedingly rare.

Interestingly, men who present to fertility clinics have a varicocele prevalence of 20–40%¹⁰, whereas 80% of men with a varicocele diagnosed during adolescence are fertile¹¹. This discordance emphasizes the need for a thorough understanding of the underlying pathophysiology to help identify the patients who would benefit from treatment prior to attempts at paternity.

Etiology

The increased preponderance of left sided varicoceles is thought to be secondary to right and left anatomic differences. The left internal spermatic vein (ISV) is longer and inserts at a more acute angle into the renal vein compared to the right, which inserts into the inferior vena cava. Furthermore, its insertion into the renal vein can lead to outflow stasis with left renal vein disease (i.e. nutcracker phenomenon). After evaluating hundreds of right and left ISV venograms in patients with varicoceles, the investigators found a higher number of sufficient valves in the right ISV¹², making the left side more prone to varicocele development.

The etiology leading to dilated spermatic veins in the pampiniform plexus has been attributed to incompetent valves. However, collateral venous drainage has been demonstrated to play a role in some adult series^{12,13}. One retrospective review divided patients based on age (<17 years & >25 years) and the adolescent left ISVs were more likely to be incompetent (86% vs 72%), more likely to have a single ISV outflow (94% vs 72%), and have less collateral venous drainage (56% vs 71%)¹². These findings help support the theory that adolescent varicoceles are more likely secondary to congenital venous valve abnormalities. However, this must be interpreted cautiously as the same study identified a higher prevalence of nutcracker phenomenon in the adolescent group (23% vs 5%). This absent or faulty valve system or compression of the ISV from the left renal vein increases the venous pressure in the dependent scrotum causing venous dilation and stasis. The abnormal spermatic vein architecture in varicoceles is further supported by the degradation or absence of the smooth muscle layers in varicoceles¹⁴.

To maintain testicular homeostasis a temperature 2–4°C below body temperature is required¹⁵. In order to accomplish this, the scrotum lacks subcutaneous fat insulation and the scrotal surface area changes with change in temperature, thus bringing the testicles closer or further away from the core body temperature. Additionally, the thermoregulatory mechanism of the countercurrent heat exchange between the incoming arterial blood and the draining venous blood in the spermatic cord allows for pre-cooling of the arterial blood¹⁶. With the presence of dilated veins and poorly draining venous blood within the spermatic cord, the venous blood inadequately remains cooler than the arterial inflow and this temperature gradient is depressed. With the use of a percutaneous temperature gauge, elevated intratesticular and scrotal skin temperatures have been measured in patients with varicocele¹⁷. Interestingly, a unilateral varicocele was shown to elevate the contralateral scrotal surface¹⁷. This highlights that a unilateral varicocele can potentially cause contralateral testicular dysfunction. Multiple experimental studies in animal models have shown decreased testicular size, spermatogenesis, and testosterone positive leydig cells with application of exogenous heat^{18,19}. This is further supported by studies demonstrating abnormal semen parameters and infertility in men with prolonged genital heat exposure (e.g. professional drivers, paraplegic men in wheelchairs, ceramic oven operators)¹⁶. On a cellular level, hyperthermia has been shown to cause oxidative stress leading to elevated free radical production leading to both germ and leydig cell injury^{15,20}.

We have outlined how varicoceles may be toxic to the testis, which could result in size difference, abnormal SA, or infertility. Although it has been hypothesized that the varicocele adds weight to the scrotum causing tension on the spermatic cord leading to chronic, dull, aching testicular pain, the mechanism linking varicocele and testicular pain has yet to be elucidated²¹.

Clinical Evaluation and Outcome

Fertility

In adults, the gold standard to measure varicocelectomy success for infertility is paternity, and there is strong evidence that varicocelectomy improves fertility^{22–24}. Obviously, this cannot be tested in adolescents as the majority are not attempting to father children. It is

likely that adolescent varicocele persists in adulthood, since prevalence is similar. Surgery is therefore preventative, which requires stricter justification than therapeutic surgery. Even stricter criteria apply for preventive surgical procedures in adolescents, who cannot fully weigh the evidence themselves and cannot legally consent to the procedure²⁵. Therefore, strong evidence is needed before recommending surgery for fertility reasons to adolescents.

Bogaert et al. contacted patients >30 years of age that were diagnosed with a grade II or III varicocele during adolescence to evaluate paternity. Effective paternity was 85% (61/72) in the non-repaired group and 79% (67/86) in the treatment group ($p>0.05$) with similar distribution of varicocele grades and similar rate of testicular asymmetry among the groups¹¹. They concluded that adolescent varicocele repair had no influence on paternity rate. However, the incidence of testicular asymmetry (measured by Prader orchidometer) in this study was relatively low (8%)¹¹ compared to other studies where asymmetry was described in up to 50–77%²⁶, making comparison difficult and potentially underestimating the effect of varicoceles on asymmetric testicles. In addition, the varicoceles in this study were treated angiographically without evidence of resolution on follow-up, indicating the possibility of diluting any true effect, and the survey response rate was only 53%.

There is likely a subgroup who would benefit from an early repair, but we currently do not have the tools to identify these patients. At presentation, the adult patient has likely reached testicular maturity, whereas the adolescents are at varying stages of puberty and maturation making evaluation of the substitute parameters of future fertility and gonadal function (testicular size, SA, and testosterone levels) moving targets.

Testicular Volume

The European Society of Pediatric Urology (ESPU) guidelines from 2015 indicate repair for a volume difference of >2 mL or 20%⁵. Comparison of absolute testis volume is difficult as the variation of testis volume through adolescent time period can vary by ~10 mL for normal males at the same chronological age²⁷. Thus, comparison of testes volumes to each other potentially makes this our best reference. This should be done cautiously as grade III left varicoceles have been shown to correlate with smaller right testicles in Tanner stage IV & V males²⁸. The 20% cutoff for intervention is derived from testicular volume measured by ultrasound using the Lambert formula ($L*W*H*0.71$)²⁹ and SA assessment in Tanner Stage V males with left varicoceles. Sperm concentration, % motile, and total motile count (TMC) were significantly lower at >10% differential, and even more pronounced at >20% differential³⁰. Others have not been able to demonstrate the association between differential testicular volume and SA findings³¹.

With the potential that a unilateral varicocele can cause contralateral changes¹⁷ and conflicting evidence of testicular differential volumes correlation with SA^{30,31}, could evaluation of total testicular volume be more prudent? Tanner V males with a total testis volume <30 mL have an increased likelihood of low TMC^{31,32}. Even those patients with varicoceles and symmetric, normal volume testes have a 45% risk of having an abnormal TMC on initial SA³³.

Taking a single snapshot in time for either testicular differential or total testicular volume may lead to overtreatment. In an attempt to understand the temporal changes in left testicular hypotrophy, >50% who originally met the 15%³⁴ and 10%³⁵ volume differential criteria for repair were spared surgical intervention after yearly ultrasound because of asynchronous testicular growth^{34,35}.

This approach becomes even more confusing as our methods of measurement are fraught with their own inaccuracies. Volume measurement directly reported by ultrasound machines provide default measurements based on the formula for an ellipsoid ($L*W*H*0.52$)³⁶, when it should be using the Lambert formula²⁹. The use of an orchidometer when compared with ultrasound findings has been shown to have significant overestimation^{27,37} and have a very poor sensitivity (33%) when using a 20% volume differential cutoff for intervention³⁷. Conversely, subjective cursor placement when making ultrasound measurements may lead to inappropriate recommendations as well³⁸. It has also been shown that different formulas for calculating testicular volume differential vary considerably³⁹. For example, a 15% differential in one formula ($(\text{Right Testicular Volume} - \text{Left Testicular Volume})/\text{Right Testicular Volume}$) as used by Khasnavis et al³⁵ amounts to only an 8 % differential in a second formula ($(\text{Right Testicular Volume} - \text{Left Testicular Volume})/\text{Total Volume}$)³⁹. This makes comparison between studies regarding catchup growth and implications in terms of SA difficult.

There is a high probability of normalization of testis volume differential after varicocelectomy. A meta-analysis identified 14 studies (13 retrospective & 1 prospective) which demonstrated that testis volume differential was significantly reduced after surgery in studies that used 10% and 20% as the testis volume differential as the indication for repair. The average catch-up growth was 76.4%⁴⁰. The absence of a control arm in the 13-retrospective series increases the likelihood of regression to the mean (initial outliers have more normal measurements when examined serially). This is further supported by the findings of asynchronous testicular growth over time in this population without repair^{34,35}. The single prospective study from this meta-analysis that had a control arm found that 15% of the repair group and 70% of the control group had persistent testis differential >20% at 1 year follow up with scrotal ultrasound⁴¹. This supports that varicocelectomy likely aides in testicular differential normalization in the adolescent population, although this remains in question. One study suggests that at least a portion of the normalization may be attributed to interstitial edema due to division of lymphatic vessels.⁴²

Semen Analysis

Semen analysis parameters provided by the WHO were derived from normal adult males⁴³. Strong studies have been performed understanding the change in testicular volume through childhood and adolescence²⁷, but the same has not been done for SA parameters. In an attempt to understand this a few decades ago, 274 SAs from 134 normal adolescent boys were evaluated and found that from the time of first ejaculation azoospermia dominates until the fifth month, oligozoospermia from the sixth to the eleventh month, and normospermia after the twenty-first month. Additionally, TMC reaches normal levels almost two years after the first ejaculation⁴⁴. These findings are supported by the findings that 47% of Tanner V

males with symmetric normal volume testis and a varicocele with an initial poor TMC improved over time to normal TMC without surgery³³. When evaluating a similar population of males with a varicocele and normal testicular volumes, sperm concentration and forward motility were not found to be associated with age⁴⁵. For those with significant testicular volume differential, as mentioned above, there is a significant decrease in SA parameters^{30,46}, although not shown uniformly³¹. These studies strengthen the argument for longitudinal assessment of SAs in symmetric testicles and it provides a topic of debate in asymmetric testicles as we are unsure how their SAs change over time.

The studies evaluating adolescent SAs demonstrate that varicocele presence increases the likelihood for abnormal SAs, although the correlation with varicocele grade has not been made^{30,32}. A prospective study evaluating 14–18 year old males found a trend of TMC significantly decreasing with increase in varicocele grade with grade III having an average TMC of 31 million⁴⁷. Interestingly, this is still above the accepted cutoff defining a TMC of 20 million as abnormal⁴⁸. Should our TMC cutoff be higher for adolescents if we feel that the SA will worsen over time with persistent varicocele? We need to interpret the SA cautiously, but its findings may be strengthened by trending SAs overtime.

Broaching the topic of SA collection can be uncomfortable for the patient and parents⁴⁹. Additionally, a surprising fraction of practitioners are also uncomfortable or unfamiliar with the topic as multiple practitioner surveys demonstrate that only 31–47% obtain a SA during varicocele evaluation^{49–51} and only 22% obtain SAs longitudinally⁴⁹.

Assessing the improvement in SA after varicocelectomy is predicated on obtaining a SA post-operatively. Unfortunately, only 8% of practitioners routinely obtain a post-operative SA⁴⁹ and this contributes to the paucity of SA outcomes in the literature. One study demonstrated significant sperm concentration and sperm motility improvement of 9 million/mL and 11% respectively in adolescents after varicocele repair⁵². The lack of a non-surgical group in this, along with other studies evaluating this topic, makes it difficult to discriminate the normal changes seen over time in adolescent SAs with or without varicoceles^{33,44}. Improvement in TMC has been demonstrated in a group of 17 adolescents with testicular symmetry undergoing repair. While over 80% of patients had improved TMC postoperatively, only approximately half of patients achieved a normal TMC with repair⁵³. Interestingly, spontaneous improvement in TMC was seen in the same cohort with 47% achieving normal TMC without treatment of the varicocele³³. Most importantly, we don't know if changes in adolescent SA after varicocele repair leads to a change in paternity rate.

Pain

Of all the adolescent indications pain is probably the most accepted. Conservative treatment for pain relief (such as scrotal support or non-steroidal anti-inflammatory drugs) has been shown not to be effective^{54,55}. Although data on pain improvement does not exist specifically for adolescents, data from a recent meta-analysis in adults suggests that there are differences in who will benefit from surgery⁹. Overall resolution rate was 61 – 100 %, with the majority of the studies showing a resolution rate > 85%⁹. The resolution rate for patients with dull pain was slightly, but significantly higher than for those with sharp pain. No significant correlation between varicocele grade and pain resolution postoperatively could be

found. Pain resolution rate was significantly higher after subinguinal repair than after high or inguinal repair and pain resolution rate was significantly higher after microsurgery than after laparoscopic repair. Also patients with higher BMI are more likely to not experience sufficient pain resolution⁵⁶. Since persistent pain can lead to self-implemented physical restrictions and significant relief of discomfort has been demonstrated with repair, varicocele repair is indicated for these adolescents.

Hypogonadism

Androgen deficiency is an indication only 4% of surveyed pediatric urologists consider appropriate for adolescent varicocele repair⁵¹. Evaluating the pituitary-gonadal axis during the pubertal period is incredibly variable and dependent on age and Tanner stage^{26,57}. Hormonal profile evaluation in normal boys showed that 23% and 58% of Tanner IV & V boys, respectively would be considered eugonadal by adult guidelines (testosterone >350 ng/dL)^{26,57}. A meta-analysis evaluating changes in testosterone level after adult varicocele repair included 9 of 125 studies and found that with repair there was an increase in testosterone level by 97 ng/dL⁵⁸. This is encouraging, but as with testicular volume and SA this period of adolescent maturation makes it difficult to assess the varicocele's effect on testicular function without prospective studies.

Special clinical situations

Isolated right-sided varicoceles require a thorough workup with abdominal imaging to rule out a retroperitoneal mass, such as Wilms tumor⁵⁹ or situs inversus⁶⁰ as the underlying cause. There is very little data on varicoceles after previous inguinal surgery. After orchidopexy there seems to be an increased rate of intratesticular varicocele⁶¹; and in general previous inguinal surgery does not seem to affect efficiency or safety of varicocele repair⁶². There is no literature on varicoceles in solitary testis, and therefore decision-making should be based on individual situations. Although testicular loss is rare, it would lead to anorchia. Thus, waiting until the patient attempts paternity or is of age to consent for the procedure is advisable.

Conclusion

Apart from pain, all indications for varicocele repair in adolescence remain debatable and managing the balancing act between overtreatment and missing patients who would benefit from repair in adolescence will be the most important task of future studies. The published guidelines and best practice statements based on non-randomized studies, retrospective reviews, and expert opinion from the American Urological Association, European Association of Urology, American Society of Reproductive Medicine, and the ESPU all provide general recommendations for intervention with regard to testicular hypotrophy and abnormal semen parameters⁵. Other than the ESPU (testis <2 ml or 20% differential volume), specific testicular volume or SA parameter cutoffs for intervention are not included.

Randomized controlled trials (RCT) with paternity as endpoint to identify subgroups who would most benefit from treatment are needed and will be difficult to implement. An attempt

at an RCT in our institution failed to recruit. In the presence of persistent testicular hypotrophy and/or abnormal SA, both parents and the patient are likely to find it difficult to enroll in a trial where intervention bares very low risk with potential preservation of fertility. This dilemma questions the ethicality of a trial like this and illustrates the limitations of evidence-based medicine.

Although making concrete recommendations based on testicular volume and SA for adolescent repair of varicoceles is incredibly difficult because of studies with contradictory findings, different patient populations, and lack of long term follow up with paternity endpoints, we have observed themes within these studies that have led to three conclusions:

1. Since fertility cannot be measured in adolescence, substitute parameters must suffice in decision-making. Because their significance is mitigated by inherent inaccuracies or lack of confident prospective long-term data, no single parameter in isolation should be decisive.
2. Testicular size, volume differential and semen analysis should be obtained prior and if possible after repair. This will provide confidence to the physician, patient, and caregivers when deciding the need for intervention and also help with counseling regarding fertility potential after repair. SA is the next best parameter of fertility after paternity, and scarcity of available longitudinal data can be augmented by trending SAs over time.
3. Since temporal changes in testicular volume and SA emphasize the need to trend these parameters over time, asymptomatic varicocele repair should most likely not be offered after evaluation at a single time point. Repeat ultrasound and/or SA yearly will help better counsel and likely stratify those that truly need repair because of worsening parameters.

Ultimately, we as pediatric urologists are repairing varicoceles for concern of future loss of fertility. We do not know what percentage of patients will have non-recoverable infertility if we wait to perform varicocele repair after the patient attempts paternity; and because of this we unnecessarily treat a significant number of patients. Is it safe to perform yearly SA and follow testicular volume until they are of age to consent for the procedure themselves? Or until we identify persistence or worsening of these parameters? Probably, but when will we have the prospective longitudinal data to support this?

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