Curr Urol Rep (2012) 13:311–317
DOI 10.1007/s11934-012-0256-y

PEDIATRIC UROLOGY (R GRADY, SECTION EDITOR)

Varicocele in Adolescence: Where Are We Now?

Laura S. Merriman · Andrew J. Kirsch

Published online: 27 May 2012

Abstract The exact pathophysiology of varicocele and the subsequent alteration of spermatogenesis has been the subject of much debate. Despite an enormous amount of literature on the subject, the appropriate management of varicocele in the adolescent patient population has not yet been clearly elucidated. While not every male with varicocele will be subfertile, the possibility potentially lends credence to early diagnosis for those in whom treatment will have an impact.

Keywords Varicocele · Adolescent · Pediatric urology

Introduction

In 1954, Dr. J. K. Russell observed a relationship between varicocele and poor semen quality. He concluded that it was imperative to "challenge the traditional attitude that varicocele is an innocuous condition and to stress the need for more extensive investigation into the natural history of varicocele and the effect which it may have upon fertility" [1]. Nearly 60 years later, we continue to grapple with the question of varicocele and its impact on fertility.

The bothersome dilation of the pampiniform plexus and testicular vein affects up to 15 % of postpubertal adolescents, an incidence approaching that of adults [2]. The matched incidence as well as the potentially devastating consequence of infertility gives weight to the diagnosis of varicocele. However, while 40 % of men with primary infertility have a varicocele [3], only 20 % of men with clinically proven varicocele are infertile [4]. The primary rationale for the management of varicocele in adolescence is the preservation of future fertility. However, for all the studies showing a direct correlation between varicocele and infertility, there are just as many that question this tenet.

L. S. Merriman (✉) · A. J. Kirsch
Children's Healthcare of Atlanta, Emory University,
5445 Meridian Mark Road,
Atlanta, GA 30342, USA
e-mail: laura.stansell@emory.edu

Taken in isolation, this incongruous data could lead to overtreatment and unnecessary surgery in adolescent males; therefore, it is necessary to understand how varicocele may potentially affect fertility to determine how it might impact the individual patient.

Diagnosis

Most simply, varicocele is an abnormal dilation of a venous plexus as a result of incompetent or congenitally absent venous valves. Varicocele has been identified on the left more than 90 % of the time [5]. It is the more cephalad course of the left gonadal vessels and insertion into the comparably smaller renal vein, as opposed to the inferior vena cava, that might explain this predilection. Certainly, more men would be diagnosed with varicocele by virtue of typical anatomy; therefore, it is more likely that varicocele is a composite result of multiple factors. Secondary varicocele is described as an abnormal dilation of veins as a result of extrinsic compression (ie, retroperitoneal mass).

Varicocele typically presents as painless or occasionally uncomfortable scrotal mass. The most common differential diagnoses include hydrocele, hernia, epididymal cyst, and spermatocele. It should be noted that secondary varicoceles might not noticeably decompress with a change in position to supine; therefore, it is imperative to perform the physical exam in both standing and supine positions. Valsalva maneuver is a necessary adjunct to aid the clinician in examination of subtle dilations of the venous plexus. A survey from Kubal and colleagues suggest that a significant number of pediatricians (from an 11 % respondent rate) do not routinely perform an appropriate physical exam to detect varicocele [6]. The classification of varicocele according to Dubin and Amelar [7] is listed in Table 1.

It is also the clinician's responsibility to give careful assessment of testicular size and turgor in relation to each testis. This data may be most useful in the setting of serial exams to document changes in volume over time. Accuracy of different techniques to determine testicular size, such as the Prader or Takihara orchidometers, is subject to the clinician's experience [8]. The use of ultrasound should be considered the most accurate method of measuring testicular volume [9]. Diamond et al. [9] evaluated 65 men (age range: 7–24 years) in whom ultrasound and orchidometer assessment were compared for accuracy. They found the sensitivity of manual orchidometers in detecting a volume difference was less than 50 %; therefore, more than half the patients with a significant volume differential would be missed on physical exam alone.

Consequences

Correction of varicocele has been recognized as a maneuver to improve fertility in adult men [10]. The diagnosis of varicocele in adolescence presents a special population for which the natural history of varicocele might be impacted by early treatment. It is currently unknown whether fertility potential is improved, impaired, or unchanged by aggressive management of varicocele in adolescence. It was the conclusion of a Cochrane review of eight randomized controlled trials that treatment of varicocele showed no benefit in conception outcomes when it is the only proven finding in an infertile couple [11]. However, observations in the literature of impaired testicular growth and altered semen parameters in adolescents continue to evoke a measure of concern.

Numerous etiologic factors have been implicated as the source of testicular dysfunction that results from the presence of varicocele. Among these are hypoxic conditions, elaboration of reactive oxygen species, and hormonal derangements, which may have direct consequences on testicular growth and spermatogenesis.

Table 1 Classifications of varicocele

Subclinical	Impalpable Veins>3 mm on ultrasound Doppler proven reflux with valsalva maneuver
Grade I	Palpable with Valsalva maneuver only
Grade II	Palpable at rest (without Valsalva)
Grade III	Easily visible at rest

Hypoxia/Oxidative Stress

The pathophysiology of subnormal spermatogenesis has been theorized to be the result of oxidative stress through elevated scrotal temperature and the production of free radicals [12]. Although alterations in temperature have been well documented, it is the consequence of hypoxia that may be the root cause of impaired spermatogenesis. Hypoxia within the testicular microenvironment and the proliferation of reactive oxygen species may occur through a variety of mechanisms. Through analysis of fluid mechanics, Gat et al. [13] sought to implicate hydrostatic pressure as the source of hypoxia through observation of more than 700 venographies at the time of sclerotherapy. The authors conjectured that elevated pressure within the venous microcirculation disallows arterial inflow, resulting in a hypoxic state. Kilinc et al. [14] support hypoxia as the potential etiologic factor for impaired spermatogenesis by demonstrating an upregulation of hypoxia inducible factor (HIF) and vascular endothelial growth factor in experimentally induced varicocele in rats. The upregulation of HIF might represent an adaptive response of the testis to protect itself in a low oxygen environment. In adults, Lee et al. [15] also observed an increase in HIF in patients with grade 3 varicocele as compared to control patients. Perhaps the relative magnitude of upregulation may confer prognosis; the more the testis is exposed to hypoxic conditions, the more HIF will be produced.

Beyond simple observation of hypoxia, others have focused on the toxic byproducts of anoxic conditions. Hendin and colleagues [16] confirmed the occurrence of oxidative stress in the presence of varicocele; however, they stopped short of identifying a direct relationship between reactive oxygen species and altered spermatogenesis. They noted presence of reactive oxygen species in 80 % of their cohort, comprised of infertile men with varicocele, compared to 20 % of control patients. Furthermore, they noted a significant number of men (77 %) with incidental finding of varicocele, irrespective of fertility status, were noted to have elevated reactive oxygen species. In terms of spermatogenesis, Gomez and colleagues [17] have noted that immature spermatozoa produce higher concentrations of reactive oxygen species. This in turn, may affect mature sperm, as Gil-Guzman et al. [18] have found a higher incidence of DNA damage observed in mature sperm in the presence of immature spermatozoa.

To evaluate the effects of surgical intervention on the resolution of oxidative damage, Chen et al. [19] prospectively examined the semen quality of 30 infertile men diagnosed with varicocele by either ultrasound or physical exam.

In their study, 40 % of the cohort exhibited elevated markers of oxidative DNA damage before surgery, which decreased to 13 % after surgical intervention. Overall, 73 % of their cohort had improved semen parameters on a single sample after surgical intervention; however, there was no correlation to fertility status. Cocuzza and colleagues [20••] performed an interesting comparison between fertile men with grade 3 varicoceles and a control group of infertile men with varicocele as the only identifiable cause of infertility. They noted a significant difference between sperm concentration and the presence of reactive oxygen species among varicocele grades. They noted a higher concentration of reactive oxygen species and decreased sperm count in grade 3 varicocele in both fertile and infertile men.

Hormone Imbalance

Because the frequency of testicular dysfunction is difficult to quantify in adolescents, gonadotropin response has been utilized as a proxy to determine the effect of varicocele on the hormonal milieu. To this end, gonadotropin-releasing hormone (GnRH) is injected to evaluate the negative feedback loop involving luteinizing hormone (LH) and follicle-stimulating hormone (FSH). If the feedback loop is defective, then elevated levels of LH might indicate Leydig cell dysfunction and a surge in FSH might indicate failure of the seminiferous tubules. Kass et al. [21] evaluated 104 boys to correlate pituitary gonadal dysfunction and varicocele, and found an altered hormonal response in 30 % of the cohort. However, difficulties arise in hormone testing because levels may fluctuate in peripubertal children. In adult studies, it has been suggested that a poor initial result from GnRH stimulation may predict men who will be most at risk for future infertility as well as those who might derive the greatest benefit from surgical intervention [22, 23].

Testicular Growth

In 1955, W. Selby Tulloch reported on the impact of varicocele repair on fertility. In men with varicocele, he observed that the testis was “sometimes smaller than normal and showed evidence of softening to a varying degree” [24]. Arrest of testicular maturation in terms of volume is the most often cited consequence of varicocele in adolescents. More than half of the constituent makeup of the testis is reflected in the development of seminiferous tubules and germinal elements. In puberty, the size differential may be amplified due to the exponential growth of the testis expected at this stage. Testicular size is a useful and easily observable parameter; however, it suffers the limitation of interobserver variability that may affect the interpretation of clinical studies. There are conflicting reports in the literature: those that both positively correlate the degree of varicocele to hypotrophy [25] and those that negate this relation [26].

Kass and Belman [27] noted the potential for reversal of testicular hypotrophy with surgical correction in a prospective evaluation. They observed “catch-up” growth in 80 % of their cohort. Many have corroborated this evidence of catch-up growth; however, the question as to whether this will impact future fertility remains the primary concern. Hypothetically, testicular growth may be a positive stimulus for the development and maturation of seminiferous tubules and germ cells. In an attempt to correlate the occurrence of growth arrest and varicocele size, Thomas et al. [25] retrospectively reviewed 117 male patients (ages 7 to 18 years) treated nonoperatively for evidence of testicular growth arrest on initial or subsequent examinations. They found that the presence of varicocele, irrespective of size or grade, is at risk for testicular hypotrophy, with a slightly higher risk demonstrated in grade 3 varicocele.

Akbay et al. [28] theorized varicocele is a potentially progressive disease by the observation that the incidence of varicocele in adolescence increases with age. Authors have historically come to the conclusion that hypotrophied testes are observed with increasing frequency in the peripubertal age group, leading to a conclusion that earlier development of varicocele has a greater impact on testicular growth [29]. Diamond et al. [30] refuted this concept by following 41 boys (ages 7.3 to 19 years) with unilateral varicocele over at least two sequential exams separated by a mean of 16 months. They found no change in grade or testicular volume over time. The disparity in the literature casts aspersion on the hypothesis of testicular hypotrophy as a direct correlate to impaired spermatogenesis. It seems hypotrophy is an imperfect surrogate for future fertility potential. The problem of testicular hypotrophy is further clouded by the fact that up to 70 % of adolescents with varicocele will present with impaired testicular growth on the initial exam [28, 31]. The influence of puberty on testicular growth in the setting of varicocele is not easily discernible, and may cloud interpretation of studies showing improvement with surgical intervention.

If varicocele was progressive or if testicular hypotrophy conferred possible future infertility, then treatment at an early stage would potentially confer a benefit. The parameters most readily observed in children and adolescents are testicular size and turgor, the measurement of which suffers from an assortment of possible techniques and interobserver variability. It is vitally important to note the methods of measurement, the consistency of application, and the threshold for volume discrepancy utilized in the literature.

Cayan et al. [32] measured 39 children and adolescents 11 to 19 years of age using the Prader orchidometer and gauged a physiologically significant difference as a 10 % discrepancy. In their study, 19 of the 39 patients presented with testicular atrophy, with 10 of these regaining “normal testicular growth”; however, they used a stricter threshold of discrepancy than the more often cited 20 % difference. They further observed that repair of varicocele at younger than 14 years of age conferred a benefit in terms of catch-up growth while repair after 14 years of age did not.

Spinelli et al. [33] evaluated 54 patients (ages 13 to 16 years) with unilateral varicocele using 20 % as their threshold for discrepancy. In this cohort, volumes were measured with ultrasound using the prolate ellipsoid formula. The patients were separated into treatment and observation groups and followed for 1 year. They noted significant catch-up growth in 85 % of the immediate surgery group compared to 30 % of the observation group. The authors astutely recognize the possibility of testicular growth without surgical intervention, citing data from Children’s Hospital of Philadelphia in which 71 % of their cohort improved volume differentials over a period of observation [34]. However, one must ask how these results would change if a 10 % difference was used as the threshold.

Fundamentally, it remains to be shown if the improvement in testicular volume is a reflection of true histologic growth and maturation of seminiferous elements or merely a consequence of either testicular edema due to iatrogenically altered venous drainage or normal pubertal growth. When surveying the literature, the raw data varies significantly with different thresholds for assessing hypotrophy as well as methods of measurement. Are the differences in size a reflection of a comparative size differential or as an absolute increase or decrease over time? There are no studies that indicate a 10 %, 15 %, or 20 % disparity is indicative of definitive fertility loss. Nonetheless, careful assessment and documentation of size discrepancy has emerged as a key proxy in the determination of operative intervention in an otherwise asymptomatic male.

Semen Parameters

In adults, although imperfect, semen analysis is utilized to predict fertility potential [35]. Varicocelectomy has been shown to improve sperm density, morphology, and motility in adults after surgical intervention [36].

Multiple retrospective studies in adults have confirmed that more than two thirds of patients will have improved semen parameters after varicocele ligation [37]. In a review of 118 men, Boman et al. [38] noted a significant increase in motile sperm count as well as a higher rate of spontaneous pregnancy (65 % vs 32 %) in those managed with varicocelectomy versus observation.

Clinical decision making for adolescents with varicocele is hampered by lack of data specific to this population, leading us to infer from adult studies as to the potential benefit of surgical correction. Certainly, rates of spontaneous pregnancy cannot be ascertained as a desirable outcome. Additionally, there are no set normal values for adolescent semen analysis, notwithstanding the ethical issues of specimen acquisition. The World Health Organization 2010 update for the analysis of semen recognizes that the parameters for “normal” semen may encompass a subset of fertile and infertile men. In fact, many of the threshold values were significantly decreased [39••].

In the attempt to correlate degree of testicular growth arrest with altered spermatogenesis, Diamond et al. [40] concluded in an analysis of 57 postpubertal male patients (ages 14 to 20 years) that volume differentials of 10 % or greater correlate with a significantly decreased sperm concentration and total motile sperm count [40]. Importantly, they did not note volumetric differential and semen quality to have an absolute correlation. Instead, they recommend semen analysis in adolescents with size differentials greater than 10 % to more accurately determine need for surgical intervention.

In a similar evaluation, Laven et al. [41] performed a prospective study on 88 adolescents with varicocele and randomly assigned them to treatment or observation groups. They observed a significant increase in sperm concentration; however, there was no change in semen quality in the untreated versus treated groups at 1 year. Varicocele correction did have a significant impact on testis volume, approaching that of normal control patients without varicocele. It is difficult to interpret these studies in the absence of long-term follow-up and without accounting for the multiple confounding factors that might affect fertility potential.

While some have shown no correlation between the grade of varicocele and semen parameters [26], others have noted a distinct association [25]. It stands to reason that the patients who require surgery will have larger varicoceles with greater volumetric asymmetry; however, correlations between the grade of varicocele and poor semen parameters have not been shown with regularity in the literature [40].

Zampieri and colleagues [42] pursued evaluation of semen parameters in 214 adolescents with unilateral grade 2 or 3 varicocele. The cohort was split into three groups: surgically treated with testicular hypotrophy, surgically treated with a normal testis, and observed with a normal testis. About half of the surgically treated patients underwent the Palomo procedure with the others undergoing the arterial sparing modification, which was randomly chosen. Semen analysis was only performed when the patients had attained 18 years of age. No preoperative semen analyses were done. The post-hoc analyses noted no significant differences in semen quality according to surgical technique with the exception of improved motility and vitality noted in the arterial sparing group who had preoperative testicular atrophy. No statistically significant differences in semen quality were found between the observed group and the surgically treated groups. There was selection bias imparted by the lack of both a control group as well as an observation group with an “abnormal” testis; however, in comparing the observed “normal” testes, there were no measurable improvements in semen quality conferred by surgical treatment.

In terms of pregnancy rates, one of the most often cited statistics stems from the Madgar et al. [43] randomized controlled trial of varicocelectomy for infertile adults. They noted a sixfold greater pregnancy rate as compared to the observation group. A Belgian study of 374 men with varicocele noted no correlation between degrees of varicocele, age at intervention or pregnancy rate. They did note a mean improvement in all semen parameters after varicocelectomy; however, this did not seem to translate to improved pregnancy outcomes. The authors warn against extrapolating adult data to the justification of varicocele repair in adolescents [44]. Ku and colleagues [45] retrospectively compared three different groups of men before and after varicocelectomy: adolescents, fertile adults, and infertile adults [45]. While they noted that the percentage of normal sperm improved after varicocelectomy, the proportion of normal to abnormal sperm remained unchanged in all three groups. However, they did note the baseline semen parameters in adolescents were more equivalent to that of fertile adults after varicocelectomy, thus only adding to the speculation surrounding early repair.

Treatment

Indications for treatment include patient request, discomfort, or volumetric discrepancy (usually more than 20 %). Surgical correction of varicocele has been found to improve morphologic parameters in up to 60 % of patients, with the most common improvement being motility [37]. Abnormal semen analysis and desire for fertility are indications for repair in adults; however, we do not yet know the impact of varicocele correction on these end points in the adolescent population.

The goals of surgical intervention are to disrupt venous stagnation while preserving arterial and lymphatic flow. A variety of surgical approaches have been described in the management of varicocele; however, superiority of any one technique has not been definitively shown in the literature. As such, surgical correction of varicocele should be performed in the method of which the surgeon is most comfortable.

Techniques vary as to the level at which the veins are ligated (subinguinal, inguinal, or retroperitoneal), with or without arterial sparing, and with the use of optical magnification or laparoscopic instruments.

Complications of varicocele repair include hydrocele, recurrence, and discomfort. Incidence of postoperative hydrocele formation is between 3 % and 33 %, primarily due to disruption of the lymphatic drainage of the tunica vaginalis [46]. Recurrence rates for the Palomo technique range from 0 % to 2 % [27, 47]. To address the concern for the possibility of testicular hypotrophy after arterial ligation, Hosli and colleagues [48] evaluated the application of the Palomo technique in adolescents with varicocele and did not find any significant occurrence of atrophy.

Al-Kandari et al. [49] employed randomization to compare their surgical outcomes among open inguinal, laparoscopic, and subinguinal microscopic varicocelectomy in adults. Postoperative hydrocele was noted in none of the microscopic group, 13 % of the open group, and 20 % of the laparoscopic group. Recurrence occurred in none of the microscopic group, 18 % of the open group, and 23 % of the laparoscopic group. With respect to semen parameters, all three groups had comparable improvements with no significant differences in pregnancy rates at 1 year. Microsurgical varicocelectomy may be technically more challenging, require special equipment, and incur longer operative times; however, advocates for microsurgical techniques cite a lower incidence of hydrocele formation due to the prevention of iatrogenic lymphatic obstruction. Cayan et al. [50] prospectively compared high ligation with and without the aid of a microscope in 468 patients. In terms of fertility rates, they noted 43 % and 34 % rates of successful pregnancy in the groups with and without microscopic assistance, respectively. The benefit of microsurgical ligation was conferred in lower recurrence rates (2 % vs 16 %) and lower hydrocele rates (0.69 % vs 9 %).

In pediatric patients, Pintus et al. reported on their series of 99 patients who underwent surgical intervention with a variety of techniques [47]. They conclude the open Palomo procedure as the most effective approach with one recurrence in the 54 patients treated as such. However, it would be difficult to ascertain true recurrence across techniques without a method of randomization. Cayan et al. [51] have corroborated these findings in the adolescent population. In a comparative study of surgical technique, Zampieri et al. [52] substantiated Kass and Belman’s [27]finding in that 80 % of their cohort demonstrated catch-up growth; however, only 32 % approached testicular volumes equal to the unaffected side. They did not find any differences related to laparoscopic or open techniques. Likewise, there were no statistically significant differences in semen analysis results [52].

There are some reports in the literature questioning the unilateral prevalence of varicocele in adult and pediatric populations. The existence of a subclinical varicocele has been purported to be a confounding factor in the postoperative assessment of semen quality and, thus, fertility potential. Gat and colleagues [53] evaluated 286 men with clinical varicocele and noted subclinical varicocele involving the contralateral testis 80.8 % of the time. The authors also emphasize that physical exam alone is insufficient for the diagnosis of bilateral varicocele and instead sonography, thermography, or venography should be utilized. More study as to the effect of subclinical varicocele would be required, as this would suggest a requirement for surgery in a significant number of patients.

Conclusions

The management of varicocele in the adolescent population continues to be fraught with contention [54]. The harmful effects of varicocele have been well documented [55]. It is the concern for progressive impairment of spermatogenesis over time that drives the need for appropriate diagnosis and management in the adolescent patient. Many reports express concern regarding testicular hypotrophy, impaired spermatogenesis, and the production of free radicals as culprits of future infertility; however, these have yet to be proven in the adolescent population as they grow into adulthood. The evaluation of testicular volumetric difference is currently the best guide to determine the need for surgical correction, despite the fact that testicular size incongruity has not been shown to specifically correlate to infertility in adult data. It is our recommendation that these patients be examined at regular intervals with referral to an urologist if volumetric discrepancy or altered semen parameters manifest.

Disclosures No potnetial conflicts of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Russell JK, Mitchell AP. Clinical approach to infertility. Lancet. 1954;266:1161–2.
2. Skoog SJ, Roberts KP, Goldstein M, Pryor JL. The adolescent varicocele: what's new with an old problem in young patients? Pediatrics. 1997;100:112–21.
3. Dubin L, Amelar RD. Etiologic factors in 1294 consecutive cases of male infertility. Fertil Steril. 1971;22:469–74.
4. World Health Organization. The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. Fertil Steril. 1992;57:1289–93.
5. Lipshultz LI, Howards SS. Infertility in the male. New York: Churchill Livingstone; 1983;336–359.
6. Kubal A, Nagler HM, Zahalsky M, Budak M. The adolescent varicocele: diagnostic and treatment patterns of pediatricians. A public health concern? J Urol. 2004;171:411–3.
7. Dubin L, Amelar RD. Varicocele size and results of varicocelectomy in selected subfertile men with varicocele. Fertil Steril. 1970;21:606–9.
8. Behre HM, Nashan D, Nieschlag E. Objective measurement of testicular volume by ultrasonography: evaluation of the technique and comparison with orchidometer estimates. Int J Androl. 1989;12:395–403.
9. Diamond DA, Paltiel HJ, DiCanzio J, et al. Comparative assessment of pediatric testicular volume: orchidometer versus ultrasound. J Urol. 2000;164:1111–4.
10. Sharlip ID, Jarow JP, Belker AM, et al. Best practice policies for male infertility. Fertil Steril. 2002;77:873–82.
11. Evers JH, Collins J, Clarke J. Surgery or embolisation for varicoceles in subfertile men. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD000479.
12. Gomez E, Buckingham DW, Brindle J, Lanzafame F, Irvine DS, Aitken RJ. Development of an image analysis system to monitor the retention of residual cytoplasm by human spermatozoa: correlation with biochemical markers of the cytoplasmic space, oxidative stress, and sperm function. J Androl. 1996;17:276–87.
13. Gat Y, Zukerman Z, Chakraborty J, Gornish M. Varicocele, hypoxia and male infertility. Fluid Mechanics analysis of the impaired testicular venous drainage system. Hum Reprod. 2005;20:2614–9.
14. Kilinc F, Kayaselcuk F, Aygun C, Guvel S, Egilmez T, Ozkardes H. Experimental varicocele induces hypoxia inducible factor-1alpha, vascular endothelial growth factor expression and angiogenesis in the rat testis. J Urol. 2004;172:1188–91.
15. Lee JD, Jeng SY, Lee TH. Increased expression of hypoxia-inducible factor-1alpha in the internal spermatic vein of patients with varicocele. J Urol. 2006;175:1045–8. discussion 8.
16. Hendin BN, Kolettis PN, Sharma RK, Thomas Jr AJ, Agarwal A. Varicocele is associated with elevated spermatozoal reactive oxygen species production and diminished seminal plasma antioxidant capacity. J Urol. 1999;161:1831–4.
17. Gomez E, Irvine DS, Aitken RJ. Evaluation of a spectrophotometric assay for the measurement of malondialdehyde and 4-hydroxyalkenals in human spermatozoa: relationships with semen quality and sperm function. Int J Androl. 1998;21:81–94.
18. Gil-Guzman E, Ollero M, Lopez MC, et al. Differential production of reactive oxygen species by subsets of human spermatozoa at different stages of maturation. Hum Reprod. 2001;16:1922–30.
19. Chen SS, Huang WJ, Chang LS, Wei YH. Attenuation of oxidative stress after varicocelectomy in subfertile patients with varicocele. J Urol. 2008;179:639–42.
20. •• Cocuzza M, Athayde KS, Alvarenga C, Srougi M, Hallak J. Grade 3 varicocele in fertile men: a different entity. J Urol. 2012;187:1363–8. *This article provides an interesting look into the disparity between infertility and the presence of varicocele.*
21. Kass EJ, Freitas JE, Salisz JA, Steinert BW. Pituitary gonadal dysfunction in adolescents with varicocele. Urology. 1993;42:179–81.
22. Segenreich E, Israilov S, Shmuele J, Niv E, Baniel J, Livne P. Evaluation of the relationship between semen parameters, pregnancy rate of wives of infertile men with varicocele, and gonadotropin-releasing hormone test before and after varicocelectomy. Urology. 1998;52:853–7.
23. Hudson RW, Perez-Marrero RA, Crawford VA, McKay DE. Hormonal parameters of men with varicoceles before and after varicocelectomy. Fertil Steril. 1985;43:905–10.
24. Tulloch WS. Varicocele in subfertility; results of treatment. Br Med J. 1955;2:356–8.

25. Thomas JC, Elder JS. Testicular growth arrest and adolescent varicocele: does varicocele size make a difference? J Urol. 2002;168:1689–91. discussion 91.
26. Alukal JP, Zurakowski D, Atala A, et al. Testicular hypotrophy does not correlate with grade of adolescent varicocele. J Urol. 2005;174:2367–70. discussion 70.
27. Kass EJ, Belman AB. Reversal of testicular growth failure by varicocele ligation. J Urol. 1987;137:475–6.
28. Akbay E, Cayan S, Doruk E, Duce MN, Bozlu M. The prevalence of varicocele and varicocele-related testicular atrophy in Turkish children and adolescents. BJU Int. 2000;86:490–3.
29. Lyon RP, Marshall S, Scott MP. Varicocele in childhood and adolescence: implication in adulthood infertility? Urology. 1982; 19:641–4.
30. Diamond DA, Zurakowski D, Atala A, et al. Is adolescent varicocele a progressive disease process? J Urol. 2004;172:1746–8.
31. Decastro GJ, Shabsigh A, Poon SA, Laor L, Glassberg KI. Adolescent varicocelectomy—is the potential for catch-up growth related to age and/or Tanner stage? J Urol. 2009;181:322–7. discussion 7.
32. Cayan S, Akbay E, Bozlu M, et al. The effect of varicocele repair on testicular volume in children and adolescents with varicocele. J Urol. 2002;168:731–4.
33. Spinelli C, Di Giacomo M, Lo Piccolo R, Martin A, Messineo A. The role of testicular volume in adolescents with varicocele: the better way and time of surgical treatment. J Urol. 2010;184:1722–6.
34. Kolon TF, Clement MR, Cartwright L, et al. Transient asynchronous testicular growth in adolescent males with a varicocele. J Urol. 2008;180:1111–4. discussion 4–5.
35. Smith R, Kaune H, Parodi D, et al. Increased sperm DNA damage in patients with varicocele: relationship with seminal oxidative stress. Hum Reprod. 2006;21:986–93.
36. Agarwal A, Deepinder F, Cocuzza M, et al. Efficacy of varicocelectomy in improving semen parameters: new meta-analytical approach. Urology. 2007;70:532–8.
37. Pryor JL, Howards SS. Varicocele. Urol Clin N Am. 1987;14:499–513.
38. Boman JM, Libman J, Zini A. Microsurgical varicocelectomy for isolated asthenospermia. J Urol. 2008;180:2129–32.
39. •• Lu JC, Huang YF, Lu NQ. WHO Laboratory Manual for the Examination and Processing of Human Semen: its applicability to andrology laboratories in China. Zhonghua nan ke xue Natl J Androl. 2010;16:867–71. *From this article, it is important to be aware that the reference values have been broadened.*
40. Diamond DA, Zurakowski D, Bauer SB, et al. Relationship of varicocele grade and testicular hypotrophy to semen parameters in adolescents. J Urol. 2007;178:1584–8.
41. Laven JS, Haans LC, Mali WP, te Velde ER, Wensing CJ, Eimers JM. Effects of varicocele treatment in adolescents: a randomized study. Fertil Steril. 1992;58:756–62.
42. Zampieri N, Zuin V, Corroppolo M, Chironi C, Cervellione RM, Camoglio FS. Varicocele and adolescents: semen quality after 2 different laparoscopic procedures. J Androl. 2007;28:727–33.
43. Madgar I, Weissenberg R, Lunenfeld B, Karasik A, Goldwasser B. Controlled trial of high spermatic vein ligation for varicocele in infertile men. Fertil Steril. 1995;63:120–4.
44. Vereecken RL, Boeckx G. Does fertility improvement after varicocele treatment justify preventive treatment at puberty? Urology. 1986;28:122–6.
45. Ku JH, Kim SW, Park K, Paick JS. Benefits of microsurgical repair of adolescent varicocele: comparison of semen parameters in fertile and infertile adults with varicocele. Urology. 2005;65:554–8.
46. Miller J, Pfeiffer D, Schumacher S, Tauber R, Muller SC, Weidner W. Varicocele testis in childhood and adolescence. Der Urologe Ausg A. 2002;41:68–75. quiz 6–7.
47. Pintus C, Rodriguez Matas MJ, Manzoni C, Nanni L, Perrelli L. Varicocele in pediatric patients: comparative assessment of different therapeutic approaches. Urology. 2001;57:154–7.
48. Hosli PO. Varicocele—results following early treatment of children and adolescents. Zeitschrift fur Kinderchirurgie: organ der Deutschen, der Schweizerischen und der Osterreichischen Gesellschaft fur Kinderchirurgie. Surg Infancy Childhood. 1988;43:213–5.
49. Al-Kandari AM, Shabaan H, Ibrahim HM, Elshebiny YH, Shokeir AA. Comparison of outcomes of different varicocelectomy techniques: open inguinal, laparoscopic, and subinguinal microscopic varicocelectomy: a randomized clinical trial. Urology. 2007;69:417–20.
50. Cayan S, Kadioglu TC, Tefekli A, Kadioglu A, Tellaloglu S. Comparison of results and complications of high ligation surgery and microsurgical high inguinal varicocelectomy in the treatment of varicocele. Urology. 2000;55:750–4.
51. Cayan S, Acar D, Ulger S, Akbay E. Adolescent varicocele repair: long-term results and comparison of surgical techniques according to optical magnification use in 100 cases at a single university hospital. J Urol. 2005;174:2003–6. discussion 6–7.
52. Zampieri N, Mantovani A, Ottolenghi A, Camoglio FS. Testicular catch-up growth after varicocelectomy: does surgical technique make a difference? Urology. 2009;73:289–92.
53. Gat Y, Bachar GN, Zukerman Z, Belenky A, Gornish M. Varicocele: a bilateral disease. Fertil Steril. 2004;81:424–9.
54. Will MA, Swain J, Fode M, Sonksen J, Christman GM, Ohl D. The great debate: varicocele treatment and impact on fertility. Fertil Steril. 2011;95:841–52.
55. Paduch DA, Niedzielski J. Semen analysis in young men with varicocele: preliminary study. J Urol. 1996;156:788–90.