

VARICOCELE IN ADOLESCENCE PATIENTS: DEFINITION, PREVELANCE, ETIOLOGY, PATHOPHYSIOLOGY AND EVALUATION

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DEFINITION

Varicocele is defined as an abnormal dilation and tortuosity of the internal spermatic veins within the pampiniform plexus (1). In a study performed by World Health Organization (WHO), left-sided varicoceles were found in 90% of cases and bilateral varicoceles were 10%. A isolated right-sided palpable varicocele was seen in less than 1% of patients (2). Later studies also confirmed that most of the varicoceles (78–93%) were found on the left side (3-5). However, there are different outcomes in different studies with regard to bilateral varicocele and isolated right varicocele. Akbay et al. assessed varicocele in 4052 Turkish boys with an age range of 2–19. The authors found that 10.8% of boys had bilateral varicoceles and only one boy had a right-sided varicocele (3). In Clavijo et al's study, bilateral varicocele and an isolated right-sided varicocele were reported to be 1.1% and 0.2%, respectively (6). In other studies, bilateral palpable varicoceles were found to be 3% (7,8).

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REFERENCES

1. Zundel S, Szavay P, Stanasel I. Management of adolescent varicocele. *Semin Pediatr Surg*. 2021 Aug;30(4):151084. doi: 10.1016/j.sempedsurg.2021.151084. Epub 2021 Jul 14.
2. The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. *World Health Organization. Fertil Steril*. 1992 Jun;57(6):1289-93.
3. 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 Sep;86(4):490-3. doi: 10.1046/j.1464-410x.2000.00735.x.
4. Oster J. Varicocele in children and adolescents. An investigation of the incidence among Danish school children. *Scand J Urol Nephrol*. 1971;5(1):27-32. doi: 10.3109/00365597109133569.
5. Baazeem A, Belzile E, Ciampi A, Dohle G, Jarvi K, Salonia A, Weidner W, Zini A. Varicocele and male factor infertility treatment: a new meta-analysis and review of the role of varicocele repair. *Eur Urol*. 2011 Oct;60(4):796-808. doi: 10.1016/j.eururo.2011.06.018. Epub 2011 Jul 5.
6. Clavijo RI, Carrasquillo R, Ramasamy R. Varicoceles: prevalence and pathogenesis in adult men. *Fertil Steril*. 2017 Sep;108(3):364-369. doi: 10.1016/j.fertnstert.2017.06.036.
7. Chung JM, Lee SD. Current Issues in Adolescent Varicocele: Pediatric Urological Perspectives. *World J Mens Health*. 2018 May;36(2):123-131. doi: 10.5534/wjmh.170053. Epub 2018 Mar 22.
8. Macey MR, Owen RC, Ross SS, Coward RM. Best practice in the diagnosis and treatment of varicocele in children and adolescents. *Ther Adv Urol*. 2018 Jun 22;10(9):273-282. doi: 10.1177/1756287218783900.
9. Kim HH, Goldstein M. Adult varicocele. *Curr Opin Urol*. 2008 Nov;18(6):608-12. doi: 10.1097/MOU.0b013e3283136493.
10. Rais A, Zarka S, Derazne E, Tzur D, Calderon-Margalit R, Davidovitch N, Afek A, Carel R, Levine H. Varicocele among 1 300 000 Israeli adolescent males: time trends and association with body mass index. *Andrology*. 2013 Sep;1(5):663-9. doi: 10.1111/j.2047-2927.2013.00113.x.
11. Liu J, Zhang S, Liu M, Wang Q, Shen H, Zhang Y, Yan D. Prevalence of varicocele and its association with body mass index among 39,559 rural men in eastern China: a population-based cross-sectional study. *Andrology*. 2017 May;5(3):562-567. doi: 10.1111/andr.12345.
12. Pfeiffer D, Berger J, Schoop C, Tauber R. A Doppler-based study on the prevalence of varicocele in German children and adolescents. *Andrologia*. 2006 Feb;38(1):13-9. doi: 10.1111/j.1439-0272.2006.00680.x.
13. Kumanov P, Robeva RN, Tomova A. Adolescent varicocele: who is at risk? *Pediatrics*. 2008 Jan;121(1):e53-7. doi: 10.1542/peds.2007-0340.
14. Isaikhan B, Alrabeeah K, Delouya G, Zini A. Epidemiology of varicocele. *Asian J Androl*. 2016 Mar-Apr;18(2):179-81. doi: 10.4103/1008-682X.172640.
15. Jacobson DL, Johnson EK. Varicoceles in the pediatric and adolescent population: threat to future fertility? *Fertil Steril*. 2017 Sep;108(3):370-377. doi: 10.1016/j.fertnstert.2017.07.014. Epub 2017 Aug 10.
16. Damsgaard J, Joensen UN, Carlsen E, Erenpreiss J, Blomberg Jensen M, Matulevicius V, Zilaitiene B, Olesen IA, Perheentupa A, Punab M, Salzbrunn A, Toppari J, Virtanen HE, Juul A, Skakkebaek NE, Jørgensen N. Varicocele Is Associated with Impaired Semen Quality and Reproductive Hormone Levels: A Study of 7035 Healthy Young Men from Six European Countries. *Eur Urol*. 2016 Dec;70(6):1019-1029. doi: 10.1016/j.eururo.2016.06.044. Epub 2016 Jul 14.
17. 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 Sep;20(9):2614-9. doi: 10.1093/humrep/dei089. Epub 2005 Jun 2.

18. Nagler HM, Grotas AB. Varicocele. In: Lipshultz LI, Howards SS, Niederberger CS, editors. *Infertility in the male*. 4th ed. New York: Cambridge University Press; 2009. p. 331–61].
19. Kass EJ. Adolescent varicocele. *Pediatr Clin North Am*. 2001 Dec;48(6):1559–69. doi: 10.1016/s0031-3955(05)70391-6.
20. Parekh N and Sabanegh E. Anatomic Theories of Varicocele Origin. Chapter 2, pp: 17–26, *Varicocele and Male Infertility*, Eds: Esteves SC, Cho CK, Majzoub A, Agarwal A. Springer, (2019).
21. Ahlberg NE, Bartley O, Chidekel N. Right and left gonadal veins. An anatomical and statistical study. *Acta Radiol Diagn (Stockh)*. 1966 Nov;4(6):593–601. doi: 10.1177/028418516600400601.
22. Ozbek E, Yurekli M, Soylu A, Davarci M, Balbay MD. The role of adrenomedullin in varicocele and impotence. *BJU Int*. 2000 Oct;86(6):694–8. doi: 10.1046/j.1464-410x.2000.00853.x.
23. Gat Y, Gornish M, Chakraborty J, Perlow A, Levinger U, Pasqualotto F. Azoospermia and maturation arrest: malfunction of valves in erect poster of humans leads to hypoxia in sperm production site. *Andrologia*. 2010 Dec;42(6):389–94. doi: 10.1111/j.1439-0272.2010.01083.x.
24. Shin JI, Lee JS, Kim MJ. The prevalence, physical characteristics and diagnosis of nutcracker syndrome. *Eur J Vasc Endovasc Surg*. 2006 Sep;32(3):335–6. doi: 10.1016/j.ejvs.2006.04.030. Epub 2006 Jun 15.
25. Shin JI, Park JM, Lee JS, Kim MJ. Effect of renal Doppler ultrasound on the detection of nutcracker syndrome in children with hematuria. *Eur J Pediatr*. 2007 May;166(5):399–404. doi: 10.1007/s00431-006-0252-7. Epub 2006 Oct 19.
26. Okada M, Tsuzuki K, Ito S. Diagnosis of the nutcracker phenomenon using two-dimensional ultrasonography. *Clin Nephrol*. 1998 Jan;49(1):35–40.
27. Park SJ, Lim JW, Cho BS, Yoon TY, Oh JH. Nutcracker syndrome in children with orthostatic proteinuria: diagnosis on the basis of Doppler sonography. *J Ultrasound Med*. 2002 Jan;21(1):39–45; quiz 46. doi: 10.7863/jum.2002.21.1.39.
28. Raman JD, Walmsley K, Goldstein M. Inheritance of varicoceles. *Urology*. 2005 Jun;65(6):1186–9. doi: 10.1016/j.urology.2004.12.057.
29. Mohammadali Beigi F, Mehrabi S, Javaherforooshzadeh A. Varicocele in brothers of patients with varicocele. *Urol J*. 2007 Winter;4(1):33–5.
30. Mokhtari G, Pourreza F, Falahatkar S, Kamran AN, Jamali M. Comparison of prevalence of varicocele in first-degree relatives of patients with varicocele and male kidney donors. *Urology*. 2008 Apr;71(4):666–8. doi: 10.1016/j.urology.2007.11.116. Epub 2008 Feb 15.
31. Gökçe A, Davarci M, Yalçinkaya FR, Güven EO, Kaya YS, Helvacı MR, Balbay MD. Hereditary behavior of varicocele. *J Androl*. 2010 May-Jun;31(3):288–90. doi: 10.2164/jandrol.109.008698. Epub 2009 Oct 15.
32. Shiraishi K, Takihara H, Naito K. Testicular volume, scrotal temperature, and oxidative stress in fertile men with left varicocele. *Fertil Steril*. 2009 Apr;91(4 Suppl):1388–91. doi: 10.1016/j.fertnstert.2008.04.044. Epub 2008 Aug 5.
33. Dahl EV, Herrick JF. A vascular mechanism for maintaining testicular temperature by counter-current exchange. *Surg Gynecol Obstet*. 1959 Jun;108(6):697–705.
34. Mariotti A, Di Carlo L, Orlando G, Corradini ML, Di Donato L, Pompa P, Iezzi R, Cotroneo AR, Romani GL, Merla A. Scrotal thermoregulatory model and assessment of the impairment of scrotal temperature control in varicocele. *Ann Biomed Eng*. 2011 Feb;39(2):664–73. doi: 10.1007/s10439-010-0191-3. Epub 2010 Oct 26.
35. Fujisawa M, Yoshida S, Matsumoto O, Kojima K, Kamidono S. Decrease of topoisomerase I activity in the testes of infertile men with varicocele. *Arch Androl*. 1988;21(1):45–50. doi: 10.3109/01485018808986732.
36. De Amicis F, Perrotta I, Santoro M, Guido C, Morelli C, Cesario MG, Bruno R, Aquila S. Human sperm anatomy: different expression and localization of phosphatidylinositol 3-kinase in

- normal and varicocele human spermatozoa. *Ultrastruct Pathol*. 2013 May;37(3):176-82. doi: 10.3109/01913123.2013.763881. Epub 2013 May 1.
37. Comhaire F, Kunnen M. Selective retrograde venography of the internal spermatic vein: a conclusive approach to the diagnosis of varicocele. *Andrologia*. 1976;8(1):11-24. doi: 10.1111/j.1439-0272.1976.tb01638.x.
 38. Comhaire F, Kunnen M, Nahoum C. Radiological anatomy of the internal spermatic vein(s) in 200 retrograde venograms. *Int J Androl*. 1981 Jun;4(3):379-87. doi: 10.1111/j.1365-2605.1981.tb00722.x.
 39. Agarwal A, Hamada A, Esteves SC. Insight into oxidative stress in varicocele-associated male infertility: part 1. *Nat Rev Urol*. 2012 Dec;9(12):678-90. doi: 10.1038/nrur.2012.197. Epub 2012 Nov 20.
 40. Ito H, Fuse H, Minagawa H, Kawamura K, Murakami M, Shimazaki J. Internal spermatic vein prostaglandins in varicocele patients. *Fertil Steril*. 1982 Feb;37(2):218-22. doi: 10.1016/s0015-0282(16)46043-7.
 41. MacLeod J. Seminal cytology in the presence of varicocele. *Fertil Steril*. 1965 Nov-Dec;16(6):735-57. doi: 10.1016/s0015-0282(16)35765-x.
 42. Franco A, Proietti F, Palombi V, Savarese G, Guidotti M, Leonardo C, Ferro F, Manna C, Franco G. Varicocele: To Treat or Not to Treat? *J Clin Med*. 2023 Jun 15;12(12):4062. doi: 10.3390/jcm12124062.
 43. 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 Mar;175(3 Pt 1):1045-8; discussion 1048. doi: 10.1016/S0022-5347(05)00417-9.
 44. Wang H, Sun Y, Wang L, Xu C, Yang Q, Liu B, Liu Z. Hypoxia-induced apoptosis in the bilateral testes of rats with left-sided varicocele: a new way to think about the varicocele. *J Androl*. 2010 May-Jun;31(3):299-305. doi: 10.2164/jandrol.108.007153. Epub 2009 Dec 17.
 45. Shafik A, Wali MA, Abdel Aziz YE, el-Kateb S, el-Sharkawy AG, Olfat E, Saleh M. Experimental model of varicocele. *Eur Urol*. 1989;16(4):298-303. doi: 10.1159/000471596.
 46. Sofikitis N, Miyagawa I. Bilateral effect of unilateral varicocele on testicular metabolism in the rabbit. *Int J Fertil Menopausal Stud*. 1994 Jul-Aug;39(4):239-47.
 47. Kazama T. [Effect of experimental left varicocele on rat Leydig cell function]. *Nihon Hinyokika Gakkai Zasshi*. 1995 Feb;86(2):308-15. Japanese. doi: 10.5980/jpnjurol1989.86.308.
 48. Zalata AA, Mokhtar N, Badawy Ael-N, Othman G, Alghobary M, Mostafa T. Androgen receptor expression relationship with semen variables in infertile men with varicocele. *J Urol*. 2013 Jun;189(6):2243-7. doi: 10.1016/j.juro.2012.11.112. Epub 2012 Nov 28.
 49. Swerdloff RS, Walsh PC. Pituitary and gonadal hormones in patients with varicocele. *Fertil Steril*. 1975 Oct;26(10):1006-12. doi: 10.1016/s0015-0282(16)41416-0.
 50. Schiff I, Wilson E, Newton R, Shane J, Kates R, Ryan KJ, Naftolin F. Serum luteinizing hormone, follicle-stimulating hormone, and testosterone responses to gonadotropin-releasing factor in males with varicoceles. *Fertil Steril*. 1976 Sep;27(9):1059-61. doi: 10.1016/s0015-0282(16)42076-5.
 51. Hudson RW, Crawford VA, McKay DE. The gonadotropin response of men with varicoceles to a four-hour infusion of gonadotropin-releasing hormone. *Fertil Steril*. 1981 Nov;36(5):633-7.
 52. Kessopoulou E, Tomlinson MJ, Barratt CL, Bolton AE, Cooke ID. Origin of reactive oxygen species in human semen: spermatozoa or leucocytes? *J Reprod Fertil*. 1992 Mar;94(2):463-70. doi: 10.1530/jrf.0.0940463.
 53. Garrido N, Meseguer M, Simon C, Pellicer A, Remohi J. Pro-oxidative and anti-oxidative imbalance in human semen and its relation with male fertility. *Asian J Androl*. 2004 Mar;6(1):59-65.
 54. Aitken RJ. Free radicals, lipid peroxidation and sperm function. *Reprod Fertil Dev*.

- 1995;7(4):659-68. doi: 10.1071/rd9950659.
55. Burton GJ, Jauniaux E. Oxidative stress. *Best Pract Res Clin Obstet Gynaecol*. 2011 Jun;25(3):287-99. doi: 10.1016/j.bpobgyn.2010.10.016. Epub 2010 Dec 3.
56. Sharma RK, Agarwal A. Role of reactive oxygen species in male infertility. *Urology*. 1996 Dec;48(6):835-50. doi: 10.1016/s0090-4295(96)00313-5.
57. Mostafa T, Anis TH, El-Nashar A, Imam H, Othman IA. Varicocelectomy reduces reactive oxygen species levels and increases antioxidant activity of seminal plasma from infertile men with varicocele. *Int J Androl*. 2001 Oct;24(5):261-5. doi: 10.1046/j.1365-2605.2001.00296.x.
58. Halliwell B. Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? *Lancet*. 1994 Sep 10;344(8924):721-4. doi: 10.1016/s0140-6736(94)92211-x.
59. Agarwal A, Saleh RA. Role of oxidants in male infertility: rationale, significance, and treatment. *Urol Clin North Am*. 2002 Nov;29(4):817-27. doi: 10.1016/s0094-0143(02)00081-2.
60. Allamaneni SS, Naughton CK, Sharma RK, Thomas AJ Jr, Agarwal A. Increased seminal reactive oxygen species levels in patients with varicoceles correlate with varicocele grade but not with testis size. *Fertil Steril*. 2004 Dec;82(6):1684-6. doi: 10.1016/j.fertnstert.2004.04.071.
61. Cocuzza M, Athayde KS, Agarwal A, Pagani R, Sikka SC, Lucon AM, Srougi M, Hallak J. Impact of clinical varicocele and testis size on seminal reactive oxygen species levels in a fertile population: a prospective controlled study. *Fertil Steril*. 2008 Oct;90(4):1103-8. doi: 10.1016/j.fertnstert.2007.07.1377. Epub 2007 Nov 26.
62. Hurtado de Catalfo GE, Ranieri-Casilla A, Marra FA, de Alaniz MJ, Marra CA. Oxidative stress biomarkers and hormonal profile in human patients undergoing varicocelectomy. *Int J Androl*. 2007 Dec;30(6):519-30. doi: 10.1111/j.1365-2605.2007.00753.x. Epub 2007 Jun 15.
63. Mostafa T, Anis T, Imam H, El-Nashar AR, Osman IA. Seminal reactive oxygen species-antioxidant relationship in fertile males with and without varicocele. *Andrologia*. 2009 Apr;41(2):125-9. doi: 10.1111/j.1439-0272.2008.00900.x.
64. Pasqualotto FF, Sundaram A, Sharma RK, Borges E Jr, Pasqualotto EB, Agarwal A. Semen quality and oxidative stress scores in fertile and infertile patients with varicocele. *Fertil Steril*. 2008 Mar;89(3):602-7. doi: 10.1016/j.fertnstert.2007.03.057. Epub 2007 May 7.
65. Agarwal A, Sekhon LH. Oxidative stress and antioxidants for idiopathic oligoasthenoteratospermia: Is it justified? *Indian J Urol*. 2011 Jan;27(1):74-85. doi: 10.4103/0970-1591.78437.
66. Shiraishi K, Naito K. Nitric oxide produced in the testis is involved in dilatation of the internal spermatic vein that compromises spermatogenesis in infertile men with varicocele. *BJU Int*. 2007 May;99(5):1086-90. doi: 10.1111/j.1464-410X.2007.06800.x. Epub 2007 Mar 6.
67. Guo J, Jia Y, Tao SX, Li YC, Zhang XS, Hu ZY, Chiang N, Lue YH, Hikim AP, Swerdloff RS, Wang C, Liu YX. Expression of nitric oxide synthase during germ cell apoptosis in testis of cynomolgus monkey after testosterone and heat treatment. *J Androl*. 2009 Mar-Apr;30(2):190-9. doi: 10.2164/jandrol.108.005538. Epub 2008 Oct 2.
68. Beltrán B, Orsi A, Clementi E, Moncada S. Oxidative stress and S-nitrosylation of proteins in cells. *Br J Pharmacol*. 2000 Mar;129(5):953-60. doi: 10.1038/sj.bjp.0703147.
69. Abbasi M, Alizadeh R, Abolhassani F, Amidi F, Hassanzadeh G, Ejtemaei Mehr S, Dehpour AR. Aminoguanidine improves epididymal sperm parameters in varicocelized rats. *Urol Int*. 2011;86(3):302-6. doi: 10.1159/000322154. Epub 2010 Nov 18.
70. Abbasi M, Alizadeh R, Abolhassani F, Amidi F, Ragerdi KI, Fazelpour S, Hoshino Y, Sato E, Dehpour AR. Effect of aminoguanidine in sperm DNA fragmentation in varicocelized rats: role of nitric oxide. *Reprod Sci*. 2011 Jun;18(6):545-50. doi: 10.1177/1933719110393028. Epub 2011 Feb 1.
71. Alizadeh N, Abbasi M, Abolhassani F, Amidi F, Mahmoudi R, Hoshino Y, Sato E, Ragerdikashani I. Effects of aminoguanidine on infertile varicocelized rats: A functional and morphological study. *Daru*. 2010;18(1):51-6.

72. DeFoor WR, Kuan CY, Pinkerton M, Sheldon CA, Lewis AG. Modulation of germ cell apoptosis with a nitric oxide synthase inhibitor in a murine model of congenital cryptorchidism. *J Urol*. 2004 Oct;172(4 Pt 2):1731-5; discussion 1735. doi: 10.1097/01.ju.0000138846.56399.de.
73. Parsell DA, Lindquist S. The function of heat-shock proteins in stress tolerance: degradation and reactivation of damaged proteins. *Annu Rev Genet*. 1993;27:437-96. doi: 10.1146/annurev.ge.27.120193.002253.
74. Mehraban D, Ansari M, Keyhan H, Sedighi Gilani M, Naderi G, Esfehiani F. Comparison of nitric oxide concentration in seminal fluid between infertile patients with and without varicocele and normal fertile men. *Urol J*. 2005 Spring;2(2):106-10.
75. Schlesinger MH, Wilets IF, Nagler HM. Treatment outcome after varicocelectomy. A critical analysis. *Urol Clin North Am*. 1994 Aug;21(3):517-29.
76. Dada R, Shamsi MB, Venkatesh S, Gupta NP, Kumar R. Attenuation of oxidative stress & DNA damage in varicocelectomy: implications in infertility management. *Indian J Med Res*. 2010 Dec;132(6):728-30.
77. Mroz K, Hassold TJ, Hunt PA. Meiotic aneuploidy in the XXY mouse: evidence that a compromised testicular environment increases the incidence of meiotic errors. *Hum Reprod*. 1999 May;14(5):1151-6. doi: 10.1093/humrep/14.5.1151.
78. Reichart M, Eltes F, Soffer Y, Zigenreich E, Yogev L, Bartoov B. Sperm ultramorphology as a pathophysiological indicator of spermatogenesis in males suffering from varicocele. *Andrologia*. 2000 May;32(3):139-45. doi: 10.1046/j.1439-0272.2000.00355.x.
79. Santana VP, Miranda-Furtado CL and dos Reis RM. Genetics and Epigenetics of Varicocele Pathophysiology. Chapter 4, Pp: 37-53. *Varicocele and Male Infertility*. Eds. Esteves SC, Cho CL, Majzoub A, Agarwal A, Springer 2019.
80. Naughton CK, Nangia AK, Agarwal A. Pathophysiology of varicoceles in male infertility. *Hum Reprod Update*. 2001 Sep-Oct;7(5):473-81. doi: 10.1093/humupd/7.5.473.
81. Peterson AC, Lance RS, Ruiz HE. Outcomes of varicocele ligation done for pain. *J Urol*. 1998 May;159(5):1565-7. doi: 10.1097/00005392-199805000-00043.
82. Ebiloglu T, Aydogmus Y, Kaya E, Oral E, Kaplan O, Kibar Y. The effect of physical activity on varicocele pain and resolution of this pain by different varicocelectomy techniques. *Can J Urol*. 2016 Jun;23(3):8285-90.
83. Vanlangenhove P, Dhondt E, Everaert K, Defreyne L. Pathophysiology, diagnosis and treatment of varicoceles: a review. *Minerva Urol Nefrol*. 2014 Dec;66(4):257-82. Epub 2014 Nov 14.
84. Lomboy JR, Coward RM. The Varicocele: Clinical Presentation, Evaluation, and Surgical Management. *Semin Intervent Radiol*. 2016 Sep;33(3):163-9. doi: 10.1055/s-0036-1586143.
85. Khera M, Lipshultz LI. Evolving approach to the varicocele. *Urol Clin North Am*. 2008 May;35(2):183-9, viii. doi: 10.1016/j.ucl.2008.02.001.
86. Chen SS. Factors predicting symptomatic relief by varicocelectomy in patients with normospermia and painful varicocele nonresponsive to conservative treatment. *Urology*. 2012 Sep;80(3):585-9. doi: 10.1016/j.urol.2012.05.014. Epub 2012 Jul 10.
87. Çayan S, Bozlu M, Akbay E. Update on the novel management and future paternity situation in adolescents with varicocele. *Turk J Urol*. 2017 Sep;43(3):241-246. doi: 10.5152/tud.2017.01033. Epub 2017 Aug 1.
88. Dubin L, Amelar RD. Varicocele size and results of varicocelectomy in selected subfertile men with varicocele. *Fertil Steril*. 1970 Aug;21(8):606-9. doi: 10.1016/s0015-0282(16)37684-1.
89. Mohammed A, Chinegwundoh F. Testicular varicocele: an overview. *Urol Int*. 2009;82(4):373-9. doi: 10.1159/000218523. Epub 2009 Jun 8.
90. Mohammed A, Chinegwundoh F. Testicular varicocele: an overview. *Urol Int*. 2009;82(4):373-9. doi: 10.1159/000218523. Epub 2009 Jun 8.

91. Freeman S, Bertolotto M, Richenberg J, Belfield J, Dogra V, Huang DY, Lotti F, Markiet K, Nikolic O, Ramanathan S, Ramchandani P, Rocher L, Secil M, Sidhu PS, Skrobisz K, Studniarek M, Tsili A, Tuncay Turgut A, Pavlica P, Derchi LE; members of the ESUR-SPIWG WG. Ultrasound evaluation of varicoceles: guidelines and recommendations of the European Society of Urogenital Radiology Scrotal and Penile Imaging Working Group (ESUR-SPIWG) for detection, classification, and grading. *Eur Radiol.* 2020 Jan;30(1):11-25. doi: 10.1007/s00330-019-06280-y. Epub 2019 Jul 22.
92. Sakamoto H, Saito K, Ogawa Y, Yoshida H. Effects of varicocele repair in adults on ultrasonographically determined testicular volume and on semen profile. *Urology.* 2008 Mar;71(3):485-9. doi: 10.1016/j.urology.2007.11.040.
93. Zampieri N, Cervellione RM. Varicocele in adolescents: a 6-year longitudinal and followup observational study. *J Urol.* 2008 Oct;180(4 Suppl):1653-6; discussion 1656. doi: 10.1016/j.juro.2008.03.114. Epub 2008 Aug 20.
94. Zhou T, Zhang W, Chen Q, Li L, Cao H, Xu CL, Chen GH, Sun YH. Effect of varicocelectomy on testis volume and semen parameters in adolescents: a meta-analysis. *Asian J Androl.* 2015 Nov-Dec;17(6):1012-6. doi: 10.4103/1008-682X.148075.
95. La Vignera S, Condorelli R, Vicari E, D'Agata R, Calogero AE. Effects of varicocelectomy on sperm DNA fragmentation, mitochondrial function, chromatin condensation, and apoptosis. *J Androl.* 2012 May-Jun;33(3):389-96. doi: 10.2164/jandrol.111.013433. Epub 2011 Jun 2.
96. Condorelli RA, Calogero AE, Vicari E, Mongioi' L, Burgio G, Cannarella R, Giaccone F, Iacoviello L, Morgia G, Favilla V, Cimino S, La Vignera S. Reduced Seminal Concentration of CD45pos Cells after Follicle-Stimulating Hormone Treatment in Selected Patients with Idiopathic Oligoasthenoteratozoospermia. *Int J Endocrinol.* 2014;2014:372060. doi: 10.1155/2014/372060. Epub 2014 Jan 14.
97. Diamond DA, Zurakowski D, Bauer SB, Borer JG, Peters CA, Cilento BG Jr, Paltiel HJ, Rosoklija I, Retik AB. Relationship of varicocele grade and testicular hypotrophy to semen parameters in adolescents. *J Urol.* 2007 Oct;178(4 Pt 2):1584-8. doi: 10.1016/j.juro.2007.03.169. Epub 2007 Aug 16.
98. Moursy EE, ElDahshoury MZ, Hussein MM, Mourad MZ, Badawy AA. Dilemma of adolescent varicocele: long-term outcome in patients managed surgically and in patients managed expectantly. *J Pediatr Urol.* 2013 Dec;9(6 Pt B):1018-22. doi: 10.1016/j.jpuro.2013.01.017. Epub 2013 Mar 20.
99. Fiogbe MA, Alao MJ, Biaou O, Gbenou SR, Yekpe P, Sossou R, Metchihoungbe SC. Ultrasound diagnosis of varicocele in the adolescent: our experience from Benin. *Afr J Paediatr Surg.* 2013 Oct-Dec;10(4):295-8. doi: 10.4103/0189-6725.125403.
100. Vaganée D, Daems F, Aerts W, Dewaide R, van den Keybus T, De Baets K, De Wachter S, De Win G. Testicular asymmetry in healthy adolescent boys. *BJU Int.* 2018 Oct; 122 (4): 654-666. doi: 10.1111/bju.14174. Epub 2018 Mar 23.
101. Oehme NHB, Roelants M, Saervold Bruserud I, Madsen A, Eide GE, Bjerknes R, Rosendahl K, Juliusson PB. Reference data for testicular volume measured with ultrasound and pubic hair in Norwegian boys are comparable with Northern European populations. *Acta Paediatr.* 2020 Aug; 109 (8):1612-1619. doi: 10.1111/apa.15159. Epub 2020 Jan 22.
102. Patil N and Javali T. Varicocelectomy in adolescents - Does it safeguard future fertility? A single centre experience. *J Ped Urol* 2022; 18: 5e1-5e10. doi: 10.1016/j.jpuro.2021.11.020. Epub 2021 Dec 5.
103. Dabaja AA, Wosnitzer MS, Bolyakov A, Schlegel PN, Paduch DA. When to ask male adolescents to provide semen sample for fertility preservation? *Transl Androl Urol.* 2014 Mar; 3(1): 2-8. doi: 10.3978/j.issn.2223-4683.2014.02.01.
104. Paduch DA, Niedzielski J. Semen analysis in young men with varicocele: preliminary study. *J*

- Urol. 1996 Aug;156(2 Pt 2):788-90. doi: 10.1097/00005392-199608001-00063.
105. Fine RG, Gitlin J, Reda EF, Palmer LS. Barriers to use of semen analysis in the adolescent with a varicocele: Survey of patient, parental, and practitioner attitudes. *J Pediatr Urol*. 2016 Feb;12(1):41.e1-6. doi: 10.1016/j.jpuro.2015.06.015. Epub 2015 Aug 10.
106. Rajfer J. Varicoceles: practice guidelines. *Rev Urol*. 2007 Summer;9(3):161.
107. Naughton CK, Nangia AK, Agarwal A. Pathophysiology of varicoceles in male infertility. *Hum Reprod Update*. 2001 Sep-Oct;7(5):473-81. doi: 10.1093/humupd/7.5.473.
108. Rajfer J, Turner TT, Rivera F, Howards SS, Sikka SC. Inhibition of testicular testosterone biosynthesis following experimental varicocele in rats. *Biol Reprod*. 1987 May;36(4):933-7. doi: 10.1095/biolreprod36.4.933.
109. Di Bisceglie C, Bertagna A, Baldi M, Lanfranco F, Tagliabue M, Gazzera C, Gandini G, Maniari C. Varicocele sclerotherapy improves serum inhibin B levels and seminal parameters. *Int J Androl*. 2007 Dec;30(6):531-6. doi: 10.1111/j.1365-2605.2007.00747.x. Epub 2007 Mar 22.
110. Pierik FH, Abdesselam SA, Vreeburg JT, Dohle GR, De Jong FH, Weber RF. Increased serum inhibin B levels after varicocele treatment. *Clin Endocrinol (Oxf)*. 2001 Jun;54(6):775-80. doi: 10.1046/j.1365-2265.2001.01302.x.
111. Sirvent JJ, Bernat R, Navarro MA, Rodriguez Tolra J, Guspi R, Bosch R. Leydig cell in idiopathic varicocele. *Eur Urol*. 1990;17(3):257-61. doi: 10.1159/000464051.
112. Hayden RP, Tanrikut C. Testosterone and Varicocele. *Urol Clin North Am*. 2016 May;43(2):223-32. doi: 10.1016/j.ucl.2016.01.009. Epub 2016 Mar 21.
113. Comhaire F, Vermeulen A. Plasma testosterone in patients with varicocele and sexual inadequacy. *J Clin Endocrinol Metab*. 1975 May;40(5):824-9. doi: 10.1210/jcem-40-5-824.
114. Pirke KM, Vogt HJ, Sintermann R, Spyra B. Testosterone in peripheral plasma, spermatic vein and in testicular tissue under basal conditions and after HCG-stimulation in patients with varicocele. *Andrologia*. 1983 Nov-Dec;15(6):637-41. doi: 10.1111/j.1439-0272.1983.tb00179.x.
115. Cayan S, Kadioglu A, Orhan I, Kandirali E, Tefekli A, Tellaloglu S. The effect of microsurgical varicocelectomy on serum follicle stimulating hormone, testosterone and free testosterone levels in infertile men with varicocele. *BJU Int*. 1999 Dec;84(9):1046-9. doi: 10.1046/j.1464-410x.1999.00353.x.
116. Hudson RW. The endocrinology of varicoceles. *Fertil Steril*. 1988 Feb;49(2):199-208. doi: 10.1016/s0015-0282(16)59700-3.
117. Hassanin AM, Ahmed HH, Kaddah AN. A global view of the pathophysiology of varicocele. *Andrology*. 2018 Sep;6(5):654-661. doi: 10.1111/andr.12511. Epub 2018 Jul 6.
118. Niu XB, Tang J, Wang HB, Yan L, Zhang CY, Wang GC, Liang J, Dou XY, Fu GB. [Inhibin B level helps evaluate the testicular function of prepubertal patients with varicocele]. *Zhonghua Nan Ke Xue*. 2018 Jul;24(7):618-621. Chinese.