VARICOCELE: A REVIEW

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ABSTRACT

The link between varicocele and infertility was first reported by Celsius in the first century AD, but it was not widely acknowledged until Tulloch and colleagues reported the improvement of sperm parameters in 26 of 30 patients undergoing varicocelectomy. The World Health Organization also reported that varicocele was present in 25% of patients with abnormal sperm parameters and 12% of patients with normal sperm parameters. Varicocele is the most frequently encountered surgical disease causing male infertility.

Keywords: Male infertility, varicocele, varicocelectomy.

INTRODUCTION

The link between varicocele and infertility was first reported by Celsius in the first century AD.[1] A varicocele was described as a 'bag of worms' by Dubin and Amelar in 1970,[2] although a more scientific definition would be: an abnormal venous dilatation of the pampiniform plexus caused by various aetiologies. The first usage of the word 'varicocele' was by Curling in 1843.[3] Varicocele remained out of the spotlight until Tulloch and colleagues[4] reported the improvement of sperm parameters in 26 of 30 patients undergoing varicocelectomy. The World Health Organization reported that varicocele is present in 25% of patients with abnormal sperm parameters and 12% of patients with normal sperm parameters.[5] The condition is commonly encountered in the left testicular side: 90% of cases are isolated in the left side and only 2% are isolated in the right side; this phenomenon can be explained by the venous anatomy.[6]

AETIOLOGY

There are three commonly accepted theories:

- Differences between left and right testicular venous drainage anatomy: The left internal spermatic vein has about 8-10 mm H_2O higher blood pressure and relatively slower blood flow compared with the right side. This is mainly caused by the drainage of the left testicular vein to the left renal vein with a perpendicular angle, whereas in the right testicular vein the drainage is to the vena cava at a steeper angle. This causes less cranial venous drainage.
- Venous reflux: Reflux to the pampiniform plexus is caused by the lack of valves in the internal spermatic vein and/or the reflux caused by venous collateral flow. The lack of valves in the junction of the left renal and internal spermatic veins was shown by Shiraishi and Naito.[7] Braedel and colleagues[6] demonstrated a lack of venous valves in 73% of 659 male patients with varicocele.
- Partial obstruction of testicular veins: This phenomenon, called 'the nutcracker phenomenon,' occurs when a specific vein is compressed by arteries. In proximal type, the left renal vein is compressed by the aorta and the superior mesenteric artery. In distal type, the left common iliac artery compresses the left common iliac vein.

PATHOPHYSIOLOGY

The underlying pathophysiology can be summarised in the following hypotheses. It is

proposed that varicocele is associated with increased testicular blood flow; Grasso Laenza and colleagues[8] reported increased blood flow in patients with varicocele compared with healthy controls in colour Doppler studies. An increase in interstitial fluid was described in animal models of varicocele formation,[9] with the increased number of leukocytes potentially attributable to this increase. In addition, a higher testicular temperature may inhibit spermatogenesis. In both animal models and humans, an increased intra and intertesticular temperature was shown in the presence of varicocele.[10,11] Increased venous pressure caused by reflux may contribute to decreased testicular flow,[12] while Tek et al.[13] demonstrated a higher apoptotic index in patients with varicocele (0.693 versus 0.206; $p<0.05$). Varicocele also causes impairment of the blood—testis barrier,[14] which leads to the formation of anti-sperm antibodies.[15]

DIAGNOSIS

Diagnosis is made using physical examination. Physical examination should be completed in both sitting and standing positions inside a warm and comfortable room. The scrotum should be inspected first and then palpated to evaluate spermatic cord and testes. The diagnosis is finally made by observing and/or palpating a dilated or tortuous segment.[16] Varicocele can be classified as one of three grades:

Grade 1: Dilated veins are palpable only with Valsalva manoeuver.

Grade 2: Dilated veins are seen whilst the patient is standing but not without Valsalva manoeuver, the physician can palpate dilated veins.

Grade 3: Tortuous and dilated veins can be seen in scrotum skin.

Radiology can assist in diagnosis: scrotal ultrasonography (USG) is not indicated for diagnosis of varicocele, but can be helpful if the diagnosis is inconclusive, such as in patients with morbid obesity, previous scrotal surgery, or accompanying ipsilateral hydrocele. The spermatic cord and epididymis can be evaluated with conventional USG. The assessment of testicular volume can also be helpful for indicating a need for intervention. Nowadays, because of the wide usage of Doppler USG and the subjectivity of physical examination, Doppler USG has become a standard diagnostic tool. It is recommended that patients should have at least one diagnostic imaging modality combined with physical examination. Through the use of Doppler USG, blood flow to the testes and reflux can be evaluated. Hirsh et al.[17] graded varicocele according to the reflux observed in Doppler USG:

Grade 1: No spontaneous venous reflux.

Grade 2: Intermittent spontaneous venous reflux.

Grade 3: Continuous spontaneous venous reflux.

However, an objective grading system is lacking and a validated Doppler grading system is needed. The most sensitive test for diagnosing varicocele is venography, but, due to its invasiveness and relatively high cost, it is no longer recommended unless a therapeutic occlusion is planned. The success rate of the occlusion procedure is as high as 85% for recurrent varicoceles.[18] Scrotal thermography is another tool for diagnosis although it is not a widely used method, mainly due to the widespread use of Doppler USG. This method can be used to document elevated temperature of the scrotum due to varicocele.

TREATMENT INDICATIONS

Guidelines from the European Association of Urology[19] recommend treatment in the case of clinical varicocele, oligozoospermia, infertility lasting longer than 2 years, and unexplained infertility. The American Urological Association recommends treatment when the following criteria are met: palpable varicocele on physical examination (may be validated via ultrasound), known infertility, normal female fertility potential, and abnormal semen parameters.[20]

TREATMENT OPTIONS

The main aim of treatment is to disrupt internal spermatic venous drainage whilst preserving arterial and lymphatic blood flow. There are several defined methods, the most widely used of which are the inguinal,[21] subinguinal, and microscopic subinguinal approaches. Although not very commonly used, retroperitoneal,[22] scrotal,[23] and laparoscopic approaches[24] have been described. Furthermore, a minimally invasive method, angiography, and embolisation for internal spermatic veins, have also been defined.[25]

TREATMENT OUTCOMES

In 2009, a meta-analysis suggested that varicocele repair did not improve the likelihood of conception.[26] After the meta-analysis was published, it was greatly criticised for heterogeneity among enrollment and having normal semen parameters of patients suffering from infertility.[27-29] Furthermore, the study included one of the most debatable topics in urology, the subclinical varicocele, which will be discussed in more detail below. In contrast to this meta-analysis, several papers published in subsequent years advocated the use of varicocelectomy to improve sperm parameters and reported improvement of sperm parameters and paternity rates.[30]

Subinguinal varicocelectomy can yield high improvement rates: 75.2% improvement in semen parameters and 45.5% in pregnancy rates.[31] Abdel-Meguid et al.[30] treated patients with varicocelectomy and followed their progress. They revealed a significant improvement in the treatment arm of the study, and a 3.04-times higher rate of spontaneous pregnancy.[30] There is a debate as to whether varicocele repair improves pregnancy rates. Nilsson et al.[32] reported the first comparative study of varicocele repair and did not reveal a significant difference in pregnancy rates among patients treated with varicocele repair. Krause and colleagues[33] conducted a study of 65 men treated with sclerotherapy and revealed no significant improvement compared with those who received no treatment. However, both studies have been criticised for low cohort size and poor follow-up.

On the other hand, Okuyama et al.[34] compared patients treated using Palomo repair with those who received no treatment and revealed significantly higher pregnancy rates in the treatment arm (30% versus 18%; $p<0.05$). Schlegel[35] wrote a review on varicocele treatment outcomes and revealed a 33% pregnancy rate in patients with varicocele repair compared with 16% in the no-treatment group. Varicocele can cause scrotal pain and some surgeons prefer surgery to treat this painful disease. In several studies pain was shown to be resolved with conservative treatment (e.g. oral anti-inflammatory medicine and limiting physical activity) in 5-15% of patients.[36,37] Several studies reported success rates between 75-91%.[38-44]

PROGNOSTIC FACTORS

Not all patients improve after a successful varicocelectomy. Patients with a disease history <2 years and who have high-grade varicoceles are more likely to improve following varicocelectomy. Patients with a total motile sperm count <5 million, who have genetic disorders, altered follicle-stimulating hormone (FSH)/testosterone levels, small testis volume, or concomitant metabolic syndrome have worse treatment outcomes.[44-46]

COMPLICATIONS

Recurrence rates can be as high as 29% with high ligations and about 2% with microscopic techniques. When optical enhancement is not an option, hydrocele may be observed in 7-10% of cases following varicocelectomy. Following the improvement of the technique with microscopy, one of the most feared complications, testicular atrophy, is encountered at a rate of only 1%. Ilioinguinal nerve damage may be seen with the loss of sensation in the scrotum and inner thigh. Haematoma and infections may be encountered in about 2-5% of cases.[46,47]

Patients with Non-Obstructive Azoospermia

The need for varicocelectomy in patients with non-obstructive azoospermia is debatable. Palpable varicocele can be found in approximately 4-14% of cases.[48] Even after varicocele repair, most of these men will be subfertile.[48] One of the most comprehensive meta-analyses was conducted by Weedin and colleagues,[49] and stated that 39% of a total of 233 patients had motile sperm in semen analysis performed after successful varicocelectomy. They concluded that histopathological examination was a key factor in treatment success, with those with maturation arrest being the most likely to benefit from surgery, whereas Sertoli-cell-only syndrome had the worst outcome ($p<0.001$). Daitch et al.[50] proposed a higher rate of pregnancy following surgical repair. Esteves et al.[51] reported better outcomes following intracytoplasmic sperm injection therapy.

Patients with Subclinical Varicocele

Subclinical varicocele is defined as varicocele that is only diagnosed radiologically. Several investigators have conducted trials concerning treatment of subclinical varicocele and do not recommend treatment.[28,29,52] Both the European

and American Urological Associations do not recommend treatment of subclinical varicocele.[20]

Paediatric and Adolescent Varicocele

Indications for treatment are: varicocele associated with small testis, additional testicular condition affecting fertility, bilateral palpable varicocele, pathological sperm quality, and symptomatic varicocele.[53] Çayan and colleagues[54] compared studies of paediatric varicocelectomy and proposed that a 10% volume difference in the affected testis should be the indication for surgical repair; they reported that 53% of patients gained normal sperm volume following the operation before 14 years of age. With the subinguinal microscopic approach, recurrence rates are usually <10%.[55-57]

KEY MESSAGES

- The WHO reported that varicocele was present in 25% of patients with abnormal sperm parameters and 12% of patients with normal sperm parameters.
- Diagnosis is made using physical examination. Nowadays, because of the wide usage of Doppler USG and subjectivity of physical examination, Doppler USG has become a standard diagnostic tool. It is recommended that patients should have at least one diagnostic imaging modality combined with physical examination.
- The main aim of treatment is to disrupt internal spermatic venous drainage while preserving arterial and lymphatic blood flow. There are several methods defined, with the most widely used being the inguinal, subinguinal, and microscopic subinguinal approaches.
- Patients with a disease history <2 years and with high-grade varicoceles are more likely to improve following varicocelectomy.
- Not all patients improve after a successful varicocelectomy. Patients with a total motile sperm count <5 million, who have genetic disorders, altered FSH/testosterone levels, small testis volume, or concomitant metabolic syndrome have worse treatment outcomes.
- Both European and American Urological Associations do not recommend the treatment of subclinical varicocele.
- Following the improvement of the technique with microscopy, one of the most feared complications, testicular atrophy, is encountered at a rate of only 1%.
- Several papers advocate for varicocelectomy in improving sperm parameters, and report improvement of sperm parameters and paternity rates.

REFERENCES

1. Zerhouni EA et al. Elevated pressure in the left renal vein in patients with varicocele: preliminary observations. J Urol. 1980;123(4):512-3.

2. Dubin L, Amelar RD. Varicocele size and results of varicocelectomy in selected subfertile men with varicocele. Fertil Steril. 1970;21(8):606-9.

3. Herman JR. Varicocele: some interesting early approaches. Urology. 1978;12(4):498C-498D.

4. Tulloch WS. Varicocele in subfertility. Results of treatment. 1955. J Urol. 2002;167(2 Pt 2):1184-5; discussion 1186.

5. Agarwal A et al. Efficacy of varicocelectomy in improving semen parameters: new meta-analytical approach. Urology. 2007;70(3):532-8.

6. Braedel HU et al. A possible ontogenic etiology for idiopathic left varicocele. J Urol. 1994;151(1):62-6.

7. Shiraishi K, Naito K. Increased expression of Leydig cell haem oxygenase-1 preserves spermatogenesis in varicocele. Hum Reprod. 2005;20(9):2608-13.

8. Grasso Leanza F et al. [Volocimetric evaluation of spermatic vessels with echo color doppler in patients with idiopathic varicocele]. Minerva Urol Nefrol. 1997;49(4):179-82.

9. Turner TT, Miller DW. Protein synthesis and secretion by the rat seminiferous tubule in vivo not affected by experimental varicocele. J Urol. 1996;156(5):1881-7.

10. Sofikitis N, Miyagawa I. Left adrenalectomy in varicocelized rats does not inhibit the development of varicocele-related physiologic alterations. Int J Fertil Menopausal Stud. 1993;38(4):250-5.

11. Lerchl A et al. Diurnal variations in scrotal temperature of normal men and patients with varicocele before and after treatment. Int J Androl. 1993;16(3):195-200.

12. Shafik A, Bedeir GA. Venous tension patterns in cord veins. I. In normal and varicocele individuals. J Urol. 1980;123(3):383-5.

13. Tek M et al. The effect of vascular endothelial growth factor on spermatogenesis and apoptosis in experimentally varicocele-induced adolescent rats. Fertil Steril. 2009;91(5 Suppl):2247-52.

14. Mieusset R et al. Association of scrotal hyperthermia with impaired spermatogenesis in infertile men. Fertil Steril. 1987;48(6):1006-11.

15. Turner TT et al. Experimental varicocele does not affect the blood-testis barrier, epididymal electrolyte concentrations, or testicular blood gas concentrations. Biol Reprod. 1987;36(4):926-32.

16. Stahl P, Schlegel PN. Standardization and documentation of varicocele evaluation. Curr Opin Urol. 2011;21(6):500-5.

17. Hirsh AV et al. The Doppler assessment of varicoceles and internal spermatic vein reflux in infertile men. Br J Urol. 1980;52(1):50-6.

18. Punekar SV et al. Post-surgical recurrent varicocele: efficacy of internal spermatic venography and steel-coil embolization. Br J Urol. 1996;77(1):124-8.

19. Jungwirth A et al. Guidelines on male infertility. European Association of

Urology. 2014.

20. Sharlip ID et al. Report on varicocele and infertility. An AUA best practice policy and ASRM Practice Committee Report. American Urological Association Inc. 2001.

21. Ivanissevich O. Left varicocele due to reflux; experience with 4,470 operative cases in forty-two years. J Int Coll Surg. 1960;34:742-55.

22. Palomo A. Radical cure of varicocele by a new technique; preliminary report. J Urol. 1949;61(3):604-7.

23. Fretz PC, Sandlow JI. Varicocele: current concepts in pathophysiology, diagnosis, and treatment. Urol Clin North Am. 2002;29(4):921-37.

24. Ding H et al. Open non-microsurgical, laparoscopic or open microsurgical varicocelectomy for male infertility: a meta-analysis of randomized controlled trials. BJU Int. 2012;110(10):1536-42.

25. Hart RR et al. Intraoperative spermatic venography during varicocele surgery in adolescents. J Urol. 1992;148(5):1514-6.

26. Evers JH et al. Surgery or embolisation for varicoceles in subfertile men. Cochrane Database Syst Rev. 2009;(1):CD000479.

27. Ficarra V et al. Treatment of varicocele in subfertile men: The Cochrane Review--a contrary opinion. Eur Urol. 2006;49(2):258-63.

28. Grasso M et al. Low-grade left varicocele in patients over 30 years old: the effect of spermatic vein ligation on fertility. BJU Int. 2000;85(3):305-7.

29. Unal D et al. Clomiphene citrate versus varicocelectomy in treatment of subclinical varicocele: a prospective randomized study. Int J Urol 2001;8(5):227-30.

30. Abdel-Meguid TA et al. Does varicocele repair improve male infertility? An evidence-based perspective from a randomized, controlled trial. Eur Urol. 2011;59(3):455-61.

31. Peng J et al. Spontaneous pregnancy rates in Chinese men undergoing microsurgical subinguinal varicocelectomy and possible preoperative factors affecting the outcomes. Fertil Steril. 2015;103(3):635-9.

32. Nilsson S et al. Improvement of semen and pregnancy rate after ligation and division of the internal spermatic vein: fact or fiction? Br J Urol. 1979;51(6):591-6.

33. Krause W et al. Does treatment of varicocele improve male fertility? Results of the 'Deutsche Varikozelenstudie', a multicentre study of 14 collaborating centres. Andrologia. 2002;34(3):164-71.

34. Okuyama A et al. Surgical repair of varicocele: effective treatment for subfertile men in a controlled study. Eur Urol. 1988;14(4):298-300.

35. Schlegel PN. Is assisted reproduction the optimal treatment for varicocele-associated male infertility? A cost-effectiveness analysis. Urology. 1997;49(1):83-90.

36. Yaman O et al. Effect of microsurgical subinguinal varicocele ligation to treat pain. Urology. 2000;55(1):107-8.

37. Chen SS. Factors predicting symptomatic relief by varicocelectomy in patients with normospermia and painful varicocele nonresponsive to conservative treatment. Urology. 2012;80(3):585-9.

38. Al-Buheissi SZ et al. Predictors of success in surgical ligation of painful varicocele. Urol Int. 2007;79(1):33-6.

39. Ribé N et al. Clinical follow-up after subinguinal varicocele ligation to treat pain. Arch Ital Urol Androl. 2002;74(2): 51-3.

40. Karademir K et al. Evaluation of the role of varicocelectomy including external spermatic vein ligation in patients with scrotal pain. Int J Urol. 2005;12(5):484-8.

41. Shridharani A et al. Varicocelectomy in the treatment of testicular pain: a review. Curr Opin Urol. 2012;22(6):499-506.

42. Maghraby HA. Laparoscopic varicocelectomy for painful varicoceles: merits and outcomes. J Endourol. 2002;16(2):107-10.

43. Kim HT et al. Microsurgical ligation for painful varicocele: effectiveness and predictors of pain resolution. Yonsei Med J. 2012;53(1):145-50.

44. Park HJ et al. Predictors of pain resolution after varicocelectomy for painful varicocele. Asian J Androl. 2011;13(5):754-8.

45. Ozturk U et al. The effect of metabolic syndrome upon the success of varicocelectomy. ScientificWorldJournal. 2012;2012:985201.

46. Choi WS, Kim SW. Current issues in varicocele management: a review. World J Mens Health. 2013;31(1):12-20.

47. Salama N, Blgozah S. Immediate development of post-varicocelectomy hydrocele: a case report and review of the literature. J Med Case Rep. 2014;8:70.

48. Czaplicki M et al. Varicocelectomy in patients with azoospermia. Arch Androl. 1979;3(1):51-5.

49. Weedin JW et al. Varicocele repair in patients with nonobstructive azoospermia: a meta-analysis. J Urol. 2010;183(6):2309-15.

50. Daitch JA et al. Varicocelectomy improves intrauterine insemination success rates in men with varicocele. J Urol. 2001;165(5):1510-3.

51. Esteves SC et al. Clinical outcome of intracytoplasmic sperm injection in infertile men with treated and untreated clinical varicocele. J Urol. 2010;184(4):1442-6.

52. Yamamoto M et al. Effect of varicocelectomy on sperm parameters and pregnancy rate in patients with subclinical varicocele: a randomized prospective controlled study. J Urol. 1996;155(5):1636-8.

53. Tekgul S et al. Guidelines on paediatric urology. European Society for Paediatric Urology. European Association of Urology. 2013.

54. Çayan S et al. The effect of varicocele repair on testicular volume in children and adolescents with varicocele. J Urol. 2002;168(2):731-4.

55. Marmar J, Benoff S. New scientific information related to varicoceles. J Urol. 2003;170(6 Pt 1):2371-3.

56. Kocvara R et al. Lymphatic sparing laparoscopic varicocelectomy: a microsurgical repair. J Urol. 2005;173(5):1751-4.

57. Riccabona M et al. Optimizing the operative treatment of boys with varicocele: sequential comparison of 4 techniques. J Urol. 2003;169(2):666-8.