Suez Canal University Medical Journal Vol. 28 (6), 2025
Pages 1-8

Intra-testicular Doppler Ultrasound Parameters among Varicocele Patients: A Review

Omar M. Shehata[1], Mohammad A. Al-Shatouri[2], Hashem M. Rashwan[1], Essam A. Shalaby[1], Ahmed I. El-Sakka[1]*

[1]*Department of Urology, Suez Canal University, Ismailia, Egypt*
[2]*Department of Diagnostic Radiology, Suez Canal University, Ismailia, Egypt*

Abstract:

Background: **Varicocele is characterized by the abnormal enlargement, elongation, and tortuosity of the pampiniform plexus veins, which are responsible for testicular venous drainage. While varicocele affects approximately 15% of the male population, its prevalence rises significantly among infertile men (19–41%) and reaches 70–80% in cases of secondary infertility. Although the etiology of varicocele remains uncertain, it is generally accepted as multifactorial, with proposed contributors including the nutcracker phenomenon, weak mesenchyme syndrome and defective venous valves.** ***Aim:*** **To explore the impact of varicocele on hormonal profiles, particularly estradiol and testosterone levels, and to assess the associated hemodynamic changes detectable by Doppler ultrasound.** ***Materials and Methods:*** **Previous studies assessing hormonal changes in men with varicocele, specifically those with oligoasthenoteratozoo-spermia, were reviewed. Doppler ultrasound findings evaluating peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistive index (RI) were also analyzed in relation to varicocele presence.** ***Results:*** **Men with varicocele, especially those with abnormal semen parameters, have been found to exhibit elevated estradiol concentrations and reduced total testosterone levels, resulting in a decreased testosterone-to-estradiol (T: E) ratio. Additionally, varicocele has been associated with increased sperm DNA damage, adversely affecting fertility. Doppler ultrasound studies have consistently demonstrated significant alterations in testicular blood flow parameters (PSV, EDV, RI) in affected individuals.** ***Conclusions:*** **Varicocele contributes to hormonal imbalances and impaired sperm parameters, leading to reduced fertility. Evaluation using Doppler ultrasound aid in detecting hemodynamic abnormalities, and surgical intervention such as subinguinal varicocelectomy help restore hormonal balance and improve fertility.**

Keywords: doppler ultra-sound, infertility, varicocele.

Introduction

The Varicocele definition is the abnormal enlargement of the pampiniform plexus of veins located in the spermatic cord. Its severity is typically classified into four grades: grade 0 (subclinical), which can only be detected through imaging; grade 1, which becomes noticeable or palpable solely while performing the Valsalva maneuver; grade 2, which can be felt by examination but not seen while standing in a room-temperature environment; and grade 3, which is visibly apparent under the same conditions. Approximately 85% of varicocele cases are on the left side and are unilateral. The majority of the remaining instances are bilateral, while isolated right-sided varicoceles are infrequent. While many affected men remain asymptomatic, some may experience testicular discomfort or pain, as well as

**Corresponding author: aielsakka@yahoo.com*

concerns related to the cosmetic aspect of the condition [1].

Varicoceles are characteristic with the abnormal expansion and coiling of veins within the pampiniform plexus, a venous network essential for draining blood from the testes. These veins primarily flow into the internal spermatic (gonadal) vein. On the right, this vein typically enters the anterolateral side of the inferior vena cava (IVC) below the right renal vein. In contrast, the left internal spermatic vein drains at a right angle into the left renal vein, a configuration that makes it more prone to venous congestion, especially under increased pressure within the left renal vein. This condition is worsened by compression of the left renal vein between the aorta and the superior mesenteric artery—a situation known as "nutcracker syndrome." Furthermore, the left spermatic vein is much longer compared to the right increases the incidence of varicoceles on the left sides, Due to this anatomical variance, isolated right-sided varicoceles are uncommon, prompting some experts to recommend further investigation for possible retroperitoneal tumors. Another contributing factor to the development of varicoceles on the left is the potential compression of the left spermatic vein by the descending colon [2].

Absence or dysfunction of venous valves has a potential role in the occurrence of reflux of venous blood, which is much frequently observed in the left internal spermatic vein. Research has shown that valves are absent in 40% of left spermatic veins compared to the veins of the right-side which is 23% [3].

Besides the internal spermatic vein, the testes utilize several auxiliary venous drainage routes, listed according to importance. These include the external pudendal vein, which drainage is into the great saphenous vein; the vasal vein, which connects to the internal iliac vein; and the cremasteric (or external spermatic) vein, which empties to the inferior epigastric and external iliac veins. Another collateral pathway may involve venous connections with the retroperitoneal, peritoneal, ureteral, colonic, splenic, and adrenal systems. Notably, relation between the right and left internal spermatic veins have also been observed near the level of the third lumbar vertebra (L3) [4].

Etiology

Varicoceles are generally believed to form due to impaired venous return in the internal spermatic vein, leads to blood pooling and vein dilation that is often clinically palpable on scrotal examination [5].

Three primary anatomical mechanisms have been proposed:

Failure of the anti-reflux valve at the junction of the internal spermatic vein and left renal veins, leading to backward flow of blood;

The junction between the left internal spermatic and left renal veins is angled, that can impair flow;

The "nutcracker effect" is compression of the left renal vein between the aorta and the superior mesenteric artery—a condition can restrict venous outflow. This anatomical obstruction of the left spermatic vein has been reported in as many as 50% or more of cases [6].

Less common causes of varicocele include thrombosis in the deep veins, renal arteriovenous malformations, and clot formation within the pampiniform plexus (Brahmbhatt et al., 2021).

Additional risk factors for male infertility include tobacco use and genetic variations such as mutations in the glutathione S-transferase Mu 1 gene [7].

When varicoceles negatively impact semen quality, they often produce a distinctive "stress pattern" on semen analysis, marked

by a reduced sperm count, poor motility, and a higher proportion of morphologically abnormal sperm [8].

Epidemiology

Varicoceles affect approximately 15% to 20% of adult males and are found in as many as 40% of men being assessed for infertility [9]. Despite this, delays in assessing the male partner during infertility evaluations are not uncommon. Notably, 18% of men with infertility who were referred after undergoing assisted reproductive procedures were eventually found to have varicoceles and were suitable candidates for varicocelectomy. Notably, in about 70% of these couples, no fertility-related issues were detected in the female partner [10].

Complications

If left untreated, clinically significant varicoceles can lead to discomfort or pain and may impair fertility. In younger individuals, particularly adolescents, varicoceles can also interfere with testicular growth and development [11].

Although atrophy of the testis is uncommon—even when the artery is accidentally tied off during surgery (reported in around 5% of cases)—this is due to the presence of alternative arterial supplies from the cremasteric and vasal arteries. Risk of damaging the artery during surgical intervention can be reduced by employing magnification techniques, such as surgical loupes, or by using microsurgical approaches. Despite treatment, varicoceles can recur in up to 10% of patients [12].

Postoperative scrotal pain may occur, and several potential causes have been proposed, including hydrocele formation, nerve irritation, injury to the ureter, recurrence of the varicocele, Nutcracker syndrome, or pain referred from other anatomical areas [13].

Pathophysiologic Mechanisms Associated with Varicocele

Subfertility is typically the main clinical concern associated with varicoceles. Although many men with varicoceles remain fertile, others may experience issues related to sperm count, motility, morphology, or overall function. One proposed explanation is that elevated scrotal temperatures from venous pooling led to oxidative stress, which may impair sperm health. Additional contributing factors may include diminished oxygen delivery (hypoxia), mechanical pressure damage to testicular tissue, accumulation of toxins, autoimmune responses, or exposure to elevated levels of adrenal steroids. This last mechanism is particularly plausible on the left side, where adrenal veins drain into the left renal vein, near the entrance of the internal spermatic vein [14].

Varicoceles are also linked to increased DNA fragmentation of the sperms and oxidative stress, both of which can negatively impact various aspects of sperm functionality [15].

Although most varicoceles are asymptomatic, 2% to 10% of cases may present with pain. Possible causes for this discomfort include increase of testicular temperature, elevated the pressure of the veins, oxidative stress, hormonal disturbances, backflow of harmful substances from the kidneys or adrenal glands, hypoxia, or nerve fibers stretch in the spermatic cord caused by vein enlargement [16].

Varicoceles can also affect the testosterone in the Leydig cells of the testes, especially in older men. [17].

Hypoperfusion and hypoxia

The testicular microvasculature is characterized by notably low blood pressure within both the pre-capillary and post-capillary arterioles and venules, making the environment within the testicular tissue

particularly susceptible to even slight fluctuations in vascular pressure [18]. In varicocele patients, the abnormal dilation of the pampiniform veins leads to blood pooling and a reversal of flow within the venous system. This venous congestion disrupts the countercurrent heat exchange mechanism, resulting in elevated scrotal temperatures. Additionally, increased venous pressure can trigger compensatory vasoconstriction in the pre-capillary arterioles, a physiological attempt to regulate arterial inflow and stabilize intratesticular pressure [19].

The vasoconstriction associated with varicocele leads to decreased blood flow (hypoperfusion) in the testes, restricting the supply of oxygen and nutrients to the testicular cells. high levels of hypoxia-inducible factor 1α (HIF-1α) have been detected in the testicular veins of varicocele patients, suggesting that these tissues are subjected to lower oxygen levels [20]. HIF-1α and related hypoxia-inducible factors are critical regulators of cellular responses to low oxygen environments. Under hypoxic conditions, these factors promote survival by stimulating new blood vessel formation and shifting cellular metabolism toward anaerobic pathways. However, whether these factors facilitate survival or induce cell death depends on the type of tissue and the extent of oxygen deprivation [21].

Heat stress

The testicular artery, located within the spermatic cord, is encircled by several veins forming the pampiniform plexus. In 1959, Dahl and Herrick introduced the countercurrent heat exchange theory, which posits that venous blood returning through the pampiniform veins cools the arterial blood that enter the testicular artery. This mechanism helps maintain a scrotal temperature that is a few degrees lower than the core temperature of the body, which is essential for optimal testicular function [22].

In varicocele patients, the dilation of the veins of the pampiniform plexus can lead to pooling of the blood and backward venous flow, disrupting this finely tuned thermal regulation. As a result, the cooling of incoming arterial blood is compromised, which leads to elevated temperatures in the scrotum. Studies in both humans and animal models have confirmed that varicoceles cause increased scrotal and intratesticular temperatures [23]. This rise in local temperature may be one of the key factors contributing to the effect of varicocele on sperm development and overall function of sperm [24].

Central role of oxidative stress

Varicoceles are thought to impair male fertility through several mechanisms, with oxidative stress (OS) playing a central role. OS occurs when the generation of reactive oxygen species (ROS) exceeds the ability of the body to counteract them with antioxidants. Extensive research has demonstrated that this imbalance can make oxidative damage to sperm membranes and DNA, interfere with spermatogenesis, and diminish sperm motility [25].

Testicular hypoxia

In varicoceles, impaired venous drainage can lead to localized hypoxia in the testes, as evidenced by elevated expression of hypoxia-inducible factor-1α in the tissue within the testis of rats with varicocele [26].

Complications of varicocele

Hormonal disturbance

Oxidative stress (OS) can adversely affect steroidogenesis in Leydig cells, disrupting

spermatogenesis and reducing the production of mature spermatozoa. In a retrospective study, varicocele repair led to an average increase of 109.1 ± 12.8 ng/dl in serum testosterone levels among 78 patients [27].

Likewise, a prospective study found a significant correlation between baseline testosterone and the changes in testosterone following varicocelectomy [28]. Hu et al. demonstrated that adrenomedullin, a polypeptide hormone linked to increased oxidative stress (OS), reduces both antioxidant defense and steroidogenesis [28]. In the male reproductive system, reactive oxygen species (ROS) can also affect other hormonal pathways. For example, the hypothalamus-pituitary-adrenal (HPA) activation axis leads to elevated cortisol levels, which suppress pituitary hormones [29]. also, OS in the hypothalamus-pituitary-thyroid (HPT) axis can decrease thyroid hormone production, lowering the expression of steroidogenic acute regulatory (StAR) protein in Leydig cells, thus impairing testosterone production [30].While OS has long been known to contribute to infertility by disrupting local hormonal environments, its effects may extend more broadly. Additional research is important to comprehensively understand the systemic effect of OS on spermatogenesis and semen quality, particularly in men diagnosed with varicocele [31].

Testicular Dysfunction

Around 40% of men undergoing infertility evaluation are diagnosed with a varicocele [32]. The multifactorial nature of infertility in varicocele patients certainly adds complexity to treatment strategies. The interplay between elevated scrotal temperature, retrograde blood flow, and increased oxidative stress underscores the importance of targeting multiple mechanisms when managing varicocele-related infertility. The effect on sperm quality and testicular function—such as the potential for testicular atrophy—highlights how varicoceles can have long-term consequences even in individuals without overt symptoms of infertility.

Interestingly, the various factors you mentioned—like catecholamine effects from retrograde blood flow and oxidative damage to spermatozoa—suggest a systemic imbalance that could be more difficult to reverse once established. However, if addressed early, the effects of varicocele, such as testicular atrophy, might be mitigated or even reversed, particularly with surgical interventions like varicocelectomy [33].

This reduction in testicular size is often accompanied by dysfunction of the testicular tissue, as demonstrated by biopsy studies of testicles affected by varicocele [34].

Approach to evaluating varicocele.

Clinical assessment

Varicoceles are commonly detected during routine physical examinations or as part of an infertility assessment. While they are typically asymptomatic, 2% to 10% of patients may report discomfort. The pain is generally described as dull, aching, or throbbing, with sharp or stabbing pain being rare. Some patients may also experience a sensation of heaviness in the scrotum [35].

Large varicoceles are easily visible during inspection and often present with the characteristic "bag of worms" appearance. Medium-sized varicoceles can be felt through palpation or physical examination without the need for the patient to strain. Small varicoceles are detectable only with a pronounced Valsalva maneuver.

Subclinical varicocele, on the other hand, cannot be detected during physical examination and are diagnosed using ultrasound imaging [16].

When evaluating Color Doppler ultrasonography (CDUS) results, it is important to use the formula 'volume = 0.71 × length × width × height' for a more precised calculation of testicular ellipsoid volume, replacing the older formula 'volume = 0.52 × length × width × height' [36].

Clinical grading

The Dubin and Amelar clinical grading system for varicocele severity remains widely utilized, categorizing varicoceles into three grades: grade 1 (detectable only during a Valsalva maneuver), grade 2 (palpable without Valsalva), and grade 3 (visibly evident). The World Health Organization (WHO) later introduced the concept of grade 0, or "subclinical" varicocele, that cannot be detected through physical examination, either during rest by the Valsalva maneuver. Subclinical varicoceles diagnosis is typically identified using thermography or color Doppler ultrasonography (CDUS) [8].

In adults, studies have shown that vein diameter correlates with the likelihood of venous reflux, although the exact threshold values differ among reports. One investigation proposed that a minimum vein diameter (MVD) of 3 mm is significant; men with an MVD below this level has venous reflux in 62.3% of cases, whereas reflux was present in 94.4% of those with an MVD above 3 mm [37].

Similarly, Pilatz et al. In a study involving 270 adult men, it was determined that a varicocele diagnosis could be made with a minimum vein diameter (MVD) of 2.45 mm at rest (with a sensitivity of 84% and specificity of 81%) or 2.95 mm during the Valsalva maneuver (with a sensitivity of 84% and specificity of 84%) [38].

Hemodynamic assessment

Doppler color flow mapping ultrasonography is widely regarded as a valuable diagnostic tool in clinical urology for assessing varicoceles. The 2011 guidelines from the European Association of Urology (EAU) recommend its use for the diagnosis of venous reflux, detecting subclinical varicoceles, and evaluating the size of the testos to identify hypoplasia [39].

However, the use of hemodynamic parameters has yet to be validated through prospective randomized studies or included in pediatric and adolescent patient's guidelines. Despite this, many clinicians rely on hemodynamic classification in practice to better characterize varicoceles and determine surgical candidates. As these parameters gain broader use, they may be incorporated into future guidelines. [8].

For hemodynamic evaluation of varicocele, high-frequency linear probes and devices capable of assessing the flow of blood are recommended for Color Doppler Ultrasound (CDUS) (Hamada et al., 2015). The perfusion of the testis is evaluated using color Doppler (CD), power Doppler, and spectral Doppler ultrasound techniques. The waveform of testicular arteries generally demonstrates low resistance and an average resistive index (RI) of 0.62 (range 0.48–0.75) in adults and post pubertal boys [40].

Subsequent studies have shown that CDUS has high sensitivity in detecting changes in circulation inside in testes affected by varicocele. These studies indicate significant reductions in testicular arterial blood flow, along with increases in resistive index and peak systolic velocity in patient with varicocele.

References:

1. Macleod R, et al. Varicocele. BMJ Clin Evid. 2015 Jul 20; 2015:1806.
2. Baigorri BF, Dixon RG. Varicocele: a review. Semin Interventional Radiology. 2016 Sep;33(3):170-176.

3. Bernstein AP, Najari BB. Varicocele Treatment and Serum Testosterone. Androgen Clinical Research and Therapeutic. 2022;3(1):133-137.
4. Ramírez-González JA, Sansone A. Male reproductive system. In: Fertility, Pregnancy, and Wellness. Elsevier; 2022. p. 23-36.
5. Reesink DJ, Huisman PM, Wiltink J, Boeken Kruger AE, Lock TM. Sneeze and pop: a ruptured varicocele; analysis of literature, guided by a well-documented case-report. BMC Urol. 2019;19(1):1-6.
6. Malasevskaia I, Al-Awadhi AA, Raza FA. Fertility outcomes after varicocele repair: are there any benefits? A traditional review. Fortune J Health Sci. 2021;4(2):284-298.
7. He J, Mu Y, Liu M, Che BW, Zhang WJ, Chen KH, Tang KF. Glutathione S-transferase genetic polymorphisms and fluoride-induced reproductive toxicity in men with idiopathic infertility. Asian J Andrology. 2023;25(3):404.
8. Cannarella R, et al. Management and treatment of varicocele in children and adolescents: an endocrinologic perspective. J Clin Med. 2019;8(9):1410.
9. Wang NN, Dallas K, Li S, Baker L, Eisenberg ML. The association between varicocoeles and vascular disease: an analysis of US claims data. Andrology. 2018;6(1):99-103.
10. Jacobson DL, Johnson EK. Varicoceles in the pediatric and adolescent population: threat to future fertility? Fertility and Sterility. 2017;108(3):370-377
11. Zavattaro M, Ceruti C, Motta G, Allasia S, Marinelli L, Di Bisceglie C, et al. Treating varicocele in 2018: current knowledge and treatment options. J Endocrinol Invest. 2018; 41:1365-1375.
12. Leslie SW, Sajjad H, Siref LE. Varicocele. In: Stat Pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2023 Jan–. Available from:
13. Lai CZ, et al. Scrotal Pain after Varicocelectomy: A Narrative Review. Biomedicines. 2023;11(4):1070.
14. Lomboy JR, Coward RM. The varicocele: clinical presentation, evaluation, and surgical management. Semin Intervent Radiol. 2016 Sep;33(3):163-169.
15. Brannigan RE. Introduction: varicoceles: a contemporary perspective. Fertile Sterile. 2017;108(3):361-363.
16. Paick S, Choi WS. Varicocele and testicular pain: a review. World J Mens Health. 2019;37(1):4.
17. Çayan S, et al. Effect of varicocele and its treatment on testosterone in hypogonadal men with varicocele: review of the literature. Balkan Med J. 2020;37(3):121.
18. Majzoub A, et al. Scrotal hyperthermia, hormonal disturbances, testicular hypoperfusion, and backflow of toxic metabolites in varicocele. In: Varicocele and Male Infertility: A Complete Guide. 2019. p.27-35.
19. Tsili AC, et al. Potential role of imaging in assessing harmful effects on spermatogenesis in adult testes with varicocele. World J Radiology. 2017;9(2):34.
20. Kuroda S, Usui K, Mori K, Sanjo H, Takeshima T, Kawahara T, et al. The efficacy of microsurgical varicocelectomy as a salvage option for grade 1 varicocele: a retrospective study. Glob Reproductive Health. 2020;5(3): e46.
21. Babaei A, et al. Expression of hypoxia-inducible factor1-α in varicocele disease: a comprehensive systematic review. Reprod Sci. 2022;29(10):2731-2743.
22. Dv EV, JF H. A vascular mechanism for maintaining testicular temperature by counter-current exchange. Surg Gynecol Obstet. 1959;108(6):697-705.
23. Nguyen HT, Rossini G. Hernia, hydrocele, testicular torsion, and varicocele. In: The Kelalis–King–Belman Textbook of Clinical Pediatric Urology. CRC Press; 2018. p.1313-1333.
24. Arya D, Balasinor N, Singh D. Varicocele-associated male infertility: Cellular and molecular perspectives of pathophysiology. Andrology. 2022;10(8):1463-1483.
25. Majd NE, Sadeghi N, Tavalaee M, Tabandeh MR, Nasr-Esfahani MH. Evaluation of oxidative stress in testis and sperm of rat following induced varicocele. Urol J. 2019;16(3):300.
26. Hu W, et al. Roles of adrenomedullin and hypoxia-inducible factor 1 alpha in patients with varicocele. Andrologia. 2015;47(8):951-957.

27. Hsiao W, et al. Varicocelectomy is associated with increases in serum testosterone independent of clinical grade. Urology. 2013;81(6):1213-1218.
28. Abdel-Meguid TA, et al. Effects of varicocele on serum testosterone and changes of testosterone after varicocelectomy: a prospective controlled study. Urology. 2014;84(5):1081-1087.
29. Hu W, et al. Roles of adrenomedullin and hypoxia-inducible factor 1 alpha in patients with varicocele. Andrologia. 2015;47(8):951-957.
30. Darbandi M, Darbandi S, Agarwal A, Sengupta P, Durairajanayagam D, Henkel R, Sadeghi MR. Reactive oxygen species and male reproductive hormones. Reprod Biol Endocrinol. 2018;16(1):1-14.
31. Monageng E, Offor U, Takalani NB, Mohlala K, Opuwari CS. A review on the impact of oxidative stress and medicinal plants on Leydig cells. Antioxidants (Basel). 2023;12(8):1559.
32. Chaudhuri GR, Das A, Kesh SB, Bhattacharya K, Dutta S, Sengupta P, Syamal AK. Obesity and male infertility: multifaceted reproductive disruption. Middle East Fertil Soc J. 2022;27(1):8.
33. Yan S, Shabbir M, Yap T, Homa S, Ramsay J, McEleny K, Minhas S. Should the current guidelines for the treatment of varicoceles in infertile men be re-evaluated? Hum Fertil (Camb). 2019;22(1):1-6.
34. Bernstein AP, Najari BB. Varicocele treatment and serum testosterone. Androg Clin Res Ther. 2022;3(1):133-137.
35. Kang C, Punjani N, Lee RK, Li PS, Goldstein M. Effect of varicoceles on spermatogenesis. Semin Cell Dev Biol. 2022; 121:114-124.
36. Leslie SW, Sajjad H, Siref LE. Varicocele. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. Available from:
37. Kocakoc E, et al. Color Doppler sonographic evaluation of inter-relations between diameter, reflux and flow volume of testicular veins in varicocele. Eur J Radiol. 2003;47(3):251-256.
38. Pilatz A, Altinkilic B, Köhler E, Marconi M, Weidner W. Color Doppler ultrasound imaging in varicoceles: is the venous diameter sufficient for predicting clinical and subclinical varicocele? World J Urol. 2011; 29:645-650.
39. Shridharani A, et al. The significance of clinical practice guidelines on adult varicocele detection and management. Asian J Androl. 2016;18(2):269.
40. Dogra VS, et al. Sonography of the scrotum. Radiology. 2003; 227:18-36.