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REVIEW

Potential role of imaging in assessing harmful effects on spermatogenesis in adult testes with varicocele

Athina C Tsili, Olga N Xiropotamou, Anastasios Sylakos, Vasilios Maliakas, Nikolaos Sofikitis, Maria I Argyropoulou

Athina C Tsili, Olga N Xiropotamou, Vasilios Maliakas, Maria I Argyropoulou, Department of Clinical Radiology, University of Ioannina, Medical School, University Campus, 45110 Epirus, Greece

Anastasios Sylakos, Nikolaos Sofikitis, Department of Urology, University of Ioannina, Medical School, University Campus, 45110 Epirus, Greece

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Correspondence to: Athina C Tsili, MD, Assistant Professor, Department of Clinical Radiology, University of Ioannina, Medical School, University Campus, Ioannina, 45110 Epirus, Greece. a_tsili@yahoo.gr
Telephone: +30-69-76510904
Fax: +30-26-51007862

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Abstract

Varicocele is characterized by an abnormal dilatation and retrograde blood flow in the spermatic veins. Varicocele is the leading correctable cause of male infertility. Although it is highly prevalent in infertile men, it is also observed in individuals with normal fertility. Determining which men are negatively affected by varicocele would enable clinicians to better select those men who will benefit from treatment. To assess the functional status of the testes in men with varicocele, color Doppler sonographic parameters were evaluated. Testicular arterial blood flow was significantly reduced in men with varicocele, reflecting an impairment of spermatogenesis. An improvement in the testicular blood supply was found after varicocelectomy on spectral Doppler analysis. Testicular contrast harmonic imaging and elastography might improve our knowledge about the influence of varicocele on intratesticular microcirculation and tissue stiffness, respectively, providing possible information on the early damage of testicular structure by varicocele. Magnetic resonance imaging (MRI), with measurement of apparent diffusion coefficient has been used to assess the degree of testicular dysfunction and to evaluate the effectiveness of varicocele repair. Large prospective studies are needed to validate the possible role of functional sonography and MRI in the assessment of early defects of spermatogenesis in testes with varicocele.

Key words: Varicocele; Spermatogenesis; Diagnostic imaging; Ultrasonography; Doppler ultrasound imaging; Magnetic resonance imaging; Functional

Core tip: Varicocele is known as one of the main causes of male infertility. However, many controversies exist regarding the effect of varicocele on male reproductive potential, which patients to treat and whether repair leads to an improvement of the fertility status. Non-

invasive imaging modalities, including functional sonography and magnetic resonance imaging, might provide useful information on the early damage of testicular structure by varicoceles, therefore helping clinicians target repair efforts to those men who will benefit from varicocele treatment.

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INTRODUCTION

Male infertility is a social problem, representing the causal factor for infertility in 50% of cases and the sole cause in 30% of infertile couples[1-3]. Varicocele is the most common andrological disorder between adolescents and adult males. Its clinical significance is mainly related to fertility, as it represents the most common cause of impaired male fertility and the most common treatable cause of infertility[4-10]. The origin of the word varicocele comes from varico (a combining form meaning "varix" in Latin) and cele (a combining form meaning "tumor" in Greek) and dates to 1730-1740.

Varicocele has been one of the most controversial topics of debate in the fields of andrology and urology, regarding the effect of varicocele on male infertility and whether repair leads to improvement of fertility status[4-10]. While most men with varicocele are able to father children, most evidence suggests that varicocele has detrimental effects on male reproductive potential. A non-invasive imaging technique providing answers to questions regarding which patients with varicocele are at risk for infertility and which will benefit from varicocele repair, would be extremely useful.

DEFINITION AND EPIDEMIOLOGY

Varicocele is clinically defined as an abnormal dilation of the veins of the pampiniform venous plexus and the testicular veins with continuous or intermittent reflux of venous blood[4,5,11]. Primary varicoceles are due to venous reflux into the pampiniform plexus from the internal spermatic vein because of incontinent venous valves, and they usually occur on the left side. Secondary varicoceles are the result of increased pressure in the testicular veins, which can be related to several causes, such as hydronephrosis, abdominal and retroperitoneal neoplasms, and the so-called nutcracker phenomenon, which involves compression of the left renal vein between the superior mesenteric artery and aorta[4,12-15]. Although varicoceles are almost always more common and larger on the left side, they are bilateral in 50% of cases[14]. The uncommon, isolated right-sided varicocele always necessitates further investigation, as this finding may be associated with situs inversus or retroperitoneal malignancies[4,14].

Varicocele epidemiology is incompletely understood[14]. A clinical varicocele is found in approximately 15% of all adult males, up to 35% of infertile men and 81% of men presenting with secondary infertility. When classified according to semen analysis parameters, 12% of infertile men with normal semen analyses and 25.4% of those with abnormal results were found to have clinical varicocele[4,5,8,12,14]. This disorder may be present at birth or in young children, but the incidence substantially increases in adolescents coinciding with pubertal development[4,5,14]. The prevalence of varicocele also increases with advancing age, with an increase of approximately 10% per decade of life, probably because of the aging of venous valves[14].

An association between varicocele and varicose veins of the lower extremities and an inverse relationship between the prevalence of varicocele and body mass index have been suggested[4-16]. Hereditary factors may also play a role in the prevalence of varicocele[14,17].

ETIOLOGY AND PATHOGENESIS

The exact etiology of varicocele is still unknown, but it is probably multifactorial[4,5,12,13,18]. The cause for the high incidence of left varicocele is that the left internal spermatic vein runs vertically to drain into the ipsilateral renal vein at a right angle, when the man is in the standing position, and thus, the endoluminal pressure in the renal vein is transmitted backward, opposing flow from the internal spermatic vein. On the right side, the internal spermatic vein runs tangentially to join the inferior vena cava, resulting in less flow turbulence and back pressure in the vein and therefore in a lower incidence of venous dilation on the right side. However, Gat *et al*[19] reported that varicocele is mainly a bilateral disease, expressed earlier on the left side, with a right-sided venous return problem presenting in 86% of infertile men with clinically significant varicocele.

Several other theories related to the etiological factors of varicocele have been proposed, including the following: Incompetence or absence of venous valves in the spermatic veins, obstructed venous drainage, vascular contractions of the left testicular vein caused by catecholamines from the left adrenal gland and the so-called nutcracker phenomenon[4,5,12,13,18,20,21].

CLINICAL FINDINGS-CLASSIFICATION

Clinically, varicocele is characterized by an abnormal enlargement of the spermatic veins of the venous plexus, which drains the blood from the testes, associated with an anomalous intermittent or continuous backflow of blood into the plexus. In adult males, most cases are

asymptomatic, often revealed during an investigation related to infertility and/or because of an unfavorable outcome of semen analysis[5]. Rarely, it may present with scrotal pain or create esthetic problems or discomfort due to the presence of significant enlargement of the scrotum[5,12].

Clinical varicocele was found to be a significant risk factor for decreased sperm count, motility and morphology in adult infertile men[22,23]. A study conducted by the World Health Organization (WHO) reported that both sperm concentration and motility were lower in men with varicocele compared to individuals without varicocele[22]. Recently, Agarwal *et al*[23] in a systematic review assessing the effects of varicocele on semen parameters based on the new 2010 WHO laboratory criteria for the examination of the human semen, reported that varicocele was associated with reduced sperm count, motility and morphology[23].

Physical examination represents the gold standard for the diagnosis of clinically significant varicoceles[5,8,12,24]. It is used by clinical urologists and pediatricians, consisting of palpation performed with the patient in the standing position and observation of the scrotum during the Valsalva maneuver. The classification system published by Dubin and Amelar in 1970 is the most commonly used and includes the following three degrees of varicocele: Grade 1, varicocele detectable by palpation only during the Valsalva maneuver; Grade 2, varicocele detectable by simple palpation; and, Grade 3, varicocele visible on inspection and palpation[24]. However, this system has limitations because its diagnostic accuracy is closely associated with physician's experience. A study involving experienced andrologists and clinicians identified a significant inter-observer and intra-observer variability in the grading of varicoceles based on the above classification[12].

Histology from a testicular biopsy in men with varicocele has shown depressed spermatogenesis with maturation arrest, sloughing of the spermatogenic epithelium, profusion of Leydig cells, thickening of the tubular basement membrane and interstitial blood vessel wall with luminal narrowing, and increased deposition of interstitial fibrous tissue[25].

PATHOPHYSIOLOGY

The pathophysiology of impaired spermatogenesis in varicocele is multifactorial. A combination of several factors affects spermatogenesis and sperm function, and the relative involvement of these factors is different in each patient[4,7,8,25]. Several pathophysiologic mechanisms resulting in impairment of spermatogenesis in left varicocele have been proposed, including heat stress, notch signaling, cadmium accumulation, insufficiency of the hypothalamo-pituitary-gonadal axis, retrograde flow of adrenal or renal metabolites, possible disruptions of blood-testis barrier, testicular hypoxia and alterations in testicular extracellular fluid dynamics[4,7,8,25]. Interstitial lesions, including the proliferation of Leydig cells, thickening of the tubular basement membrane and blood vessel wall with luminal narrowing, and increased deposition of interstitial collagen fibers may also play an important role in varicocele-related testicular dysfunction[25].

Current evidence suggests the primary role of reactive oxygen species (ROS) and the resultant oxidative stress (OS) in the pathogenesis of varicocele-associated male infertility[4,7,8,18,25,26]. Excessive ROS has also been associated with sperm DNA fragmentation (SDF), which may mediate the clinical manifestation of poor sperm function and infertility related to varicocele[4,7,8,18,25-27]. A significantly less total acrosin activity in the spermatozoa of infertile men with varicocele and an abnormal retention of cytoplasmic droplets by human spermatozoa, which is negatively correlated with sperm motility, are other potential contributing factors for the diminished sperm function in individuals with varicocele[4,28].

Using animal models, bilateral detrimental effects on testicular temperature, blood flow, and histology have been reported to occur in cases of unilateral varicocele, probably related either to the dilatation of the right testicular vein in individuals with left varicocele or the role of the sympathetic nervous system[4,29,30]. The development of a unilateral varicocele affecting bilateral Leydig cell secretory function results in a significant reduction in bilateral intratesticular testosterone content, which, in turn, affects the Sertoli cell secretory function and epididymal maturation process, all contributing to the reduced male reproductive potential[4]. Recent advances in biomolecular techniques and mass spectrometry equipment have allowed us to better understand the molecular pathways associated with varicocele and male infertility[25,31,32].

DIAGNOSIS

In the past, various diagnostic imaging modalities were used for the evaluation of varicoceles, including venography, scintigraphy, and thermography[33-35]. Labeled blood-pool scintigraphy was reported as an accurate and noninvasive method for the detection and grading of varicocele. The main contribution of radionuclide blood-pool imaging of the scrotum was in the detection and grading of subclinical varicocele in infertile men with no other cause of infertility. The technique was also accurate in the diagnosis of recurrent varicocele[33-35]. However, the above methods have been replaced by less invasive and more easily performed diagnostic tools, especially ultrasonographic examination of the scrotum.

Ultrasonography (US) is currently the most established and widely used modality for the study of varicoceles, with 97% sensitivity and 94% specificity in the diagnosis of clinical varicocele and 83%-95% sensitivity in the diagnosis of subclinical varicocele[5,12,13,33,36,37]. The classic US features of a varicocele is that of "multiple,

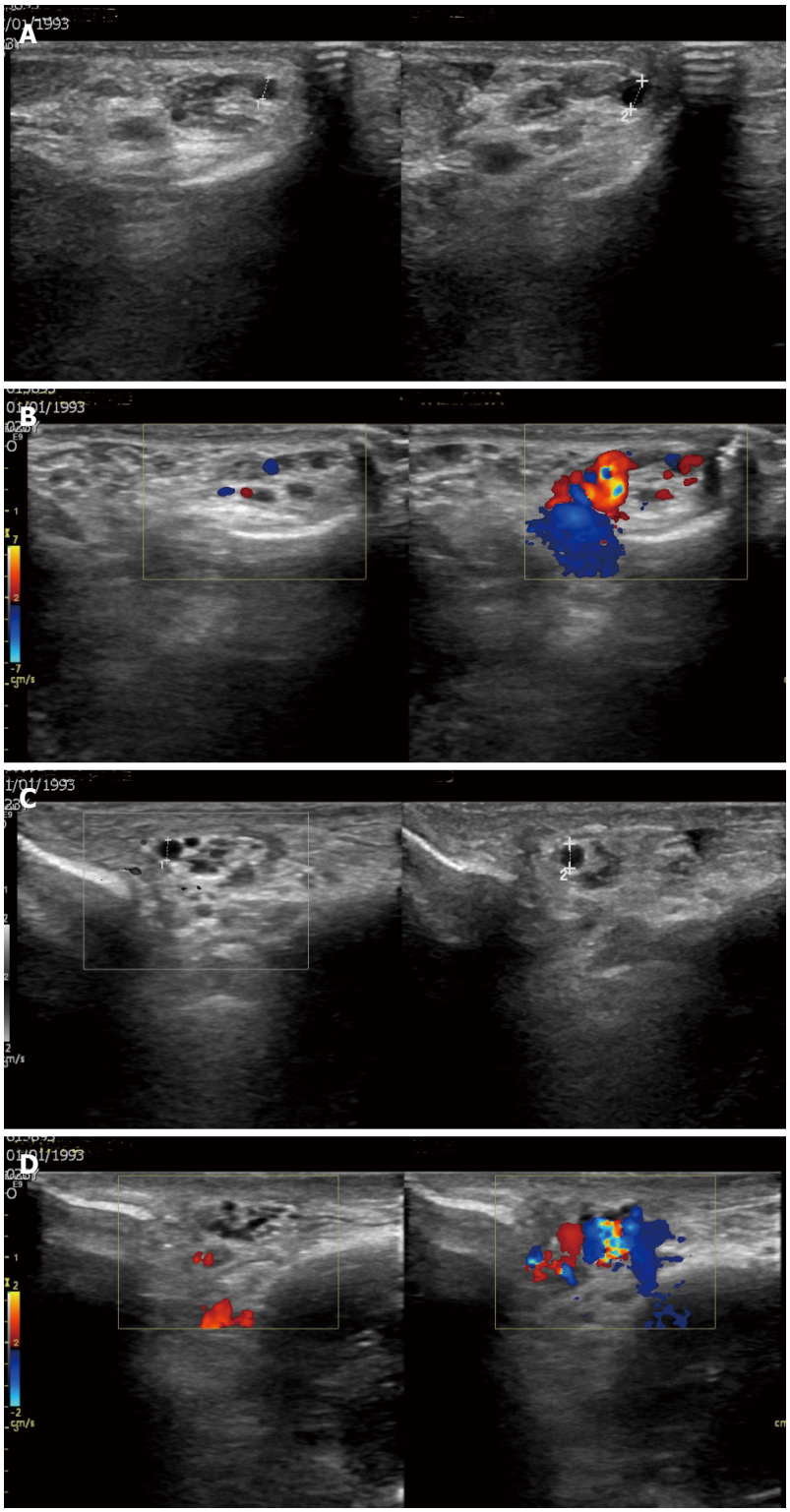

Figure 1 A 24-year-old man with bilateral varicocele. A: Gray-scale sonographic images, longitudinal sections at the supratesticular region of the left hemiscrotum at rest and during the Valsalva maneuver. The maximal diameter of the left spermatic veins is 2.5 mm at rest and 3.5 mm during the Valsalva maneuver; B: Color Doppler sonographic images, longitudinal sections same level show blood flow reversal after Valsalva maneuver; C: Gray-scale sonographic images, longitudinal sections at the right supratesticular region. The maximal diameter of the right spermatic veins is 2.3 mm at rest and 2.8 mm during the Valsalva maneuver; D: Color Doppler sonographic images, longitudinal sections show flow reversal with Valsalva maneuver.

anechoic, serpiginous, tubular structures" near the superior and lateral aspects of the testis. Color, power, or spectral Doppler US with settings optimized for low flow velocities is used complimentary to aid in the diagnosis of varicoceles. Typical Doppler findings include venous flow at rest, with intermittent or continuous flow reversal with Valsalva maneuver (Figures 1 and 2)[5,33].

However, there are no homogeneous US criteria

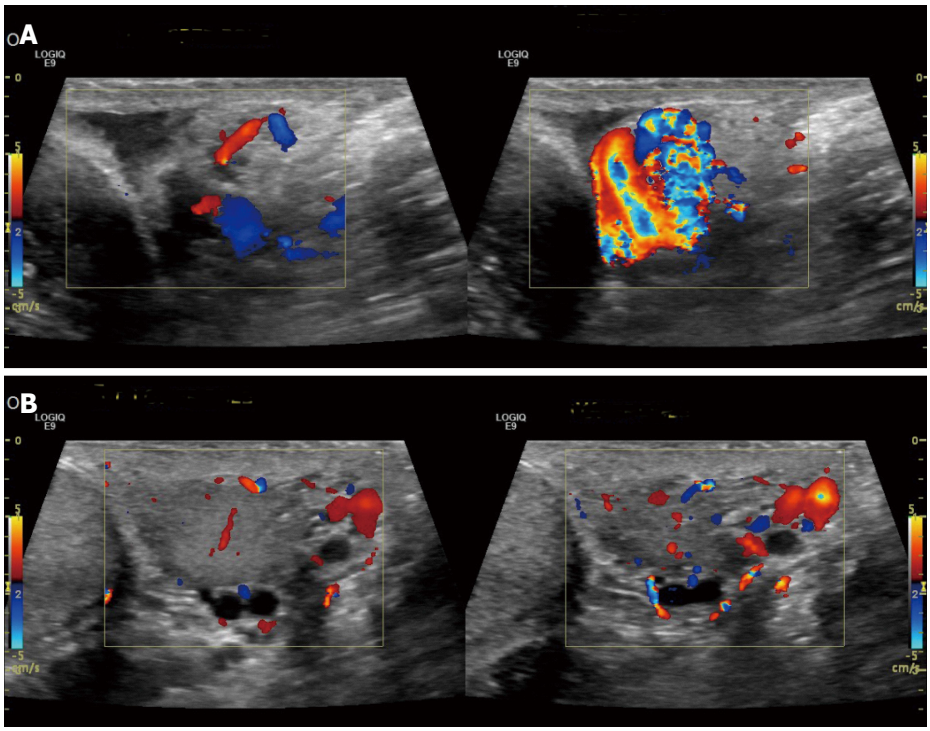

Figure 2 A 36-year-old man with left varicocele. Color Doppler sonographic images, longitudinal sections at the level of the upper (A) and lower pole (B) of the left testis depict blow flow reversal seen during the Valsalva maneuver.

Table 1 Sarteschi classification

Grade	Characteristics
1	Venous reflux at the emergence of the scrotal vein only during the Valsalva maneuver; hypertrophy of the venous wall without stasis
2	Supratesticular reflux only during the Valsalva maneuver; venous stasis without varicosities
3	Peritesticular reflux during the Valsalva maneuver; overt varicocele with early stage varices of the cremasteric vein
4	Spontaneous basal reflux that increases during the Valsalva maneuver; possible testicular hypotrophy, overt varicocele, varicosities in the pampiniform plexus
5	Spontaneous basal reflux that does not increase during the Valsalva maneuver; testicular hypotrophy, overt varicocele, varicosities in the pampiniform plexus

regarding the extent of venous dilation or reflux that must be present to meet the definition of a varicocele[5,12,13,36-45]. A widely accepted US criterion for the diagnosis of varicocele is the existence of veins larger than 2 mm in diameter, with 95% sensitivity[38]. In general, clinicians agree that clinically relevant varicoceles are more than 2.5-3 mm in diameter[33]. Multiple grading systems exist for classifying the US findings of varicocele; however, all have a low predictive value in terms of impairment of spermatogenesis, which is the main indication for any therapeutic plan[5,12,13,31,46,47]. The Sarteschi (Table 1) and Chiou *et al*[47] (Table 2) classifications systems are among the most commonly used.

Advances in US and magnetic resonance imaging (MRI) provide the potential to expand the role of imaging beyond that of visual confirmation and characterization of varicoceles. The ability to identify the early signs of testicular dysfunction based on imaging findings may have implications for the selection of patients for varicocele repair.

US IN THE EVALUATION OF INTRATESTICULAR MICROCIRCULATION IN TESTES WITH VARICOCELE

The testis gets its arterial supply mainly from the testicular artery (TA) supplemented with the cremasteric artery and the deferential artery, all coursing through the deep inguinal canal to enter the spermatic cord[48-51]. TA penetrates the tunica albuginea along the posterior surface of the testis and divides into capsular arteries. These capsular branches then give rise to the centripetal arteries which carry blood from the capsular surface, centrally towards the mediastinum along the testicular septa. Branches of the centripetal arteries then course backward towards the capsular surface, known as recurrent rami. In approximately 50% of testes, the transtesticular artery can also be seen passing directly from the testicular artery at the mediastinum into the parenchyma[48-51]. Testicular perfusion can be evaluated with color Doppler (CD), power Doppler, and spectral

Table 2 Chiou *et al*[47] classification (total score of ⩾ 4 defined as varicocele)

Characteristics	Grade
Maximum vein diameter (mm)	
< 2.5	0
2.5-2.9	1
3-3.9	2
⩾ 4	3
Plexus/sum of diameter of veins	
No plexus identified	0
Plexus (+) with sum diameter < 3 mm	1
Plexus (+) with sum diameter 3-5.9 mm	2
Plexus (+) with sum diameter ⩾ 6 mm	3
Change of flow velocity on Valsalva maneuver	
< 2 cm/s or duration < 1 s	0
2-4.9	1
5-9.9	2
⩾ 10	3
Total score	0-9

Doppler US. The spectral waveform of the intratesticular arteries characteristically has a low-resistance pattern, with a mean resistive index (RI) in adults and postpubertal boys of 0.62 (range, 0.48-0.75)[48].

Several clinical studies have assessed the effects of varicocele on testicular blood flow by US[49,50-56]. In an early study, Ross *et al*[52] compared the testicular blood flow in 248 patients with varicocele and 34 fertile volunteers with color Doppler ultrasonography (CDUS) and reported no significant differences[52]. A similar result was reported by Grasso Leanza *et al*[53]. In this study, the peak systolic velocity (PSV) of the testicular arteries was evaluated in men with varicocele and healthy subjects with normal or impaired spermatogenesis using CDUS. No significant difference was found in relation to the presence or degree of varicocele[53].

However, in subsequent studies, CDUS proved to be sensitive in assessing alterations in intratesticular circulation in testes with clinical varicocele[37,49,54-56]. A significant decrease in testicular arterial blood flow and an increase in RI and PSV in testes with clinical varicocele were reported[37,49,54-56]. Semiz *et al*[37] concluded that spectral Doppler parameters might be used as a noninvasive method to assess the hemodynamic changes and testicular microcirculation in cases of clinical varicocele[37]. The PSV, end-diastolic velocity (EDV), RI and pulsatility index (PI) from capsular and intratesticular arteries in 50 men with clinical varicocele were measured and correlated with semen analysis parameters, including count, motility, volume and morphology. PSV significantly correlated with sperm count in men with unilateral and bilateral varicocele. No significant correlation between EDV, RI, PI and semen analysis results was found[37]. Unsal *et al*[54] evaluated the effects of clinical varicocele on testicular microcirculation comparing PSV, EDV, RI and PI from capsular and intratesticular arteries in 15 men with left clinical varicocele and 34 controls[54]. The authors found a significantly greater RI and PI of capsular branches of the left testes (RI = 0.68 ± 0.04; PI = 1.22 ± 0.15) compared to the control group (RI = 0.64 ± 0.06; PI = 1.07 ± 0.18)[54].

Biagiotti *et al*[55] reported that spectral Doppler traces from the TA can be used to differentiate the various causes of impaired spermatogenesis[55]. The RI and PSV proved the most reliable indicators for routine clinical use to identify infertile men in this study, whereas EDV, FSH and TV were not. Specifically, men with varicoceles or, varicoceles and male accessory glans inflammation or fertile men with varicoceles had the highest PSV and RI[55].

In cases of subclinical varicocele, no significant changes in intratesticular perfusion are probably seen on CDUS[50]. Akcar *et al*[50] assessed the testicular volume (TV) and the RI from centripetal intratesticular arteries in 27 men with left varicocele, 96% of which were subclinical. The authors found that subclinical varicocele is not associated with testicular atrophy and does not affect the intratesticular arterial resistance[50].

Testicular contrast harmonic imaging has been proposed as an adjuvant diagnostic tool in the assessment of the effects of varicocele on intratesticular microcirculation[57]. Caretta *et al*[57] in a study of 90 patients with left varicocele, associated with either normozoospermia or oligospermia calculated contrast material arrival time in the arteriolar circulation (wash-in), time to peak arterial circulation, arrival time in the venular circulation (washout) and mean transit time in each testis after intravenous administration of contrast agent containing phospholipid stabilized microbubbles filled with sulfur hexafluoride. All parameters were significantly higher in patients with varicocele plus normozoospermia or oligospermia compared to controls, although they did not correlate with varicocele grading. A negative linear correlation between total sperm count and left mean transit time was found in patients with varicocele. In the multivariate analysis, left mean transit time was the only independent predicting parameter of oligospermia in this study[57].

Tissue elastography (TE) is a relatively new imaging technique that measures the stiffness of tissue[58-60]. TE has been reported as a useful diagnostic tool, further enhancing the characterization of focal testicular lesions[58-60]. Acoustic radiation force impulse (ARFI) elastography represents one of the main types of elastography currently in use, involving the estimation of shear wave speed. In a prospective controlled study of 30 men with clinical varicocele and 30 controls, Dede *et al*[61] concluded that ARFI elastography may be used to assess the early damage of testicular structure by varicocele[61]. Mean elastography results were significantly different between the two groups and significantly lower in testes with varicoceles. Significant negative correlations between FSH and testis elasticity was also reported. Additionally, a negative correlation was determined between varicocele grade and elasticity

of testes[61].

ROLE OF MRI

Although US represents the primary imaging modality in the assessment of scrotal diseases, MRI has recently emerged as an important supplemental diagnostic tool, used both as a problem-solving technique in patients with inconclusive US findings and as a primary imaging modality[62-64]. Recently, functional MRI techniques, including diffusion-weighted imaging (DWI), dynamic contrast-enhanced (DCE) MRI and MR spectroscopy have added important diagnostic information to the interpretation of testicular diseases[65-75].

DWI, with the calculation of apparent diffusion coefficient (ADC), is an evolving technique that can be used to improve tissue characterization if interpreted in combination with the findings of conventional MR sequences. DWI applications in scrotal pathology include characterization of intratesticular lesions, diagnosis of testicular torsion and detection and localization of nonpalpable undescended testes[65-67]. Karakas *et al*[72] in a preliminary study of 25 men with varicocele and 25 healthy volunteers recommended the potential role of DWI for the early detection and the determination of the degree of testicular damage due to varicocele[72]. The authors found lower ADC both in the ipsilateral and contralateral testicular parenchyma of patients with varicocele, compared to that of healthy volunteers. A significant negative correlation between the mean ADC and venous diameter was also found[72]. Decreased ADC of the ipsilateral testis in patients with varicocele might be associated with hypoxia and fibrosis. Decreased ADC of the contralateral testis might be related to hormonal and autoimmune factors and heat stress[72].

DCE-MRI evaluates the kinetics of the distribution of the paramagnetic contrast medium in the microvessels and the interstitial spaces of the tissues used. The technique has been useful in the characterization of scrotal lesions and the discrimination of various causes of acute scrotal pain[68,69,73-75]. Normal testes enhance slowly, moderately and homogeneously with a linear increase in signal intensity during the entire dynamic period (type Ⅰ curve)[68,69]. This pattern of enhancement is probably related to an intact "blood-testis" barrier. Minor disruptions of the blood-testis barrier could be associated with alterations of testicular perfusion in testes with varicocele and could be detected using DCE-MRI[73].

Although MRI is not routinely used in the assessment of testes with varicocele, large prospective studies evaluating functional MRI data might validate the possible role of this technique in the investigation of harmful effects on spermatogenesis.

TREATMENT

There are numerous surgical and non-surgical techniques for treating clinically significant varicocele, although there is no consensus on which might be considered the treatment of choice[4,5,7,8,11,25,76-78]. Microsurgical varicocelectomy is the most recommended type of therapy and is associated with fewer complications and lower recurrence rates, compared to the other techniques[4,11].

Varicocele embolization represents a technically feasible, minimally invasive and outpatient treatment option for men with varicocele, with high success rates. A major advantage of embolization over surgery is the ability to simultaneously perform intra-operative venography[79-83]. Postoperative recurrence of varicocele has been mainly attributed to the persistence of collaterals or anomalous veins missed during surgical ligation[84-86]. Better anatomic delineation on pre-embolization venography enables the identification of these veins, therefore reducing the possibility of future recurrences[79-86]. Embolization may be suggested for patients with recurrence, although no strong evidence to recommend the ideal treatment for recurrent varicocele exists[79-86].

The diagnosis and treatment of varicoceles are embraced by the American Society for Reproductive Medicine (ASRM), American Urological Association (AUA) and European Urological Association, and the recommendations are presented in Table 3[8,76-78]. If varicocele repair is decided, it is advisable to include both sides, if a clinically palpable varicocele is present bilaterally. For now, the available data indicate no benefit for subclinical varicocele treatment[11].

Another controversial topic in urology is the effects of varicocele treatment on male infertility[11]. Several studies indicated that varicocele repair improves semen parameters, including sperm density, count, concentration, motility and morphology and the percentage of progressively motile sperm in most treated men with clinical varicocele and abnormal semen parameters[4,5,9]. In addition to the improvement in semen parameters, varicocele repair may allow a couple with severely impaired semen parameters to have less invasive treatment. Men with severe oligospermia who would otherwise require *in vitro* fertilization/intra cytoplasmic sperm injection (IVF-ICSI) to conceive may have adequate improvement in semen analysis to allow intrauterine insemination instead of IVF-ICSI, and those with oligospermia may have sufficient improvement in semen parameters to allow natural conception in some cases. Surgical varicocele repair also proved useful in alleviating OS-associated infertility and improving sperm nuclear DNA integrity. Temporal changes in the testicular histology after varicocelectomy, including maturation of the germ cells, with the absence of meiotic abnormalities and normalization of the number of Leydig cells, have been reported[8].

The debate about the role of varicocele repair in male infertility mainly lies on its actual positive effect on improving natural fertility. Several studies attempting to investigate this issue have yielded equivocal results. However, most of the existing data agree that varicocele repair increases natural pregnancy rates and mitigates

Table 3 Summary of recommendations for the diagnosis and treatment of varicoceles

	ASRM/SMRU	AUA	EAU
Guideline title	Report on varicocele and infertility: A committee opinion	The optimal evaluation of the infertile male: AUA best practice statement	Guidelines on male infertility
Infertile male evaluation	Medical and reproductive history, physical examination and at least two semen analyses	Complete medical history, physical examination by a urologist or other specialist in male reproduction and at least two semen analyses	Medical history and physical examination, including semen analysis: One semen analysis is sufficient if normal, two will be performed if the first one is abnormal based on WHO 2010 criteria
Optimal method to detect varicocele	Physical examination; varicoceles graded, 1 to 3	Physical examination; varicoceles graded, 1 to 3	Physical examination; varicoceles graded, 1 to 3
Role of scrotal US	For inconclusive physical examination	Indicated in those patients in whom physical examination is difficult or inadequate or a testicular mass is suspected	Used to confirm presence of varicocele identified on physical examination
Indications for treatment of varicocele	If the male partner of a couple attempting to conceive has a varicocele, treatment should be considered if most or all the following are met: clinically palpable varicocele; abnormal semen parameters; known infertility; female partner has normal fertility or a potentially treatable cause of infertility; time to conception is not a concern. An adult male who is not currently attempting to achieve conception but has a palpable varicocele, abnormal semen analyses and a desire for future fertility, and/or pain related to the varicocele is also a candidate for varicocele repair	Not stated	Varicocele repair may be effective in men with abnormal semen analysis, a clinical varicocele and otherwise unexplained infertility of duration > 2 yr
Contraindications to treatment	Patients with either normal semen analysis, isolated teratozoospermia, or a subclinical varicocele; and, if IVF or IVF-ICSI is otherwise required for the treatment of a female factor infertility	Not stated	
Method of treatment	There are two types of varicocele management, surgical repair and percutaneous embolization. Multiple types exist within each category. None of these has been proven superior to the others in its ability to improve fertility, although there are differences in recurrence rates with microsurgical subinguinal varicocelectomy having the lowest recurrence rates	Not stated	Reviews all types of treatment within guidelines and provides complication and recurrence rates of each, without specific recommendations

ASRM: American Society of Reproductive Medicine; SMRU: Society of Male Reproduction and Urology; AUA: American Urological Association; EAU: European Association of Urology; WHO: World Health Organization; IVF: *In vitro* fertilization; ICSI: Intracytoplasmic sperm injection.

the need for multiple assisted reproductive technology cycles[87-89]. Recently, there is increased evidence that clinically significant varicocele may influence testosterone production, and some researchers advocate varicocele repair in cases of decreased testosterone levels, including patients with non-obstructive azoospermia[90-92].

US ASSESSMENT OF TESTICULAR BLOOD FLOW AFTER VARICOCELE REPAIR

Several groups have assessed the effects of varicocelectomy on testicular arterial blood flow by CDUS[51,93-98]. Sun *et al*[93] used CDUS to assess the changes in testicular perfusion following laparoscopic varicocele clipping in 14 children and reported no significant change[93]. However, the authors evaluated only the magnitude of arterial perfusion, not using any arterial flow parameters[93]. Student *et al*[94] reported no major changes in RI after laparoscopic varicocelectomy in comparing cases with spermatic artery ligation to those with spermatic artery preservation[94]. Tanriverdi *et al*[96] compared microsurgery and high ligation varicocelectomy by evaluating intratesticular arterial flow 7 d after surgery and reported no significant difference between the preoperative and postoperative RI in both groups[96]. A similar study comparing two laparoscopic surgical methods of varicocelectomy at 3 mo follow-up demonstrated that mean RI in the group of patients with spermatic artery ligation was comparable to the group of spermatic artery preservation.

However, subsequent studies reported a correlation between CDUS parameters and the effects of varicocele repair[51,97,98]. Balci *et al*[97] assessed the long-term effects of varicocele repair on intratesticular arterial RI in 26 infertile men with left varicocele, undergoing

subinguinal varicocelectomy. CDUS was performed before and 6 mo after the operation, and spectral Doppler indexes were measured in the intratesticular arteries and correlated with semen analysis results. RI, PI and EDV decreased significantly after surgery, but no significant change was observed in PSV. Surgery resulted in a significant increase in total sperm count, motility, morphology, and total motile sperm count, although no significant correlation was found between sperm parameters and RI[97]. CDUS was performed by Tarhan *et al*[98] in 30 men with left clinical varicocele who underwent a microsurgical inguinal varicocelectomy before, 3 and 6 mo after surgery[98]. Spectral Doppler parameters, including PSV, EDV, RI and PI, were measured from testicular, capsular, and intratesticular arteries and were correlated with preoperative and postoperative semen analysis results. A significant improvement in both testicular blood supply and sperm parameters was found. Specifically, PSV and EDV in the left TA increased, whereas RI and PI in the left capsular and intratesticular arteries decreased significantly after surgery, both reflecting an increase in testicular arterial blood flow. Regarding semen analysis, significant increases in sperm concentration, morphology percentage, and total motile sperm concentration were seen 3 mo after surgery[98]. Recently, Zhang *et al*[51] evaluated the effects of laparoscopic varicocelectomy (LV) and microsurgical subinguinal varicocelectomy (MV) on testicular microcirculation using CDUS and concluded that the RI and the PI of ipsilateral capsular artery (CA) and intratesticular artery (ITA) probably represent important indexes for the prognosis after varicocelectomy[51]. Specifically, the authors found a significant decrease in the mean values of PSV, PI and RI of CA and ITA after LV and MV, but no significant change in EDV. In comparing the two groups, the RI and PI of left CA and ITA in the third month and of ITA in the sixth month postoperatively in the MV group were significantly lower than those in the LV group. Both types of surgery resulted in a significant increase in the sperm density, morphology and total motile sperm count. Moreover, the PI and RI of ipsilateral CA and ITA seemed negatively correlated with sperm quality[51].

CONCLUSION

Varicocele is a common medical condition entangled with many controversies. Determining which patients are negatively affected by varicocele would help clinicians better select those men who will benefit the most from therapy. Functional imaging techniques, including US and MRI, might provide early indications of testicular dysfunction in testes with varicocele. Large prospective studies are needed to validate the potential role of non-invasive imaging, including US and MRI, in the assessment of the functional status of the testis in men with varicocele, thereby helping to differentiate causal from incidental varicocele.

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