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Imaging and Interventional Therapy for Varicoceles

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Abstract Varicocele is a common treatable cause of testicular pain, male infertility, and Leydig cell dysfunction. Scrotal ultrasonography has become the modality of choice in the diagnosis and post-treatment follow-up of varicocele. Visualization of dilated veins and reflux into the pampiniform plexus enables accurate diagnosis. Although the pathophysiology of varicocele in testicular dysfunction remains unclear, numerous studies have established significant improvement in the seminal parameters and pregnancy rates after varicocele repair. Interventional therapy is a minimally invasive effective treatment option for primary and salvage varicocele repair. This review discusses sonographic criteria used in the pre- and post-procedural evaluation of varicocele and various interventional techniques for varicocele treatment.

Keywords Varicocele · Male infertility · Testicular pain · Leydig cell dysfunction · Scrotal color Doppler ultrasonography · Interventional therapy · Venography · Percutaneous embolization · Sclerotherapy · Spontaneous pregnancy · Recurrence · Hydrocele formation

Introduction

Varicocele is characterized by abnormal tortuosity and dilatation of the veins in the pampiniform plexus of the spermatic cord caused by reflux of blood in the internal spermatic or gonadal veins [1]. The incidence of varicocele is approximately 16 % in the young healthy male population [2, 3]. The prevalence of varicocele increases with age, reaching approximately 42 % in the elderly population [4, 5].

The etiology of primary varicocele is still unclear but believed to be multifactorial. Various theories have been proposed, including anatomical variations, congenital valvular absence or valvular incompetence, and venous obstruction. Anatomically, the left gonadal vein is longer than the right. In addition, the left spermatic vein inserts into the left renal vein while the right inserts directly into the IVC. These anatomical variations result in longer blood column and greater hydrostatic pressure in the left spermatic vein. Some authors believe that this is the reason for earlier and more common expression of varicocele in the left side [6].

Congenital valvular absence or valvular incompetence is also believed to facilitate venous reflux in the pampiniform plexus [7]. Rarely, compression of the left renal vein between the superior mesenteric artery and the aorta (nutcracker syndrome) results in an increase in renal venous pressure [8]. Secondary varicocele can result from compression or obstruction of the venous drainage by pelvic, abdominal, or renal tumors [9, 10].

Clinical Presentation

While many patients with varicocele remain asymptomatic, varicocele can cause infertility, testicular pain, and impaired testosterone production [11•]. It is the most common and treatable cause of male infertility, with a prevalence of up to 40 % of the population [12, 13]. There is a large body of evidence indicating that varicocele is associated with abnormal semen parameters, testicular atrophy, and Leydig cell dysfunction [11•, 14–16]. Leading theories for the

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development of these symptoms include elevated scrotal temperature, hypoxia secondary to venous stasis, and reflux of renal and adrenal metabolites. Research has recently focused on the role of reactive oxygen species on testicular dysfunction and impaired spermatogenesis [17]. A 2009 meta-analysis reported significant improvement in semen parameters and overall spontaneous pregnancy rate of 39 % after varicocelectomy or radiologic embolization [18••]. More recent studies have reported significant improvement in both spontaneous pregnancy rate and pregnancy via in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) after varicocele ligation. These studies also noted a significant decrease in sperm DNA damage that has been linked to oxidative stress and poor pregnancy rates with both natural and assisted conception [19, 20].

Varicocele is clinically diagnosed on physical examination and appreciated as a "bag of worms" on palpation. Patients are evaluated in the upright positions and asked to perform the Valsalva maneuver in order to accentuate venous dilatation [21]. Based on the findings at physical examination, varicocele is classified as grade 0 (no palpable varicocele), grade I (palpable only during Valsalva maneuver), grade II (palpable at rest), or grade III (visible and palpable at rest) [22].

Imaging

Scrotal ultrasonography is the modality of choice for evaluating varicocele. Using a high-frequency transducer (7–10 MHz) with pulsed and color Doppler capabilities, sonographic examination is performed with the patient in the upright position while performing the Valsalva maneuver. Scrotal ultrasonography provides objective measurement of the venous dilatation and real-time visualization of reflux in the pampiniform plexus. This enables accurate diagnosis with higher sensitivity and specificity than physical examination, which is subject to inter-observer variability [23]. While the American Urological Association and American Society for Reproductive Medicine limits the role of scrotal ultrasonography to cases of inconclusive physical examination [24, 25], routine sonographic examination is advocated by some authors in the workup of male infertility and pediatric varicocele [21, 26]. In addition, pre- and post-treatment sonographic measurements provide reproducible means of determining the technical success of varicocele repair. Postoperative complications such as hydrocele formation or testicular atrophy from testicular artery ligation can be effectively evaluated as well [27].

On gray-scale sonography, the vessels of the pampiniform plexus are visualized superior and lateral to the upper pole of the testis and head of the epididymis. Normal vessels range between 0.5 mm and 1.5 mm in diameter, with a main draining vein measuring up to 2 mm [1]. In contrast, varicocele demonstrates multiple dilated peritesticular veins. Pilatz et al. showed that clinical varicoceles (grade I–III) can be reliably predicted with greater than 80 % sensitivity and specificity using cutoff vein diameter values of 2.45 mm in rest and 2.95 mm during the Valsalva maneuver [28•].

On color Doppler sonography, reflux into the pampiniform plexus is demonstrated with augmentation of flow during the Valsalva maneuver [29]. Many authors have compared the accuracy and sensitivity of physical examination and ultrasonography in the diagnosis of the left and/or right varicocele. These authors used retrograde flow of contrast material through the internal spermatic vein toward the testis as the venographic criterion for the diagnosis. Petros et al. reported a sensitivity of 95 % for color Doppler ultrasonography when presence of increased venous flow in the pampiniform plexus during the Valsalva maneuver was used as the criterion [23]. Similar results were shown by Trum et al. when Valsalva-induced reflux greater than 1 second was used as the criterion [30]. Chiou et al. showed that a scoring system incorporating the maximal venous diameter, presence of a venous plexus, sum of the diameters of veins in the plexus, and change of flow during Valsalva maneuver reliably diagnosed varicocele with a sensitivity of 93 % and a specificity of 85 % [31].

Patient Selection

Varicocele treatment is indicated in patients with palpable varicocele and infertility with abnormal semen parameters or abnormal sperm function tests [24]. In adolescents, a 20 % differential in testicular volume that is persistent for over one year is indication for varicocele repair [21]. Additionally, varicocele repair can be considered in patients with testicular pain or impaired testosterone production [11•].

Surgical Repair

There are several varicocele ligation techniques, including open or laparoscopic retroperitoneal (Palomo), macroscopic inguinal (Ivanissevich), and microscopic subinguinal varicocelectomy. Recently, Cayan et al. analyzed the outcomes in 4,473 subfertile or infertile men after varicocele treatment utilizing various surgical and radiologic techniques. 39 % of the patients achieved spontaneous pregnancy after varicocele repair. The highest spontaneous pregnancy rate of 42 % was seen in patients treated with microscopic subinguinal technique. Overall recurrence rates ranged from 1 % to 15 % and postoperative hydrocele formation rates from 0.4 % to 8.2 %. Lower recurrence and hydrocele formation rates were seen in patients treated with microscopic subinguinal technique [18••]. Rare complications included testicular atrophy after incidental artery ligation and intraperitoneal injury to bowel, bladder, or neurovascular bundles [24].

Interventional Therapy

Percutaneous embolization is a minimally invasive treatment option for varicocele. Shlansky-Goldberg et al. retrospectively compared the outcomes in 346 subfertile or infertile men after varicocele treatment with surgical ligation and percutaneous embolization. Both groups showed comparable improvement in seminal parameters and pregnancy rates of 39 % and 34 % after embolization and surgery, respectively [32]. Recurrence rates range from 0 % to 3.6 %, and thrombophlebitis is the most common post-procedural complication (Table 1). Advantages of percutaneous varicocele embolization include precise anatomic delineation of the complex venous collaterals and lack of perivenous dissection sparing injury to the lymphatic drainage and testicular artery. While hydrocele formation is a major postoperative complication after surgical ligation, it has never been reported after embolization.

Embolization is performed under fluoroscopic guidance on an outpatient basis. Intravenous sedation and local anesthesia is generally provided for patient comfort. Shielding with limited fluoroscopy is used to minimize the radiation dose to patients. Limiting radiation dose is particularly essential for adolescent and young adult male patients.

Venography

The right femoral vein is generally accessed under sonographic guidance. In conjunction with a hydrophilic guide wire, a 5-French Cobra catheter is used to catheterize the left renal vein and then the orifice of the left gonadal vein. Coaxial catheterization using a 6-French preformed long sheath or guiding catheter provides the stability needed for distal catheterization and embolization of the left gonadal vein. The origin of the right gonadal vein is usually located on the right anterolateral IVC just below the right renal vein. Internal jugular or basilic vein approach can be used if the femoral approach results in unsuccessful catheterization of the right gonadal vein. This approach is used primarily by interventional radiologists and takes advantage of the less-acute angle with the right gonadal vein origin, facilitating its catheterization.

After catheterizing the gonadal vein, pre-embolization venography is performed, with the patient performing the Valsalva maneuver. If given intravenous sedation, the patient can be placed in the reverse Trendelenburg position before performing venography. Venograms are obtained at various levels while advancing the catheter from the orifice of the gonadal vein to the level of the pubic symphysis. Venospasm or venous perforation can be avoided by gently advancing catheters and guide wires. Microcatheters are used to catheterize small-caliber veins. Although venospasm spontaneously resolves within 5–10 min, careful maneuvers with microcatheters and guide wires are required in order to cross a perforated venous segment (Fig. 1).

The role of venography is twofold: confirmation of the diagnosis and mapping of the highly variable venous collaterals. In an autopsy study of human cadavers, Wishahi demonstrated branching of the gonadal vein into the medial and lateral divisions at the L4 level. The medial division drained into the left renal vein or IVC, and was joined by the periureteral veins to form a venous plexus ascending or descending along the ureter. The lateral division was joined by the renal capsular and/or colonic veins [33]. Cross-communication between the left and right spermatic veins was seen in 55 % of the human cadavers. Unsuccessful interruption of these collateral pathways is believed to contribute to the persistence or recurrence of varicoceles. Sze et al. analyzed the venograms of patients with persistent or recurrent varicoceles after surgical repair [34]. The study revealed duplication of the gonadal vein in the pelvic or inguinal region as the most common collateral pathway (65 %), followed by communication with other retroperitoneal veins such as the lumbar, renal capsular, iliac, and rarely, circumaortic renal veins (Fig. 2). Similar venographic findings were demonstrated by other authors, underscoring the importance of thorough assessment of venous drainage in planning varicocele repair [35, 36•].

Table 1 Postembolization spontaneous pregnancy rates and resolution of varicocele or testicular pain among different embolic agents

Techniques	Authors	n[a]	n[b]	Recurrence
Sclerotherapy	Gandini et al., 2008	23/59 (39 %)	164/170 (96.5 %)	3.6 %
	Li et al., 2010	NA	53/58 (91.4 %)	0 %
Coils	Nabi et al., 2004	18/45 (40 %)	NA	2 %
Sclerotherapy and coils	Reiner et al, 2008	NA	16/16 (100 %)	0 %
	Storm et al., 2010	NA	19/21 (91 %)	0 %
Tissue adhesive	Sze et al., 2008	NA	17/17 (100 %)	0 %

[a] Reported number of patients who were assessed for spontaneous pregnancy

[b] Reported number of patients who were assessed for resolution of varicocele or testicular pain

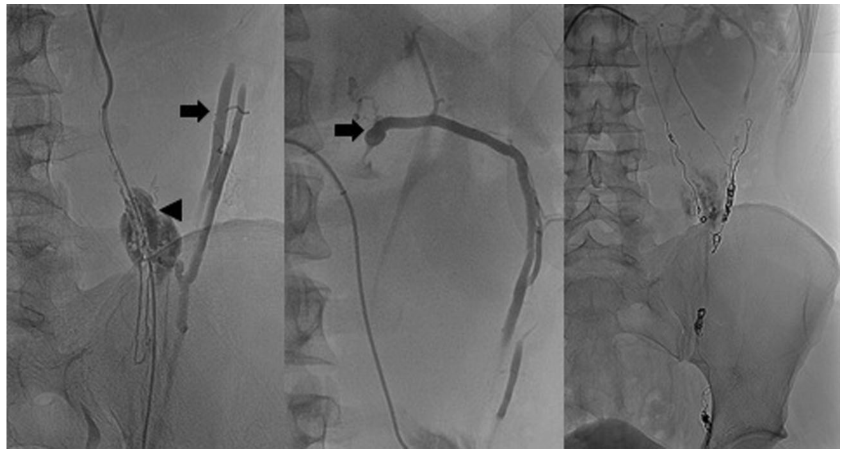

Fig. 1 25-year-old male with left scrotal pain. The left gonadal and accessory gonadal veins join dilated renal capsular veins which drain into the left renal vein (arrows). Tissue extravasation is seen at the confluence (arrow head)

Embolic Agents

Embolic agents commonly utilized for gonadal vein embolization include pushable or detachable coils, Amplatzer vascular plugs, and sclerosing agents. Coils are the most commonly used embolic agents, and all FDA-approved coils are now MRI-compatible [37]. Unlike pushable coils, detachable coils can be repositioned for precise deployment or safely withdrawn in cases of inappropriate size before release. Fibered coils occlude the lumen by inducing thrombosis around the fibers on the coils, and hydrogel-coated coils mechanically occlude the lumen by expanding up to 9 times their original volume after contact with blood [38]. Embolization begins with placing a nest of coils below the lowest collateral branch of the gonadal vein, usually at the level of the pubic symphysis. Microcoils are available if a microcatheter is utilized for catheterization at this level. While retracting the catheter and/or microcatheter toward the renal vein, additional coils are deployed at various levels to ensure complete isolation of the gonadal vein from collateral pathways (Fig. 1). Amplatzer vascular plugs offer a simple, efficient method for occlusion of the proximal gonadal vein. In a retrospective study by Nabi et al., 71 subfertile or infertile patients underwent percutaneous coil embolization for varicocele treatment. The study reported 96 % technical success, with statistically significant improvement in the seminal morphology and motility, and spontaneous pregnancy in 40 % of 45 patients [39]. Similar success rates were reported by Bechara et al. in a retrospective study that compared the outcomes after laparoscopic varicocelectomy and microcoil embolization [40].

The various sclerosing agents that have been used include boiling contrast material, ethanol, sodium tetradecyl sulfate, and sodium morrhuate [37]. Thermal or chemical injury is believed to produce inflammatory reaction, resulting in endothelial necrosis. Sodium tetradecyl sulfate is currently the only FDA-approved sclerosant in the United States. Foam sclerosants are produced by agitating sodium tetradecyl sulfate with air between two syringes through a three-way stopcock (Tessari technique). Many studies have demonstrated the safety and effectiveness of foam sclerotherapy for varicocele treatment. Gandini et al. retrospectively analyzed the outcomes in 244 patients with varicoceles who had undergone sclerotherapy using sodium tetradecyl sulfate. In this series, 39 % of the 59 patients who had presented with abnormal seminal parameters achieved spontaneous pregnancy after sclerotherapy, while 96.5 % of the 170 patients who had

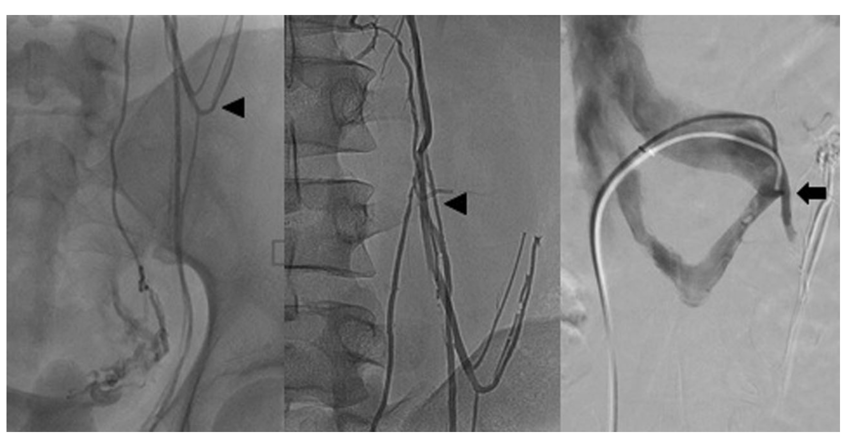

Fig. 2 24-year-old male with bilateral scrotal pain elicited when lifting weights. Duplicated gonadal veins join retroperitoneal veins (arrow heads) at the level of the upper sacroiliac joint. The left gonadal vein drains into the circumaortic renal vein

presented with testicular pain experienced resolution of symptoms. The overall recurrence rate was 3.6 % [41]. Li et al. evaluated the safety and efficacy of sodium morrhuate foam sclerotherapy and reported resolution of grade II/III varicocele in 91.4 % of 58 patients and no recurrence [42]. These outcomes were comparable to those after microscopic subinguinal varicocelectomy. Sclerotherapy is often associated with significant inflammatory pain during injection, however, and reflux of sclerosing agents into the undesired venous beds can result in complications such as pampiniform thrombophlebitis or renal vein thrombosis.

Coils and sclerosants can be used together in what is sometimes referred to as the “sandwich technique.” The first nest of coils is placed at the level of the inguinal canal prior to sclerotherapy in order to avoid reflux of the sclerosing agent into the pampiniform plexus. The advantage of this technique lies in the ability to occlude the collateral channels that are too small to be catheterized. Reiner et al. reported resolution of varicocele in 94 % of 16 adolescent patients after varicocele embolization with coils and foam sclerosant [43]. Similarly, Storm et al. reported resolution of pain and catch-up growth in cases of testicular asymmetry in 91 % of 21 patients after varicocele treatment using the sandwich technique [44].

N-butyl 2-cyanoacrylate (NBCA) has been used by some authors in varicocele embolization. After contact with ionic medium such as blood, saline, or contrast, NBCA polymerizes into an embolic agent or “glue.” A varying amount of ethiodized oil is used to adjust the polymerization time and viscosity of the mixture [45]. In a small series, Sze et al. reported resolution of symptomatic varicocele in all 17 patients treated with NBCA [34].

Conclusions

Along with physical examination, color Doppler ultrasonography is an integral component in the pre- and post-treatment evaluation of varicocele. Venous dilatation and reflux during the Valsalva maneuver are the sonographic criteria for the diagnosis of varicoceles, which has a higher sensitivity and specificity than physical examination. With the use of sonography, resolution of varicocele and postsurgical complications such as hydrocele formation and testicular atrophy can be effectively evaluated.

Interventional therapy is an effective minimally invasive treatment option for varicocele, yielding significant improvement in seminal parameters and spontaneous pregnancy. Venography provides the advantage of mapping of the potentially complex venous collateral pathways, allowing for effective embolization. Surgical complications such as hydrocele and testicular atrophy do not occur following embolization. With similar outcomes and a lower overall complication rate, percutaneous embolization provides an excellent alternative to surgical varicocelectomy.

Compliance with Ethics Guidelines

Conflict of Interest Dr. No Kwak and Dr. David Siegel each declare no potential conflict of interest relevant to this article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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