The Varicocele

Puneet Masson, MD[a], Robert E. Brannigan, MD[b,*]

KEYWORDS

• Infertility • Microsurgery • Pampiniform plexus • Sperm • Testicle • Varicocele • Varicocelectomy

KEY POINTS

- Varicoceles are present in 35% to 40% of infertile men and represent a highly treatable form of male infertility.
- Varicoceles can result in disordered spermatogenesis, germ cell sloughing within the seminiferous tubules, testicular atrophy, and decreased testosterone secretion.
- Microsurgical varicocelectomy results in improved semen parameters and reproductive outcomes with low rates of recurrence and postoperative morbidity.
- Varicocelectomy is more cost-effective than both IUI and in vitro fertilization as a treatment option for affected infertile couples.

HISTORICAL PERSPECTIVE

The association of the varicocele with male infertility derives back to the first century AD when Celsius reported a link between dilated scrotal veins and testicular atrophy.[1] Besides supportive clothing, no known intervention was offered for symptomatic painful varicoceles until the nineteenth century when various methods were established to ligate these dilated veins. Among them was the Woods operation, which consisted of the passing of wire loops around the scrotal vessels and applying tension until they eventually cut themselves out.[2] Another popular modality involved the use of Andrew varicocele clamp, which removed the dilated vessels along with the scrotal skin covering these vessels.[3] Several modifications were made on these "varicocelectomy" techniques, but the main indication for surgery was scrotal discomfort secondary to varicocele.

The benefits of varicocelectomy with regards to male reproduction were not recognized until the late nineteenth century. In 1885, Barwell[4] reported on 100 men with varicoceles who underwent placement of wire loops around dilated scrotal veins and observed an improvement in testicular size and consistency. Testicular function was augmented by Bennet[5] in 1889, when he reported an improvement in semen quality in a patient who underwent bilateral varicocelectomy. In 1929, Macomber and Sanders[6] further elucidated the reproductive benefit to varicocelectomy by reporting normal semen parameters and fertility after the procedure in an oligozoospermic subfertile patient. Despite these early reports, varicocelectomy did not gain popularity as a surgical treatment of male infertility until the work of Tulloch in 1955. In his series of 30 patients undergoing unilateral or bilateral varicocelectomy, he demonstrated an improvement in semen parameters in 26 patients, of which 10 had return to normal fertility with successful pregnancy.[7] His conclusion that "where a varicocele is associated with subfertility, the varicocele should be cured" has become part of the backbone of reproductive medicine, and numerous studies have followed demonstrating an improvement in semen parameters and pregnancy rates in infertile men undergoing this procedure. These more contemporary series on varicoceles and treatment options, including outcomes data, are reviewed in further sections.

[a] Division of Urology, Department of Surgery, Perelman School of Medicine, University of Pennsylvania, 3rd Floor, West Pavilion, 3400 Civic Center Boulevard, Philadelphia, PA 19104, USA; [b] Department of Urology, Northwestern University, Feinberg School of Medicine, Galter Pavilion, Suite 20-150, 675 North Saint Clair Street, Chicago, IL 60611, USA
* Corresponding author.
E-mail address: r-brannigan@northwestern.edu

Urol Clin N Am 41 (2014) 129–144
http://dx.doi.org/10.1016/j.ucl.2013.08.001
0094-0143/14/$ – see front matter

The varicocele clamps and wire loops were discontinued in the early twentieth century as the ligation or excision of the pampiniform plexus transformed to varicocelectomy through the inguinal or scrotal route. Because of the high failure rate and the risk of injury to end arteries through the scrotal approach, Ivanissevich advocated "high ligation of the internal spermatic vein" through either the high inguinal or retroperitoneal approach.[2] In 1960, he further documented his experience with 4470 operative cases, demonstrating both low complication and failure rates, and many surgeons continue to use some modification of this technique today.[8] More advances in varicocelectomy came through the use of microsurgery in the 1980s, when several published series demonstrated not only greater efficacy but also a reduction in morbidity through better preservation of the internal spermatic artery and lymphatic channels with higher magnification.[9–11]

ANATOMY

A varicocele is defined as a dilatation or tortuosity of the veins of the pampiniform plexus. Clinically, they are found more commonly on the left side, although there is wide variation among the reported prevalence of bilateral varicoceles, which range from 30% to 80%.[12] An isolated right-sided varicocele is extremely rare and raises concern about an underlying retroperitoneal mass.

The reason for the prevalence of left varicoceles can be clarified by retroperitoneal anatomy. The left internal spermatic vein drains perpendicularly into the left renal vein, whereas the right internal spermatic vein drains obliquely into the vena cava. This basic finding has 2 ramifications that contribute to the left-sided predisposition. For one, the course of the left internal spermatic vein results in a length of approximately 8 to 10 cm longer than its right-sided counterpart. This added length, coupled with upright posture, results in increased hydrostatic pressure, which can overcome valvular mechanisms in certain men and lead to dilatation and tortuosity of spermatic veins. Second, the perpendicular insertion of the left internal spermatic vein into the left renal vein exposes the left spermatic vein to pressure elevations within the left renal vein. The oblique insertion of the right internal spermatic vein into the vena cava, on the contrary, shields the right internal spermatic vein from the increased pressures within the vena cava.[13] The basis for increased hydrostatic pressure and varicocele formation is best elucidated by the work of Shafik and Bedeir,[14] who studied venous tension patterns in spermatic cord veins in 32 patients with a left varicocele and 30 controls. They demonstrated that patients with left varicoceles have a venous tension that is considerably higher both during rest and during Valsalva maneuver compared with that in control subjects, with average increases of 19.7 mm Hg and 22 mm Hg, respectively.

The predisposition to varicocele formation is also related to abnormalities in valvular mechanisms among certain patients. In a well-quoted study, Ahlberg and colleagues[15] performed anatomic examination of 30 normal men at autopsy and revealed the complete absence of valves in 40% of the left spermatic veins and 23% of the right spermatic veins. In a follow-up study, Ahlberg and colleagues[16] performed selective phlebography in patients with varicoceles and control subjects in the erect position; they demonstrated retrograde left internal spermatic vein filling in 22 patients with varicoceles and right internal spermatic vein filling in 10 patients. They reported that some of these patients had no valves and others had incompetent valvular mechanics. Meanwhile, they did not observe any retrograde filling in 9 control patients and 6 patients who underwent previous varicocelectomy. These studies articulate 2 important points: first, valvular malfunction or absence does exist in a certain segment of the population, and second, the absence of valves is more common in the left internal spermatic vein.

There may also be a genetic basis to the valvular dysfunction leading to varicocele development. Raman and colleagues[17] evaluated 62 first-degree relatives of patients with varicoceles and found that 56.5% of them had a clinically palpable varicocele on physical examination, compared with a prevalence of 6.8% in 263 controls. Specifically, among the first-degree relatives with varicoceles, 74% were brothers, 41% were fathers, and 67% were sons. Although the genetic mechanisms predisposing to varicocele formation remain to be elucidated, these results suggest an inheritance pattern of this anatomic finding.

Most anatomic research has been conducted on the internal spermatic vein and varicocele formation; however, there are some data to suggest that dilated external spermatic (cremasteric) veins can also contribute to primary or recurrent varicoceles. In 1980, Coolsaet[18] retrospectively reviewed 67 patients with left varicoceles who underwent preoperative venography and demonstrated that the cause of varicoceles stems from dysfunction within the internal spermatic vein, obstruction of the common iliac vein (resulting in dilated external spermatic veins), or both mechanisms. Murray and colleagues[19] evaluated 44 varicocele recurrences and reported that 58% of

these are due to inguinal (external spermatic) collaterals. Using 4 mm as the threshold for vein dilation, Chehval and Purcell[20] identified dilated external spermatic veins in 49.5% of 93 varicoceles in 67 patients. It is generally acknowledged that these external spermatic veins can lead to varicocele formation and recurrence, and standard inguinal or subinguinal varicocelectomy calls for routine inspection and ligation of these external spermatic collaterals. In addition to demonstrating varicocele recurrences due to venous collaterals that bypass the inguinal portion of the spermatic cord, Kaufman and colleagues[21] report that 7% of recurrences are due to scrotal collaterals. This finding forms the basis for delivery of the testicle during varicocelectomy and ligation of all gubernacular veins exiting from the tunica vaginalis. Goldstein and colleagues[22] report a lower recurrence rate (0.6%) with delivery of the testis and adaption of the microsurgical technique.

PATHOPHYSIOLOGY

It is well acknowledged that varicoceles can cause progressive testicular damage and infertility. Lipshultz and Corriere demonstrated that varicoceles result in testicular atrophy in both fertile and subfertile men.[23] Multiple histologic studies have explored this phenomenon on the microscopic level. Not only is there the loss of testicular mass with varicoceles, but also there can be substantial areas of testicular dysfunction. Scott reported his findings after having performed bilateral testicular biopsies in 17 patients with unilateral varicoceles; he found hypospermatogenesis with decreased thickness of germinal epithelium in both testes.[24] Several others have confirmed his findings and have also reported areas of spermatogenic arrest, sloughing of spermatogenic cells, and "Sertoli cell only" histology associated with the presence of unilateral varicoceles.[25] Saleh and colleagues[26] reported testicular biopsy results from 37 azoospermic men with varicoceles; these revealed complete spermatogenesis with disorganization, sloughing, and low to moderate sperm counts in 30%, arrested spermatogenesis in 38%, and "Sertoli cell only" histology in 32% of cases. Despite the extensive testicular dysfunction in these azoospermic men, the authors showed that the degree of histopathologic impairment is independent of the clinical grade of the varicocele. The same degree of testicular damage was equally associated with either grade I or grade III varicoceles.

It remains unclear when an otherwise incidental varicocele may become pathologic. Gorelick and Goldstein reported that varicoceles were palpable in 35% of men presenting with primary infertility and in 81% of men with secondary infertility. The men with secondary infertility had significantly lower mean sperm concentration, poorer morphology, and higher follicle-stimulating hormone levels than did men with varicoceles and primary infertility.[27] Their findings suggest that varicoceles cause a progressive decline in fertility and can continue to induce impairment of spermatogenesis, despite prior fertility. Chehval and Purcell[28] followed men with varicoceles presenting for fertility evaluation at 9- to 96-month intervals and found a statistically significant deterioration in sperm density and motility, suggesting progressive testicular deterioration.

There are several hypotheses that attempt to explain the correlation between varicoceles and testicular dysfunction. The most widely acknowledged mechanism is that of testicular hyperthermia. Human testicles are approximately 1°C to 2°C less than normal body temperature. Scrotal thermoregulation is maintained by thin scrotal skin, which lacks subcutaneous fat and a countercurrent heat exchange system involving the pampiniform plexus. This system, first proposed by Dahl and Herrick,[29] allows arterial blood to be cooled as it is delivered to the testis and enables the lower temperatures ideal for testicular function. In most men, scrotal temperatures are lowest during the standing position; however, standing also intensifies varicoceles and may prevent the reduction in testicular temperature.[30] In 1973, Zorgniotti and Macleod[31] reported that oligozoospermic patients with varicoceles had bilateral intrascrotal temperatures that were significantly higher by 0.6°C to 0.7°C than those of normal controls. Goldstein and Eid[32] used sensitive needle thermistors to measure intratesticular and bilateral scrotal surface temperatures in anesthetized infertile men with unilateral varicoceles and normal controls, and they demonstrated an average temperature increase of 2.5°C in men with varicoceles. Several other studies have demonstrated an increase in intrascrotal temperature in men with varicoceles, although there is controversy on the amount of elevation.

Animal and human studies show that this additional heat can be detrimental to spermatogenesis. Lue and colleagues[33] exposed the scrota of rats to 43°C for 15 minutes, which resulted in increased apoptosis for spermatocytes and spermatids. Yin and colleagues,[34] using an adult mouse model of experimental unilateral cryptorchidism, showed that exposure of the testis to abdominal temperature results in increased DNA fragmentation, loss of testicular weight, histologic evidence of germ cell loss, and widespread apoptosis of germ cells (particularly primary spermatocytes and round

spermatids). Although human studies also confirm the association between varicoceles, elevated scrotal temperatures, and testicular dysfunction, not all men with varicoceles share this phenomenon. Lewis and Harrison[35] demonstrated that men with varicoceles and abnormal spermatogenesis had higher scrotal temperatures compared with men with varicoceles and normal results in semen analyses. To confound the picture further, Mieusset and colleagues[36] demonstrated that infertile men with abnormal spermatogenesis have higher scrotal temperatures compared with fertile men, regardless of the presence of a varicocele. Although the scrotal temperatures of infertile men with varicoceles were significantly higher than those of fertile men, they did not differ significantly from those of infertile men without varicoceles.

The persistence of scrotal hyperthermia and abnormal semen parameters in only some men with varicoceles remains a clinical mystery. Numerous studies have investigated various molecular markers in men with varicoceles to see why these dilated tortuous veins have a harmful effect on spermatogenesis in only some men. One interesting theory involves the heat shock proteins (HSPs) and heat shock factors (HSFs), both of which generally have a protective function. Activated by increased temperature and stress, HSPs and HSFs serve as molecular chaperones that mitigate the stress-induced denaturation of other proteins, allowing cells to survive in potentially lethal conditions.[37] Lima and colleagues[38] have shown that the gene expression of one particular HSP, HSPA2, is downregulated in adolescents with varicoceles and oligozoospermia compared with both adolescents without varicoceles and adolescents with varicoceles and normal sperm concentration. Yeşilli and colleagues[39] confirmed that HSPA2 level is lower in patients with varicoceles and abnormal semen parameters and that this expression increases significantly after varicocelectomy. These studies suggest that HSPA2 expression may be a marker of thermal tolerance in men with varicoceles. Other studies have demonstrated additional HSPs and HSFs in ejaculated sperm of men with varicoceles and impaired spermatogenesis, although the clinical significance of these molecular markers requires further investigation.[40]

Hypoxia and oxidative stress also play a role in varicocele pathophysiology. In a rat varicocele model, Kilinç and colleagues[41] demonstrated that the levels of various markers for hypoxia and angiogenesis, namely, hypoxia inducible factor-1alpha (HIF-1alpha) and vascular endothelial growth factor, were significantly elevated in rats with surgically induced varicoceles compared with a sham operated cohort and a control group. In men with a grade 3 unilateral varicocele undergoing varicocelectomy, Lee and colleagues[42] demonstrated that HIF-1alpha expression is 7-fold higher in the internal spermatic vein compared with control subjects. Both these studies confirm that varicoceles are associated with increased hypoxia, and this may contribute to testicular dysfunction. Further, increased oxidative stress has also been associated with varicoceles. Hendin and colleagues[43] demonstrated that patients with varicoceles had significantly higher reactive oxygen species (ROS) levels compared with controls; however, these levels did not differ significantly between infertile men with varicoceles and fertile men with varicoceles. Likewise, total antioxidant levels were significantly lower among men with varicoceles, regardless of fertility status. Other markers for oxidative stress, namely, nitrotyrosine and 4-hydroxy-2-nonenal–modified proteins, have also been identified in men with varicoceles.[44,45] ROS production in semen has been associated with loss of sperm motility, decreased capacity for sperm-oocyte fusion, and loss of fertility.[46] Surgical correction of the varicocele is associated with decreased oxidative stress; Mostafa and colleagues[47] reported that varicocelectomy results in a significant reduction in ROS levels and also an increase in the antioxidant capacity of semen in infertile men.

The reflux of renal and adrenal metabolites into the spermatic vein is also hypothesized to contribute to varicocele pathophysiology. Given venography studies, which demonstrate reflux of blood from the renal vein to the spermatic vein, along with venous pooling secondary to the dilation and tortuosity of the varicocele, it is thought that these renal and adrenal metabolites can be toxic to testicular function. However, there is considerable inconsistency among studies examining the presence of these metabolites in reproductive tissues. Comhaire and Vermeulen[48] reported increased catecholamine levels in the internal spermatic vein of patients with varicoceles, but other investigators were unable to confirm this finding.[48–50] Elevated levels of prostaglandins E and F, both of which are antispermatogenic in animal models, have been identified in the internal spermatic vein in patients with varicoceles.[51,52] In addition, elevated levels of the potent vasodilator adrenomedullin have been identified in the spermatic vein of patients presenting for varicocele repair; it is thought that this metabolite may disturb the countercurrent heat exchange system of the spermatic cord.[53]

Hormonal dysfunction has also been associated with varicoceles and can contribute to their

pathophysiology. Animal studies using surgically induced varicoceles show subsequent reductions in serum and intratesticular testosterone levels.[54,55] Comhaire and Vermeulen[56] have demonstrated that decreased plasma testosterone concentrations are found in men with varicoceles. In one of the largest studies to date, the World Health Organization published data on 9034 men presenting for an infertility evaluation and reported that men older than 30 years with varicoceles had significantly lower testosterone levels than younger men with varicoceles. Meanwhile, this trend was not observed in men without varicoceles, suggesting a progressive detrimental effect of the varicocele on Leydig cell function.[57] However, other reputable series have not shown any significant differences in plasma testosterone in men with varicoceles compared with normal men.[58,59] Additional studies suggest Leydig cell dysfunction and decreased testosterone synthesis in some men with varicoceles. Weiss and colleagues[60] reported that the testicular tissue of men with varicoceles and severe oligozoospermia have suppression of in vitro testosterone synthesis compared with normal controls. Sirvent and colleagues[61] studied testicular histology in men with varicoceles and reported increased Leydig cell cytoplasmic vacuolization and atrophy and a decrease in the total number of Leydig cells; this was true of bilateral testicular tissue in men with a unilateral varicocele.

The reversibility of Leydig cell dysfunction with varicocele treatment remains controversial. With retroperitoneal varicocelectomy, historical studies by Hudson and colleagues[49] and Segenriech and colleagues[62] report an insignificant increase in testosterone from preoperative levels, although both study populations were small (14 and 24 patients, respectively). Conversely, Su and colleagues[63] reported a statistically significant increase in serum testosterone levels in 53 infertile men with varicoceles undergoing microsurgical inguinal varicocelectomy. Mean serum testosterone increased from a preoperative level of 319 to 409 ng/dL, suggesting that varicocelectomy can improve Leydig cell function in men with varicoceles. In addition, they found an inverse correlation between preoperative testosterone levels and change in testosterone levels after varicocelectomy, which suggests that patients with lower preoperative serum testosterone levels and potentially more testicular dysfunction might achieve the greatest benefit from varicocele treatment. Tanrikut and colleagues[64] reported data on 200 men undergoing varicocelectomy and reported a significant increase in serum testosterone levels in 70% of patients; however, they did not find any association between change in testosterone level and age, laterality of varicocele, or varicocele grade. These findings confirm the benefit to varicocelectomy in improving testicular function in some men and also suggest that the improvement in testosterone biosynthesis is independent of age and varicocele severity. Nonetheless, the reversibility of hormonal dysfunction by varicocelectomy remains controversial, and, to date, no best practice policy statements or guidelines advocate varicocelectomy for isolated hypogonadism.

PRESENTATION

Varicoceles are present in 15% to 20% of the general population but in approximately 35% to 40% of men presenting for an infertility evaluation.[30,65] Any man presenting with a known varicocele who has a possible interest in future paternity should be offered a thorough medical and reproductive history, a physical examination, a hormone profile, and semen analysis testing.

Diagnosis

A meticulous physical examination is paramount to accurately diagnosing a varicocele. Ideal conditions include a warm room, a comfortable and cooperative patient, and a skilled clinician. To facilitate examination of the scrotal contents, the scrotum should be warm and relaxed. A cold environment or uncomfortable patient may result in shrinkage or tightening of the scrotum, which can make a varicocele more difficult to palpate. Some clinicians have even recommended a heating pad to ensure the accuracy of the physical examination.[66] The patient should be examined in both the recumbent and upright positions.

These tortuous dilated veins have been described as a “bag of worms” by Dubin and Amelar[67] and may be significantly reduced or even disappear when the patient is in the supine position. When a varicocele is suspected but not clearly palpable, the patient should perform a Valsalva maneuver in the standing position. This exercise will enable the dilated veins to become more engorged, and the clinician may palpate a discrete pulse when examining the cord. Typical findings include dilated veins above the testis within the spermatic cord, most commonly on the left side, along with ipsilateral or bilateral testicular atrophy. Although isolated right varicoceles do occur, they are extremely rare and should raise the question of an underlying retroperitoneal process such as lymphadenopathy. Furthermore, varicoceles that do not reduce in the supine position should raise the same concern and merit further investigation.

The varicocele grading system, as proposed by Dubin and Amelar,[67] as is follows:

Grade 1, small	Palpable only with the patient standing and performing a concurrent Valsalva maneuver
Grade 2, moderate	Palpable with the patient standing, without a Valsalva maneuver
Grade 3, large	Visible through the scrotal skin and palpable with the patient standing

Clinical varicoceles are defined as varicoceles that are palpable on physical examination, and only these varicoceles have been associated with infertility. Although there are several radiologic modalities available, routine use of imaging studies is not recommended for the detection of subclinical varicoceles in patients without a palpable abnormality.[68]

Ultrasonography

Scrotal ultrasonography is not indicated for routine evaluation of men with varicoceles. However, in a situation in which the physical examination is inconclusive, scrotal ultrasound examination can be used for clarification. Chiou and colleagues[69] demonstrated a sensitivity of 93% and specificity of 85% for color flow Doppler ultrasonography (CDU) when compared with physical examination (Fig. 1). All moderate to large varicoceles found on physical examination were detected by CDU diagnosis. Petros and colleagues[70] demonstrated that CDU detected 93% of varicoceles found on physical examination and provided the best correlation with venography. Thus, in situations in which physical examination may be challenging due to scrotal size or skin thickness, CDU may be a useful adjunct to the diagnosis of varicocele.

Caution with scrotal ultrasonography persists because of the detection of subclinical varicoceles and the controversy surrounding their management. Mihmanli and colleagues[71] used CDU in 208 testes units in infertile patients without clinical varicoceles on physical examination and detected 94 subclinical varicoceles. However, correction of subclinical varicoceles has not been proved to positively affect fertility. Grasso and colleagues[72] randomized 68 infertile patients with subclinical varicoceles to varicocelectomy versus observation and found no improvement in sperm quality or paternity. Yamamoto and colleagues[73] reported similar findings in 85 infertile patients; they noted an improvement in sperm density, but there were no significant differences in sperm motility, morphology, or pregnancy rate. Because of the dearth of data showing any reproducible benefit for the treatment of subclinical varicoceles, widespread use of ultrasonography to screen for dilated spermatic veins is not advocated.

Scrotal ultrasonography is useful in patients who have undergone prior surgery and in whom recurrence or persistence of varicocele is suspected. In addition, ultrasonography is more accurate than physical examination or orchidometer when assessing testicular size, especially when there is the concern for progressive testicular atrophy. Thus, although ultrasonography is not routinely used in the diagnosis of varicocele, it may supplement physical examination findings in some cases and should be used at the discretion of the treating clinician.

Venography

Retrograde spermatic venography is generally considered to be the most sensitive test for the detection of varicoceles. However, it is fairly invasive and usually only performed in conjunction with therapeutic occlusion. Access is usually obtained via the right femoral vein or right internal jugular vein, as described by Seldinger, and a catheter is advanced to the testicular vein and a

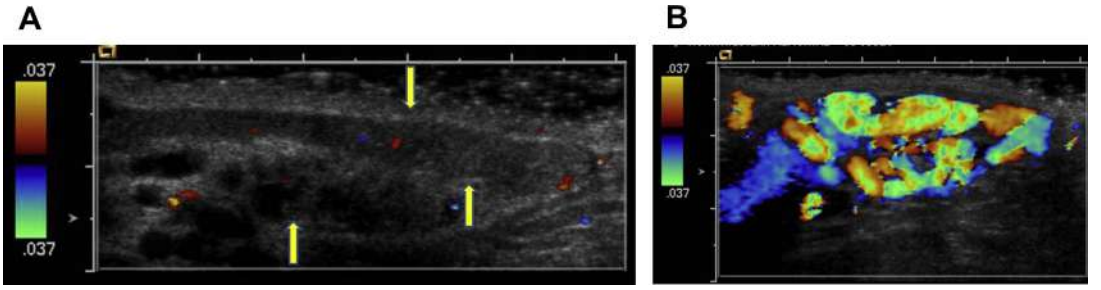

Fig. 1. (*A*) Scrotal ultrasonography demonstrated dilated tortuous veins consistent with varicocele (*arrows*). (*B*) Doppler flow in patient with grade 3 varicocele.

contrast agent injected.[74] In patients with palpable varicoceles, reflux has been reported in 100% of patients.[16] However, the specificity of this modality has been questioned, as there is a considerable false-positive rate. Netto Júnior and colleagues[75] demonstrated no statistically significant differences in the presence of spermatic vein reflux in subfertile patients with varicoceles, fertile patients with varicoceles, and normal controls.

There is also considerable technical variability with diagnosis,[76] and thus venography is considered an adjunct to physical examination and usually reserved for situations where treatment can be pursued in the same setting. An interesting concept proposed by Hart and colleagues[77] advocates intraoperative spermatic venography during varicocelectomy, with a reported 16% collateral drainage rate that could have resulted in varicocele persistence if those specific veins were not ligated. Given the low recurrence rate and advances with microsurgery, intraoperative spermatic venography is not routinely performed; however, it can provide a more precise anatomic definition of venous anatomy in postsurgical patients with varicocele persistence or recurrence. For this reason, a common indication for venography is a recurrent or persistent postsurgical varicocele; thus, difficult venous anatomy can be well delineated and simultaneous treatment offered. Punekar and colleagues[78] reported a success rate of 85% in patients with recurrent varicoceles using stainless steel coil embolization.

TREATMENT INDICATIONS

Infertility

As per the American Urological Association Best Practice Policy "Report on Varicocele and Infertility," varicoceles should be treated when all the following conditions are met:

1. Varicocele is palpable on physical examination of the scrotum.
2. The couple has known infertility.
3. The female partner has normal fertility or a potentially treatable cause of infertility.
4. The male partner has abnormal semen parameters or abnormal results from sperm function tests.[68]

With regards to infertility, varicocele treatment is not indicated if semen parameters are normal or if the varicocele is subclinical. Adult men who are not actively trying to conceive but present with an incidental varicocele should be counseled on fertility risk and offered at least 1 semen analysis to evaluate their reproductive capacity. Although not all men with varicoceles have abnormal semen parameters, a substantial proportion of them may have reduced counts, decreased motility, and/or abnormal morphology.[13,25] Because they may try to achieve conception sometime in the future, men with clinically palpable varicoceles and abnormal semen parameters should be informed of definitive varicocele treatment options.

Men with clinically palpable varicoceles and normal semen parameters may be at risk for future testicular dysfunction. Witt and Lipshultz[79] demonstrated that varicoceles are capable of causing progressive fertility loss. In their date-matched retrospective analysis, they noted that varicoceles were identified as the cause of infertility in 69% of men with secondary infertility compared with 50% of men with primary infertility, suggesting that varicoceles are progressive lesions resulting in the loss of previously established fertility. Gorelick and Goldstein's work, as previously discussed, supported this finding.[27] For this reason, young adult men with clinically palpable varicoceles, normal semen parameters, and a desire for future paternity should be offered monitoring with serial semen analyses every 1 to 2 years. If abnormal results are obtained, semen analyses should be repeated, and if progressive dysfunction persists, they can be offered definitive treatment of varicocele. In addition, men with secondary infertility and clinically palpable varicoceles should be offered the same treatment as individuals presenting with primary infertility.

Young men with clinically palpable varicoceles and objective evidence of testicular atrophy may also be considered for varicocele treatment. Semen analyses can be offered to further clarify reproductive potential in this population, although reduced ipsilateral testicular size may alone indicate testicular dysfunction secondary to varicocele.[80] Sigman and Jarow[81] reported that patients with unilateral left varicoceles and ipsilateral testicular hypotrophy had significantly reduced semen parameters compared with patients without hypotrophy. Thus, adolescents and young men with varicocele-associated testicular growth retardation should be offered treatment. In patients with varicoceles but with normal (ipsilateral) testicular size, routine follow-up should include objective measurements of testicular size and/or semen analyses to detect the earliest sign of testicular dysfunction.

With the advent of advanced assisted reproductive technologies (ARTs), many couples with male-factor infertility secondary to varicocele may ultimately choose between varicocele treatment and IUI or in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI). Although many factors may influence this decision, couples should be

routinely counseled that varicocele repair might offer a permanent solution to male-factor infertility, whereas IUI or IVF/ICSI must be used for each pregnancy attempt. Moreover, there is considerably greater cost savings for varicocele treatment versus IUI/IVF or IVF in patients with isolated varicocele-related infertility.[82,83]

Varicocele treatment is not routinely recommended when IVF is necessary secondary to a female factor. However, in certain cases with both male and female factor components, varicocelectomy can augment ART efforts. In some azoospermic or cryptozoospermic patients, varicocele repair can lead to improved numbers of ejaculated sperm, thereby sparing these men a testicular sperm extraction. Kim and colleagues[84] reported that approximately 43% of patients with azoospermia had return of sperm in the ejaculate after unilateral or bilateral varicocelectomy. These patients also underwent simultaneous testicular biopsy, which revealed that only men with severe hypospermatogenesis and maturation arrest spermatid stage had improvement in sperm density (patients with Sertoli-cell-only or maturation arrest spermatocyte stage did not demonstrate a benefit). Although all couples eventually required some form of ART to achieve a pregnancy, this study contends that certain patients with spermatogenic failure and varicoceles may be candidates for varicocele repair, instead of resorting to testicular sperm extraction in preparation for ICSI. Additional studies regarding the benefit of varicocelectomy with ART are discussed a subsequent section.

Hypogonadism

The progressive negative effect of varicoceles on Leydig cell function has been previously discussed along with the association of varicoceles and low serum testosterone in some men. With greater public awareness of hypogonadism and concern for varicoceles as a significant risk factor for androgen deficiency, there is an ongoing debate regarding the benefit of varicocelectomy for improving serum testosterone. Earlier studies did not show a statistically significant increase in serum testosterone after varicocelectomy; however, many of these studies were smaller scale[49,62] and included patients with normal to above-normal baseline testosterone levels.[85,86] Meanwhile, studies by Su and colleagues[63] and Tanrikut and colleagues[64] have shown not only that varicocelectomy leads to an improvement in serum testosterone but also that men with lower preoperative testosterone levels derived the most benefit. Hsiao and colleagues[87,88] corroborated this finding in infertile men with baseline lower testosterone values and confirmed that significant increases in serum testosterone post-varicocelectomy are independent of varicocele grade or age.

Although this biochemical response in previously hypogonadal men is interesting, it is worthwhile to also assess the effects of varicocele treatment on the signs and symptoms of hypogonadism. Many younger men with hypogonadism may present with low energy, diminished libido, and erectile dysfunction (ED). Srini and Veerachari[89] evaluated 200 heterosexual, hypogonadal infertile men with clinical varicoceles and divided them into 2 groups: those who underwent varicocelectomy and those who underwent ART. In the varicocelectomy group, they observed a statistically significant increase in serum testosterone levels with 78% of patients becoming eugonadal. As expected, there was no change in serum testosterone levels in the hypogonadal men with varicoceles who underwent ART. However, they observed a reduction in ED among patients in the varicocelectomy group; the prevalence of ED decreased from 44% to 31%. Meanwhile, there was a mild increase from 39% to 41% in ED among those who were in the ART group and did not have correction of their serum testosterone. Zohdy and colleagues[90] performed a similar study with 141 heterosexual infertile hypogonadal men with clinical varicoceles divided into a varicocelectomy treatment arm and an ART arm. They also reported a significant increase in serum testosterone levels in the varicocelectomy arm with normalization of testosterone levels in 75.5% of these men. Moreover, they reported a significant increase in the International Index of Erectile Function 5 questionnaire results in hypogonadal men undergoing varicocelectomy, suggesting clinical improvement with regards to erectile function in symptomatic men.

Varicocelectomy for men with low testosterone levels is a controversial and an evolving concept; it is not at this time considered to be a standard of care. To date, the body of evidence regarding varicocele treatment and low testosterone has primarily focused on populations of infertile men. Furthermore, there are no studies on the long-term maintenance of higher testosterone levels after varicocele repair. Nonetheless, there is emerging evidence to suggest that microsurgical varicocelectomy may be a promising alternative to the medical treatment of hypogonadism and potentially prevent future androgen deficiency in some men.

Symptomatic Varicoceles

Varicoceles can also present with pain, which is typically a dull ache and localized to the scrotum

or inguinal area. There is tremendous variability in the frequency, character, and intensity of this discomfort, and other potential causes of pain must be explored before the varicocele is treated. Common conservative measures include scrotal support/elevation, antiinflammatory medications, and analgesic agents. Patients may also benefit from a referral for pelvic floor physical therapy or consultation with a pain medicine specialist.

When conservative measures prove inadequate, definitive treatment of the varicocele can be offered, although patients should be counseled that surgery may not relieve their discomfort. There is considerable variability regarding surgical outcomes for symptomatic varicoceles, but most reports show a high rate of success in relieving discomfort. These studies include subjects ranging from 11 to 284 patients, although the majority includes data on less than 100 patients. Rates for resolution of pain and improvement of pain after varicocelectomy range from 53% to 94% and 42% to 100%, respectively.[91] Most contemporary studies use the microsurgical subinguinal approach,[92] although all other options such as laparoscopic and robotic techniques have also been used with respectable results.[93,94]

TREATMENT OPTIONS

The cornerstone of varicocele treatment is disruption of the internal spermatic venous drainage of the testicle while preserving the internal spermatic artery, the vasal and deferential vessels, and the spermatic cord lymphatics. Definitive treatments for varicocele include surgery and radiographic venous embolization. Although all approaches have been shown to be effective, there is the general preference among many urologists to favor surgery given their expertise with various surgical approaches to varicocelectomy and its minimal complication rate. There are several surgical options available, and they are discussed later.

Inguinal and Subinguinal Approach

Most varicocele repairs are conducted using either of these 2 approaches. The inguinal approach, initially described by Ivanissevich,[8] necessitates exposure and incision of the external oblique aponeurosis. Care should be taken to avoid injury to the ilioinguinal nerve. The spermatic cord is then identified and mobilized at the level of the pubic tubercle, and it is carefully elevated and secured with a Penrose drain. This exposure also facilitates exposure of large external cremasteric vessels that can contribute to the varicocele.[13] With Loupe magnification or microsurgery, the inguinal approach allows excellent identification of the internal spermatic artery and vein before considerable branching transpires.

The subinguinal approach does not involve incision of the external oblique fascia and has been shown to minimize postoperative discomfort.[95,96] This approach is preferred at our and many other centers. After making a skin incision at the level of the external inguinal ring, the spermatic cord is mobilized immediately below at the level of the pubic tubercle and secured with a Penrose drain. Any large external cremasteric vessels should be identified and ligated. Because there is considerable branching of the internal spermatic vein at the subinguinal level, most urologists use microsurgery with this approach to effectively recognize and preserve the testicular artery, vas deferens, and lymphatic vessels.

Microsurgical varicocelectomy has been shown to have a higher success rate and minimal complication rates when compared with nonmicrosurgical modalities.[97,98] Large-scale retrospective studies have documented extremely low recurrence and complication rates; these complications can include hydrocele formation, testicular atrophy, recurrent pain, and infection.[22,99] All patients should be counseled about the indications, risks, and benefits of surgery, including realistic assessments with regards to their outcome of interest (eg, fertility, pain). These procedures can be performed under local, regional, or general anesthesia, although we favor use of general anesthesia with either a laryngeal mask airway or endotracheal tube. The patient is supine on the operating room table with standard perioperative precautions such as padding, deep venous thromboembolism prophylaxis, and intravenous antibiotics for prophylaxis against gram-positive skin organisms. We use an operating microscope with a dual ocular system for our procedures.

A 2.5- to 3-cm oblique incision is typically made over the external inguinal ring and then deepened through Camper and Scarpa fascias. Using Richardson retractors, the spermatic cord is exposed and gently dissected by sliding a finger longitudinally from the external ring to the upper scrotum. The cord is then manipulated, placed over a 1-inch Penrose drain, and carefully delivered to skin level. We typically expose and maneuver the cord using manual dissection, but some favor use of a Babcock instrument to gently grasp the cord and aid in delivery.[66] Through manual retraction of the spermatic cord with the Penrose drain, perforating external spermatic vessels are identified and carefully ligated.

At this point, the operating microscope is brought into the field and the cord is examined under 8 to 15 power magnification. Many different approaches to cord dissection have been described in the literature. We use Gerald pickups and Bovie electrocautery to carefully dissect through the external and internal spermatic fascias. The spermatic cord is secured under the operating surgeon's index finger (usually standing on the contralateral side of the table), and the vas deferens with associated vessels is maneuvered medially. The edges of the external and internal spermatic fascia are secured medially and laterally, thus exposing and flattening out the internal spermatic vessels. This exposure transforms the cord from a cylindrical, 3-dimensional structure to a more 2-dimensional configuration, facilitating identification of individual vessels. The dissection is carried out as proximally as possible to the external inguinal ring.

The micro-Doppler is introduced to help locate the internal spermatic arteries before fine dissection begins. We request that the anesthesiologist maintain the patient's systolic blood pressure greater than 100 mm Hg to assist us in isolating an arterial Doppler signal and also to help us visualize subtle pulsations that indicate arterial flow. If there is the concern for vasospasm, we irrigate the field with lidocaine 1% solution. Other surgeons recommend papaverine (30 mg/mL) diluted in a 1:5 ratio with saline to help dilate the arteries.[100] Once the artery is identified, care is taken to protect it and reidentify it several times through the fine dissection to confirm preservation. All internal spermatic veins are ligated with 3-0 or 4-0 silk and divided, although some surgeons use surgical clips for venous occlusion. Any lymphatics are also identified and preserved. Dissection is then carried out through the cremasteric fibers, and any cremasteric arteries identified are also preserved. All cremasteric veins are ligated and divided. The cord is repeatedly examined to ensure no other veins (other than those preserved in the vas deferens packet) are visualized. The internal spermatic arteries are also reassessed with Doppler to ensure flow.

At the completion of the varicocelectomy, the spermatic cord should have patency of only testicular and cremasteric arteries, lymphatics, and vas deferens with its associated vessels. After confirming adequate hemostasis, the wound is irrigated and the cord is returned to its orthotopic position. Scarpa and Camper fascia are closed with absorbable sutures, and the incision is infiltrated with a local anesthetic. The skin is closed with a running subcuticular closure and reinforced with Steri-strips, followed by a dry sterile dressing.

Alternative Surgical Approaches

The retroperitoneal approach, originally described by Palomo,[101] involves ligation of the internal spermatic vein superior to the internal ring. The skin incision is made at the level of the internal ring medial of the anterior superior iliac spine, and dissection is carried out through the external and internal oblique fascia and muscles. The internal spermatic vein is visualized and then ligated and divided. A principle advantage of this technique is that it enables identification of the internal spermatic vein before it extensively branches; a significant disadvantage of this approach is that it does not allow access to the external spermatic veins, which have been shown to contribute to varicoceles.[18] Furthermore, some patients may have more pain during the recovery period due to dissection of the abdominal musculature.[98]

The scrotal approach, addressed here for historical reasons, is no longer favored because of its substantial rate of injury to the spermatic arteries and resultant testicular atrophy/loss.[30] Although it can be performed under local anesthesia, this approach has an unacceptably high complication rate, which includes a 40% incidence of hydroceles.[102] This technique is no longer considered a viable option for performing varicocelectomy.

With advancements in minimally invasive surgery and the increasing familiarity that many urologists have with laparoscopy, laparoscopic varicocelectomy provides another mode of treatment. It is an intraperitoneal procedure, which has its own inherent risks, and involves high ligation of the spermatic vein. The procedure is similar to the open retroperitoneal approach in that external spermatic vessels are not identified and may put the patient at risk for varicocele persistence or recurrence. However, there is less postoperative pain and faster return to normal activities following laparoscopic surgery compared with the retroperitoneal technique. One additional advantage of the laparoscopic approach is that it enables bilateral ligations in an efficient and expeditious manner. Unilateral or bilateral varicocelectomy can also be executed resourcefully if a patient is undergoing another laparoscopic procedure at the same time. Overall, laparoscopy has been shown to be safe and efficacious when performed by experienced surgeons, although the incidence of postoperative hydrocele and varicocele recurrences was higher than in microsurgical varicocelectomy.[103]

Percutaneous Venous Occlusion

Embolization is considered a nonoperative approach to varicocelectomy, and the technique

has been described earlier in this article. The advantage of radiological venous embolization is quicker recuperative time and less pain. Success rates of varicocele treatment are slightly less than that of open surgery, with most large series ranging from 85% to 95%.[104,105] Complications can include vascular perforation, coil or balloon migration, and the risk of allergic contrast reaction.[30] Furthermore, concern exists regarding radiation exposure and its potential effect on spermatogenesis in a population of subfertile men.

TREATMENT OUTCOMES

Most studies reporting efficacy data on varicocelectomy are nonrandomized retrospective analyses and report improvements in semen parameters and fertility. Although their results are promising, they generally contain a diverse patient population with varied inclusion or exclusion criteria, inadequate study designs, and limited data on preoperative and postoperative parameters, all of which make a meta-analysis of the data challenging. Further, several studies suggest no benefit, especially with regards to pregnancy outcomes.[106–108] To clarify this issue, the National Institutes of Health supported a multicenter randomized controlled trial on varicocele repair to obtain better data on pregnancy and live birth rates. However, this trial was stopped after 2.5 years because of low recruitment (only 3 patients were randomized), reflecting the general unwillingness of most fertility-desiring couples to be placed in the placebo arm.[109]

A review of the earlier literature in 1994 by Schlesinger and colleagues[110] demonstrated an improvement in semen parameters after varicocelectomy in subfertile men. A recent meta-analysis by Agarwal and colleagues[111] confirms this finding. Their inclusion criteria was stricter than previous meta-analyses; they included only studies with infertile men with clinically palpable unilateral or bilateral varicoceles, and at least one abnormal semen parameter who had undergoing surgical varicocelectomy, and insisted on at least 3 semen analyses per patient. Seventeen studies were included, and the combined analysis demonstrated that sperm concentration increased by 9.71 million/mL and motility increased by 9.92% after microsurgical varicocelectomy. After high-ligation varicocelectomy, the combined analysis revealed that sperm concentration increased by 12.03 million/mL and motility increased by 11.72%. Morphology increased by 3.16% with both approaches. In this thorough meta-analysis, these investigators have shown that surgical varicocelectomy is an effective treatment for improving semen parameters of infertile men with a clinically palpable varicocele.

Despite these improvements, treatment of varicoceles for fertility remains controversial. There is considerable variability with regards to pregnancy outcomes after varicocele repair in infertile couples. A recent Cochrane review concluded that, although there is evidence suggesting that varicocele repair may improve a couple's chance of pregnancy, the quality of available evidence is low.[112] Marmar and colleagues[113] explored the efficacy of varicocelectomy with regards to spontaneous pregnancy. In their meta-analysis, which focused exclusively on pregnancy outcomes, they found that infertile men with a clinically palpable varicocele were 2.63 to 2.87 times more likely to achieve a spontaneous pregnancy following surgical varicocelectomy compared with observation.

A recent randomized controlled trial by Abdel-Meguid and colleagues[114] corroborates this finding. A total of 145 infertile men with clinical varicoceles were allocated in a one-to-one fashion to either an observation (control) arm or subinguinal microsurgical varicocelectomy. There were no changes in the semen analysis in the control arm, but the treatment arm demonstrated significant improvements in sperm concentration, motility, and morphology. Moreover, patients in the treatment arm were 3.04 times more likely to achieve a spontaneous pregnancy compared with their counterparts.

For patients with nonobstructive azoospermia, testicular sperm extraction coupled with in vitro fertilization and intracytoplasmic sperm injection is typically required for conception. Clinically palpable varicoceles are found in 4.3% to13.3% of men with azoospermia or severe oligozoospermia, and the role of varicocelectomy in these men has been controversial given the probability that these men may still be subfertile after the surgery.[115] Weedin and colleagues[116] conducted a meta-analysis on varicocele repair in this patient population using 11 publications during the past 20 years. Their total patient population was 233 men with azoospermia undergoing varicocelectomy, and 39.1% of them had motile sperm in the ejaculate after surgery. A total of 14 spontaneous pregnancies were reported. However, testicular pathology was identified as a predictor of success; patients with maturation arrest (42.1%) or hypospermatogenesis (54.5%) were significantly more likely to benefit than patients with Sertoli-cell-only histopathology (11.3%, $P<.001$). Thus, these investigators advocate that, although varicocelectomy may have a role in nonobstructive azoospermia, histopathology should be considered before varicocele repair.

Even if the use of ART is inevitable, varicocele repair can augment the chance of a successful pregnancy. In a small series, the IUI success rate was higher after varicocele repair.[117] Esteves and colleagues[118] evaluated the effect of varicocelectomy on intracytoplasmic sperm injection and found that infertile men undergoing varicocelectomy have an improved number of motile sperm and a decreased sperm defect score. In addition, they observed significantly higher clinical pregnancy and live birth rates and a decreased miscarriage rate in the varicocele-treated group. Thus, even in situations requiring some form of ART, treatment of clinical varicocele in men with markedly decreased semen quality increases the couple's ability to conceive. With improvement in semen parameters, varicocele repair may also enable some couples to undergo IUI before proceeding to more advanced ART.

VARICOCELECTOMY IN 2034: WHAT DOES THE FUTURE HOLD?

No one has a "crystal ball" or other tool to foresee the future, but that should not preclude one from considering the future and all of the possibilities that it might provide diagnostically and therapeutically. Varicoceles are a highly prevalent condition, and it is known that, although some men suffer marked reproductive or endocrine impairment as a result, other patients remain unscathed. We envision that an additional 20 years of academic investigation and technical advances will afford us more "front end" tools to determine which patients will be more susceptible to the pathophysiology caused by varicoceles and which patients will remain less adversely affected. As is the case in so many domains of medicine, there is likely a genetic component to these outcomes. Several investigators are already working on sperm and seminal markers of susceptibility for damage wrought by varicoceles, and we suspect that in 20 years we might be able to more effectively stratify patients for this risk based the basis of such clinical markers. Technically, further advances in microsurgical optics and instrumentation will surely come to pass. The incredible advances of the preceding 20 years have included increased precision in instrumentation, smaller Doppler probes with enhanced functionality, and more optimized microsurgical optics. Although some researchers are currently investigating the role of robotics in the setting of varicocelectomy, it is unclear how much, if any, technical advantage this approach affords in performing the procedure. In 20 years, this question will surely have been answered with greater clarity.

Ultimately, the "holy grail" of varicocele treatment would be a reliable, safe, specific, and effective treatment that does not involve a surgical incision or percutaneous access of the great veins. These authors suspect that much more than 20 years will need to pass for this "holy grail" treatment to be realized.

REFERENCES

1. Kaufman SL, Nagler HM. The varicocele: concepts of pathophysiology – present and future. World J Urol 1986;4:88–97.
2. Glezerman M. A short historical review and comparative results of surgical treatment for varicoceles. In: Glezerman M, Jecht EW, editors. Varicocele and male infertility II. New York: Springer; 1984. p. 87–93.
3. Herman JR. Andrew's varicocele clamp. Urology 1975;6:252.
4. Barwell R. 100 cases of varicocele treated by the subcutaneous wire loop. Lancet 1885;1:978.
5. Bennet WH. Varicocele, particularly with reference to its radical cure. Lancet 1889;1:261–3.
6. Macomber D, Sanders MB. The spermatozoa count: its value in the diagnosis, prognosis, and treatment of sterility. N Engl J Med 1929;200:981–4.
7. Tulloch WS. Varicocele in subfertility: results of treatment. Br Med J 1955;2(4935):356–8.
8. 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.
9. Wosnitzer M, Roth JA. Optical magnification and Doppler ultrasound probe for varicocelectomy. Urology 1983;22:24–6.
10. Kaye KW. Modified high varicocelectomy: outpatient microsurgical procedure. Urology 1988;32:13–6.
11. Gilbert BR, Goldstein M. New directions in male reproductive microsurgery. Microsurgery 1988;9:281–5.
12. Gat Y, Bachar GN, Zukerman Z, et al. Varicocele: a bilateral disease. Fertil Steril 2004;81:424–9.
13. Nagler HM, Grotas AB. Varicocele. In: Lipshultz LI, Howards SS, Niederberger CS, editors. Infertility in the male. 4th edition. New York: Cambridge University Press; 2009. p. 331–61.
14. Shafik A, Bedeir GA. Venous tension patterns in cord veins in normal and varicocele individuals. J Urol 1980;123:383–5.
15. Ahlberg NE, Bartley O, Chidekel N. Right and left gonadal veins: an anatomical and statistical study. Acta Radiol Diagn (Stockh) 1966;4:593–601.
16. Ahlberg NE, Bartley O, Chidekel N, et al. Phlebography in varicocele scroti. Acta Radiol Diagn (Stockh) 1966;4:517–28.
17. Raman JD, Walmsley K, Goldstein M. Inheritance of varicoceles. Urology 2005;65:1186–9.

18. Coolsaet BL. The varicocele syndrome: venography determining the optimal level for surgical management. J Urol 1980;124:833–9.
19. Murray RR Jr, Mitchell SE, Kadir S, et al. Comparison of recurrent varicocele anatomy following surgery and percutaneous balloon occlusion. J Urol 1986;135:286–9.
20. Chehval MJ, Purcell MH. Varicocelectomy: incidence of external spermatic vein involvement in the clinical varicocele. Urology 1992;39:573–5.
21. Kaufman SL, Kadir S, Barth KH, et al. Mechanisms of recurrent varicocele after balloon occlusion or surgical ligation of the internal spermatic vein. Radiology 1983;147:435–40.
22. Goldstein M, Gilbert B, Dicker AP. Microsurgical inguinal varicocelectomy with delivery of the testis: an artery and lymphatic sparing technique. J Urol 1992;148:1808–11.
23. Lipshultz LI, Corriere JN Jr. Progressive testicular atrophy in the varicocele patient. J Urol 1977;117:175–6.
24. Scott LS. Varicocele: a treatable cause of subfertility. Br Med J 1961;1:788–90.
25. Saypol DC. Varicocele. J Androl 1981;2:61–71.
26. Saleh R, Mahfouz RZ, Agarwal A, et al. Histopathologic patterns of testicular biopsies in infertile azoospermic men with varicocele. Fertil Steril 2010;94:2482–5.
27. Gorelick JI, Goldstein M. Loss of fertility in men with varicocele. Fertil Steril 1993;59:613–6.
28. Chehval MJ, Purcell MH. Deterioration of semen parameters in men with untreated varicocele: evidence of progressive testicular damage. Fertil Steril 1992;57:174–7.
29. Dahl EV, Herrick JF. A vascular mechanism for maintaining testicular temperatures by countercurrent exchange. Surg Gynecol Obstet 1959;108:697–705.
30. Fretz PC, Sandlow JI. Varicocele: current concepts in pathophysiology, diagnosis, and treatment. Urol Clin North Am 2002;29:921–37.
31. Zorgniotti AW, Macleod J. Studies in temperature, human semen quality, and varicocele. Fertil Steril 1973;24:854–63.
32. Goldstein M, Eid JF. Elevation of intratesticular and scrotal skin surface temperature in men with varicocele. J Urol 1989;142:743–5.
33. Lue YH, Sinha-Hikim AP, Swerdloff RS, et al. Single exposure to heat induces stage-specific germ cell apoptosis in rats: role of intratesticular testosterone on stage specificity. Endocrinology 1999;140:1709–17.
34. Yin Y, Hawkins AP, Wang C, et al. Heat stress causes testicular germ cell apoptosis in adult mice. J Androl 1997;18:159–65.
35. Lewis RW, Harrison RM. Contact scrotal thermography: application to problems of fertility. J Urol 1979;122:40–2.
36. Mieusset R, Bujan L, Mondinat C, et al. Association of scrotal hyperthermia with impaired spermatogenesis in infertile men. Fertil Steril 1987;48:1006–11.
37. Feder ME, Hofmann GE. Heat-shock proteins, molecular chaperones, and the stress response: evolutionary and ecological physiology. Annu Rev Physiol 1999;61:243–82.
38. Lima SB, Cenedeze MA, Bertolla RP, et al. Expression of the HSPA2 gene in ejaculated spermatozoa from adolescents with and without varicocele. Fertil Steril 2006;86:1659–63.
39. Yeşilli C, Mungan G, Seçkiner I, et al. Effect of varicocelectomy on sperm creatine kinase, HspA2 chaperone protein (creatine kinase-M type), LDH, LDH-X, and lipid peroxidation product levels in infertile men with varicocele. Urology 2005;66:610–5.
40. Ferlin A, Speltra E, Patassini C, et al. Heat shock protein and heat shock factor expression in sperm: relation to oligozoospermia and varicocele. J Urol 2010;183:1248–52.
41. Kilinç F, Kayaselcuk F, Aygun C, et al. Experimental varicocele induces hypoxia inducible factor 1alpha, vascular endothelial growth factor expression and angiogenesis in the rat testis. J Urol 2004;172:1188–91.
42. Lee JD, Jeng SY, Lee TH. Increased expression of hypoxia-inducible factor 1alpha in the internal spermatic vein of patients with varicocele. J Urol 2006;175:1045–8.
43. Hendin BN, Kolettis PN, Sharma PK, et al. Varicocele is associated with elevated spermatozoal reactive oxygen species production and diminished seminal plasma antioxidant capacity. J Urol 1999;161:1831–4.
44. Romeo C, Ientile R, Impellizzeri P, et al. Preliminary report on nitric oxide-mediated oxidative damage in adolescent varicocele. Hum Reprod 2003;18:26–9.
45. Shiraishi K, Naito K. Increased expression of Leydig cell haem oxygenase-1 preserves spermatogenesis in varicocele. Hum Reprod 2005;20:2608–13.
46. Griveau JF, LeLannon D. Reactive oxygen species and human spermatozoa: physiology and pathology. Int J Androl 1997;20:61–9.
47. Mostafa T, Anis TH, El-Nashar A, et al. Varicocelectomy reduces reactive oxygen species levels and increases antioxidant activity of seminal plasma from infertile men with varicocele. Int J Androl 2001;24:261–5.
48. Comhaire F, Vermeulen A. Varicoceles: cortisol and catecholamines. Fertil Steril 1974;25:88–95.
49. Hudson RW, Perez-Marrero RA, Crawford VA, et al. Hormonal parameters of men with varicocele before and after varicocelectomy. Fertil Steril 1985;43:905–10.

50. Steeno O, Koumans J, De Moor P. Adrenal cortical hormones in the spermatic vein of 95 patients with left varicocele. Andrologia 1976;8:101–4.
51. Free ML, Jaffe RA. Dynamics of circulations in the testis of the conscious rat. Am J Physiol 1972; 223:241–8.
52. Ito H, Fuse H, Minagawa H, et al. Internal spermatic vein prostaglandins in varicocele patients. Fertil Steril 1982;37:218–22.
53. Ozbek E, Yurekli M, Soylu A, et al. The role of adrenomedullin in varicocele and impotence. BJU Int 2000;86:694–8.
54. Shafik A, Wali MA, Abdel Azis YE, et al. Experimental model of varicocele. Eur Urol 1989;16: 298–303.
55. Turner TT, Evans WS, Lopez TJ. Gonadotroph and Leydig cell responsiveness in the male rat. Effects of experimental left varicocele. J Androl 1990;11: 555–62.
56. Comhaire F, Vermeulen A. Plasma testosterone in patients with varicocele and sexual inadequacy. J Clin Endocrinol Metab 1975;40:824–9.
57. World Health Organization. The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. Fertil Steril 1992;57:1289–92.
58. Swerdloff RS, Walsh PC. Pituitary and gonadal hormones in patients with varicocele. Fertil Steril 1975; 26:1006–12.
59. Adamopoulos D, Lawrence DM, Vassilopoulos P, et al. Hormone levels in the reproductive system of normospermic men and patients with oligospermia and varicocele. J Clin Endocrinol Metab 1984; 59:447–52.
60. Weiss DB, Rodriguez-Rigau LJ, Smith KD, et al. Leydig cell function in oligospermic men with varicocele. J Urol 1978;120:427–30.
61. Sirvent JJ, Bernat R, Navarro MA, et al. Leydig cell in idiopathic varicocele. Eur Urol 1990;17:257–61.
62. Segenreich E, Shmuely H, Singer R, et al. Andrological parameters in patients with varicocele and fertility disorders treated by high ligation of the left spermatic vein. Int J Fertil 1986;31:200–3.
63. Su LM, Goldstein M, Schlegel PN. The effect of varicocelectomy on serum testosterone levels in infertile men with varicoceles. J Urol 1995;154: 1752–5.
64. Tanrikut C, Goldstein M, Rosoff JS, et al. Varicocele as a risk factor for androgen deficiency and effect of repair. BJU Int 2011;108:1480–4.
65. Clarke BG. Incidence of varicocele in normal men and among men of different ages. JAMA 1966; 198:1121–2.
66. Zini A, Boman J. Varicocele. In: Goldstein M, Schlegel PN, editors. Surgical and medical management of male infertility. 1st edition. New York: Cambridge University Press; 2013. p. 137–49.
67. Dubin L, Amelar RD. The varicocele and infertility. In: Amelar RD, Dubin L, Walsh PC, editors. Male infertility. Philadelphia: Saunders; 1977. p. 57–68.
68. Sharlip ID, Jarow JP, Belker AM. AUA best practice policy: report on varicocele and infertility. Baltimore (MD): American Urological Association Inc; 2001.
69. Chiou RK, Anderson JC, Wobig RK, et al. Color Doppler ultrasound criteria to diagnose varicoceles: correlation of a new scoring system with physical examination. Urology 1997;50: 953–6.
70. Petros JA, Andriole GL, Middleton WD, et al. Correlation of testicular color Doppler ultrasonography, physical examination, and venography in the detection of left varicoceles in men with infertility. J Urol 1991;145:785–8.
71. Mihmanli I, Kurugoglu S, Cantasdemir M, et al. Color Doppler ultrasound in subclinical varicocele: an attempt to determine new criteria. Eur J Ultrasound 2000;12:43–8.
72. Grasso M, Lania C, Castelli M, et al. Low-grade left varicocele in patients over 30 years old: the effect of spermatic vein ligation on fertility. BJU Int 2000;85:305–7.
73. Yamamoto M, Hibi H, Hirata Y, et al. Effect of varicocelectomy on semen parameters and pregnancy rate in patients with subclinical varicocele: a randomized prospective controlled study. J Urol 1996;155:1636–8.
74. Sigman M, Jarow JP. Male infertility. In: Walsh PC, Retik AB, Vaughan ED, et al, editors. Campbell's urology, vol. 2, 8th edition. Philadelphia: Saunders; 2002. p. 1475–515.
75. Netto Júnior NR, Lerner JS, Paolini RM, et al. Varicocele: the value of reflux in the spermatic vein. Int J Fertil 1980;25:71–4.
76. Nadel SN, Hutchins GM, Albertsen PC, et al. Valves of the internal spermatic vein: potential for misdiagnosis of varicoceles by venography. Fertil Steril 1984;41:479–81.
77. Hart RR, Rushton HG, Belman AB. Intraoperative spermatic venography during varicocele surgery in adolescents. J Urol 1992;148:1514–6.
78. Punekar SV, Prem AR, Ridhorkar VR. Post-surgical recurrent varicocele: efficacy of internal spermatic venography and steel-coil embolization. Br J Urol 1996;77:124–8.
79. Witt MA, Lipshultz LL. Varicocele: a progressive or static lesion? Urology 1993;42:541–3.
80. Paduch DA, Niedzielski J. Repair versus observation in adolescent varicocele: a prospective study. J Urol 1997;158:1128–32.
81. Sigman M, Jarow JP. Ipsilateral testicular hypotrophy is associated with decreased sperm counts in infertile men with varicoceles. J Urol 1997;158: 605–7.

82. Schlegel PN. Is assisted reproduction the optimal treatment for varicocele-associated male infertility? A cost-effectiveness analysis. Urology 1997;49: 83–90.
83. Penson DF, Paltiel AD, Krumholz HM, et al. The cost-effectiveness of treatment for varicocele related infertility. J Urol 2002;168:2490–4.
84. Kim ED, Leibman BB, Grinblat DM, et al. Varicocele repair improves semen parameters in azoospermic men with spermatogenic failure. J Urol 1999;162: 737–40.
85. Di Bisceglie C, Bertagna A, Baldi M, et al. Varicocele sclerotherapy improves serum inhibin B levels and seminal parameters. Int J Androl 2007;30:531–6.
86. Zheng YQ, Gao X, Li ZJ, et al. Efficacy of bilateral and left varicocelectomy in infertile men with left clinical and right subclinical varicoceles: a comparative study. Urology 2009;73:1236–40.
87. Hsiao W, Rosoff JS, Pale JR, et al. Varicocelectomy is associated with increases in serum testosterone independent of clinical grade. Urology 2013;81:1213–8.
88. Hsiao W, Rosoff JS, Pale JR, et al. Older age is associated with similar improvements in semen parameters and testosterone after subinguinal microsurgical varicocelectomy. J Urol 2011;185:620–5.
89. Sathya Srini V, Belur Veerachari S. Does varicocelectomy improve gonadal function in men with hypogonadism and infertility? Analysis of a prospective study. Int J Endocrinol 2011;2011:916380.
90. Zohdy W, Ghazi S, Arafa M. Impact of varicocelectomy on gonadal and erectile functions in men with hypogonadism and infertility. J Sex Med 2011;8: 885–93.
91. Schlegel PN, Goldstein M. Alternate indications for varicocele repair. Fertil Steril 2011;96:1288–93.
92. Chawla A, Kulkarni G, Kamal K, et al. Microsurgical varicocelectomy for recurrent or persistent varicoceles associated with orchialgia. Urology 2005; 66:1072–4.
93. Maghraby HA. Laparoscpic varicocelectomy for painful varicoceles: merits and outcomes. J Endourol 2002;16:2.
94. Parekattil SJ, Brahmbhatt JV. Robotic approaches for male infertility and chronic orchialgia microsurgery. Curr Opin Urol 2011;21:493–9.
95. Marmar JL, Kim Y. Subinguinal microsurgical varicocelectomy: a technical critique and statistical analysis of semen and pregnancy data. J Urol 1994;152:1127–32.
96. AL-Kandari AM, Shabaan H, Ibrahim HM, et al. Comparison of outcomes of different varicocelectomy techniques: open inguinal, laparoscopic, and subinguinal microscopic varicocelectomy: a randomized clinical trial. Urology 2007;69:417–20.
97. Cayan S, Kadioglu TC, Tefekli A, et al. Comparison of results and complications of high ligation surgery and microsurgical high inguinal varicocelectomy in the treatment of varicocele. Urology 2000;55:750–4.
98. Ghanem H, Anis T, El-Nashar A, et al. Subinguinal microvaricocelectomy versus retroperitoneal varicocelectomy: comparative study of complications and surgical outcome. Urology 2004;64:1005–9.
99. Grober ED, O'Brien J, Jarvi KA, et al. Preservation of testicular arteries during subinguinal microsurgical varicocelectomy: clinical considerations. J Androl 2004;25:740–3.
100. Bodie JA, Sandlow JI. Microsurgical subinguinal varix ligation: techniques and technical pearls. In: Sandlow JI, editor. Microsurgery for fertility specialists. 1st edition. New York: Springer; 2013. p. 35–48.
101. Palomo A. Radical cure of varicocele by a new technique: preliminary report. J Urol 1949;61:604–7.
102. Iacono F, Capparelli G, Darmiento M. Bilateral varicocele repair by transscrotal extratunica vaginalis procedure in outpatients: a novel technique. Tech Urol 2000;6:196–200.
103. Ding H, Tian J, Du W, et al. Open non-microsurgical, laparoscopic, or open microsurgical varicocelectomy for male infertility: a meta-analysis of randomized controlled trials. BJU Int 2012;110:1536–42.
104. Nabi G, Asterlings S, Greene DR, et al. Percutaneous embolization of varicoceles: outcomes and correlation of semen improvement with pregnancy. Urology 2004;63:359–63.
105. Ferguson JM, Gillespie IN, Chalmers N, et al. Percutaneous varicocele embolization in the treatment of infertility. Br J Radiol 1995;68:700–3.
106. Kamischke A, Nieschlag E. Varicocele treatment in the light of evidence-based andrology. Hum Reprod Update 2001;7:65–9.
107. Krause W, Muller HH, Schafer H, et al. Does treatment of varicocele improve male fertility? Results of the "Deutsche Varikozelenstudie," a multicentre study of 14 collaborating centres. Andrologia 2002;34:164–71.
108. Rageth JC, Unger C, DaRugna D, et al. Long-term results of varicocelectomy. Urol Int 1992;48: 327–31.
109. Sigman M. There is more than meets the eye with varicoceles: current and emerging concepts in pathophysiology, management, and study design. Fertil Steril 2011;96:1281–2.
110. Schlesinger MH, Wilets IF, Nagler HM. Treatment outcome after varicocelectomy: a critical analysis. Urol Clin North Am 1994;21:517–29.
111. Agarwal A, Deepinder F, Cocuzza M, et al. Efficacy of varicocelectomy in improving semen parameters: new meta-analytical approach. Urology 2007;70: 532–8.
112. Kroese AC, de Lange NM, Collins J, et al. Surgery or embolization for varicoceles in subfertile men. Cochrane Database Syst Rev 2012;(10):CD000479.

113. Marmar JL, Agarwal A, Prabakaran S, et al. Reassessing the value of varicocelectomy as a treatment for male subfertility with a new meta-analysis. Fertil Steril 2007;88:639–46.
114. Abdel-Meguid TA, Al-Sayyad A, Tayib A, et al. Does varicocele repair improve male infertility? An evidence-based perspective from a randomized, controlled trial. Eur Urol 2011;59:455–61.
115. Czaplicki M, Bablok L, Janczewski Z. Varicocelectomy in patients with azoospermia. Arch Androl 1979;3:51–5.
116. Weedin JW, Khera M, Lipshultz LI. Varicocele repair in patients with nonobstructive azoospermia: a meta-analysis. J Urol 2010;183:2309–15.
117. Daitch JA, Bedaiwy MA, Pasqualotto EB, et al. Varicocelectomy improves intrauterine insemination success rates among men with varicoceles. J Urol 2001;165:1510–3.
118. Esteves SC, Oliveira FV, Bertolla RP. Clinical outcome of intracytoplasmic sperm injection in infertile men with treated and untreated clinical varicocele. J Urol 2010;184:1442–6.