Invited review

Varicocele and male infertility: an evidence based review

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Abstract

Varicoceles are present in 15% of the normal male population and in approximately 40% of men presenting with infertility. The preponderance of experimental data from clinical and animal models demonstrates a deleterious effect of varicoceles on spermatogenesis. Testicular temperature elevation and oxidative stress appear to play an important role in varicocele-induced testicular dysfunction, although the exact pathophysiology is not yet completely understood. The American Urological Association and American Society of Reproductive Medicine jointly convened Best Policy Practice Groups for Male Infertility and recently stated, "Varicocele repairs may be considered the primary treatment option when a man with a varicocele has suboptimal semen quality and a normal female partner." They considered percutaneous embolization and surgery for varicocele treatment and noted that most experts performed inguinal or subinguinal microsurgical repairs to maximize preservation of arterial and lymphatic vessels while reducing the chances of persistence or recurrence. Although these comments represent the considered opinion of 12 experts and 125 consultants in the field of male infertility, anyone familiar with varicoceles knows that discussion of the pathophysiology and management continues to be hotly debated. This review offers recommendations regarding the best infertility treatment for the man with a varicocele: assisted reproduction or varicocelectomy.

Key words: semen, varicocele, reproduction, fertilization, infertility.

Incidence

Varicocele remains an enigma in the treatment of male infertility [1-5]. Despite more than 30 years of evidence that varicocele repair results in improved fertility, the retrospective nature of most of these reports has led to controversy regarding the utility of treatment [6-8]. Evaluation of a patient with a varicocele should include a careful medical and reproductive history, a physical examination and at least two semen analyses [9, 10]. The physical examination should be performed with the patient in both the recumbent and upright positions. Imaging studies are not indicated for the standard evaluation unless the physical exam is inconclusive [9]. Therefore, when a suspected varicocele is not clearly palpable, the scrotum should be examined while the patient performs a Valsalva maneuver in a standing position.

The incidence of varicocele varies according to age. Incidence ranges from 7.2% (in boys/men 2 to 19 years old), with the following distribution: 2 to 6 years, 0.79%; 7 to 10 years, 0.96%; 11 to 14 years, 7.8% and 15 to 19 years, 14.1% [GR-A] [11]. After the 20s, incidence varies from 10 to 25% [GR-C] [12]. In the elderly, (median of 60 years) the varicocele is present in up to 42.9% of the population [13]. No prospective, randomized, controlled studies that demonstrate a relationship between varicocele and hormonal abnormalities have been published.

The incidence of varicocele is about 20% in the general population; in infertile populations the incidence is roughly 40% [GR-B] [14]. An inverse correlation between body mass index (BMI) and the incidence of varicocele [GR-B] appears to exist [15].

The reason for this discrepancy in distribution remains unknown, although it may be related to the association among infertility, intratesticular temperature and time [9, 10, 16]. The blood supply to the testes, as well as the resulting counter-current heat exchange, results in intratesticular temperatures that are cooler than body temperatures [7, 8]. Disruption of this system can result in hyperthermia of the testes. As the left side drains into a system with higher resistance, small venules may persist or open during embryogenesis. Testicular blood flow remains low before puberty, and therefore these veins do not become clinically apparent until adolescence when testicular blood flow increases. This explains the appearance of most varicoceles around puberty.

Men with varicocele who engage in intense physical activity regularly four to five times a week for 2 to 4 h/day over a period of four years have a decrease in semen parameters [GR-A] [17].

Varicocele occurs more frequently among first-degree relatives than in the general population [GR-B] [18].

Pathophysiology and typical testicular histological abnormalities in men with varicocele

The possible causes of varicocele are absence or congenital incompetence of the left spermatic vein valves or difficulties in the venous return due to obstruction or compression of the vein system [GR-B] [19]. Several theories have been suggested to explain the impact of varicocele on testicular function, although none of them alone is able to elucidate the variable effects of varicocele in spermatogenesis and male infertility [GR-B] [19]. These theories include hyperthermia [19] [GR-B], hypoxia [19, 20] [GR-B], decrease in intratesticular and epididymal blood flow, intratesticular hormonal abnormalities [19] [GR-B], oxidative stress [20] [GR-B] and renal and adrenal metabolite reflux [19] [GR-B].

Pathognomic testicular histological abnormality does not occur in patients with varicocele [GR-B] [21]. It may cause Leydig cell hyperplasia, maturation arrest, decrease in the number of Sertoli cells per seminiferous tubule and germinal epithelium displacement [GR-B] [21, 22]. Tissue abnormalities are similar to the ones found in patients with spermatogenesis abnormalities without the presence of varicocele [GR-B] [21, 22].

Varicocele as a cause of infertility

Varicocele remains the most common cause of male infertility, although the literature shows conflicting data in this regard. Additionally, many of the studies present only weak evidence for the association between varicocele and infertility, and some of them lack adequate statistical power.

The World Health Organization (WHO), in an observational study involving 9,034 men, verified that 25.6% of patients with abnormal semen analysis have varicocele, and these men exhibit a significant decrease in the ipsilateral testicle volume compared with the contralateral testicle. This decrease in testicular volume does not occur in men with infertility without varicocele [GR-B] [23].

Varicocele diagnoses

A gold standard for the diagnosis of varicocele [GR-D] does not exist [24]. The physical examination, with the patient standing in a 25°C room temperature, has been the method most commonly used [GR-C] [25], but the sensitivity and specificity of this method are only 70% [GR-A] [26].

Varicoceles diagnosed by physical examination are considered "clinical", and they are classified according to their size. The larger (grade III) varicoceles are the ones visually detected; moderate (grade II) varicoceles are detected through palpation without the Valsalva maneuver; the smallest (grade I) varicoceles are detected through physical examination with the Valsalva maneuver [GR-C] [25, 27]. Radiological tests are not able to differentiate clinical from subclinical varicoceles [GR-A] [26, 28].

Spermatic vein venography is the most widely recognized method for the diagnosis of pampiniform plexus vein reflux (clinical vs. subclinical varicocele) [GR-B] [29, 30]. In comparison to venography, the color Doppler ultrasound has more than 90% sensitivity and specificity [GR-A] [26], while scrotal thermography and cintilography have variable results [GR-A] [26, 28, 29].

Clinical treatment for varicocele

Few well-designed studies focusing on medical, nonsurgical treatment for varicocele have been published.

The use of carnitine combined with non-hormonal anti-inflamatory drugs for 6 months in patients with clinical varicocele and infertility did not resolve the problem [GR-A] [31, 32].

In patients with subclinical varicocele, clompiphene citrate did not improve sperm concentration and motility to the level that surgery does, although it did promote a significant improvement in semen quality as well as in pregnancy rates [GR-A] [33]. The literature lacks sufficient information to validate the use of clompiphene citrate in patients with clinical varicocele.

In a study involving 65 patients, the use of kallikrein for 3 months in 38 men showed a statistical improvement in sperm motility as well as morphology compared with the control group [GR-B] [34].

The association of menotropin for 3 months before the varicocelectomy is related to a better outcome compared to the surgery alone. In this study, the sooner introducing the clinical treatment, the better [GR-A] [35].

Data supporting the use of vitamins and antioxidants in the treatment of varicocele are insufficient.

Subclinical varicocele – a different entity

Subclinical varicocele is identified only with the help of complementary tests beyond physical examination [36]. It may be associated with male infertility [GR-B] [19]. Scrotal Doppler ultrasound may be indicated to evaluate infertile men when the physical examination is inconclusive or for the detection of venous reflux [GR-D] [37, 38].

The ideal treatment for men with subclinical varicocele [GR-D] is undefined in the medical literature [39, 40]. Therefore, varicocele treatment for infertility is not indicated for patients with either normal semen quality or subclinical varicocele.

Surgery versus embolization

The treating physician's experience and expertise, together with the options available, should determine the choice of treatment for varicocele. Only two methods for the treatment of varicocele are well-described in the literature, surgical vein ligation and percutaneous embolization [GR-D] [37, 41-43]. Surgery may be performed through a retroperitoneal, inguinal, subinguinal or laparoscopic approach [GR-A] [43]. Marmar et al. [41] introduced the subinguinal microsurgical varicocelectomy with ligation and sclerosis, and Goldstein et al. [42] modified the microsurgical technique with delivery of the testis in search of scrotal collaterals, including the gubernacular veins.

Percutaneous embolization is performed by occluding the internal spermatic vein [GR-A] [44].

None of these methods have been proven to be superior to the others in fertility improvement; however, differences in the complication and recurrence rates have been described [GR-A] [45].

Subinguinal varicocelectomy with optical magnification increases the probability of arterial and lymphatic vessel preservation. This significantly decreases the risks of recurrence and postoperative complications in relation to laparoscopy and surgeries without magnification [GR-A] [45] [GR-C] [46] [GR-D] [42, 47].

Percutaneous embolization is associated with recurrence rates that are higher than those associated with conventional surgical approaches. Complications related to the percutaneous embolization method itself also should be taken into account to create a true picture of the outcomes and risks related to this technique [GR-A] [48].

Patients with bilateral clinical varicocele should be submitted to a bilateral varicocelectomy [GR-A] [49].

Azoospermia and varicocele

Varicocele repair must be considered for all men with azoospermia who have a palpable varicocele. Azoospermic patients with germ cell aplasia in a single large testis biopsy may have an improvement in semen quality following varicocelectomy. Due to the possibility of a relapse into azoospermia after an initial improvement in semen quality following varicocelectomy, patients should be informed of the possibility of sperm cryopreservation. In azoospermic patients, the surgical treatment of varicocele may promote spermatogenesis, avoiding the need to obtain sperm from the testicle for assisted reproduction [GR-A] [50-54].

Improvement in semen parameters after varicocelectomy

Varicocele repair, intrauterine insemination (IUI) and *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) are options for the management of couples with male factor infertility associated with a varicocele [55-60]. The decision as to which method to use is influenced by many factors. Most importantly, varicocele repair has the potential to reverse a pathological condition and effect a permanent cure for infertility, as opposed to IUI or the assisted reproduction technologies (ART) required for each attempt at pregnancy [58]. Other factors to be considered are age of the female partner, the potential long-term health effects of IVF and ICSI on the offspring resulting from these techniques, and the possibly greater cost-effectiveness of varicocele treatment compared with IVF with or without ICSI [59, 60]. Finally, failure to treat a varicocele may result in a progressive decline in semen parameters, further reducing a man's chances for future fertility.

Several studies evaluating semen quality following varicocelectomy have been published. However, they lack standardization in selection methods, diagnostic techniques, forms of treatment and variables evaluated.

One randomized study demonstrated semen quality improves in 50% of cases following varicocelectomy [GR-A] [61].

A meta-analysis of clinical randomized studies demonstrated that surgery or embolization for varicocele in infertile men does not increase the chance of natural pregnancy [GR-A] [43]; however, several criticisms have been raised regarding the selection of the studies included in this article [GR-A] [62]. Another recent meta-analysis demonstrated that the chances of natural pregnancy increased 2.8 times after varicocelectomy compared with patients who receive no treatment or medical treatment [GR-A] [63].

Testicular size, varicocele grade, seminal parameters and hormonal levels may be considered prognostic parameters for men with varicocele [GR-D] [64]. However, it is not possible to conclude which parameters are predictive of treatment outcomes [GR-B] [14] [GR-A] [65, 66]. Future repair is usually not indicated as the primary treatment for couples when IVF is necessary for treatment of female factor infertility [56]. Nevertheless, certain circumstances occur in which treatment of a varicocele should be undertaken before initiating ART even when female factor infertility is present. Specifically, varicocele repair has been shown to restore at least low numbers of sperm to the ejaculate of some men with nonobstructive azoospermia [50-54]. In these cases, varicocele repair may restore sperm to the ejaculate, making IVF/ICSI possible without testicular sperm aspiration or extraction. Therefore, testicular biopsy and varicocele repair may be offered to these men.

A large body of literature suggests improved semen parameters and fertility following varicocelectomy. However, some investigators have challenged the benefit of these procedures because the favorable results are reported in case-controlled studies rather than prospective, randomized trials [67-71]. Statistical evaluation of these data is the subject of an ongoing debate, and the fertility outcomes of varicocele repair have been described in numerous published studies [72-75]. Most of these studies lack adequate numbers of patients, randomization and/or controls, and it is not possible, therefore, to reach a clear conclusion on fertility outcomes [43].

Recently, Evers and Collins reported a meta-analysis including seven prospective, randomized trials that evaluated varicocelectomy and pregnancy outcomes [43]. They claimed that evidence was insufficient to conclude that treatment of clinical varicocele improved the likelihood of conception for couples with male infertility. They stated that the routine treatment of the male partner of subfertile couples was unadvisable. This conclusion is regrettable because the data in the meta-analysis were questionable. Specifically, several patients in the study groups had normal semen analysis. Of the seven studies, four included men with subclinical varicoceles. Two of the studies had questionable outcomes data for controls. One of these reported a cumulative pregnancy rate for controls of 47%, and the other reported a 24.5% pregnancy rate among controls with counseling [76, 77]. The pregnancy rates for controls among the remaining studies in the meta-analysis ranged between 4.5 and 10%. Finally, varicocele treatment did not include microsurgical procedures as suggested by the Best Practice Study Groups, and follow-up information regarding recurrence with either high ligation or embolization was limited [9].

In fact, the majority of the published controlled studies have failed to use randomization, men with palpable varicoceles, men with abnormal semen analyses and/or men with normal female partners [78, 79]. Most of these trials, however, show improvement in fertility after varicocele treatment, with only a few indicating that varicocele treatment has little or no effect on fertility. A review of 12 controlled studies found a pregnancy rate over one year of 33% in couples in which the male had received varicocele treatment, as compared with 16% in untreated couples [80].

A Cochrane review identified five randomized controlled trials that examined outcomes in couples with male factor infertility and varicoceles and concluded that they did not show sufficient evidence regarding the treatment of varicoceles to warrant their repair [43, 58, 59, 61, 81, 82]. However, these studies were chosen for this review only because of their status as randomized clinical trials; no evaluation of the methods was performed. A review of these trials shows that one examined only subclinical varicoceles, and three others exhibited methodological problems, including the use of embolization, high pregnancy rates in untreated couples (25% in a one-year period), and inherent selection bias in the study (many couples opted to pursue ART rather than enter the study).

Only two well-designed, randomized, controlled studies using men with palpable varicoceles, abnormal semen parameters and normal wives have been published [76, 77]. While one of the studies showed no greater likelihood of pregnancy following varicocele repair, it did demonstrate a significant improvement in testis volume and semen quality as compared with those of controls [77]. The one study that did show sizeable benefit was a randomized crossover design in which more

than 60% of couples who underwent repair achieved pregnancy, compared with 10% of untreated couples [77]. When the untreated couples were then crossed over and treated, another 50% became pregnant in the following year. However, men with severe oligospermia were excluded from this trial. Furthermore, preliminary data from an ongoing, prospective, randomized, controlled trial have shown a fourfold increase in the spontaneous pregnancy rate in men with treated varicoceles compared with the control group.

Although few randomized controlled trials show the benefit of treating varicocele-related infertility, many nonrandomized studies support this concept [78-80]. Based on a review of numerous studies, most of them retrospective, several conclusions were drawn. Most participants showed improvement in postoperative sperm density and motility. Natural pregnancy rates varied, but the overall average was 37%, a clearly higher figure than any reported for non-treatment. Although many of these studies suffer from the flaws of non-randomized trials, these results would be difficult to explain on the basis of chance alone.

Varicocele in the adolescent

The main challenge in the management of varicocele in adolescents is establishing criteria for treatment – in other words, identifying which patients will benefit from surgery.

Adolescent males who have unilateral or bilateral varicoceles and objective evidence of reduced testicular size ipsilateral to the varicocele should be considered candidates for varicocele repair [4, 9, 83]. If objective evidence of reduced testis size is not present, adolescents with varicoceles should be followed up with annual objective measurements of testis size and/or semen analysis to detect the earliest sign of varicocele-related testicular injury [9, 10]. Varicocele repair should be offered at the first detection of testicular or semen abnormality.

In the adolescent population, the hypotrophy rate caused by varicocele is 9%. It always should be related to the child's/adolescent's development according to the Tanner Kass classification (GR-D) [84].

In adults, varicocele grade is related to testicular volume. A grade I varicocele has a minimal impact on testicular volume; grade II is related to unilateral atrophy; and grade III is related to bilateral abnormalities [GR-D] [84]. Despite these associations, varicocele grade is not related to the presence or gravity of testicular disproportion in adolescents [GR-C] [85].

The criteria for definition of testicular hypotrophy are arbitrary because they were not compared with fertility in a long-term follow-up. The definitions of hypotrophy include:

1) difference in testicular size of 10 to 25% [GR-C] [86, 87],
2) an absolute difference between the testicles of 2 to 3 ml [GR-D] [88].

Scrotal pain appears to be uncommon in adolescents with varicocele, with an incidence of 2 to 4% [GR-D] [89]. No studies have been published that evaluate the indications for varicocelectomy in these cases.

The same techniques for varicocele repair in adults are routinely used in adolescents [GR-C] [90-94].

The improvement in sperm motility following varicocelectomy is higher in adolescents compared with adults [GR-C] [95]. An increase in size of the affected testis occurs in 50 to 90% of adolescent cases [47] [GR-C].

In the presence of bilateral normal testicular development and absence of symptoms, evidence is lacking to support the benefits of surgical varicocele repair. These adolescents must be followed annually with physical exam, ultrasound and semen analysis [GR-D] [89]. In cases of testicular hypotrophy and/or abnormalities in the semen, surgical repair of the varicocele must be considered.

Benefits of surgery in assisted reproduction technologies

Studies indicate that IVF/ICSI seem to be no more effective than varicocelectomy in managing male factor infertility associated with a varicocele, but ART is more expensive than the surgical procedure [58-60]. In their meta-analysis, Penson et al. reported that the probability of a live birth after varicocelectomy was 29.7% (with 1% having twins), compared with 25.4% after IVF/ICSI (with a multiple gestation rate of 39%) [60]. In a separate study, Schlegel reported that the cost per baby delivered with IVF/ICSI was $89,091, compared with $26,268 after varicocelectomy [59]. Thus, varicocele surgery seems desirable for selected varicocele cases.

The surgical treatment of varicocele has the capacity of improving semen parameters, leading to an increase in the total motile sperm count and improved sperm morphology, decreasing oxidative stress and resulting in an improvement in the function of the male gamete [GR-B] [20].

Surgical varicocele repair may help a couple avoid the need for ART or reduce the treatment complexity grade when ART is indicated [GR-D] [56, 58].

In azoospermic patients, the surgical treatment of varicocele may promote spermatogenesis, avoiding the need to obtain sperm from the testicle for assisted reproduction [GR-C] [50-54].

Patients should be evaluated after varicocele treatment for persistence or recurrence of the varicocele. If the varicocele persists or recurs, internal spermatic venography may be performed

to identify the site of persistent venous reflux. Either surgical ligation or percutaneous embolization of the refluxing veins may be used. Semen analysis should be performed after varicocele treatment at about 3-month intervals for at least one year or until pregnancy is achieved. IUI or ART should be considered for couples in whom infertility persists after anatomically successful varicocele repair [9, 10].

Conclusions

Despite the absence of definitive studies on fertility outcomes after varicocele repair, varicocele treatment should be considered as an option for appropriate infertile couples. Varicocele repair has been proven to improve semen parameters in most men; varicocele treatment may possibly improve fertility, and the risks of varicocele treatment are small.

Varicoceles continue to stimulate controversy among reproductive experts. Despite conflicting evidence from both randomized and nonrandomized trials, clinical experience still favors the surgical treatment of clinical varicoceles in men with infertility. However, fertility specialists must design and recruit participants (or patients) in randomized, properly controlled trials to reach a definitive conclusion.

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