

Varicocele: How this condition and its management affects men's health

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Abstract

Varicocele is a relatively common condition that can impact men's health in various ways. Unfortunately, its prevalence and the availability of various different methods of repairing it might lead to unnecessary treatment. An understanding of the various ways that this condition can impact men's health is necessary in order to manage it appropriately. At present, there is substantial evidence to support varicocele repair in men who present with infertility, abnormal semen parameters, clinical varicocele and a female partner with normal fertility (or one with a potentially correctable abnormality). Varicocele repair appears to improve seminal fluid quality and might improve pregnancy rates. It might also have a role in managing men with non-obstructive azoospermia. Varicocele can also be a cause of scrotal pain that is usually of a dull character. Varicocele repair is an effective method of managing this type of pain, especially once proper measures have been taken to exclude other possible causes of orchalgia. Conservative measures are generally not effective in managing varicocele-related scrotal pain. There is growing evidence to suggest that varicocele repair might have a role in improving the serum testosterone level in men with hypogonadism, especially in the sub-fertile population. Well-designed prospective studies are needed to support the utilization of varicocele repair in

managing these patients, as well as in preventing testicular dysfunction on a prophylactic basis.

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Key words: Varicocele; Varicocelectomy; Infertility; Azoospermia; Pain

Core tip: The prevalence of varicocele and the availability of various different methods of repairing it might lead to unnecessary treatment. An understanding of the various ways that this condition can impact men's health is necessary in order to manage it appropriately. An overview of this disorder is given, together with different indications of treating it in adult men.

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INTRODUCTION

A varicocele is a tortuous spermatic vein that is abnormally dilated. It is a relatively common condition. A clinical varicocele has been described to be palpable in around 15% of all men^[1]. However, in a more recent study, it was found to be present in 24.2% of healthy young men^[2]. Furthermore, its prevalence has been described to be as high as about 35% of men who present for assessment of infertility^[3]. Varicocele repair is currently considered to be the most commonly performed procedure to treat male infertility. This relatively high prevalence of varicocele, coupled with the availability of a multitude of relatively low-risk methods of repair, might lead to over-treating it^[4]. The aim of this review is to examine how varicocele can affect men's health and the theories on how it exerts these effects. In addition, the potential out-

comes of repairing varicocele for various indications will be assessed.

ASSOCIATIONS AND ETIOLOGY

Varicocele occurs predominantly on the left side. Several factors have been proposed to explain this disproportion in laterality, including the more frequent occurrence on the left side of absent or incompetent spermatic vein valves, a longer spermatic vein, retro-aortic left renal veins, the nut-cracker phenomenon (the compression of the left renal vein between the superior mesenteric artery and the aorta) as well as the insertion of the spermatic vein into the higher pressure left renal vein^[5-8].

There appears to be an association between varicocele and conditions such as peripheral varicose veins and coronary artery ectasia, suggesting a diffuse vascular abnormality^[9,10]. Its prevalence appears to rise with advancing age, increasing by about 10% with each decade^[11]. The prevalence in the elderly was described to reach 42% in a study that involved men with a mean age of 60.7 years^[12]. A higher prevalence of varicocele has been described in first-degree relatives, suggesting a hereditary component as well^[13,14]. Varicocele also appears to be positively correlated with adolescent gynecomastia and inversely related to the body mass index^[15,16].

DIAGNOSIS AND CLASSIFICATION

Varicocele is typically diagnosed by physical examination. The classical description of it is that of a "bag of worms" when the patient is examined in the standing position, in a warm room. Varicoceles are usually classified according to the Dubin system^[17]: Grade I: palpable distension of intrascrotal veins only with the Valsalva maneuver; Grade II: palpable, but not visible, distension of the intrascrotal veins without the Valsalva maneuver; Grade III: distention of intrascrotal veins that is visible through the scrotal skin.

"Grade 0" is sometimes used to classify subclinical varicoceles that are not palpable, but rather are detected using ancillary diagnostic measures (*e.g.*, ultrasonography, venography, thermography and scintigraphy). Ultrasonography is one of the most popular of these ancillary measures and there are described systems of classifying varicocele using it^[18]. Scintigraphy and thermography have been suggested as methods that are comparable or even superior to ultrasonography in detecting varicocele^[19,20]. With the exception of venography, these techniques are considered simple and non-invasive.

Advocates of using ultrasonography contend that it helps avoid the risk of subjectivity that is associated with physical examination. However, no clear cut-off measurements have been agreed upon to establish the diagnosis of varicocele on ultrasonography^[21]. Therefore, while it continues to be used widely to diagnose and classify varicocele, and is certainly indicated in cases where physical examination is inconclusive, some authorities caution that such procedures that detect subclinical varicoceles should

be avoided^[22].

INDICATIONS FOR REPAIR

Varicocele repair in adults has been described to address several conditions. These include: (1) male infertility, including non-obstructive azoospermia (NOA); (2) pain; and (3) low serum testosterone.

VARICOCELE AND MALE FACTOR INFERTILITY

In 1992, the World Health Organization assessed the influence of varicocele in more than nine thousand men who presented as partners in couples consulting for infertility across 24 countries^[23]. A clinically palpable varicocele was detected in 11.7% of men with normal semen analyses, compared to 25.4% in those with abnormal analyses. Varicocele was associated with a reduced left testicular size and semen count. Interestingly, there was a wide range of varicocele detection among different centers (6%-47%), with the presence of a urologist or andrologist helping increase the detection rate. Also noteworthy is that the spontaneous pregnancy rate was not significantly different between men with and without varicocele.

The exact mechanism by which varicocele may negatively affect male fertility potential remains undetermined. However, several mechanisms that may contribute to this detrimental effect have been proposed. These include: (1) reflux of toxic adrenal and renal metabolites through the renal vein^[24]; (2) elevated intrascrotal temperatures^[25]; (3) elevated spermatozoal oxygen species^[26,27]; (4) local hypoxia and ischemia^[28,29]; (5) sperm chromosome aneuploidy^[30]; and (6) sperm nuclear DNA damage^[27,31].

Varicocele repair can be considered when a man has a clinically palpable varicocele, abnormal semen analysis results and his female partner has normal (or correctable) fertility potential^[22]. The role of varicocele repair in managing men with male factor infertility has been a matter of heavy debate. A meta-analysis of randomized controlled trials (RCTs) to assess the influence of varicocele repair on pregnancy rates concluded that the treatment of varicocele in managing men from couples with unexplained infertility cannot be recommended^[32]. This study was criticized for including men with subclinical varicocele as well as those with normal semen parameters. Several meta-analyses proposed a contrary perspective. A meta-analysis of the same RCTs in the above-mentioned study, after exclusion of those including men with subclinical varicocele and/or normal semen parameters showed that pregnancy rates in the treatment group were significantly higher in the treatment group on "as-treated" analysis^[33]. A meta-analysis that included RCTs and observational studies that were scored for bias concluded that surgical repair of varicocele significantly improved the odds of spontaneous pregnancy^[34]. An update of the aforementioned Cochrane Collaboration meta-analysis

found pregnancy outcomes that favored varicocele treatment over observation^[35]. These results were even more pronounced when men with subclinical varicocele or normal semen parameters were excluded from analysis. However, the authors emphasized, as in most of these meta-analyses, the heterogeneity of the studies involved. Finally, a meta-analysis of RCTs involving only surgical repair of varicocele compared to observation found an even higher odds ratio (OR) of 4.15 favoring surgical repair after excluding men with normal semen parameters and subclinical varicocele^[36].

Although pregnancy is the obvious desired principal outcome when managing men with infertility, there is a disadvantage to using it when assessing the effect of therapeutic interventions involving the male partner. This outcome inherently involves potential female partner factors that might impact the observed effect of treatment. Therefore, the role of semen analysis as a predictor of male fertility potential is probably just as important as that of pregnancy rates when assessing the benefit of varicocele repair on male fertility. There is evidence to suggest an improvement in sperm concentration, motility and morphology following varicocele repair^[37-39]. According to a meta-analysis involving 22 prospective studies that addressed sperm concentration before and after varicocele repair, the combined post-repair improvement in sperm concentration postoperatively was 12.32×10^6 sperm/mL^[40]. Furthermore, in the same study, the combined improvements in total and progressive sperm motility were 10.86% and 10.67%, respectively. All of these findings were statistically significant. Significant improvements in seminal oxidative stress and sperm DNA damage following varicocele repair were also found in this meta-analysis. Sperm ultramorphology has also been shown to improve following surgical varicocele repair in a non-randomized prospective controlled study^[41].

A review that compared the various methods of varicocele repair in more than 5000 patients concluded that the microsurgical approaches (subinguinal or inguinal) offer better outcomes in terms of pregnancy, recurrence and complication rates^[42]. Retrograde radiographic-guided embolization or sclerotherapy carries with it several potential advantages. It minimizes the risk of post-procedure hydrocele formation and of testicular artery injury and subsequent testicular atrophy. There is also no risk of injury to the vas deferens and the recovery time is rapid. However, it also comes with its unique set of potential complications, including those related to intravenous contrast media administration, puncture site complications (e.g., hematoma formation) and coil migration. A recent review of 158 patients who underwent varicocele embolization revealed an 18.9% failure rate when treating bilateral varicocele^[43]. This relatively high failure rate was mainly due to technical difficulties when treating the right side. This brought the authors to suggest a microsurgical approach when treating bilateral varicocele. However, embolization remains a suitable option when treating left-sided varicocele.

VARICOCELE AND NON-OBSTRUCTIVE AZOOSPERMIA

Patients with NOA represent possibly the most challenging patients with male factor infertility in terms of achieving pregnancy. They might require sperm retrieval procedures which, if successful, would be followed by assisted reproductive techniques (ARTs), such as *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI). The aim when managing these patients would be to help achieve a return of sperm to the ejaculate with enough quality that would help achieve the goal of spontaneous pregnancy or improve semen quality in order to "upgrade" the couple to be considered for intra-uterine insemination, or help the male partner avoid sperm retrieval procedures by restoring sperm in the ejaculate for use in IVF/ICSI, or at least potentially improve spermatogenesis to a degree that might hopefully improve the success of future sperm retrieval attempts.

The return of sperm to the ejaculate following varicocele repair has been described in several series of men with a clinical varicocele and NOA, with success rates ranging between 20.8%-56.2%^[44-48]. A meta-analysis that involved 233 patients from 11 retrospective studies found that motile sperm returned to the ejaculate in 39.1% following varicocele repair^[49]. Fourteen patients (6%) achieved spontaneous pregnancy and 10 (4%) IVF/ICSI pregnancies. After an initial return of sperm to the ejaculate, 11 patients (4.6%) reverted back to azoospermia within 2-6 mo. When available, the histopathological picture can help predict the outcomes of varicocele repair, with hypospermatogenesis and maturation arrest associated with significantly higher success rates than Sertoli cell-only. Several studies have found an increase in sperm retrieval procedure success rates following varicocele repair when compared to proceeding with retrieval attempts without repairing the varicocele^[50-52]. However, a retrospective study that included men with subclinical varicocele showed similar sperm retrieval rates between the two groups^[48].

PROPHYLACTIC VARICOCELECTOMY

Progressive, duration-dependant, deterioration in semen quality has been described in infertile men with a clinical varicocele who originally had normal semen parameters and were followed over time, albeit in a small-sized study^[53]. Furthermore, the incidence of varicocele in men with secondary infertility is significantly higher than those with primary infertility, suggesting that prior fertility does not offer protection from possible varicocele-induced impairment of testicular function^[54]. This potentially deleterious effect of varicocele on male fertility, coupled with the relative safety and low complication rates of modern microsurgical procedures, has led to consideration by some of varicocele repair in men with normal semen parameters and a clinically palpable varicocele, especially if there is ipsilateral testicular hypotrophy. However, there

is not enough evidence to strongly support the use of this theory in the clinical setting. No RCTs or prospective studies have been conducted to address the use of prophylactic varicocelectomy in this setting.

VARICOCELE AND SCROTAL PAIN

Varicocele has been reported as a cause of scrotal pain^[55]. The character of the pain has been described as dull and one that is aggravated by exercise and straining^[56]. It has been estimated to occur in 2%-14% of men with varicocele^[57]. Conservative measures that have been traditionally used to manage varicocele-associated pain include utilizing scrotal support, non-steroidal anti-inflammatory analgesics and limiting physical activity which are impractical and of limited benefit^[56,58]. In a study of 140 patients who were treated conservatively for up to 8 wk, only 5 patients had an improvement in symptoms, and even those 5 patients eventually opted for surgical management for recurrent pain^[58]. A low success rate (0.04%) for conservative management was also seen in another study when it was attempted for a mean of 4 wk^[59]. There is some evidence, based on the experience with a small number of patients, to suggest a possible benefit from the venotonic drug micronized purified flavonoid fraction in reducing varicocele-associated pain in men with normal sperm concentration^[60].

Studies, the vast majority of which are retrospective, that assess the effect of varicocele repair on pain are relatively few. Most of these series showed a relatively high rate of post-procedure complete or partial pain resolution, ranging between 76.7%-94.8%^[56-59,61-67]. However, one of the earliest studies to address this issue described failure to resolve pain in 52% of the patients who underwent high ligation^[55]. To date, there are no studies that assess the effect of subclinical varicocele repair on scrotal pain.

Other potential causes of scrotal pain should be ruled out prior to treating varicocele in order to help reduce treatment failures. The character of pain experienced by the patient can provide a clue to the cause of the patient's symptoms. Atypical pain properties such as sharp pain might be due to causes other than varicocele. Indeed, the presence of a dull aching or dragging pain has been reported as a predictor of treatment success, while sharp or throbbing pain was associated with a higher rate of recurrence, persistence or even worsening of symptoms^[62]. In another study, post-operative success was significantly and independently higher in patients who were operated on for dull rather than "dragging" or "aching" pain and for mild or moderate rather than severe pain (≥ 7 on the 11-point numeric rating scale)^[68]. Yaman *et al*^[59] suggested that the grade of a painful varicocele might also influence the outcome of repair, as did Kim *et al*^[57]. However, this association was not observed in other studies^[56,62,66,68]. Further support for the notion that a cause other than varicocele might be a reason behind treatment failure is noted in the finding that failure rates were significantly higher in patients with a duration of symptoms of less than 3 mo^[66],

but this association with symptom duration was not supported by findings in other studies^[56,68]. In one of the few prospective studies that assessed varicocele repair for pain management, neither preoperative varicocele grade, pain character or duration of symptoms were predictive of post-operative outcomes^[64]. In this study, among the patients who were available for their 3 mo post-operative assessment, 95% stated that they would recommend the procedure for their relatives.

Various techniques have been reported when treating varicocele for pain, including high ligation, subinguinal and inguinal microsurgery, conventional inguinal (Ivanissevich), scrotal and laparoscopic approaches, as well as percutaneous interventional radiological procedures such as sclerotherapy or embolization with reasonable results. Microsurgical approaches might have a higher post-operative pain resolution rate^[69]. No difference in outcome was detected in a study that compared non-microsurgical approaches (inguinal, subinguinal and high ligation)^[62].

Failure of varicocele resolution and its recurrence after treatment have been reported with varying rates. This might be a cause of persistent or recurrent scrotal pain following treatment^[57]. Chawla *et al*^[70] reported a series of 11 patients who presented with recurrent varicocele and pain and were treated with microsurgical subinguinal varicocelectomy. Ten of the patients had complete or partial resolution of pain and nine of them stated that they would undergo the same procedure for their presenting complaint.

VARICOCELE AND HYPOGONADISM

Although the potential effect of varicocele and varicocelectomy on serum testosterone levels is one that has been studied in the past, this topic is garnering increasing interest more recently^[71]. A possible dysfunction in testosterone production in infertile men has been described^[72]. Tanrikut *et al*^[73] described significantly lower serum testosterone levels in men with varicocele than a control group of men undergoing vasectomy reversal. The effect of varicocele repair on serum testosterone levels has been debated. Some studies showed no increase in serum testosterone levels following repair^[74-76]. However, the baseline serum testosterone level in these studies was normal or somewhat higher, making it difficult to document an improvement following repair.

A meta-analysis involving 9 studies (one prospective and 8 retrospective observational studies) in which men with clinical varicocele underwent surgical repair showed a significant post-operative increase in serum testosterone from baseline by 97.48 ng/dL^[77]. In a retrospective review of men who underwent microsurgical subinguinal varicocelectomy, men who had a baseline serum testosterone level of 400 ng/dL or less had a significant increase in their levels after surgery in all age groups^[78]. In an interesting non-randomized prospective study, a hundred infertile men with clinical varicocele and low serum testosterone (< 280 ng/dL) who underwent microsur-

cal subinguinal repair were compared to a control group of hypogonadal varicocele patients who opted for ART utilization^[79]. While there was a slight decrease in serum testosterone level in the control group at follow-up, the varicocelectomy group showed a significant increase in serum testosterone. Indeed, 78% of the men in the treatment arm went on to reach normal serum testosterone levels at follow-up, compared to only 16% in the control group. Similarly, serum testosterone and erectile function significantly improved from baseline after microsurgical subinguinal varicocelectomy in hypogonadal (serum testosterone < 300 ng/dL) infertile men with clinical varicocele when compared to a similar control group who refused surgery and opted for ARTs^[80]. It is worth emphasizing that most of these studies involved men who also complained of infertility and may not represent the general population. Findings in this group of patients would be difficult to extrapolate to the general population.

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