

Varicocele and Male Infertility: Current Issues in Management-A Review

Krishna Reddy SV*

Associate Professor, Narayana Medical College, Andhra Pradesh, India

Abstract

Varicocele is the most common correctable cause of male factor infertility. The role of varicocele in the etiology of male infertility is still controversial regarding to whom varicocelectomy should be done and the selection should be meticulous. With the recent advances in biomolecular and development of novel sperm functional tests, it has been possible to better understand the mechanism involved in damage provoked by varicocele and therefore, propose ways to reverse them. Clinical studies have shown that varicocele surgery can improve semen quality sufficient to downgrade the type of assisted reproductive technology (ART) procedure required. This review discusses current concepts on the mechanisms for varicocele induced testicular damage and efficacy of varicocelectomy for treatment of infertility. We also review the current guidelines and need for proper case selection before surgery. The authors critically reviewed the cost effectiveness of the surgical treatment of a varicocele compared with assisted reproductive techniques.

Keywords: Varicocele; Male infertility; Varicocelectomy

Introduction

Infertility is the inability of sexually active, non-contracepting couple to achieve pregnancy in one year [1]. Infertility is considered one of the main public health issues, as it affects about 15% of the couples of reproductive age [2]. The male factor is involved in 40-50% of infertility cases [3]. The most common type male infertility is idiopathic infertility, which is characterized by the presence of one or more abnormal semen parameters with no identifiable cause [4]. Another common cause of male infertility is varicocele which is found to affect 4.4-22% of general population, 21-41% of men with primary infertility and 75-81% of those with secondary infertility have this condition [5]. The term varicocele was originally coined by British surgeon T.B. Curling in 1843 to describe the pathologic dilatation of veins of the spermatic cord [6]. The earliest descriptions of treatment for varicoceles came from the Roman encyclopedist Celsus, who practised from 25-35 AD. While early varicocelectomy was performed for pain or cosmetic improvement, it was not until 1952 that association between varicocele and infertility was recognized. T.S. Tulloch published a case report of a man with testicular biopsy-proven maturation arrest in whom sperm count improved after varicocelectomy [7]. Other reports of similar findings soon followed, thus shifting the focus of varicoceles from pain to subfertility [6]. Almost all varicocele are detected after puberty. The higher incidence in secondary infertility implicates varicocele in producing progressive decline in testicular function over time. In clinical practice, most reports show persistent abnormality of sperm count, motility, or morphology [8]. The "stress pattern," which consists of elongated, tapered sperm head and amorphous cells, is commonly, though not consistently, attributed to varicocele patients [9].

A varicocele is an abnormal dilation and tortuosity of veins of pampiniform plexus that drains the testis. There are three accepted theories on the causes of varicoceles. First that, the testicular vein drains into the renal vein on the left side at a right angle and into inferior vena cava on the right side at an acute angle. This disparity leads to increase in the hydrostatic pressure of the left testicular vein which is subsequently transferred to the pampiniform plexus causing its dilation [10]. A second theory is based on the observation that left internal spermatic vein lack functional valves which are more often absent on the left side than the right which can lead regression of blood. Braedel et al. [11] demonstrated that the venographic pattern of 659 men with varicoceles showed that 73% of men had absent venous valves. Finally, a third theory suggests that there is partial obstruction of the left spermatic vein between the aorta and superior mesenteric artery ("the nutcracker phenomenon") [10]. These factors have

been proposed to be responsible for the preponderance of left sided varicocele (90%) compared to bilateral varicocele (10%). Isolated right-sided varicoceles are rare and should prompt investigations to rule out retroperitoneal pathology.

Pathophysiology of Varicocele

The exact pathophysiological mechanism by which varicocele impairs fertility in affected men remains unknown. Recent laboratory work has demonstrated various changes that may occur at molecular level due to the effect of varicoceles. Proposed mechanisms include hypoxia and stasis, elevated testicular temperature, reflux of adrenal catecholamines, and increased oxidative stress. Scrotal temperature is maintained a few degrees below bodycore temperature in order to optimize the environment for normal testicular function by the countercurrent heat exchange first postulated by Dhal and Herrick in 1959 [11]. Impairment of testicular microcirculation has been proposed as a part of the pathologic effects of varicocele. In a recent study using newer power doppler ultrasonography, Unsal et al. [12] has shown significant increase in resistance to blood flow as measured by the resistive index and pulsatility index of capsular branches in varicocele patients compared with controls. Increased resistive index and pulsatility index of capsular branches indicates impaired microcirculation, persistent hypoperfusion, stasis and hypoxia. Elevated testicular temperature in men with reduced sperm quality and varicocele has been demonstrated as well as the reduction in temperature following varicocele repair [13]. However, the mechanism by which temperature affects spermatogenesis is not clearly understood. Increased concentration of regressed toxic metabolites in the testis (e.g. catecholamines from the adrenal glands) can cause vasoconstriction and subsequent dysfunction of the spermatic epithelium [14]. Elevated catecholamine concentrations may be exchanged from the veins to the testicular artery at the level of the pampiniform plexus via the countercurrent exchange mechanism, resulting in increased testicular artery noradrenaline concentrations, and causing vasoconstriction of

*Corresponding author: Krishna Reddy SV, Associate Professor, Narayana Medical College, Urology, Nellore, Andhra Pradesh 524001, Tel: +918612321828; Fax: +918612300068; E-mail: vijaya.nel@gmail.com

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intratesticular arterioles; contributing to testicular hypoxia. A well-studied exogenous toxic agent known to affect spermatogenesis relates to smoking [15]. Cadmium workers and cigarette smokers are known to have increased serum levels of cadmium [16]. Cadmium exposure and its accumulation are known to impair spermatogenesis and sperm function and lead to impaired reproductive potential in men [16].

Furuya et al. [17] documented a blood-testis barrier and immunoregulatory proteins at the level of the sertoli cells, rete testis, and efferent ductules that provide immunological protection of sperm antigens and inhibit lymphocyte proliferation and complement-mediated cell lysis. Disruption of this barrier is believed to result in the production of antisperm antibodies. Hass et al. [18] in his study had a prevalence of antisperm antibodies in the general male population reported to be 0-2%. Bronson et al. [19] demonstrated antisperm antibodies which are shown to cause agglutination and immobilization of spermatozoa, sperm cytotoxicity, impairment of sperm penetration into cervical mucus, prevention of capacitation or the acrosome reaction in response to zona pellucida, and enhanced phagocytosis of spermatozoa by macrophages. The role of varicoceles in unexplained idiopathic male infertility has been investigated. The defect is believed to exit in sperm function rather than morphology or quantity, and is thought to involve the acrosome reaction during zona pellucida binding [20,21]. The mannose binding assay may be used to determine acrosomal activity [22].

Over last decade, research into the pathophysiology of varicoceles has focused on following areas. These are oxidative stress-related damage, tissue hypoxia and hormonal imbalances. It is speculated that the main mechanism is DNA damage in sperm heads due to oxidative stress due to presence of high levels of reactive oxygen species (ROS) or reduced total antioxidant capacity (TAC) which was confirmed in fertile as well as in infertile men with varicocele [23].

Reactive oxygen species (ROS) include superoxide anions, the hydroxyl radical, nitrous oxide, hypochlorous acid and hydrogen peroxide [24]. Schreck et al. [25] documented that production of ROS by spermatozoa is a normal physiological process which serves as an important mediator in signal transduction mechanism. de Lamirande et al. [26] demonstrated regulation of sperm hyper activation/ capacitation, and facilitation of the acrosome reaction and spermatozoon-oocyte attachment. In normal healthy men, the seminal plasma contains natural scavengers or antioxidants to neutralize the effects of excessive ROS generation. Hendin et al. [23] found the levels of ROS to be significantly higher in men with varicocele than in controls, but no difference between fertile and infertile men with varicoceles. Thus it is obvious that oxidative stress is directly related to varicocele, independent of fertility status. Nevertheless, oxidative stress is known to have adverse effects on sperm structure and function, such as membrane lipid alteration, disruption of sperm metabolism, reduction of sperm motility [27], DNA fragmentation [28] and reduced overall sperm quality [29]. A World health organization (WHO) multi-center study on influence of varicocele on fertility parameters demonstrated that the mean testosterone concentration of men aged 30 years and with varicocele was significantly lower than that of younger patients with varicoceles, whereas this trend was not observed in men without varicoceles [30]. However this study failed explain whether the reduced levels of testosterone are due to varicocele or coexistence of primary testicular failure. On the other hand, it has been demonstrated that testosterone levels in men with varicocele and no other testicular pathology are within the normal range [31].

Apoptosis is the mechanism of spontaneous, regulated, cell death

that ensures the maintenance of a normal cell life. Increased apoptosis may be responsible for depletion of germ cells, and consequently poor semen parameters. It may also induce spontaneous death of mature sperms. Cam et al. [32] and Barqawi et al. [33] in their experimental rat model studies of varicocele found an increased rate of apoptosis in varicocele group, when compared to the sham surgery group. This apoptosis may be ROS mediated, and could be reversed through the use of antioxidants (i.e. glutathione, carnitine) [34]. Nitric acid may also induce free radical mediated cellular damage. These may be elevated in isolation in spermatic vein with normal peripheral levels. Turkyilmaz et al. [35] in a study comparing adolescents with and without varicoceles, spermatic vein levels of nitric oxide were significantly higher in adolescents with varicoceles. Genetic and lifestyle factors may predispose patients to more severe damage from a varicocele. For example, patients with deletions in antioxidant glutathione S-transferase M1 enzyme display elevated levels of 8-hydroxy-2'-deoxyguanosine in their sperm DNA, have deletions in mitochondria DNA, and have impaired sperm motility [36]. Genotypes of the glutathione S-transferase enzyme have also been shown to predict clinical benefit from varicocelectomy [37]. In addition, alteration in sperm membrane fatty acid composition associated with varicoceles may also increase susceptibility to ROS-induced damage [38].

Diagnosis of Varicocele

Physical examination with the patient standing in a warm room is currently the preferred method for varicocele diagnosis and it has a sensitivity and specificity of around 70% compared with other diagnostic tools [39]. The term clinical varicocele refers to those detectable by either visual inspection or palpation. The most widely used classification is the Dubin grading system [40].

Grade 3: visible and palpable at rest,

Grade 2: palpable at rest,

Grade 1: palpable during valsalva maneuver,

Subclinical: not palpable or visible at rest or under valsalva maneuver but detectable by doppler ultrasound.

Whenever physical examination is inconclusive or difficult to perform as in cases of low-grade varicocele, previous surgery, obesity, concomitant hydrocele imaging studies are recommended. Among the noninvasive modalities, color doppler ultrasound (CDU) has been the best diagnostic tool. Using a cutoff value of 3mm for vein diameter CDU has a sensitivity of about 50% and specificity of 90% compared to physical examination [41]. A valsalva maneuver has a sensitivity of 84% and a specificity of 84% [42]. A pencil probe doppler (9 MHz) is inexpensive tool that may be helpful in diagnosing varicocele. Examination should be carried out with the patient in standing position and a venous "rush" produced by the blood reflux should be heard under valsalva maneuver [43]. Although simple, this method was also shown to be positive in men harbouring subclinical varicocele [44]. Currently, the standard diagnostic assessment of varicocele is physical examination and scrotal ultrasound/Doppler [45]. Nevertheless, scrotal thermography was demonstrated as a useful diagnostic method, especially in low grade varicocele [46]. Recent development of digital infrared thermographic Focal plane array cameras offers the opportunity to revitalize this diagnostic method and further improve its accuracy. Various diagnostic criteria for varicocele were suggested based on digital thermography imaging. However, the standardized diagnostic criteria for varicocele with this method have not yet been established. Recent introduction of radiologic methods for the percutaneous occlusion of blood vessels now allows the diagnostic

procedure of spermatic venography using jugular vein approach, to be combined with definitive occlusion of spermatic vein when indicated [47].

Progressive Effect of Varicoceles

There is a great deal of clinical data suggesting that varicocele exert a progressive deleterious effect upon male infertility, over time during adolescence. Haans et al. [48] and Sayfan et al. [49] studies have shown that testicular volume either fails to increase or actually decrease in size of testis that are associated with varicoceles. The hypothesis that varicocele can cause testicular damage was further confirmed on pubertal boys in which the reduction in testicular size ipsilateral to the pathology was restored after surgical repair [49]. It should be noted, however that catch-up testicular growth among adolescents following varicocele repair is not universal and may be dependent on several factors including patient age [50]. Accordingly, some investigators have recommended to follow-up postoperative serum androgens to better assess testicular function after varicocele repair [51]. Said et al. [31] in his study showed that men with varicocele have shown to have lower sperm count and testosterone levels, as well as reduced testicular size on the same side of varicocele compared with those without varicocele.

Unfortunately, there is few data on the effect of varicoceles and varicocele repair upon semen parameters in adolescent age group. Despite these impediments, Okuyama et al. [52] and Yamamoto et al. [52] have assessed semen parameters in a group of adolescents with varicoceles who were followed prospectively. Significant semen improvement was observed in both studies while Okuyama et al. [52] noted a progressive decline of semen parameters in the untreated group. The question remains whether or not varicoceles exert a progressive deleterious effect during adulthood. The evidence that has been used to support this hypothesis, is increased prevalence of varicocele amongst men with secondary infertility as compared to men with primary infertility [53-55]. The increased prevalence of varicoceles amongst men with secondary infertility suggests that this vascular lesion has a progressive rather than static effect upon male fertility.

A topic of considerable debate over the past is whether or not varicocele size affects outcome of varicocele. Steckel et al. [56] observed a direct relationship between varicocele size and seminal improvement following varicocele repair. They found that men with large varicoceles tend to have significantly worse baseline parameters but much more improvement following varicocele repair as compared with small varicoceles. In contrast, only 41% of the patients with a subclinical varicocele experienced significant improvement in semen parameters and the mean total motile sperm count for the entire group was unchanged. Despite the above mentioned, it remains unclear the reasons why about 2/3 of men with varicocele retain their fertility [52,57] and not all of them achieve fertility improvement after varicocelectomy [58,59]. Moreover, reports on the ineffectiveness of varicocele treatment to increase the chances of conceiving are intriguing. A Key to resolving this problem is to identify patients who could benefit from treatment. Fretz and Sandlow [60] summarized these variables and they are shown in Table 1.

In view of these issues, the American urological association and American society of reproductive medicine has clear guidelines for the evaluation and management of these patients [61,62]. These guidelines state that a varicocele should be corrected when all of the following are present:

- 1) A varicocele is palpable;
- 2) The couple has documented infertility;
- 3) The female has normal fertility or potentially correctable infertility;

and 4) The male partner has one or more abnormal semen parameters or sperm function test results.

Adult men who have a palpable varicocele and abnormal semen analyses but are not currently attempting to conceive should also be offered varicocele repair.

Young men who have a varicocele and normal semen analyses should be followed with semen analyses every one to two years.

Adolescents who have a varicocele and objective evidence of reduced ipsilateral testicular size should be offered varicocele repair. Adolescents who have a varicocele but normal ipsilateral testicular size should be offered following monitoring with annual objective measurements of testicular size and/or semen analyses.

In 2010, the World health organization (WHO) established new reference values for human semen characteristics, which are markedly lower than those previously reported [63]. Current guidelines propose that varicocele should be treated if palpable and in presence of abnormal semen analysis. Application of new WHO reference values into clinical practice will result in patients previously deemed as candidates for varicocele repair are now ineligible for treatment if their semen parameters are above new cutoff reference values. This should be looked at with caution the adequate timing to intervene and prevent testicular damage.

Treatment Options and Outcomes

Current recommendations propose for couples with documented infertility whose male partner has clinical varicocele and atleast one abnormal semen parameter. Non-surgical treatment modalities for varicocele-related infertility are poorly studied, and there is a need for well-designed trails. The gold standard treatment currently accepted for varicocele is surgical repair either by open approach associated or not with magnification, laparoscopy, or through percutaneous embolization of the internal spermatic vein. Regardless of chosen technique, the ultimate goal relies on occlusion of dilated veins that compose the pampiniform plexus. The high retroperitoneal (Palomo), radiologic, and laparoscopic approaches allow the ligation of the gonadal vein. The inguinal (Ivanissevich) and sub inguinal approaches permit ligation of the external spermatic and cremasteric veins that may contribute to the varicocele and may play a role in the recurrence.

Percutaneous embolization offers a rapid recovery and can give good success rate, but the technique demands interventional radiologic expertise and has potential serious complications, including vascular perforation, coil migration, thrombosis of pampiniform plexus [64,65]. Lima et al. have recently pioneered natural orifice transluminal endoscopic surgical procedures (NOTES) to perform varicocelectomy as an important minimally invasive approach [66,67]. In addition, various studies have described the safety and efficacy of laproendoscopic single-site (LESS) surgical repair of varicoceles [68,69]. Laparoscopic varicocelectomy provides high magnification, but hydrocele formation

	Pre-operative Predictors
01	High-grade varicocele (grade III)
02	Lack of testicular atrophy
03	Normal Serum FSH
04	Total motility >60%
05	Total motile sperm count >5x10 ⁶
06	Positive GnRH Stimulation test

FSH: Follicle Stimulating Hormone; GnRH: Gonadotropin-Releasing Hormone

Table 1: Pre-operative predictors of seminal improvement after varicocelectomy.

and recurrence can occur in 5-10% of the cases. Also, specific training and high cost materials are needed. Inherent complications of a laparoscopic procedure such as vascular and intestinal injuries are noted [70,71]. Open surgical varicoectomy is performed by retroperitoneal, inguinal, or subinguinal approaches. The main difference between the subinguinal and the inguinal approach is that the opening of the external oblique muscle aponeurosis is avoided in the former, which may implicate in shorter and less painful post-operative recovery. However, there is no objective data to substantiate a clear advantage of one over the other. Cayan et al. [65] in a systematic review involving 4,473 men aimed to define the best modality of treatment in palpable varicocele in infertile men. The authors concluded that open inguinal or subinguinal artery and lymphatic sparing microsurgical techniques resulted in higher spontaneous pregnancy rate, fewer recurrence and complications compared to laparoscopic, radiologic embolisation, macroscopic inguinal or retroperitoneal procedures. Varicoectomy is believed to improve one or more semen parameters in 65% of those men who are treated [65]. In a recent meta-analysis study conducted by Borruto et al. [72] surgical approaches and post-operative complications were compared between the classic open surgical techniques and minimal invasive surgical approaches. The meta-analysis showed that there was no statistical difference between laparoscopic surgery and open surgery regarding recurrence rate and post-operative hydrocele rate. Moreover, the laparoscopic approach has the advantage to treat simultaneously bilateral varicocele. The mean time for semen improvement and spontaneous pregnancy after surgery is approximately 5 and 7 months, respectively [73]. The reasons why fertility potential is not always improved are still obscure, and consistent data is lacking to determine prognostic factors that might help to identify the best candidates for treatment.

Assisted Reproductive Technology vs. Varicoectomy

Assisted reproductive technology (ART), including *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI), is routinely used to treat male factor infertility. Most importantly, varicocele repair has a potential to reverse a pathological condition and to achieve a permanent cure for infertility, as opposed to IUI or ART which are required for each attempt at pregnancy. Because of success of ART, the optimal method to achieve pregnancy with male infertility has been debated. Meng et al. [74] made decision analysis-based comparisons of ART and varicoectomy suggest that varicocele repair is more cost-effective than the use of ART in men with impaired semen parameters. In addition, the indication of varicocele repair prior to IVF/ICSI may be considered in certain circumstances. Men with nonobstructive azoospermia (NOA) and favorable testicular histopathology may resume sperm production following repair of clinical varicocele [75]. Sperm restoration, even if minimal, yields the possibility of IVF/ICSI without the need of sperm retrieval techniques (SRT). Although assisted reproductive technology (ART) provides an opportunity to families with infertility, the potential medical risks of these procedures include ovarian hyperstimulation and multiple-gestations [76,77]. Varicoectomy has the potential to obviate the need for ART or downstage the level of ART needed to bypass male factor infertility [78]. Esteves et al. [79] studied 242 infertile men with treated and untreated clinical varicocele who underwent intracytoplasmic sperm injection (ICSI) and found significantly higher live birth rates after ICSI in the group of men who underwent artery and lymphatic sparing sublingual microsurgical varicocele repair before ART (46.2%) as compared to the ones undergoing ICSI in the presence of a clinical varicocele (31.4%). Schlegel et al. [80] reported a comparison of varicocele repair using a 'cost per delivery' analysis and concluded that primary treatment with varicoectomy was more

cost-effective than sperm retrieval/ICSI, while providing comparable delivery rates. After varicocele repair, a couple can proceed with ART if pregnancy is not achieved. Varicocele repair may allow some couples to proceed with IUI prior to proceeding with more advanced assisted reproductive techniques, since studies suggest that varicoectomy improves the effectiveness of subsequent IUI [81,82].

Conclusions

Varicocele remains a common finding in infertile men and is often the sole identifiable cause of infertility in couples. There is convincing evidence that varicocele produce a progressive harmful effect upon the testis resulting in decline of semen parameters. The main goal of varicoectomy is to preserve testicular function and initiate pregnancy in infertile couples. However even when pregnancy is not achieved, improved seminal quality after surgery can obviate or downstage the need for assisted reproductive techniques. Controversy still remains regarding the benefit of varicocele repair to improve male fertility. Evidence exist both in favor and against it, but as of now, due to limited number of randomized, controlled clinical trials, new meta-analysis supports improvements in pregnancy rates with varicocele ligation. Although ART can achieve rapid results, considering the higher expenses involved and potential safety issues as well as the fear of unnecessary burden of invasive treatment in healthy female partner, current literature indicates that evaluating and treating the specific male cause is more cost beneficial for infertile couples.

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