Testicular Varicocele: An Overview

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Abstract
Testicular varicocele or varicocele is one of the common causes of scrotal swelling. It is predominantly found in the adolescent and young adult age group and it can adversely affect testicular function in a variety of ways. There is a considerable debate about the effects of varicoceles on future fertility, but the current evidence suggests that varicoceles are found in a higher percentage among males attending the infertility clinics and that treatment of varicoceles is associated with increased spontaneous conception rates among infertile couples. In this article we give an overall view on the aetiology, adverse effects and management of varicoceles.

Introduction

A varicocele is a vascular lesion characterised by dilation and tortuosity of the spermatic veins. It is commonly found in adolescents and young adults. Varicocele is found in approximately 15% of adult males, but the incidence could go as high as 40% in patients attending infertility clinics and up to 80% in those with secondary infertility [1–3]. Varicoceles predominantly affect the left side (90% of cases) with bilateral varicoceles present in 10% of patients [4, 5].

Varicoceles were first described by the French surgeon Ambroïse Paré (1500–1590) in the 16th century as caused by melancholic blood. Later on, Barfield, a British surgeon, proposed a relationship between infertility and varicocele in the late 19th century [6].

Anatomical Considerations

The inguinal canal is a short and oblique passage through the lower abdominal wall that runs medially from the internal inguinal ring (a defect in the fascia transversalis) to the external inguinal ring (a defect in the external oblique aponeurosis). It contains the spermatic cord in males and the round ligament in females in addition to the ilioinguinal nerves in both sexes. The canal is lined by the aponeuroses of the three muscles forming the anterolateral abdominal wall namely the external oblique, the internal oblique and the transversus abdominis. For the components of the spermatic cord see table 1.

The difference in the configuration of the right and left spermatic veins determines variation in the incidence of varicocele on both sides. The right spermatic vein drains into the inferior vena cava obliquely, while the left spermatic vein drains into the left renal vein at a right angle. In addition, the insertion of the left spermatic vein is 8–10 cm higher than that of the right spermatic vein which results in 8–10 cm greater pressure on the flow of blood from the left spermatic veins. The spermatic veins contain valves which help to prevent retrograde flow of blood. Therefore, absent or defective valves will subsequently lead to an increase in the pressure within the spermatic veins and subsequent varicocele formation.
Another factor leading to increased venous pressure in the spermatic vein is the 'nutcracker phenomenon'. This phenomenon was first described by de Schepper [7] from Belgium in 1972 and is caused by entrapment of the left renal vein between the aorta and the superior mesenteric artery, resulting in left renal vein hypertension and subsequent varicocele formation [8–11].

Varicoceles usually arise from the spermatic veins, but the cremasteric veins can also be implicated [12]. However, the role of the cremasteric veins as a cause of recurrence following varicocele surgery has not yet been proven [13]. The deferential veins on the other hand do not appear to play a role in the formation of varicoceles.

Varicoceles can be primary or secondary to increased pressure on the spermatic veins. Secondary varicocele is usually manifested on the right side. Common causes of secondary varicocele are listed in table 2.

Varicocele has also been correlated with the body height and weight. It has been found to be more prevalent in tall and heavy adolescents [15, 16]. However in a study by Handel et al. [17], the prevalence of varicocele was inversely correlated with the body mass index.

### Grading of Varicocele

Clinical varicoceles have been classified into three grades by Dubin and Amelar [18]. This has helped clinicians to determine the timing of the definitive treatment and prognosis [19]. The grades are described as: (1) grade I = small size only palpable during Valsalva manoeuvre; (2) grade II = medium size palpable at rest, and (3) grade III = large size visible at rest.

Subclinical varicocele is not visible or palpable at rest or during Valsalva manoeuvre but can be demonstrated by special tests such as colour Doppler ultrasound scan.

In addition, varicoceles can be classified according to the degree of reflux identified by colour Doppler ultrasound scan [20]: (1) grade I = reflux induced by Valsalva manoeuvre with pattern 1, only very little reflux at the beginning of the Valsalva, or pattern 2, reflux during the full length of the Valsalva; (2) grade II = intermittent spontaneous venous reflux, and (3) grade III = continuous spontaneous venous reflux.

### Adverse Effects of Varicoceles

Varicoceles are associated with deleterious effects on the testes [21]. These are described below.

#### Failure of Testicular Growth and Development

It is well known that the ipsilateral testis in patients with varicoceles is smaller than the other side [22, 23]. This is more evident in teenage boys owing to the rapid increase in the testicular volume. Haans et al. [24] demonstrated that the loss of testicular volume in patients with varicoceles was associated with decreased sperm count. The relationship between varicocele grade and testicular volume was studied by Sigman and Jarow [25] who found that left testicular varicoceles were associated with decreased testicular volumes in 73, 53 and 43% in grade III, II and I varicoceles, respectively. Sokamoto et al. [26] studied the relationship between varicoceles and testicular volume in infertile males using scrotal ultrasound. They found that left clinical varicocele was associated with significant ipsilateral testicular hypotrophy. However there was a significant difference in the testicular volume between infertile and fertile males regardless of the presence of varicocele, suggesting the presence of factors other than varicocele affecting the testicular volume. Subclinical varicoceles however were not associated with significant changes in testicular volume [26]. In another retrospective study by Zini et al. [27] subclinical varico-
Varicocele was shown to be associated with decreased testicular volume using scrotal ultrasound for patients attending the infertility clinic. The decrease in the ipsilateral testicular size in patients with varicocele was found to be reversed by varicocele surgery. Two randomised controlled trials showed increases in the sizes of the ipsilateral and contralateral testes in patients following repair of varicocele [28, 29]. Kass and Belman [30] demonstrated that 80% of patients with clinical varicoceles of grades II and III would have hypertrophy of the ipsilateral testis following varicocele surgery with an average follow-up of 3.3 years. This has also been studied by Culha et al. [31] who showed that both the ipsilateral and contralateral testicular volumes increased significantly after operation in patients with grade II and III varicoceles. The right testicular volume showed more improvement than the left in the majority of patients [31]. This has further been proved by Yamamoto et al. [32] in their study. In a similar study on the effects of varicocele treatment on testicular size, Saka moto et al. [33] followed 44 males with clinical varicocele who underwent varicocele surgery. The mean volume of the ipsilateral testes was significantly higher after repair of the varicocele [33]. However two studies from the United States showed no evidence of progression of hypotrophy in the long-term follow-up of adolescents with varicoceles and no correlation of hypotrophy with the grade of varicocele [34, 35].

**Semen Abnormalities**

Varicocele is associated with impairment in spermatogenesis mainly in the form of low or absent count (oligozoospermia), decreased sperm motility (asthenozoospermia) and abnormal sperm morphology (teratozoospermia) in infertile males presenting with varicoceles. These abnormalities can occur in isolation or in combination (known as oligoasthenoteratospermia or OAT syndrome). This effect was first described in 1965 by MacLeod [36] who described the above seminal abnormalities in patients with varicocele. He also introduced the concept of ‘stress pattern’ of semen analysis based on the presence of more than 15% tapered forms of sperms. These deranged semen qualities associated with varicoceles can be found in adolescents as early as 17 years of age [37]. A number of mechanisms have been attributed to semen abnormalities.

**Increased Scrotal Temperature.** The spermatic veins leaving the testicles form a communicating meshwork of veins (the pampiniform plexus) that encircle the arteries. This produces a counter-current heat-exchange mechanism to cool the arterial blood as it enters the testicles [38]. This mechanism is abolished in patients with varicocele causing elevated scrotal temperatures. This will eventually lead to an abnormal elevation in temperature in the intratesticular microvascular blood and interstitial fluid with the subsequent increase in the metabolic activity leading to depletion of the intracellular glycogen with the resultant testicular injury [39]. Furthermore, spermatic enzyme activity controlling DNA synthesis and polymerase activity function optimally at 33–34°C and therefore are inhibited at higher temperatures [40]. This can be reversed after varicocele surgery [41].

**Oxidative Stress (OS).** There has been great emphasis recently on the role of OS on the pathogenesis of infertility in patients with varicocele. Reactive oxygen species (ROS) are produced in a controlled fashion in living aerobic cells. These ROS are usually counteracted by antioxidants. Excessive and uncontrolled production of ROS by seminal leukocytes or abnormal sperms result in an oxidative stress status causing impaired sperm viability and motility and increased mid-piece sperm defects impairing sperm capacitation and acrosome reaction [42–44]. In addition, ROS can lead to DNA damage. ROS are also positively correlated with a sperm deformity index calculated by dividing the total number of deformed sperms by the number of sperms evaluated. Human spermatozoa are particularly vulnerable to ROS injury owing to the excess polyunsaturated fatty acids in these cells [45, 46]. Smith et al. [47] found that infertile males have lower levels of antioxidants in their seminal plasma than fertile males. In a study by Pasqualotto et al. [48] infertile men with varicocele were found to have higher levels of ROS than healthy fertile individuals. In addition, they were found to have less total antioxidant capacity. Sakamoto et al. [49] studied the levels of the oxidative stress markers, nitric oxide (NO), 8-hydroxy-2-deoxyguanosine (8-OHdG) and hexanoyl-lysine (HEL), and the antioxidant capacity of glutamate peroxidase, catalase and superoxide dismutase (SOD) from the seminal plasma in infertile patients with or without varicocele, and the effect of varicocele repair on these levels. Patients with azoospermia or oligospermia were found to have higher HEL and SOD activity, and those with varicocele had significantly higher levels of NO, HEL and SOD in their seminal plasma. However the seminal plasma level of 8-OHdG was not significantly different between patients with and without varicocele. Furthermore varicocele treatment resulted in a marked increase in the concentration of sperms and significant decrease in the levels of NO, HEL and 8-OHdG levels and SOD activity [49]. In a similar study
by Ishikawa et al. [50], the expression of 8-OHdG in the seminiferous tubules was more prevalent in patients with varicocele, and it correlated with the grade of the varicocele being 38, 41 and 57% for grades I, II and III, respectively. Furthermore, increased NO production was found to be associated with enlargement of the varicocele which in turn adversely affected testicular function [51].

**Leydig Cell Dysfunction**

Leydig cell dysfunction is caused by interstitial fibrosis which leads to diminished intratesticular levels of testosterone. However the serum levels of FSH, LH and testosterone are not particularly abnormal in patients with varicocele [52, 53]. Patients with unilateral varicocele have exaggerated levels of FSH and LH following stimulation with GnRH with normalisation of these responses following varicocele treatment [54]. In addition, Kass et al. [55] found that exaggerated responses of FHS and LH to GnRH may indicate irreversible testicular parenchymal damage to both Leydig cells and the germinal epithelium.

Patients with unilateral varicocele and infertility were found to have histological changes in the contralateral testis as well in the form-impaired spermatogenesis, degenerative changes in the Sertoli cells and Leydig cell atrophy [56]. In addition, bilateral testicular atrophy in patients with varicocele is a marker of significant impairment of spermatogenesis [57].

**Clinical Presentations**

The majority of varicoceles are asymptomatic. Most of the patients usually present with painless scrotal swelling. Only a minority of patients present with a dragging pain or discomfort.

Physical examination of the patient should be carried out in a private environment. The examination should be repeated both in the supine and standing position and with and without Valsalva manoeuvre to detect small varicoceles. The description of ‘bag of worms’ is usually applied to varicoceles which present as a compressible mass above and occasionally surrounding the testicles.

A complementary part of the physical examination includes assessment of the testicular size and consistency. Measurement of the testicular size is usually achieved with the use of either Prader or disk orchidometer comparing the sizes of both testes. The difference in size should be confirmed by two sequential measures at 12-month intervals [58].

**Investigations**

**Seminal fluid analysis** can give an indication of the degree of impairment of testicular function. However semen analysis does not predict future infertility [59].

**Hormonal analysis** including serum testosterone and FSH and testosterone response to intravenous injection of human gonadotropin (GnRH stimulation test) is not used in the routine workup of patients with varicocele as a result of the low sensitivity and specificity [60]. GnRH stimulation test can predict the hormonal abnormalities associated with the presence of varicocele [61]. Furthermore, in a study by Guarino et al. [62], these hormonal assays were found to be good predictors of infertility.

**Ultrasound** identifies varicoceles as anechoic tubular structures that expand on Valsalva manoeuvre. It can also be used to measure the testicular volume.

**Colour-flow Doppler ultrasonography** defines the anatomic and physiologic aspects of varicoceles in real-time. The colour of the signal identifies the reflux flow in the pampiniform plexus of veins. Clinical varicocele is defined as the presence of 3 or more veins, with one of them having a minimum resting diameter of 3 mm or an increase in venous diameter with the Valsalva manoeuvre [63]. Colour Doppler ultrasound can also be used to predict the outcome of microsurgical subinguinal varicocelecmy [64].

**Venography** can identify the enlargement of the pampiniform plexus with reflux of blood into its tributaries. In addition, it can identify collateral vessels and the incompetent valves. However this method has largely been replaced with other tests that are less invasive, less time-consuming and have lower exposure to radiation [65].

Further investigations should be warranted in elderly patients with sudden onset of varicocele, right-sided varicoceles and a varicocele that is not reduced in the supine position to exclude intra-abdominal pathology. This is usually done with the use of abdominal ultrasound or CT scan [65].

**Treatment**

Varicocele treatment is indicated in patients who are investigated for infertility and who are symptomatic (painful scrotum) [66]. There is strong evidence that varicocele surgery restores testicular volumes and semen parameters [67]. In a recent meta-analysis by Marmar et al. [68], varicocele surgery was associated with improvement in the rates of spontaneous pregnancies in couples with
an impaired semen quality and a palpable varicocele in the male partner. Two other studies demonstrated a significant increase in spontaneous pregnancy rates following varicocele repair in infertile males \[69, 70\]. However there is no strong evidence that treatment of varicocele in sub-fertile males can improve the spontaneous pregnancy rates \[71\]. Patients should be carefully counselled about all the treatment alternatives including the risks and failure rates.

The treatment of varicoceles shows a great deal of contradiction among various guidelines. The American Urology Association recommends varicocele treatment in males who meet the following criteria \[72\]: (1) grade II or III varicoceles; (2) abnormal semen parameters (OAT syndrome pattern); (3) the couple has a documented infertility; (4) the female counterpart has a normal or potentially correctable cause of infertility.

The European Urology Association guidelines on the other hand recommend treatment of varicocele only in the presence of progressive failure in testicular development. However they do not support the role of varicocele treatment as a modality for the management of infertility \[73\]. The National Institute of Clinical Excellence of the United Kingdom has gone further and does not recommend varicocele treatment for infertile males \[74\].

**Transvenous Varicocele Embolisation**

Transvenous varicocele embolisation involves selective catheterisation of the internal spermatic vein(s) followed by occlusion with either a sclerosant (sodium tetradecyl sulphate) or solid embolic devices (stainless steel or platinum coils). This procedure is minimally invasive and performed on an outpatient basis under local anaesthesia. It is regarded as an effective and valuable alternative to surgery due to its safety and effectiveness \[75\].

With the patient in the supine position and gonads shielded from irradiation, the internal jugular or common femoral veins are punctured under ultrasound guidance. Using the Seldinger technique, an appropriate catheter (typically 5–7 Fr in size) is used to select the left renal vein. The catheter is advanced retrogradely down the internal spermatic vein to just above the inguinal ligament level. Venography is performed to document the position of the catheter and to demonstrate any collateral circulation. Subsequently embolisation is performed using either material. The ‘sandwich’ technique refers to the use of a combination of coils and sclerosant, whereby the coils are placed in the distal internal spermatic vein just above the inguinal ligament level. The purpose of the coils is to prevent reflux of sclerosant into the pampiniform plexus. Sclerosant is then injected slowly along the length of the internal spermatic vein while withdrawing the catheter, followed by placing coils in the cephalad internal spermatic vein.

This procedure is associated with success rates of 92.4–96% with recurrence rates of less than 2–4% \[76\]. The complications as a result of this procedure are found in 0.3–2.2% of patients and are composed of testicular atrophy, scrotal haematoma, thrombophlebitis and coil migration. The failure rate for this procedure is around 15% \[59\].

**Open Surgical Approach**

This approach can be performed using different methods. The basic principle is to identify and ligate the dilated veins.

The subinguinal (Marmar) method is a small incision made just below the level of the external inguinal ring. The spermatic cord is identified, freed from the overlying fascia and exteriorised. The external coverings of the cord are incised and the vessels are identified. With the use of loupes, the spermatic veins are isolated from the rest of the cord structures. Later, the veins are double-ligated with a non-absorbable suture. The artery is preserved in this method. Shindel et al. \[77\] showed a significant relationship between the number of veins ligated and the improvement in sperm motility postoperatively. This method is associated with recurrence rates of 0–4% \[78\]. In a randomised controlled clinical trial, Al-Kandari et al. \[79\] showed that subinguinal microsurgery was more effective than open inguinal or laparoscopic varicocelectomy in terms of improvement in semen quality and pregnancy outcome.

The inguinal (Ivanissevich) method comprises an incision made between the internal and external inguinal rings parallel to the inguinal ligament. The spermatic cord is identified and mobilised. Large cremasteric veins are ligated. The coverings of the spermatic cord are opened and the spermatic vessels are exposed. The spermatic artery is isolated and the dilated veins are double-ligated using a non-absorbable suture and divided subsequently \[80\]. This approach is associated with 13.3% recurrence rates \[81\].

The retroperitoneal (Palomo) method uses a small horizontal incision made medial and inferior to the anterior superior iliac spine, 2 cm to the internal inguinal ring. After dissecting the subcutaneous tissues, the external oblique fascia is identified and incised in the direction of its fibres. Subsequently the internal oblique and transversus abdominis muscles are opened using a blunt-tipped
instrument to expose the retroperitoneal space. The spermatic vessels can be identified lying against the peritoneal reflection. The veins are subsequently ligated and divided using non-absorbable sutures with attempts made to preserve the artery [80]. This approach has a recurrence rate of 29% [81].

Laparoscopic Approach
The laparoscopic technique typically involves 3 ports. The initial camera port is placed at the umbilicus and additional ports are placed lateral to the rectus muscle. The spermatic veins are flattened by the pneumoperitoneum and therefore the artery appears more tubular than surrounding structures. After incising through the posterior peritoneum the veins are clipped and transected. This approach has a recurrence rate of 3–7% [82].

The most common complication of the approaches mentioned above is testicular atrophy secondary to arterial damage.

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