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REVIEW ARTICLE

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Varicocele and male infertility : current status

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Abstract

The role of varicoceles in the etiology of male infertility continues to be controversial. Due to the numerous variables that impact the outcome of varicocele surgery, the results of various trials are often contrary. Recent studies at the molecular level have demonstrated that varicoceles can cause testicular nuclear DNA damage, apoptosis, and raised levels of reactive oxygen species. Clinical studies have shown that varicocele surgery can improve semen quality sufficient to downgrade the type of ART procedure required, can result in the appearance of sperm in the semen in some cases of non-obstructive azoospermia, and can reverse testicular growth retardation in cases of adolescent varicocele. Hence, despite contradictory clinical results, the best practice guidelines of many associations recommend varicocele surgery in men with sub-fertile semen, clinically evident varicoceles, and infertility. Ultrasonography to detect sub-clinical varicocles is not advocated. Medical therapy may help some men with mild to moderate varicoceles. Older technics of varicocele surgery by mass ligation or non-magnified dissection are associated with higher rates of recurrence, testicular artery damage, and hydrocele formation, as compared to microsurgical methods in which every vein is individually identified and ligated, while preserving the arteries and lymphatics. Laparoscopic ligation is no longer recommended.

Key words: varicocele, surgery for varicocele, medical treatment for varicocele, male infertility

Introduction

A varicocele is an abnormal dilatation and tortuosity of veins of the pampiniform plexus that drain the testis. It occurs within the spermatic cord and can be palpated on physical examination. Almost all varicoceles are detected after puberty and there is a prevalence of about 11-15% among adult men [1,2].

The testicular vein drains into the renal vein on the left side and into the inferior vena cava directly on the right side. This follows the arterial supply to the testis and is a reflection of its embryologic origin close to the kidney. Venous valves are more often absent on the left side than the right, and the left vein may also suffer compression under the superior mesenteric artery and the aorta [3,4]. These factors have been proposed to be responsible for the preponderance of left sided varicoceles (90%) compared to bilateral varicoceles (10%). Isolated right-sided varicoceles are rare and should prompt investigations to rule out a primary pathology such as a renal cell cancer or retroperitoneal nodes.

Varicoceles detected on a physical examination in the erect position are called clinical varicoceles. They are graded from 1 to 3 in severity, with those felt only on a Valsalva maneuver being grade 1, those felt without a Valsalva maneuver as grade 2 and directly visible, grossly dilated, tortuous veins as grade 3. Varicoceles which are not clinically evident, and are diagnosed only by an investigation such as color doppler ultrasonography, scintigraphy, venography or plethysmography are termed subclinical. However, in obese men or in men with hydroceles or scrotal inflammation, it may be difficult for even experienced clinicians to diagnose a varicocele confidently, and in such cases a doppler ultrasound study may be used to supplement a strong clinical suspicion. Such varicoceles should not be called sub-clinical.

Varicoceles are considered to be the commonest correctable cause of male infertility [5]. Their incidence among infertile men is 20-40% – about three times greater than in the general

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population [6]. The mechanism by which varicoceles affect testicular function remains unclear. The most commonly accepted hypothesis is that varicoceles result in an increase in testicular temperature that suppresses spermatogenesis [7,8]. Other proposed causes are reflux of adrenal and renal metabolites, and decreased blood flow with stasis.

Varicoceles as a cause of male infertility have been the subject of fierce debate. There are a number of issues that fuel such debate. Many men with varicoceles are fertile. On the other hand, since varicoceles are so common, a varicocele may be coincidentally – but not causatively – present in an infertile man. Thus, not all varicoceles cause infertility and not all need correction. There have been severely discordant results in the literature regarding the benefits of varicocele surgery in men with infertility. Finally, there is no universally accepted theory on the mechanism of action of varicoceles in inhibiting fertility. In this review article, we look at these issues and suggest a scientifically acceptable course of action.

Problems with varicocele studies

There are several reasons why it is difficult to find good data on the outcome of varicocele surgery.

Semen analysis is used as a surrogate marker for the fertility potential of the male. The WHO has recommended values for semen parameters that establish that a male is fertile [9]. Unfortunately, the predictive value of these parameters is limited. Smith *et al* [10]. reported that up to 25% men with sperm densities below 12.5 million/mL could father a child through spontaneous conception. On the other hand, even with counts of up to 25million/mL, which is normal by the WHO standards, 10% of men could not father a child with a fertile female [5]. These findings suggest that there may be parameters other than those assessed during a routine semen analysis that affect pregnancy and study outcomes based solely on improvement of semen parameters are not enough. Semen parameters themselves tend to show a wide variation among the same individual through the day, week, month and season. The use of one, or even two, semen analyses may thus not be representative of the true fertility potential of an individual [11]. Finally, there is enormous variation in the quality of semen analysis reported by various laboratories.

A more effective outcome parameter would be pregnancy rates since pregnancy is the ultimate end-point of therapy. When using pregnancy as the end-point of treatment outcome, it is important to consider the spontaneous pregnancy rate in supposedly infertile couples on no therapy [12]. The spontaneous pregnancy rate is about 1% per month, reaching cumulatively to 26% over 3 years [13]. Obviously, any treatment option being used should improve upon this result. On the other hand, the benefit from an intervention like varicocelectomy may be neutralized by a concomitant untreated female factor.

Good clinical trials require a placebo-controlled, double-blind format. Such a trial, with sham surgery, is ethically impossible in humans. Moreover, randomization on a large scale for such surgeries is also difficult due to the intense social pressure and stress faced by infertile couples resulting in them seeking early intervention. In Germany, during the course of a multicenter, prospective, randomized trial on radiological embolization of varicoceles, only 67 patients could be randomized in 3 years against a target of 460 [14]. Further, follow-up is a major problem amongst individuals affected by infertility since they are a young and mobile population. Varicocelectomy results are incremental and pregnancies may occur even 2 years after the surgery. It is rare to find trials that are able to provide extensive and close follow-up. Thus, in another study on surgically treated varicoceles, only 130 out of an original 480 patients remained in the study at the end of one year[15].

Pathophysiology of varicocele

In order to accept that there can be clinical benefit from treating varicoceles for infertility, there must exist an acceptable hypothesis for their deleterious effects. Earlier studies dealing with changes in scrotal temperature did not clearly indicate how this actually affected local physiology and biochemistry. Recent laboratory work has demonstrated various changes that may occur at the molecular level due to the effect of varicoceles.

Nuclear DNA damage and high oxidative stress

There is increasing interest in the role of reactive oxygen species (ROS) and oxidative stress in the causation of male infertility. ROS consist of highly reactive oxygen radicals such as the superoxide anion (O_2^-), hydroxyl radical (OH^-) and the hypochloride radical (^-OHCl). Controlled generation of ROS is essential for all aerobic life and they function as signaling molecules (secondary messengers) in various cells. However, their uncontrolled production is detrimental to cell function and there exists a large battery of cellular molecules called antioxidants that protect the cell from excessive ROS-induced lipid peroxidation [16].

Human spermatozoa are among the various cells capable of generating ROS [17]. Excessive generation of ROS with inadequate compensatory rise in anti-oxidants is called oxidative stress. Oxidative stress may also be generated by deficiency of anti-oxidants without a change in the ROS levels. ROS cause damage to cell membranes by peroxidation of their lipid content. Spermatozoa are particularly susceptible to oxidative stress-induced damage because of the large polyunsaturated fat content in their membranes [18]. Oxidative stress is also responsible for damage to the DNA structure of the spermatozoa [19].

Men with high levels of ROS may have a lower fertility potential compared to those with low ROS [16,18]. Of the patients attending an infertility clinic, 40% have detectable levels of ROS formation in their semen and 25% have levels higher than the normal limits [20]. ROS are detectable in the neat, unwashed semen samples of normal fertile men at a median concentration of 0.029 $x10^6$ counted photons per minute (cpm) by the chemiluminescence technic [21]. Levels above this are considered abnormal. Varicoceles have been evaluated as one of the potential causes of increased ROS and oxidative stress. This may, in fact, be one of the main mechanisms of action of varicoceles in inducing subfertility. In an experimental study on rats, surgical creation of varicoceles resulted in elevated levels of ROS compared with sham rats [22]. Another clinical study found higher ROS levels in both fertile and infertile men with varicoceles compared with men without varicoceles, suggesting that varicoceles cause oxidative stress [23]. Saleh *et al* [24] evaluated the levels of oxidative stress and sperm DNA damage in 31 infertile men with varicoceles and 16 fertile controls in a prospective study. Sperm DNA fragmentation index (DFI), levels of seminal ROS and total antioxidant capacity (TAC) were assessed using the sperm chromatin structure assay, chemiluminescence assay and enhanced chemiluminescence assay, respectively. Patients with varicoceles had significantly higher DFI and lower ROS-TAC scores than controls. The authors concluded that spermatozoal DNA damage in men with varicoceles was possibly related to high levels of seminal oxidative stress. Mostafa et al [25] investigated whether surgical correction of varicocele might reduce ROS or increase the antioxidant capacity of seminal plasma from infertile patients with varicoceles. In the study group of 68 patients with varicoceles, they reported a statistically significant reduction in the 3-month post-operative levels of ROS with a further significant reduction after another 3 months. They also noted a rise in 4 of the 6 antioxidants tested.

Apoptosis

ROS may also act through induction of apoptosis. In an experimental rat model, including a sham surgery group, surgical creation of a varicocele resulted in increased rate of apoptosis, suggesting molecular alterations that may involve ROS overproduction as the triggering mechanism [26]. In another study, Barqawi et al [27] created a left varicocele by partial ligation of the left renal vein in 17 adult male Sprague-Dawley rats. Five rats were sham surgical controls; another 5 rats that underwent non-surgical or other intervention served as a control group. Germ cell apoptosis was confirmed by cellular ultrastructure evaluation using transmission electron microscopy. Compared with control animals, a statistically significant increase in the number of apoptotic germ cells per tubular cross section was noted following varicocele creation in the ipsilateral testis. The association of apoptosis and varicoceles, mediated through ROS, was further suggested in a study that showed apoptosis could be prevented by the introduction of intraperitoneal melatonin in rats with surgically created varicoceles [28].

Hormonal abnormalities

Varicoceles may also affect the local hormonal milieu within the testis. Anti-mullerian Hormone (AMH) and inhibin B are reliable markers of Sertoli cell function. In a large study of 124 boys, 62 with grade II or III varicocele and 62 controls, inhibin B levels were higher in prepubertal patients with varicocele than in controls [29]. Similarly, AMH levels were higher in pubertal boys with varicoceles than in the controls. This altered serum profile of gonadal hormones in boys with varicoceles may indicate an early abnormality in the regulation of the seminiferous epithelial function.

In the adult, varicoceles may have an effect on the serum testosterone levels and thus affect fertility. In a study of 83 infertile men treated for varicoceles, mean serum testosterone concentration rose after embolization by 43% while the free testosterone concentration rose by 72% [30]. This was associated with a significant increase in the mean sperm concentration, motility and morphology.

Others

Elevated nitric oxide (NO) may be another mechanism of injury in varicoceles, independent of other free radicals. Turkyilman et al [31] evaluated 26 adolescents, 13 with a left varicocele and 13 healthy children as controls. While the peripheral NO levels were the same in the study and control groups, spermatic vein NO levels were elevated significantly (compared with the peripheral levels) in the study group.

Finally, in a rat model, Kilinc et al [32] have shown that varicoceles are associated with local testicular hypoxia and related pathophysiologic events such as angiogenesis.

Evidence favoring treatment of varicoceles

A variety of studies, addressing different clinical situations, have suggested that correction of a varicocele can be beneficial.

Improved semen parameters and spontaneous pregnancy following treatment

One of the earliest papers suggesting a possible role for varicocelectomy in the management of male infertility reported the return of sperms in the ejaculate of azoospermic men [33]. Numerous studies have subsequently attested to the role of this procedure in the management of an infertile male [34-38].

Dubin and Amelar [34] published a number of articles and consolidated their series of 986 cases followed-up for over 2 years. They noted an improved semen quality in 70% with a 53% pregnancy rate. Matthews et al [36] treated 78 men with varicoceles and either azoospermia or severe oligospermia and reported pregnancy in 31%, including 19% spontaneous conceptions. Marmar and Kim [37], one of the early proponents of the subinguinal microsurgical technic, reported their experience of 606 surgeries on 466 patients. The one-year pregnancy rate was 35.6% compared to 15.8% for 19 medically treated men with varicoceles. Kumar and Gupta [38] used a similar technic in 100 patients. In the 50 in whom there was adequate follow-up there was a 34% pregnancy rate. Another group of 272 patients with clinical varicoceles were reported to have a significant improvement in sperm count and sperm motility in nearly all cases [39]. In a report on 150 patients with infertility and varicoceles, 80% showed an improvement of semen analysis and 46.3% achieved a pregnancy [40]. Pregnancy may occur up to 2 years after surgery [41].

In a Japanese study, 64 infertile male patients with clinical varicoceles were offered surgery or conservative follow-up [42]. Thirty one underwent surgery and had a pregnancy rate of 60% compared to 28% in the group on conservative follow-up. While evaluating the effect of varicocelectomy in 90 patients with varicoceles, Kibar et al [43] reported a significant improvement in density, motility and sperm morphology evaluated using the Kruger classification. In a direct comparison with medical therapy, 146 men with primary infertility and palpable left varicoceles underwent surgery while another 62 men who refused surgery were treated with tamoxifen [44]. After a year of follow-up, pregnancy was achieved in 46.6% of the surgery group and only 12.9% of the medical therapy group. Overall 83.2% of the operated men had improved semen parameters compared to 32.3% of the controls.

These studies have looked at a variety of parameters including semen analysis and pregnancy rates. However, they have varying inclusion criteria and treatment methods as well as differing end-points and do not qualify as ideal scientific evidence. In one of the few randomized, controlled trials on the effectiveness of varicocelectomy, Madgar et al [45] prospectively randomized 45 patients to undergo varicocelectomy at diagnosis or after 1 year of observation. Clinical grade 2 and 3 varicoceles were included and patients in either arm who failed to conceive after 1 year were crossed over to the other arm. Even though the study used a high ligation technic for surgery, they noted a 60% conception rate among surgery group versus only 10% in the controls. A large study reported a one-year pregnancy rate of 34.8% after varicocele surgery and only a 16.7% pregnancy rate in the control non-operated group [46].

Down staging and improving results of ART

Varicocelectomy may be useful not just in initiation of spontaneous pregnancy but also for downgrading the level of assisted reproductive therapy required. Cayan *et al* [47] evaluated a cohort of 540 infertile men with clinical varicocele who underwent microsurgical varicocelectomy. The total motile sperm counts were evaluated for each patient preoperatively and postoperatively and the patients were divided into 4 groups according to the type of assisted reproductive technology for which they qualified: 0 to 1.5 million - intracytoplasmic sperm injection (ICSI); 1.5 to 5 million - in vitro fertilization (IVF); 5 to 20 million - intrauterine insemination (IUI); 20 million or greater - possibility of spontaneous pregnancy. These men were followed more than a year postoperatively for alterations in semen quality and conception. An overall spontaneous pregnancy rate of 36.6% was achieved after varicocelectomy with a mean time of 7 months for conception. Another 31% who preoperatively were assessed as suitable for IVF or ICSI improved enough to become candidates for IUI, while 42% of the IUI candidates gained the potential for spontaneous pregnancy.

Surgery may also help improve the results of assisted reproduction technic. In a study of 58 patients with a varicocele, patients undergoing varicocelectomy prior to IUI had higher pregnancy rates than those who had no varicocelectomy [48]. The authors also noted that while there was no significant improvement in the semen parameters in the two groups, the improved pregnancy rate may be an indicator of improved sperm function, a parameter not evaluated on routine semen analysis.

Improved testicular size and fertility in adolescents

Another source of information on the need for varicocelectomy is studies documenting an improvement in testicular size and fertility following surgery in adolescents with varicocele [49-53]. In 117 adolescent boys, Thomas and Elder [49] assessed whether testicular growth arrest is related to varicocele size. They also evaluated the impact of non-operative management in boys who had similar sized testis at presentation. They found that boys with a varicocele were at significant risk for testicular growth arrest irrespective of varicocele size, and those with a grade 3 varicocele had a higher risk of testicular growth arrest. Moreover, among boys with testes of same size at diagnosis, growth arrest was observed during adolescence in approximately 25%, irrespective of varicocele size. In an elegant study comparing testicular sizes among fertile and infertile men, with and without varicoceles, Pinto et al [52] noted that varicoceles were associated with a significant reduction in testicular size. However, they were unable to demonstrate any difference in size between fertile and infertile men. The testicular atrophy rate may also increase with increasing grade of the varicocele and may be associated with a compensatory hypertrophy of the contralateral testis [54].

Koyle et al [55] report their experience of 103 cases where 84 were operated for ipsilateral testicular hypotrophy. At one-year follow-up, 64 of 78 testes (82%) demonstrated "catch-up" growth and there was no evidence of further testicular loss in the others. In terms of fertility preservation, there are a number of studies that document the benefit of varicocelectomy [56-58].

Evidence against treatment of varicoceles

While the above studies attest to the need for varicocelectomy in correcting infertility, there have also been many studies that doubt this cause-and-effect relationship. Schlesinger et al [59] reviewed controlled studies comparing varicocelectomy with no treatment but found that most studies were either not randomized, not properly controlled, or had various design flaws. Evaluated outcomes included sperm density, motility, morphology and pregnancy rates. Out of a total of 16 studies involving 1077 patients, 12 studies incorporating 859 patients, reported a statistically significant improvement in sperm density following varicocelectomy. Out of 12 studies with 1010 patients, 5 studies involving 715 patients, showed a statistically significant improvement in motility, while 5 out of 10 studies demonstrated statistically significant improvement in morphology. Pregnancy rates ranging from 0-63% (average 32.24%) were reported in 65 studies involving 6983 patients. Based on this data the authors stated that "in spite of the occasional study which indicates that varicocelectomy does not improve infertility, the preponderance of the literature does in fact support a favorable effect". However, the authors' final conclusion was that "a definitive statement concerning the efficacy of varicocelectomy cannot be made".

In a well-designed, prospective, randomized study Nieschlag et al [60] evaluated 95 infertile couples with varicoceles that underwent varicocelectomy / radiological embolisation versus counseling. While the intervention group showed significant improvement in sperm density, there was no improvement in pregnancy rates. A subsequent follow-up on this set of patients evaluated 125 men including 62 who underwent therapy for varicoceles [61]. The pregnancy rate in the treated group was 29% versus 25% in the controls.

More vehement denouements of varicocelectomy have been made in a series of articles based primarily on the Cochrane database reviews. Three such reviews have been published. The first publication in 2001 included trials from the Cochrane Menstrual Disorders and Subfertility Group's specialized register of controlled trials [62]. The authors also conducted a MEDLINE search for the period 1966-2000 and a hand-search of 22 specialist journals in the field from their first issue till 2000. Cross-references and references from review articles were checked. Randomized, controlled trials were included if they reported pregnancy rates as an outcome measure, and if they reported data in treated (surgical ligation or radiological embolization) and untreated groups. Only six studies met the inclusion criteria for this review including one that was a follow-up of a previous study. The authors expanded this report in 2003 when they published an article in the Lancet [63] with two additional studies and again in 2004 [64] when they further added one study. After a review of all these studies, the authors concluded that "varicocele repair does not seem to be an effective treatment for male or unexplained subfertility" [63].

Since the Cochrane database is supposed to assess the best evidence available, it is important to look at these reviews carefully.Unfortunately, these reviews cannot be taken as authoritative. Of the eight studies, two included men with normal semen parameters [65,66] and another three included men with subclinical varicoceles [67-69]. Neither of these is considered an indication for varicocelectomy and hence their results are irrelevant to a discussion on this subject. Of the remaining three, one study that aimed at including 460 men from 15 centers could recruit only 67 patients after three years [14]. There remain two studies that satisfy the criteria of being randomized, controlled trials involving men with clinical varicoceles and sub-fertility, the currently accepted indications for surgery. Out of these two, one study showed a 60% pregnancy rate in the treated group compared with 10% in the controls [45]. The second study, by Nieschlag et al [60,61], failed to show a pregnancy rate improvement in the treated group. However, of the 62 patients treated, about half were embolized with histacryl glue, a modality that has not been shown to be of consistent benefit. Another half had high ligation of the veins, which is a procedure associated with higher failures than the microsurgical technic. The mean age of men and women in this study was 32.8 and 30.5 years respectively. The fertility potential at this age is per se lower and may be the reason why there was no improvement in the pregnancy rates though there was an improvement in the semen parameters. In view of these drawbacks, the conclusions of the authors can only be considered tentative.

Consensus recommendations

It is clear that the issue of whether varicoceles should be treated is far from resolved. However, to completely deny a role for varicocele surgery in the management of male infertility is also not justifiable. It is important to take a balanced approach and judge each case on its merits. In view of these issues, the American Urological Association and the American Society of Reproductive Medicine have suggested clear guidelines for the evaluation and management of these patients [70,71]. These guidelines state that a varicocele should be corrected because:

1) Surgery has the potential to reverse a pathological condition.
2) Surgery improves semen parameters in the majority.
3) It may possibly improve fertility.
4) The risks of treatment are small.

Before choosing a patient for varicocelectomy, it is also important that certain basic requirements be met. A varicocele should be corrected when:

1) It is clinically palpable.
2) The couple has infertility.
3) The female partner is fertile or has correctable infertility.
4) At least one semen parameter is abnormal.

In view of the variability in semen quality, we would like to add that at least two, and preferably more, semen analyses done at regular intervals should show a persistently low or declining semen quality before a patient is advised surgery. It is not uncommon to find patients who have been advised surgery on the basis of a single report of abnormal semen analysis, showing normal second semen analysis is without any intervention.

Medical therapy

Having established that a varicocele does have some role in the pathogenesis of male infertility, it is important to evaluate the status of various therapeutic options available for its management. A review of the pathogenesis of testicular abnormalities in patients with varicoceles would suggest that some of these should be amenable to medical therapy with drugs such as antioxidants and anti-inflammatory agents. Cavallini et al [72] compared an NSAID (cinnoxicam) with surgery in various grades of varicocele in 153 patients. They found cinnoxicam improved semen quality in grade III, but not grade IV or V, varicoceles. Stopping the drug caused a return of semen parameters to baseline levels. In an experimental study on rats, vitamin E supplementation was found to have a beneficial effect on semen parameters in rats with artificial varicoceles [72]. Another experimental study on 30 rats with artificially created varicoceles showed some protective effect of melatonin, a potent free-radical scavenger, on testicular histopathology [73]. There are no randomized controlled trials on any drugs but they seem potentially useful and certainly do no harm while awaiting a definitive decision on surgery.

Surgical therapy

The aim of surgical intervention for varicoceles is the interruption of retrograde blood flow (reflux) into the pampiniform plexus. There are two basic approaches for achieving this. The first is the intravascular approach whereby the venous channels are cannulated and occluded using a variety of non-absorbable materials i.e. percutaneous embolization. The second approach involves external ligation of the veins using either open surgery or laparoscopy.

Percutaneous embolization

Percutaneous embolization using occlusive balloons or steel coils is a minimally invasive approach. The procedure may be performed in either a retrograde or antegrade manner. The retrograde technic involves puncture of the right femoral vein with introduction of a catheter into the testicular vein, opacification of the venous system under fluoroscopy and insertion of embolization material to occlude the vessel. Complications include migration of embolization coils, thrombophlebitis, arterial puncture, a high rate (up to 30%) of being unperformable, and a recurrence rate of 3-11% [74-77]. In the antegrade technic, the pampiniform plexus is punctured directly and a sclerosant is injected after confirming flow under fluoroscopy. The antegrade technic has a lesser operative time, lower unperformable rate and lower incidence of recurrence or persistence [78-81]. The complication rate of both the technics is only 3 to 8% but rarely, testicular artery injury may occur [79]. Both these technics involve radiographic exposure that may be deleterious to an already subfertile patient. Thus, while the two technics are low-cost and can be performed under local anesthesia in a day-care setting, they are probably more suitable for recurrent varicoceles since this would avoid difficult surgical exposure in a previously operated field and allow precise delineation of the vascular channels prior to their occlusion.

Surgical anatomy

It was traditionally believed that the testis was drained through a simple system of pampiniform plexus, vasal veins, and cremasteric veins whose tributaries end in a single vein. However, recent studies have shown the drainage to be considerably more complex. A study of 70 cadavers using resin casts of the gonadal vessels demonstrated that the testicular vein invariably divides into medial and lateral divisions at the level of the fourth lumbar vertebra; the main medial branch terminates in the renal vein on the left side and the inferior vena cava on the right side while the lateral branch communicates with the colonic and renal capsular veins [82]. Communications between the medial trunk and ureteric vessels were demonstrated, as well as anastomoses between the two medial trunks across the midline in more than 50% of cases. High ligations above the 4th lumber vertebra may thus be prone to failure.

Three surgical approaches have been used: conventional open (retroperitoneal high ligation or inguinal ligation), laparoscopic, and microsurgical.

Conventional open surgery

Conventional open high ligation of a varicocele continues to be the most common technic employed with minor modifications in the form of optical loupe magnification. The major advantage of this approach is its low-cost and universal applicability with no requirement of laparoscope, microscope or fluoroscope. However, it is also associated with a higher incidence of failure and complications. High retroperitoneal ligation as per the Palomo's technic [83] is prone to a higher recurrence rate for the anatomical reasons explained above. Mass ligation increases the chances of damage to the testicular artery (which may reduce the chances of improvement), while occlusion of lymphatics often causes hydrocele formation. The large incision and the need for significant retraction add to the postoperative discomfort.

Laparoscopic ligation

A few years ago laparoscopic ligation of varicoceles was very popular. However, like the conventional high retroperitoneal ligation, ligation at this level is associated with high recurrence rates of upto 45%; there is also risk of arterial injury [84]. Failure is probably related to the ligation of only large visible veins while smaller peri-arterial veins are not touched. Similarly, dilated cremasteric veins and cross-communications are not ligated in this procedure. Although the laparoscope offers some degree of magnification, it is much less than what is achieved by the operating microscope. The instruments are not as fine as microsurgical instruments and the surgery does not offer the level of precision that open microsurgery does. Other complications such as hydroceles are also more common due to simultaneous ligation of lymphatics with the veins [77,84]. The procedure is also associated with the possible complications of transperitoneal laparoscopy such as injury to the bowel, vessels and ileus.

Microsurgical ligation

Microsurgical varicocelectomy has become established as the procedure of choice due to its high success rate and low morbidity [36-38,84-86]. It can be performed as an out-patient procedure requiring 25-45 minutes operating time per side. Microsurgical dissection affords distinctly better visualization of the cord structures. Testicular arterial injury has been shown to be associated with a risk of testicular atrophy [74] and this can be avoided by its clear visualization under the microscope. Moreover, the magnification used actually permits repair of the testicular artery, if accidentally injured during surgery [87]. It also enables separation and preservation of the lymphatics from the veins leading to lower postoperative hydrocele formation, while at the same time allowing better identification of all the veins to avoid varicocele recurrence.

Hence, currently microsurgical sub-inguinal varicocelectomy with a special effort to preserve the testicular artery and lymphatics is considered the surgical gold standard since it has the lowest rates of recurrence, testicular atrophy, post-operative hydroceles, and causes the least morbidity as no fascial or muscular planes are opened [83]. This statement also holds true for surgery on adolescent varicoceles when compared with published results of the retroperitoneal, mass-ligation technic, which has a 15% overall complication rate and a 7-9% hydrocele occurrence rate. Schiff et al [88] reported that the microsurgical subinguinal approach offered less morbidity, with a 1% hydrocele rate.

Predictors of success of intervention

It is clear that only a certain proportion of men who are suitable for, and undergo this surgery, actually benefit from it. It would therefore be clinically relevant if the success or failure of surgery could be predicted from certain pre-operative parameters. A number of clinical and biochemical indices have been evaluated to answer this question.

Preoperative semen report

It seems quite logical that the initial semen analysis report would have an impact on the final outcome following surgery. In a review of 159 infertile couples that underwent microsurgical varicocelectomy, significantly higher spontaneous pregnancy rates (61% vs 8%) were observed in couples in whom the initial sperm concentration was greater than 5 million/mL compared to those in whom the initial sperm concentration was lower [89]. Marks *et al* [15] also reported that pre-operative semen parameters were important predictors of success. However, values of the parameters used by them were actually those that would be considered normal and therefore their patients may not really have been candidates for surgery. However, a more recent study reasserts the importance of baseline values in predicting success [90]. The issue of pre-operative semen reports brings forth another important issue in the management of varicoceles viz., the relationship between azoospermia and varicoceles.

The presence of complete, persistent azoospermia has special prognostic implications in the treatment of a varicocele. Since varicoceles cause a direct suppression of spermatogenesis, it is possible that the effect may be severe enough to cause azoospermia. However, most cases of varicocele are associated with oligozoospermia rather than azoospermia, and hence the etiological role of a varicocele in a man with persistent, total azoospermia has been controversial. Often, the presence of a varicocele in a man with azoospermia is coincidental: the azoospermia is either due to epididymal obstruction or due to complete testicular failure unrelated to the varicocele. Recently, however, there have been a few reports where varicocelectomy has resulted in return of sperm in the ejaculate of men with azoospermia, though only rarely in sufficient numbers to induce a spontaneous pregnancy [91,92].

Pasqualotto et al [91] reviewed the records of 15 azoospermic men who underwent testicular biopsy and microsurgical varicocelectomy for azoospermia. Forty-seven percent (7/15) men had return of sperm in their ejaculate following surgery with one establishing a spontaneous pregnancy. They noted that even a pre-operative biopsy showing germ cell aplasia was not a contraindication to surgery. However, the benefit was not sustained, with five of the seven relapsing to azoospermia after 6 months. In another retrospective review, Schelegel and Kaufmann [92] reported return of sperm to the ejaculate of 22% of 31 men who underwent microsurgical varicocelectomy. However, only 3 had adequate motile sperm in the ejaculate for ICSI while the rest still required testicular sperm extraction (TESE). The authors concluded that such men rarely have adequate sperm in the ejaculate after varicocele repair and most still need TESE. Cakan and Altug [93] reported 13 infertile patients who had complete azoospermia and clinical varicocele, and underwent inguinal varicocele repair. Induction of spermatogenesis was achieved in 3 (23%) patients. None could father a child spontaneously; nor did their sperm result in a successful ICSI. Matthews et al [36] obtained motile sperm in the semen of 12 out of 22 azoospermic men following varicocele repair; there were pregnancies (two unassisted and one following ICSI using ejaculated sperm). Only patients whose testicular biopsies showed hypospermatogenesis had motile sperm after surgery.

The role of varicocelectomy in non-obstructive azoospermia is unresolved. There are no well-defined predictors of success in this group of patients and while surgery may result in spontaneous conception, this eventuality is rare. Careful case selection (large varicocele, reasonable-sized testes and absence of other causes of infertility) with adequate pre-operative counseling is mandatory before considering this option.

Grade of varicocele

The size or grade of the varicocele has been used to predict the outcome of surgery. It has been suggested that the degree of spermatogenic defect and subsequent improvement is directly related to the grade of the varicocele [93]. Correction of larger varicoceles is more likely to produce significant improvement. On the other hand, sub-clinical varicoceles, detected purely on imaging investigations, should not be treated since there is no evidence to suggest that correcting these helps improve the semen parameters [70,71].

Testicular histology

The exact pattern of testicular histology associated with varicoceles has not been defined. Pasqualotto et al [95] looked at the pre-operative testicular histology to predict the surgical outcome in 60 patients who subsequently underwent a varicocelectomy. Twenty-eight patients had germ-cell aplasia while 32 had maturation arrest. They noted that while the postoperative increase in testicular size was greater in men with germ cell aplasia, pregnancy rate was higher in patients with maturation arrest. Their series of azoospermic men, however, reported benefit only in men with germ cell aplasia or maturation arrest, but no benefit in men with hypospermatogenesis [95]. This is contrary to the report by Matthews et al [36] who found greater benefit in men with hypospermatogenesis. There have been no studies that clearly demonstrate that testicular histology can predict success after varicocele surgery and, hence, testicular biopsy is no longer recommended with varicocele ligation.

However, recently there has been evidence that biochemical parameters may provide predictive markers in testicular histology. While evaluating 115 infertile men with varicoceles and five men with obstructive azoospermia with ultrasound-guided aspiration cytology of the testis, Marmar and Benoff [96] found that lower levels of cadmium and intact calcium channel mRNA sequence predicted greater than 50% increase in sperm density with 82.9% and 90.5% accuracy, respectively. Currently, such advanced investigations are purely experimental.

Age

Patients above the age of 30 years may be poor candidates for varicocelectomy. Grasso *et al*[67] prospectively randomised 68 infertile patients (30-38 years old) to surgery or no treatment. There was no improvement in sperm quality in either of the groups, and there was no difference in pregnancy rates. However, this series included only men with grade 1 varicoceles. Shiraishi et al [97] used the scrotal deep body temperature to predict success in 103 patients who underwent varicocelectomies and they concluded that men older than 30 years had a poorer outcome following surgery, despite increase in scrotal temperature. On the other hand, a recent report of 71 men randomized according to age before surgery found no role of age in predicting success and advocated surgery even for men above the age of 40 years [98].

GnRH stimulation test

The GnRH stimulation test is used to evaluate testicular feedback as a predictor of success. Levels of follicle-stimulating hormone (FSH) and leutenizing hormone (LH) are evaluated before and 45 minutes after intravenous injection of a synthetic GnRH analogue. A more than two-fold increase in FSH and a more than five-fold increase in LH is considered a positive result. Segenreich et al [99] used this test in 121 infertile men with varicocele, before surgery and 4 to 6, 9 to 12, and 16 to 18 months after surgery. Eighteen fertile men with normal semen parameters served as control patients for defining the preoperative hormone levels. Semen parameters were improved postoperatively in 80.9% of the GnRH-positive patients and in only 18.7% of the GnRH-negative patients. Corresponding pregnancy rates at 18 months in the two groups were 67.4% and 9.3%, respectively. Similarly, Atikeler et al [100] reported a significantly better improvement in sperm density, motility and morphology in patients with increased FSH and LH levels after GnRH administration compared with patients who had normal levels.

However, recent studies have reported contrary findings. In one of the largest studies on the role of the GnRH stimulation test for predicting improvement following varicocelectomy, O'Brien et al [101] tested 144 men, and concluded that the FSH response to bolus GnRH stimulation did not predict improvement in semen parameters or unassisted pregnancy outcome. This study was sufficiently powered to validate these findings. Their findings are similar to those of Fisch *et al*[102] whose smaller study of 13 adolescents concluded that in adolescents elevated FSH levels in conjunction with an increased response to the GnRH stimulation test are a normal physiological response and cannot be used to determine which adolescent would benefit from surgical repair.

Conclusions

Varicoceles are relatively common in the adult male population in general and the infertile male population in particular. In many, but not all, of these infertile men it can be the cause of their infertility. However, it is important to exercise restraint and clinical judgment before advocating surgery for these patients. Consensus guidelines advocate surgery only for infertile men with clinically obvious varicoceles and persistent seminal abnormalities. About 60% of the operated men will show good improvement in semen parameters. Surgery should also be recommended in adolescent boys with ipsilateral testicular atrophy so as to preserve future fertility. Among the various modes of therapy, microsurgical ligation is the gold standard and should be the procedure of choice. Since success is not guaranteed, and there are no clear predictors of success, it is important to counsel patients about possibility of no benefit after surgery, and discuss the alternative option of assisted reproductive technics.

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