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THE ROLE OF VARICOCELE TREATMENT IN THE ERA OF ASSISTED REPRODUCTIVE TECHNOLOGY

LYNN M. FISHER, JAY I. SANDLOW

Department of Urology, University of Iowa, Iowa City, Iowa, USA

ABSTRACT

In the era of sophisticated assisted reproductive techniques (ART), is the role of varicocelectomy in the treatment of male factor infertility anachronistic? Devroey et al. (1) assert that "conventional treatment for male factor infertility has little value and has been revised and abandoned". They further contend that "intracytoplasmic sperm injection (ICSI) is an effective treatment, even for cases of extreme oligoasthenoteratozoospermia. It has to be considered the method of choice and should replace ineffective conventional therapies". Certainly, treatment at the gamete level is feasible. However, it should not be unconditionally applied to all males seeking treatment for male factor infertility. A multi-factorial analysis, including outcomes, cost, and morbidity, all lend support to varicocele treatment in the subfertile male.

Key words: varicocele; infertility; reproduction
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HISTORICAL PERSPECTIVE

A varicocele is defined as a dilatation of the pampiniform plexus. This venous plexus bears the name "pampiniformis" because it wraps itself around the spermatic cord like a vine (Latin pampinus, or vine tendril). The first detailed report of a varicocele and its operative therapy was presented by Celsus (42BC-37AD) (2). Superficial scrotal veins were obliterated with the help of thin, sharp cauterizing irons. The wound was then covered with various paste mixtures. Single varicose veins were exposed by means of an scrotal-inguinal incision, ligated with threads, and severed. Multiple varicose veins were ligated but not severed, for fear of intra- or postoperative bleeding. According to Celsus, all other serious cases involving venous convolutions between the innermost skin and the testicles were treated by semicastration.

Throughout history, varicoceles have been treated with a variety of surgical procedures, including partial excision of the scrotum by Cooper in 1831 (3), and scrotal reduction by Hartmann in Paris in 1904 (4). In 1843, the British surgeon Curling used the term "varicocele" to describe the pathological dilation of the spermatic veins (5). In 1856, Curling reported that the testicle exhibited a decrease in the "secreting powers of the gland" when a varicocele was present, introducing the relationship between varicocele and infertility (6). An interesting array of conservative therapies was also utilized in the treatment of varicocele during this historical period. These therapies included silk, net-like suspensories, cold washes both in the morning and in the evening, powders, blistering plasters, and stool regulation (7).

In 1918, Ivanissevich & Gregorini recommended an inguinal approach to accomplish venous ligature in a higher position (8). In 1949, Palomo proposed a high-position retroperitoneal ligation and resection not only of the spermatic vein but also the artery (9). In 1955, Tulloch described a case in which a 27-year-old azoospermic man impregnated his wife one year after varicocelectomy was performed (10). Tulloch wrote, "From the results obtained, it seems justifiable that where a varicocele is associated with subfertility the varicocele should be cured". Tulloch's

paper is considered a landmark in the history of varicocele in that it regained widespread interest in the relationship between varicocele and infertility and it popularized varicocelectomy as a treatment for male infertility.

PATHOPHYSIOLOGY

Varicocele is observed in approximately 15% of the general population. However, up to 40% of infertile men have been observed to have clinical varicoceles (11,12). In 1992, the World Health Organization reported data analysis results of 9038 male partners of infertile marriages who were evaluated in 34 WHO centers in 24 countries (13). It was found that varicocele was present in 25.4% of men with abnormal semen, compared with 11.7% of men with normal semen. Furthermore, varicocele was associated with decreased testicular volume, impaired sperm quality and decline of Leydig cell secretion. It is difficult to dispute the findings of the WHO report that varicocele is associated with impairment in testicular function and infertility.

However, the exact pathophysiologic mechanisms involved in testicular dysfunction in men with varicocele remain elusive. It is known that reflux of venous blood into the pampiniform plexus is involved (14). Macroscopic and microscopic testicular damage associated with varicocele is also well documented (15). Marks et al. reported that 77% of subfertile patients with a varicocele had either unilateral or bilateral testicular atrophy (16). Using caliper measurements, Lipshultz & Corriere demonstrated that both testicles of subfertile patients with varicocele were significantly smaller than testes of patients with idiopathic oligospermia, or those of normal patients (17). Microscopic examination of both testicles in patients with unilateral varicoceles and oligospermia show thinning and sloughing of the germinal epithelium (15). Spermatogenic arrest in the late spermatid stage has also been observed (15).

Several hypotheses exist regarding the pathophysiology of varicocele and the role varicocele plays in altered spermatogenesis and infertility. The two most widely accepted hypotheses are elevation in scrotal temperature and reflux of toxic metabolites from the renal and/or adrenal vein (12,15,18-20). The latter has since been discounted, and the hyperthermia theory is the currently accepted hypothesis.

Studies on the mechanism of varicocele-induced infertility note an increase in testicular temperature due to impairment of the countercurrent heat exchange mechanism (15,21). In the healthy state, warm arterial blood in the spermatic arteries is cooled by convection via the multiple veins of the pampiniform plexus. Varicoceles are thought to increase the intratesticular temperature via loss of venous valvular function. This leads to pooling of the warm blood in the testis; thus causing altered spermatogenesis, Leydig cell dysfunction, and subsequent infertility (22).

Interestingly, it is this enigmatic pathophysiology that opponents cite in opposition to varicocele treatment. One argument raised against varicocele repair is that it is an empiric therapy; that in the majority of successfully treated cases, the pathophysiologic basis for favorable outcome remains obscure (1,18,23). However, just because the mechanism is not clearly established does not mean that there is not an effect (23). Opponents point to an additional controversy regarding the cause-effect relationship of varicocele and male infertility. There are patients who remain infertile despite surgical correction of varicocele, and conversely, patients who become fertile without therapeutic intervention, and patients with varicocele who are normally fertile (24,25).

TREATMENT

Varicoceles can be treated either by surgical intervention (varicocelectomy) or by radiologic embolization. Surgery is still the most popular treatment (25). The goal of surgical treatment is to ligate the dilated veins that drain into the pampiniform plexus. Three surgical techniques are commonly used: retroperitoneal, inguinal, and subinguinal. Currently, inguinal and subinguinal varicocelectomy are the most popular approaches (26). The main complications of varicocelectomy reported in the literature are clinical recurrence and hydrocele formation (27).

Inguinal approaches are associated with postoperative hydrocele formation in 4-15% of cases, with

an average incidence of 7% (26). Postoperative hydrocele formation occurs after 7-33% of retroperitoneal operations, owing to the difficulty in preserving lymphatics using this approach (26).

Varicocele recurrence rate is reported at 5-15% utilizing the inguinal approach, whereas recurrence rate following retroperitoneal varicocelectomy is in excess of 15% (26). Compared with retroperitoneal operations, inguinal approaches lower the incidence of varicocele recurrence (26). Irrespective of the surgical approach, persistent collateral veins may ultimately be responsible for treatment failure (28).

First described by Iaccarino et al. in 1980, embolization of the spermatic vein requires selective catheterization of the spermatic vein, followed by its occlusion with either a sclerosant or a solid embolization agent (29). Currently, sclerosants are used only in Europe; they have not been authorized for use in the United States for spermatic vein sclerosis (25). Embolization entails occluding the spermatic vein at a variable level according to the anatomy of the spermatic venous network. Coils, balloons, or gelfoam may be used as the occluding agent. Careful gonadal shielding is required to protect the testis from radiation exposure.

Technical problems reported with embolization include difficulty cannulating the testicular vein tributaries and high parallel collateral veins, perforation of a vein with extravasation, or distant migration of the embolization material (30).

Advantages of radiologic embolization include requirement of a local anesthetic only, elimination of the risk of postoperative hydrocele, and no threat of injury to the internal spermatic artery (24). Embolization is less invasive than surgery and morbidity is very low (28). Because small collateral veins are not cannulated, however, recurrence rates associated with this approach range between 3-15% (26). Moreover, it must be remembered that embolization is possible only when catheterization of the venous anatomy is possible (28). Embolization will not be possible when the refluxing veins cannot be cannulated.

When evaluating the scientific evidence with respect to varicocelectomy, two issues become apparent. First, researchers define success differently. Success may be defined as pregnancy rate, or as improvement in seminal parameters. Some studies define success as improvement in one of the three seminal parameters: sperm density, motility, or morphology. There is lack of a definable, consistent end-point for assessing the efficacy of varicocelectomy (31).

Secondly, female factors may confound results if pregnancy rate is utilized as the end-point for assessing the efficacy of varicocelectomy. Pregnancy rate is an attractive measure of success; it is, after all, the couple's goal. Be that as it may, pregnancy rate is evidence of the couple's fertility potential. Associated female-factor infertility may interfere with conclusions being drawn regarding the success of varicocele treatment (27).

The goals of varicocele repair are to improve semen parameters, improve testicular function, and improve pregnancy rates in couples with male factor infertility associated with varicocele (26). Utilization of varicocelectomy may eliminate the couple's need for ART, enhancing their in vivo conception potential. Furthermore, recent research suggests varicocelectomy may play a role in sperm enhancement prior to embarking on ART.

PUBLISHED SUCCESS RATES

The preponderance of the scientific literature supports the utility of varicocelectomy. Pryor & Howards reviewed 15 published reports involving 2466 varicocelectomies and reported an overall improvement in semen quality of 66% and a corresponding pregnancy rate of 43% (32).

Girardi & Goldstein reviewed their series of 1500 microsurgical varicocelectomies and found, when female-factor couples were excluded, 43% of couples were pregnant at one year and 69% were pregnant at two years (26).

Mordel et al. reviewed 50 published reports dating from 1954 to 1987 and found improved seminal parameters (57%) and pregnancy rates (36%) following varicocelectomy in approximately 5400 total patients (18). They discovered only 3 studies that found no beneficial effect upon sperm parameters or fertility following varicocelectomy.

In 1994, Schlesinger et al. reported on an extensive literature review of treatment outcomes af-

ter varicocelectomy and concluded that varicocelectomy does indeed appear to have a beneficial effect on sperm density (31). They reviewed 16 studies; encompassing 1,077 treated men that assessed the effect of varicocelectomy on sperm density without reference to the grade of the varicocele. Twelve of the 16 studies that compared the sperm densities before and after varicocelectomy demonstrated statistically significant improvements postoperatively; one study did not measure statistical significance. This improvement in sperm density seemed more pronounced when initial semen densities were greater than 10 million/ml.

Schlesinger et al. also evaluated 12 studies involving 1010 patients which reported the effects of varicocelectomy on sperm motility (31). In five of the 12 studies reviewed (715 patients), the mean motility after varicocelectomy improved statistically. The remaining seven studies showed no improvement in mean motility after varicocelectomy. Only one study found significant improvement in sperm motility without associated improvement in sperm concentration. Conversely, 5 studies demonstrated improved sperm density without improved sperm motility. It was concluded that motility might improve significantly after varicocelectomy when an associated rise in density has also occurred. However, isolated improvements in motility without an associated improvement in density have been reported (31).

Schlesinger et al. then reviewed the effects of varicocelectomy on sperm morphology in 10 studies involving 745 men (31). Half of these studies demonstrated statistically significant improvement in morphology after varicocele ligation. Each of these groups also demonstrated improved density. Schlesinger et al. concluded that standard morphology seems to improve after varicocelectomy if sperm density improves. If density does not improve, morphology is not expected to be altered.

Finally, Schlesinger reviewed 65 studies involving 6983 patients regarding pregnancy rate outcomes after varicocelectomy (31). The average pregnancy rate was 32.24%. The weighted average pregnancy rate (couples achieving pregnancy/participating couples) was 39.95%. The authors summarized, "In spite of the occasional study which indicates that varicocelectomy does not improve fertility, the preponderance of the literature does in fact support a favorable effect".

Emphasizing the varicocelectomy debate and controversy is the fact that the 2 prospective, randomized, controlled studies studying varicocelectomy as an effective treatment for men with clinical varicoceles came to exactly opposite conclusions (24, 33). Nieschlag et al. reported that reproductive counseling (no treatment) was as effective as varicocelectomy (either via embolization or surgical correction) in pregnancy rate outcome (33). Unfortunately, treatment was not standardized, and it is difficult to conclude that varicocelectomy is not effective based upon these results. Conversely, Madgar et al. concluded that varicocele is clearly associated with infertility and reduced testicular function and varicocelectomy improved sperm parameters and fertility rates (24). Differences in the study design, length of time for follow-up, selection of cases in relation to severity of the disease, and duration of infertility are contributing factors, which account for the opposite conclusions drawn from these studies (14). In addition, the differences in the method and efficacy of the treatment itself render these studies virtually incomparable.

Varicocelectomy not only occupies a crucial role in assisting couples to achieve pregnancy via natural conception, a role for treatment of varicoceles in the setting of ART is also being proposed. Daitch et al. conducted a retrospective study to compare the pregnancy rate for couples undergoing intrauterine insemination (IUI) after varicocelectomy to the pregnancy rate for couples in whom the men had untreated varicoceles (34). Their results demonstrated that even though untreated varicocele patients had higher sperm motility characteristics, the per cycle pregnancy rates (PR) and live birth rates (LBR) were significantly higher in patients whose varicoceles were obliterated prior to IUI than in untreated patients (PR = 11.3% vs. 4.2%, $p = 0.007$; LBR = 11.3% vs. 2.1%, $p = 0.02$). They concluded that among couples undergoing IUI, varicocelectomy improves both pregnancy rates and live birth rates.

Vasquez-Levin et al. studied the effect of varicocelectomy on Kruger morphology and semen

parameters in an effort to ascertain whether patients subjected to varicocelectomy exhibited significant improvement in the seminal parameters that are believed to predict successful outcome of in vitro fertilization (35). These researchers concluded that significant improvement in overall sperm morphology (using Kruger classification) was associated with varicocelectomy. Concentration and count improved as well. They suggest that after varicocelectomy, some patients could have improved fertilization rate, which may allow IVF to occur, obviating the need for ICSI. Furthermore, the morphological improvement may also enhance in vivo fertilization, thus eliminating the need for IVF.

In 1998, Schatte et al. published their findings from a prospective study in which they examined the effect of varicocelectomy on standard semen parameters and Kruger morphology, with specific attention to the site of improvement (36). This study identified a significant improvement in the percentage of normal forms as well as the total number of normal sperm by Kruger strict morphology after varicocelectomy. In addition, the primary benefit of improvement was in the sperm head. It is the researchers' hypothesis that the improvements in head morphology after varicocelectomy are directly related to an increase in IVF pregnancy rate, since: 1)- the sperm head is crucial to the successful sperm/egg interaction, and 2)- increased Kruger strict morphology has been correlated with increased in vitro fertilization.

Although studies have reported the effect of varicocelectomy on ability to conceive, efficacy of varicocelectomy before utilizing ART is less well researched (35). Future research in this area may clarify new roles and prospects for varicocelectomy in the ART domain.

COST EFFECTIVENESS

To our knowledge, only one report exists on the cost-effectiveness of ART in comparison with varicocelectomy (37). Schlegel's 1997 report carefully documents costs, success rates, and effectiveness of varicocelectomy in comparison with IVF/ICSI in men with varicocele -associated infertility. The average published U.S. delivery rate after one attempt of ICSI was 28%, whereas a 30% delivery rate was obtained after varicocelectomy. The cost per delivery with ICSI was found to be US$89,091 (95% confidence interval - CI; US$78,720 to US$99,462) whereas the cost per delivery after varicocelectomy was only US$26,268 (95% CI; US$19,138 to US$44,656.) These results suggest that specific treatment of varicocele-associated male factor infertility with surgical varicocelectomy is more cost effective than proceeding directly to assisted reproduction.

CONTRAINDICATIONS TO TREATMENT

When should a varicocele not be treated? There is a subset of men presenting with varicocele-associated male factor infertility in whom varicocelectomy may not provide significant benefit. Varicocele treatment has little, if any, effect on the subsequent natural conception rate if it is associated with a pathology in the female partner such as anovulation, high-grade endometriosis, or severe damage to the fallopian tubes (38).

Furthermore, a highly-elevated FSH level is an unfavorable predictor for pregnancy following varicocele repair (39). FSH elevation parallels the degree of damage to spermatogenesis (40). For these patients, IVF-ICSI should be offered (39).

There is ongoing debate concerning the indications to treat subclinical varicocele. The data remain controversial to support or disprove the contention that repair of subclinical varicoceles improves spermatogenesis (41). Although a modest percentage of men have improvement in their seminal parameters, the pregnancy rates following varicocelectomy for subclinical varicoceles is no higher than untreated men. For this reason, we do not recommend varicocelectomy to men with subclinical varicocele.

CONCLUSIONS

Even today, the treatment of varicocele continues to cause considerable discussion. Existing scientific evidence is compelling, but not definitive in establishing the efficacy of varicocelectomy. Studies have shown that varicocele repair can fulfill the goals

of therapy, that is, to improve semen parameters, improve testicular function, and improve pregnancy rates (26). Moreover, varicocelectomy is associated with low morbidity, and is a more cost-effective therapy when compared to ART. Clearly, when male-factor infertility associated with varicocele is present, the varicocele should be corrected. Tulloch's conclusions are relevant yet today (10). ICSI is not justifiable as the first line of treatment in varicocele–associated male infertility in the face of economic, morbidity, and treatment outcomes. Fundamental scientific and clinical questions remain. Not until well-designed, controlled, prospective, randomized studies (that can withstand scientific scrutiny) are conducted and replicated will varicocelectomy become the undisputed first line of treatment for varicocele-associated male-factor infertility.

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Correspondence address:
Dr. Jay I. Sandlow
Department of Urology
The University of Iowa
200 Hawkins Drive, 3 RCP
Iowa City, IA, 52242-1089, USA
Fax: + + (1) (319) 356-3900
E-mail: jay-sandlow@uiowa.edu