

Varicocele repair: does it still have a role in infertility treatment?

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Purpose of review

To review the role of varicocele repair in the treatment of male infertility.

Recent findings

Varicocele is a common finding among men with infertility and its repair has been a mainstay of surgical therapy in these men. Although each year multiple discoveries are made concerning the mechanism of varicocele-induced infertility, the exact pathophysiologic mechanism remains unknown. This study will update significant findings in regard to the pathophysiology of varicocele-induced infertility, such as increased expression of the aquaporin receptor and new findings related to testicular blood flow and vas deferens motility. Recent information concerning the effects of apoptosis and oxidative stress are also reviewed. With regard to the efficacy of varicocele repair, previous meta-analysis of the available data has been misleading due to improper selection criteria. Available clinical data are critically evaluated, with a focus on new meta-analyses that contradict the findings of the Cochrane database review, a study that has been accepted by many as evidence against varicocele repair.

Summary

We conclude that varicocele repair not only is an effective treatment for appropriately selected patients but can also be the most cost effective option.

Keywords

infertility, pathophysiology, repair, varicocelectomy

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Introduction

Among all men, varicocele is a common finding, present in approximately 15% of the general population. The prevalence is higher among infertile men, affecting about a quarter of this population. Although most can agree that varicoceles are more prevalent among infertile men, there is still no consensus on the view.

Although there have been numerous recent discoveries regarding the pathophysiology of varicocele, much remains unknown about its role in male factor infertility and the lack of answers is responsible for some of the debate. The most fundamental issue to both patient and physician, however, is whether varicocele repair improves fertility. Confusion on this issue is unnecessary and unfortunately a result of inconsistent research methods and heterogeneous patient populations. Even the most current meta-analyses come to opposite conclusions about the efficacy of varicocele repair [1,2,3^{••},4^{••}].

The present study focuses on the latest developments regarding various aspects of varicocele in relation to male infertility. In particular, recent findings related to the mechanisms of pathogenesis, a critical review of the data

to determine whether surgical repair is beneficial, discussion of appropriate patient selection, and cost analysis is included.

Pathophysiology: recent discoveries

The exact pathophysiologic mechanism by which varicocele impairs fertility in affected men remains unknown. In reality, impairment is likely a result of multiple pathophysiologic derangements rather than an isolated mechanism. Most of the recent discoveries regarding varicocele involve various etiologies of varicocele-induced infertility.

Testicular blood flow

Impairment of testicular microcirculation has been proposed as part of the pathologic effects of varicoceles [5,6]. Prior studies [7,8] evaluating testicular microcirculation with color duplex ultrasonography, however, have shown no significant difference in testicular blood flow between patients with varicoceles and control groups. In a recent study using newer power Doppler ultrasonography, Unsal *et al.* [9[•]] 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. They concluded that resistive

index and pulsatility index are more reliable parameters to assess alterations in intratesticular blood flow. They also noted the increased sensitivity of power Doppler ultrasonography over color duplex ultrasonography to detect slow flow and show organ perfusion and thus concluded that the increased resistive index and pulsatility index of capsular branches indicates impaired microcirculation in patients with clinical varicocele.

Oxidative stress and total antioxidant capacity

Another well known pathophysiologic derangement in patients with varicocele is elevated reactive oxygen species (ROS) in semen samples of both fertile and infertile men with varicocele [10,11]. In relation to elevated ROS levels, varicocele is also associated with decreased ability to resist oxidative stress as measured by the levels of total antioxidant capacity [11]. More recently, Nallella *et al.* [12] not only confirmed that patients with varicocele have elevated ROS levels and decreased total antioxidant capacity but also described elevated levels of the pro-inflammatory cytokine IL-6 in these patients and associated it with the elevated ROS levels.

Other pathologic changes associated with elevated ROS include elevated levels of malondialdehyde, which is a marker of lipid peroxidation from oxidative injury [13]. Interestingly, 4-hydroxy-2-nonenal (4-HNE) modified proteins are another marker of oxidative stress found in human testes with varicocele. In 2007, Shiraishi and Naito [14] demonstrated that 4-HNE impaired germ cell proliferation through upregulation of p-53 protein in testes with varicocele.

In a recent study [15], a higher number of mast cells were found in asthenospermic men with varicocele and mast cells have been shown to generate intracellular ROS in response to stimulation from various physiological stimuli. Very recent data [16^{*}] indicate elevated levels of mast cells in asthenospermic men with varicocele. Further details of this relationship with infertility await elucidation.

Effect of varicocele repair on oxidative stress and total antioxidant capacity

As oxidative stress has become a proven component of varicocele pathophysiology, recent studies have demonstrated the beneficial effect of varicocele repair on various markers of oxidative stress. In 2006, Shiraishi and Naito [17] showed that response to varicocele repair could be predicted by elevated preoperative 4-HNE-modified protein levels in the testis. This suggests that varicocele repair decreases the amount of oxidative stress as a mechanism for improving fertility. This point has subsequently been demonstrated by Hurtado de Catalfo *et al.* [18^{**}], who found that levels of thiobarbituric acid reactive substances, markers of oxidative stress, were significantly elevated in both seminal plasma and peripheral plasma

and returned to normal levels 1 month postvaricocelectomy. Other markers of oxidative stress were decreased and the total antioxidant capacity was increased by 6 months postvaricocelectomy. Most recently, Chen *et al.* [19^{*}] showed that the levels of 8-OHdG, a marker of oxidative stress, and the incidence of 4977 bp deletion in mitochondrial DNA, a marker of oxidant-mediated DNA damage, were significantly decreased in all patients studied after varicocele repair. They also found that antioxidant capacity was increased after varicocelectomy, adding to the mounting body of knowledge suggesting that varicocele repair exerts a beneficial effect on fertility by decreasing oxidative damage to sperm.

Apoptosis and DNA damage

As is well documented, varicocele is associated with DNA damage as measured by several methodologies [20–22] and this may be another means by which varicocele impairs fertility. High levels of DNA damage have also been associated with elevated ROS levels in patients with varicoceles when compared with normal controls [23]. Interestingly, these differences were found in men with varicocele irrespective of impairment of semen parameters.

Varicoceles are also associated with an increase in apoptosis within testicular tissue [24]. Various apoptotic factors in patients with varicocele include cadmium, androgen deprivation, heat stress, IL-6, and gonadotropin-releasing hormone, like gonadal peptide [25].

Other novel changes associated with varicocele

Aquaporins are a family of transcellular membrane proteins that mediate water transport across the cell membrane [26]. In 2005, Nicotina *et al.* [27] showed increased expression of aquaporin receptor-1 (AQP-1) on venular endothelial cell membranes and in the cell membrane of Sertoli cells, diploid germ cells, and haploid cells in patients with varicocele. This may suggest that in the setting of varicocele, the testis is attempting to overcome fluid imbalance in the tubular and interstitial compartments.

Although vas deferens motility was not traditionally thought to be associated with varicocele, Ozen *et al.* [28] have documented a novel effect of varicocele on vas deferens motility, at least in a rat model. In a recent study, they demonstrated decreased contractile response in the ipsilateral vas deferens compared with the contralateral vas in rats with induced varicoceles. This finding is unique in that it investigates other pathways besides testicular damage, but, at this time, its application to infertility in humans is hypothetical at best.

Although an exact pathway for varicocele-induced infertility has not been completely elucidated, there is a plethora of studies documenting multiple derangements

in the setting of varicocele. Owing to the scope of this study, abnormal expression of leptin receptors [29], glial cell derived neurotrophic factor specific receptor GFR- α 1 on germ cells [30], and increased expression of heme oxygenase on Leyding cells [31] cannot be discussed in detail. Only a few of the more recent studies have been discussed above and new insights are constantly being discovered.

Does varicocele repair improve fertility?

Although multiple derangements and detrimental molecular changes (only a few of which are mentioned above) have been documented in the setting of varicocele, the central issue is whether or not repair of this condition improves fertility. Much debate has centered on this question, and rightfully so, as it is the bottom-line for both clinicians and patients. Individual series yield mixed results. In one of the more recent studies finding no benefit to varicocele repair, Krause *et al.* [32] described a multicenter prospective randomized trial of sclerotherapy versus no treatment. Patients were appropriately selected in that they had at least one abnormal semen parameter and clinical (palpable) varicoceles. The authors, however, noted that they originally planned to enroll 460 patients to achieve appropriate power but were only able to randomize 67 patients. More than 50% of these patients were lost to follow-up and assumed to not be pregnant; therefore, it is not surprising that no difference was found. Breznik *et al.* [33] in 1993 and Rageth *et al.* [34] in 1992 are just some of the other researchers who previously found no benefit to varicocele repair in their studies.

In a more recent series showing benefits of varicocele repair, Kibar *et al.* [35] showed a statistically significant improvement in sperm concentration, motility, and morphology in a population of men with infertility and abnormal Kruger morphology. The study population was only 90 patients and, though pregnancy data were reported, there was no control group for comparison.

Although slightly less contemporary, Madgar *et al.* [36] in 1995 used an interesting study design to achieve a randomized controlled evaluation of varicocelectomy for fertility. Infertile men with palpable varicoceles and abnormal semen analysis were randomized into two groups, one receiving varicocelectomy immediately and the other receiving surgery delayed by 1 year. During the first year, the immediate surgery group had a pregnancy rate of 60% and the group awaiting surgery had a pregnancy rate of 10% with these differences being statistically significant. Although well done in that there was appropriate patient selection and a control group, the study size was small. A year earlier, Marmar and Kim [37] had shown a pregnancy rate of 35.6% in 186 patients receiving varicocelectomy and 15.8% in a group treated medically. Unfortunately, there

was quite a discrepancy in the size of the groups with only 19 patients in the nonoperative group.

In the absence of sufficient large randomized controlled studies with appropriately selected patients, investigators have turned to meta-analysis of the available literature to discern the role of varicocele ligation in male factor infertility. A 2004 Cochrane review [1] concluded that varicocele repair for otherwise unexplained infertility could not be recommended. This conclusion was based on their results showing an odds ratio favoring treatment over no treatment of only 1.1 (95% confidence interval 0.73–1.68). Although these results received considerable attention and may even be shaping practice patterns, there are serious errors in certain aspects of the methodology, which likely have accounted for the lack of correlation. A total of eight randomized controlled trials (RCTs) were included and three of them evaluated only men with subclinical varicoceles. As will be described in further detail later, men with subclinical varicoceles do not meet the current selection criteria for varicocele repair. Thus, almost half the studies included consisted of inappropriately selected patients. Another example of questionable patient selection is the fact that two additional studies included men with normal semen analysis. Thus, five of the eight studies used in the meta-analysis included patients who would not meet the criteria for varicocele repair based on American Urological Association and American Society of Reproductive Medicine (ASRM) recommendations [38*].

Ficarra *et al.* [2] repeated the Cochrane review excluding the five RCTs that included men with normal semen parameters or subclinical varicoceles. This left only three trials with a total of 237 patients for review. They showed a statistically significant difference in pregnancy rates between treatment (36.4%) and control (20%) groups. They also comment on the ‘poor’ methodology and statistical power of the included studies and therefore only disagree with the conclusions of the Cochrane review. The authors defer to future studies rather than recommend varicocele repair outright.

More recently, Agarwal *et al.* [3**] combined observational studies with RCTs as described by the Potsdam Consultation [39]. A sophisticated method was used to minimize selection bias. Although a total of 17 studies were included, pregnancy data were not available; therefore, only semen parameters were analyzed. Sperm density, motility, and WHO morphology were all significantly improved after varicocelectomy. Sperm density improved by 9.7–12 million/ml and motility by 9–11.7% depending on the surgical method employed.

In 2007, Marmar *et al.* [4**] in another meta-analysis did include pregnancy data and concluded that surgical

varicocelectomy significantly improved fertility in appropriately selected patients. An elaborate method of review blinded reviewers to any identifying information to minimize bias. Again, RCTs and observational studies involving only infertile men with palpable varicoceles and abnormal semen parameters were eligible. Depending on the statistical method, the study demonstrated an odds ratio of 2.63–2.87 for spontaneous pregnancy after varicocelectomy compared with observation or medical therapy.

The answer to the question of whether or not varicocelectomy improves fertility varies from study to study. This, however, is due to a wide variety of study designs and, more importantly, patient selection criteria. No definitive randomized prospective clinical trial of sufficient size exists at this time due to the inherent difficulties of establishing such a trial and enrolling infertility patients. In the absence of such a trial, critical assessment of the best quality data available leads to the conclusion that varicocelectomy can benefit appropriately selected infertile men. The ASRM agrees, citing ‘varicocele treatment should be considered as a choice for appropriately selected infertile couples...’ [38[•]].

Proper patient selection: key to successful outcomes

The ASRM in 2006 revised their previous recommendations from a 2001 joint report with the Male Infertility Best Practice Policy Committee of the American Urologic Association. They recommend offering varicocele repair when all the following criteria are met. First, varicocele is palpable. Therefore, men with subclinical varicoceles (detected by ultrasound only) should not be considered candidates for repair. Some studies [40,41] have touted repair of subclinical varicoceles. These studies, however, were small, poorly powered, and did not always assess fertility as an outcome. Second, documented infertility. Third, one or more abnormal semen parameters. Fourth, a normal female evaluation or a potentially reversible female factor. Although individual practice patterns may vary, these guidelines are generally accepted by most urologists.

In addition to the above standard selection criteria, there are other preoperative characteristics that may help identify those patients who would receive the most benefit from varicocele ligation. Reversal of blood flow in the varicocele during valsalva documented on ultrasound was shown to predict significantly better improvement in semen parameters than if reversal of flow could not be documented. The same study also noted that men with the largest vein measuring more than 3 mm on ultrasound showed significant improvement in semen parameters, whereas those with the largest vein less than 3 mm did not. Unfortunately, pregnancy data were not available [42].

Although another recent study [43] found that patients with bilateral varicoceles will improve more so after repair than those with only unilateral varicoceles, both groups noted improvement in semen parameters. Pregnancy rates were good for both groups, but were better in the group with bilateral varicocele repair (49 vs. 36%).

Nonobstructive azoospermia: special considerations

Varicocele in patients with nonobstructive azoospermia (NOA) is an area that has received recent interest. Most recently, Gat *et al.* [44] found that seven of 19 men with NOA had return of motile sperm to the ejaculate after microsurgical varicocele repair. The average sperm concentration was 0.36 million/ml and one patient reported conception by natural intercourse. In another study, 56% of 32 men with NOA had the appearance of sperm in the ejaculate after varicocele repair by embolization, with a mean concentration of 3.8 million/ml.

Despite these encouraging results, we cannot recommend varicocele repair as a routine treatment for men with NOA and varicocele. Schlegel and Kaufmann [45] found that 22% of men with NOA who underwent varicocele ligation had sperm on postoperative semen analysis, but only 9.6% had sufficient number of motile sperm for intracytoplasmic sperm injection (ICSI). It also appears that even in those men who receive benefit from varicocele repair, the results may not be durable as over half of them who show benefit return to azoospermic status within 1 year of varicocelectomy [46,47]. All studies to date are small and uncontrolled, but even if they are confirmed, it appears that varicocele repair in men with NOA is unlikely to improve semen parameters to such an extent that intrauterine insemination (IUI) is a reasonable option. If these men are destined for conception by means of IVF/ICSI, then they are probably better served with a testicular sperm harvest, as the success rates of this procedure are higher than the odds of sperm appearing in the ejaculate after varicocele repair.

Cost analysis

In the era of modern assisted reproductive technology (ART), men with varicocele-related male factor infertility have other treatment options than varicocele repair. The cost-effectiveness of these various options is a vital issue considering that infertility treatments are often not covered by insurance plans and therefore may be an ‘out-of-pocket’ expense to the patient. Most studies favor varicocelectomy over assisted reproduction even without accounting for the beneficial effect of varicocelectomy beyond the ‘treatment period’.

There are many factors that cannot be assigned a monetary value and included in these analyses, but these may be very significant to an individual couple. For some, there may be a premium on conceiving by the 'most natural' means possible that may influence their decision for varicocele repair. In contrast, the immediacy of ART may be valued by some over the time required for natural conception.

One of the first cost analyses to include IVF/ICSI found that this modality was more than three times as costly as varicocele ligation [48]. Considering improvements in ART success and decrease in cost over the last decade, the current cost difference may be less, but is likely to persist.

More recent analyses still support varicocele repair as a cost-effective approach. An analysis of various treatment strategies including observation, varicocele repair, IUI, and immediate IVF, with IVF offered after failures of other options, showed that the most cost-effective approach depended on the payer source [49]. IUI with IVF at failure of other options was the most cost-effective approach from the patient's perspective, as it was associated with a marginal cost-effectiveness of a few hundred dollars less than varicocele repair with IVF for failures. From the healthcare payer perspective, however, the marginal cost-effectiveness per additional live birth was over \$500 000 greater for IUI than for varicocele ligation. Immediate IVF was never the most cost-effective approach.

Most recently, the cost-effectiveness of varicocele repair was compared with ART by stratifying the degree of impairment of semen parameters [50]. Varicocele ligation was found to be more cost-effective than IUI in men with a total motile sperm count greater than 10 million/ml if the postoperative pregnancy rates were above 45%. If the total motile sperm count was less than 10 million/ml, varicocele repair was more cost-effective than IVF if a postoperative pregnancy rate of greater than 14% was achieved. Although the cost-effectiveness of varicocele ligation is directly related to the success of treatment, the minimum requirements for success are conservative and consistent with the published data.

Conclusion

Varicocele-associated infertility is one of the reversible causes of male infertility. The etiology of fertility impairment from varicocele continues to be better elucidated. Multiple pathophysiologic mechanisms likely contribute to the deleterious effect. Although no single randomized, controlled, prospective clinical trial exists to demonstrate the effectiveness of varicocele repair, the data from smaller studies with appropriately selected patients analyzed in

aggregate indicate improved fertility when compared with no treatment. Varicocele repair is not only effective but offers the advantage of durable improvement should more than one pregnancy be desired. From a cost-effectiveness standpoint, varicocele repair also compares favorably with other treatments for infertility and should be offered to men who meet the appropriate criteria.

Acknowledgement

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References and recommended reading

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- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 321).

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