Varicocele as a progressive lesion: positive effect of varicocele repair

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Varicoceles are the leading correctable cause of infertility in men who present to an infertility clinic for evaluation. Consequently, the surgical correction of a varicocele, known as a varicocelectomy, is the most commonly performed operation for the treatment of male infertility. The current data suggest that an individual with a varicocele, even with a previously normal semen analysis or documentation of previous fertility, is at risk for subsequent loss of testicular function and infertility. Many of these patients will need to be treated because there is convincing evidence that a varicocele may have a progressive toxic effect on the testes that may ultimately result in irreversible infertility if left untreated. Identifying those individuals with varicoceles that will ultimately cause fertility impairment is still beyond our current clinical capabilities. Current investigative modalities, e.g. semen analysis, testicular measurement, serum gonadotrophin determination, gonadotrophin-releasing hormone (GnRH) stimulation test, and testis biopsy analysis, may be employed to detect early changes in testicular physiology produced by a varicocele.

Key words: male infertility/progressive lesion/varicocele/varicocele repair

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Introduction

A varicocele is defined as a dilatation of the pampiniform venous plexus that surrounds the testis. Varicoceles are the leading correctable cause of infertility in men who present to an infertility clinic for evaluation. Consequently, the surgical correction of a varicocele, known as a varicocelectomy, is the most commonly performed operation for the treatment of male infertility. This procedure primarily involves ligation of the internal spermatic vein and its branches, which are the main source of drainage of the pampiniform plexus. Varicoceles are found in ~15% of the general population, including adolescents and adults (Belloli et al., 1993), in 35% of men with primary infertility (reported range 19–41%) (Pryor and Howards, 1987), and in 80% of men with secondary infertility (range 69–94%) (Gorelick and Goldstein, 1993; Witt and Lipschultz, 1993). There is no racial preponderance (Risser and Lipschultz, 1984). It was found (Steeno et al., 1976) that the incidence of varicocele detection gradually increases in boys aged 10–15 years to an incidence of ~15%, and the percentage of males aged >15 years with a varicocele was constant.

The recognition that the varicocele may be a factor in male infertility dates back to first-century Greece, where Celsius found that swollen scrotal veins were associated with an atrophic testicle (Kaufman and Nagler, 1986). In 1856, it was reported that the testicle exhibited a decrease in the ‘secreting powers of the gland’ when a varicocele was present (Curling, 1856), while Bennet (1889), performed bilateral varicocelectomy in a patient with subsequent improvement in semen quality. In 1929, Macomber and Sanders reported an instance in which an oligozoospermic subfertile patient underwent varicocele repair and became normozoospermic and fertile (Macomber and Sanders, 1929). After results which demonstrated that high ligation of the spermatic vessels resulted in improved fertility (Tulloch, 1955), the procedure became the mainstay of treatment for male infertility.

There are numerous studies identified in Table I which show improvement in both semen quality and pregnancy rate after varicocele repair. One group (Madgar et al., 1995), reported a randomized, controlled study in which they showed that a group receiving no varicocele treatment had a spontaneous pregnancy rate of only 10%, while men undergoing varicocele repair had a 71% pregnancy rate. However, there are several studies described in the literature (Table II) that fail to demonstrate significant improvement after varicocelectomy. Another investigation
(Vermeulen et al., 1986) is often cited by opponents of varicocelectomy. The flaws in this study are in the selection criteria and the size of the control group: 82 patients with infertility had varicoceles, of which 62 were treated and the remaining 20 were in the control group. In this control group were patients who had failed attempts at embolization of their varicoceles. In addition, patients who conceived prior to planned treatment were considered untreated and included in the control group. The pregnancy rate for the treated group was 24%, compared with 56% for the untreated group. It is important to emphasize that the 40% pregnancy rate for the ’controls’ included patients who conceived while waiting for treatment.

Diagnosis of a varicocele is principally made by physical examination. If it is determined to be impairing fertility or causing testicular atrophy and/or testicular pain, correction of this vascular lesion is recommended. Improvement in semen quality occurs in two-thirds of patients undergoing varicocele repair, and a subsequent pregnancy rate of ~40% has been reported (Schlesinger et al., 1994).

**Table I.** Studies demonstrating improvement in semen quality and pregnancy rate after varicocelectomy

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Improved semen quality (%)</th>
<th>Pregnancy rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scott and Young (1962)</td>
<td>166</td>
<td>70</td>
<td>31</td>
</tr>
<tr>
<td>Charny and Baum (1968)</td>
<td>104</td>
<td>61</td>
<td>24</td>
</tr>
<tr>
<td>MacLeod (1965)</td>
<td>108</td>
<td>74</td>
<td>41</td>
</tr>
<tr>
<td>Brown (1976)</td>
<td>251</td>
<td>58</td>
<td>41</td>
</tr>
<tr>
<td>Dubin and Amelar (1977)</td>
<td>986</td>
<td>70</td>
<td>53</td>
</tr>
<tr>
<td>Newton et al. (1980)</td>
<td>149</td>
<td>66</td>
<td>34</td>
</tr>
<tr>
<td>Marks et al. (1986)</td>
<td>130</td>
<td>51</td>
<td>39</td>
</tr>
<tr>
<td>Goldstein et al. (1992)</td>
<td>357</td>
<td>–</td>
<td>43</td>
</tr>
<tr>
<td>Ross and Ruppmann (1993)</td>
<td>488</td>
<td>77</td>
<td>–</td>
</tr>
<tr>
<td>Schlesinger et al. (1994)</td>
<td>–</td>
<td>66</td>
<td>40</td>
</tr>
<tr>
<td>Madgar et al. (1995)</td>
<td>45</td>
<td>–</td>
<td>71</td>
</tr>
</tbody>
</table>

**Table II.** Studies demonstrating no beneficial effect of varicocelectomy on pregnancy rates

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pregnancy rate (%) after varicocelectomy</th>
<th>Pregnancy rate (%) with no surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilsson et al. (1979)</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Baker et al. (1985)</td>
<td>47</td>
<td>45</td>
</tr>
<tr>
<td>Vermeulen et al. (1986)</td>
<td>24</td>
<td>56</td>
</tr>
<tr>
<td>Lund and Larsen (1998)</td>
<td>71</td>
<td>87</td>
</tr>
</tbody>
</table>

**Varicocele as a progressive lesion**

Varicoceles are the most common cause of secondary infertility. One group (Witt and Lipshultz, 1993) concluded that of 259 patients with primary infertility, 128 (50%) were found to have varicoceles while in 259 patients with secondary infertility 177 (69%) were found to have varicoceles. Other authors (Gorelick and Goldstein, 1993) reached similar conclusions after a study of 888 infertile men in whom 94% of men with secondary and 35% of men with primary infertility had varicoceles. The difference between the incidence of varicoceles in the two populations was significant, indicating an acquired and apparent progressive infertility from the presence of the varicocele. They also concluded that while the incidence of varicoceles in men with secondary infertility is higher than men with primary infertility, the serum concentration of FSH is also significantly higher in men with secondary infertility, suggesting a greater degree of seminiferous tubular damage over time.

The exact mechanism by which an incidental varicocele becomes pathological remains unclear. Varicoceles may produce a gradual temporal loss of normal spermatogenesis over time as a result of raised intratesticular temperatures and subsequent progressive germ cell injury or loss. Another possible mechanism by which an incidental varicocele may subsequently impair sperm production has been proposed (Peng et al., 1990): in a Sprague–Dawley rat varicocele model it was found that the varicocele may act as a co-factor in association with certain gonadotoxins, producing a greater degree of injury in the varicocele-associated testicle than in the testicle not associated with a varicocele. A varicocele could then predispose the testis to further noxious insults, exposure to which could most likely increase over time.

Men (n = 13) who presented for fertility evaluation were re-evaluated at a 9–96-month intervals because of persistent fertility problems (Chehval and Purcell, 1992). They found a statistically significant deterioration in sperm density and motility, which suggests that testicular deterioration in patients with varicocele occurs in a progressive manner. Similarly, in patients with varicoceles, the sperm density and testicular size were found to be significantly decreased in older patients (Lipshultz and Corriere, 1977).

**Hormonal dysfunction**

Ospina (1977) was the first author to demonstrate a supranormal gonadotrophin response to the administration of gonadotrophin-releasing hormone (GnRH) in fertile men with a varicocele. He believed that the excessive release of LH after GnRH administration is an indication of Leydig cell dysfunction and the abnormal FSH response a result of seminiferous tubular dysfunction. Nagao et al. (1986) also indicated that hormonal abnormalities can be observed in both fertile and infertile men with a varicocele, suggesting that there is some degree of testicular dysfunction in all men with a varicocele, regardless of their fertility status. This varicocele-induced testicular defect may progress and become clinically significant with advancing age. Decreased plasma testosterone concentrations were found in patients with varicocele; this hypoandrogenic state may play a part in the effects of varicocele on spermatogenesis (Comhaire and Vermeulen, 1975). Other authors (Su et al., 1995) demonstrated that serum testosterone concentrations in men with varicocele could be increased after varicocelectomy. Also, a subtle alteration in the hypothalamic– pituitary–gonadal (HPG) axis can be found in some varicocele patients. (Okuyama et al., 1981). Whether this is the mechanism of the effect of the
varicocele or the result of the primary pathophysiological effect of the varicocele is unclear.

**Varicocele repair**

There are several reports in the literature indicating that childhood varicocele may become apparent peripherally and that early corrective therapy could prevent future damage to the individual’s fertility status; however, this remains a controversial subject. As we noted previously (Lipshultz and Corriere, 1977; Chehval and Purcell, 1992), the presence of a varicocele is associated with loss of testicular mass that appears to be progressive with age. After correction of a paediatric or adolescent varicocele, a significant increase in testicular volume can be observed; a phenomenon called ‘catch-up’ growth of the affected testis (Lemach et al., 1998). Many authors have adopted the position that a paediatric varicocele should be left untreated unless there is significant testicular asymmetry or impaired testicular growth (>20% volume disparity).

An accurate comparison of outcomes using different treatment modalities is difficult because of innumerable, inconsistently controlled variables. In a review of 15 papers (Pryor and Howards, 1987), an overall rate of improvement in semen quality of 66% (range 51–78%) was reported, as was an overall reported pregnancy rate of 43% (range 24–53%). Although there are some series that show no significant effect or an adverse effect of varicocele repair, these series are relatively small and may be biased as well as statistically misinterpreted (Table II). There are more reports in the literature that support the beneficial effect of the varicocele ligation than do not (Table I).

A randomized, prospective study of patients with varicoceles, as previously described, compared those treated surgically with those treated by observation alone (Madgar et al., 1995). The results clearly demonstrated that varicocelectomy improves sperm quality and fertility rates. In this study, the average pregnancy occurred 6–9 months following surgery.

An extensive review of the literature (Schlesinger et al., 1994) concluded that varicocelectomy has a beneficial effect on sperm density. This effect seems more pronounced when initial semen densities are >10 × 10⁶ spermatozoa/ml. It has also been reported that motility and morphology may improve after varicocelectomy concomitant with an associated rise in density, although isolated improvements in either of these parameters have also been cited. Similarly, several authors have shown improvement in sperm morphology measured by Kruger’s strict criteria (Vazquez-Levin et al., 1997; Schatte et al., 1998).

In an attempt to identify prognostic factors that could predict post-operative pregnancies, a cohort of 130 patients were described (Marks et al., 1986) and four useful prognostic variables were identified. The absence of testicular atrophy was found to indicate a good prognosis; 56% of patients with normal testicular size established pregnancies, compared with a 33% pregnancy rate in patients with testicular atrophy. An initial sperm count of >50 × 10⁶/ejaculate was also associated with a higher pregnancy rate. Patients with a normal motility established a pregnancy in 60% of cases, whereas only 30% of patients with prior abnormal motility were successful. An elevation of FSH was a poor prognostic indicator. Only 25% of patients whose FSH was >300 ng/ml (normal <300 ng/ml) achieved pregnancies, whereas 46% of patients with normal FSH concentration had successful outcomes.

**Varicocele in azoospermic patients**

An interesting concept is that of performing varicocele repair for azoospermic patients. A primary benefit of varicocele repair in azoospermic men with spermatogenic failure is the possibility of promoting production of motile spermatozoa in the ejaculate. Two groups (Matthews et al., 1998; Kim et al., 1999) have independently found that varicocele repair in men with azoospermia and severe oligoasthenozoospermia resulted in the induction or enhancement of spermatogenesis for 40–60% of these patients. When a choice is possible, using motile spermatozoa from a fresh ejaculate is preferable to using testicular sperm extraction (TESE) in preparation for intracytoplasmic sperm injection (ICSI) and IVF (Palermo et al., 1992). Freshly ejaculated live spermatozoa are associated with ICSI success rates superior to those achieved with spermatozoa retrieved via TESE and, additionally, an invasive and potentially damaging procedure is avoided (Aboulghar et al., 1977).

Again, the importance of these findings is that a significant number of azoospermic men destined to undergo invasive testicular sperm retrieval procedures involving repeated open or needle biopsies in combination with ICSI now have the potential of providing spermatozoa via ejaculation or even of establishing a pregnancy without technical assistance.

**Conclusions**

The current data suggest that an individual with a varicocele, even with a previous normal semen analysis or documentation of previous fertility, is at risk for subsequent loss of testicular function and infertility. Because most varicoceles in adolescents are detected during routine physical examination and their fertility status is unknown, the accurate identification of all individuals at risk for future problems is beyond our capability. Many of these patients will need to be treated because there is convincing evidence that a varicocele may have a progressive toxic effect on the testes that may ultimately result in irreversible infertility if left untreated. However, because a varicocele can be detected in ~15% of adolescents and not everyone with a varicocele will be infertile if left untreated, routine varicocele ligation in all teenagers is not recommended. Identifying those individuals with varicoceles that will ultimately cause fertility impairment is complicated; however, it has been shown that adolescents demonstrating testicular growth retardation ipsilateral to the varicocele may represent an ‘at risk’ group (Kass et al., 1987). Current investigative modalities, e.g. semen analysis, testicular measurement, serum gonadotrophin determination, GnRH stimulation test, and testis biopsy analysis, may be employed to detect early changes in testicular physiology produced by a varicocele. If an abnormality is identified, then correction may be indicated. If an abnormality in testicular function cannot be found on evaluation of an individual with a varicocele and he is concerned about his future fertility, regular follow-up is recommended.
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