

Effects of varicocele on male fertility

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Varicoceles are vascular lesions of the pampiniform plexus and are the most common identifiable abnormality found in men being evaluated for infertility. Despite the long history associated with varicoceles, there remains much controversy regarding their diagnosis and management. The purpose of this manuscript is to address three of the most pressing controversies: (i) the association of varicoceles with male infertility, (ii) whether varicoceles exert a progressive deleterious effect and (iii) the relationship of varicocele size and outcome following varicocele repair. The current literature is reviewed in an effort to answer these questions. Based upon this analysis, conclusions can be drawn regarding the best management of varicoceles in subfertile men, adolescents, young fertile men and men with subclinical varicoceles. Although there remain many controversies due to a paucity of data, there appears to be a significant difference between adults and adolescents with respect to a progressive deterioration of semen parameters and it is clear that subclinical varicoceles do not play a major role in male infertility.

Key words: male infertility/prognosis/subclinical varicocele/varicocele

TABLE OF CONTENTS

Introduction
Varicoceles and male fertility
Progressive effect of varicoceles
Varicocele size
Conclusions
References

Introduction

A varicocele is a vascular abnormality of the scrotum that is defined as dilated veins of the pampiniform plexus. Physicians have been aware of the association between varicoceles and ipsilateral testicular damage since the time of Celsus. Although the exact pathophysiology of varicoceles is not known for certain, varicoceles are thought to impair normal testicular function by elevating scrotal temperature via reflux of warm abdominal blood through incompetent valves of the spermatic veins (Moore and Quick, 1923; Goldstein and Eid, 1989; Ali *et al.*, 1990; Hsiung *et al.*, 1991; Lerchl *et al.*, 1993). The veins that are most commonly involved are the internal spermatic veins but the external spermatic veins and cremasteric veins have also been implicated (Comhaire *et al.*, 1981; Wishahi, 1991a,b, 1992; Beck *et al.*, 1992; Chehval and Purcell, 1992a). The deferential veins do not appear to play a role in the development of varicoceles. Varicoceles are currently the most common abnormality identified in men being evaluated for infertility (Sigman and Howards, 1998). Varicoceles are normally diagnosed by physical examination through palpation of the spermatic cord before and during a Valsalva manoeuvre with

the patient in a standing position. The diagnosis is based upon the clinician's subjective impression of either venous dilation or reflux of blood. These vascular lesions have been arbitrarily divided into three grades based upon physical findings: large varicoceles are visible; medium varicoceles are palpable; and small varicoceles are only palpable during a Valsalva manoeuvre. Varicoceles detected by radiological imaging studies in patients without a palpable varicocele are labelled subclinical. There continues to be a great deal of controversy regarding the management of varicoceles today. The vast majority of physicians who manage male infertility patients believe that varicoceles are a major cause of male infertility and that repair of a varicocele will improve fertility (World Health Organization, 1992). Some controversial topics are whether or not varicoceles should be repaired prophylactically to prevent future infertility and whether varicocele size has prognostic significance. The latter issue has a major impact upon deciding whether or not subclinical (non-palpable) varicoceles should be diagnosed and repaired. However, there are many clinicians who are not convinced that varicocele repair improves male fertility (Kamischke and Nieschlag, 1999). The issues that will be discussed herein include the effect of varicoceles upon male fertility, whether varicoceles exert a progressive deleterious effect upon male fertility, and whether or not varicocele size affects prognosis.

Varicoceles and male fertility

The major evidence used to support the hypothesis that varicoceles have a deleterious effect upon male fertility are the increased

prevalence of varicoceles amongst men attending an infertility clinic, the association of varicoceles with ipsilateral testicular atrophy, testicular abnormalities observed in an animal model of varicocele and the improvement of both semen parameters and fertility in men undergoing varicocele repair. The prevalence of varicoceles in the general population is estimated to be 15-20%. These data, in general, come from population-based studies of military recruits and school physical examinations (Oster, 1970, 1971; Steeno *et al.*, 1976; Thomason and Fariss, 1979; Alcalay and Sayfan, 1984; Meacham *et al.*, 1994; Liang *et al.*, 1997; Martin-Du Pan *et al.*, 1997). In contrast, the prevalence of varicoceles amongst men attending an infertility clinic ranges from 30 to 40% (Dubin and Amelar, 1977; Greenberg *et al.*, 1978; Marks *et al.*, 1986; Sigman and Howards, 1998). The implication of this observed increase in the prevalence of varicoceles amongst subfertile men as compared with the general population is that varicoceles must be a cause of male infertility. Yet, a major criticism of this argument is that none of these studies employ the same examiner using the same method of diagnosis for both populations over the same time period. Moreover, it is very likely that the degree of care taken to detect a varicocele in these clinical scenarios is completely different. A patient being examined for infertility is examined very carefully for even small varicoceles, whereas, small or moderate sized varicoceles are very likely overlooked during a school or military induction physical examination. In a study of 841 men attending a urology clinic for reasons other than male infertility (Pinto *et al.*, 1994), a clinical varicocele was found in 211 (25%). Of 821 consecutive men being evaluated for male infertility over the same time period and examined by the same physician, 237 (29%) had evidence of a clinical varicocele. The prevalence of varicoceles in these two groups was not significantly different ($P=0.09$; χ^2 -test). These findings suggest that the prevalence of varicoceles may not be substantially higher in subfertile men, as previously proposed. However, these data must be interpreted cautiously since the two patient populations were not age-matched. The vast majority of the men in the control group were being evaluated for erectile dysfunction with a mean age of 56 years, which is significantly older than the subfertile population.

Another argument that varicoceles adversely affect male fertility is their association with ipsilateral testicular damage as reflected by reduced testicular volume. Since the time of Celsus, it has been noted that testicles associated with large varicoceles have reduced volume. Many clinical studies have objectively documented the association of reduced testis volume with a varicocele (Lipshultz and Corriere, Jr, 1977; Pinto *et al.*, 1994; Yamamoto *et al.*, 1995a). The seminiferous tubules, which produce spermatozoa, comprise the vast majority of testicular volume in the normal testis. A reduction of testicular volume is usually indicative of reduced spermatogenesis. Moreover, several studies have documented reduced semen parameters in men with varicoceles as compared with controls regardless of fertility status (Fariss *et al.*, 1981; Sigman and Jarow, 1997; Lund and Larsen, 1998). In addition, numerous studies have documented failure of testicular growth, hypotrophy, in adolescents with varicoceles (Kass and Belman, 1987; Haans *et al.*, 1991; Costabile *et al.*, 1992; Sawczuk *et al.*, 1993; Aragona *et al.*, 1994; Yamamoto *et al.*, 1995b; Paduch and Niedzielski, 1997). Thus, there is a strong association in the literature between varicoceles and testicular damage, as reflected by testicular size.

An animal model for varicocele was created (Al Juburi *et al.*, 1979) in the late 1970s through partial ligation of the left renal vein in a canine model. This same method was then later used to create varicoceles in both non-human primates (Harrison *et al.*, 1986) and in the rat (Saypol *et al.*, 1981). Using the rat model, Turner and associates were able to demonstrate that unilateral varicoceles had a bilateral effect upon testicular temperature, blood flow, and histology (Saypol *et al.*, 1981; Hurt *et al.*, 1987; Rajfer *et al.*, 1987; Turner *et al.*, 1987, 1996; Turner and Lopez, 1990). In addition, these adverse effects did not appear to be either neurologically or immunologically mediated (Green *et al.*, 1985). Most importantly, these effects were reversed after the varicocele was repaired (Green *et al.*, 1984; Hurt *et al.*, 1986). Thus, varicoceles were shown to have a direct adverse effect upon testicular function that was relieved by varicocele repair in an animal model.

There have been numerous outcome studies that assess the effects of varicocele repair upon semen quality and fertility but the vast majority of these have been uncontrolled compilations of case reports. The majority of these uncontrolled studies demonstrate improvement in semen parameters in ~65% and fertility in ~40% (Schlesinger *et al.*, 1994). Moreover, many studies have documented improvement in testicular volume following varicocele repair (Erkan *et al.*, 1990; Gentile and Cockett, 1992; Yamamoto *et al.*, 1995a; Culha *et al.*, 1998). In a review of the controlled studies of varicocele repair that were published prior to 1996, it was found (Schlegel, 1997) that the pregnancy rate for treated couples was 33% [95% confidence interval (CI), 28-39%], which was significantly higher than the pregnancy rate of 16% (95% CI, 13-20%) in untreated couples. However, there are currently only two (Madgar *et al.*, 1995; Nieschlag *et al.*, 1998) well-performed prospective, randomized controlled studies of varicocele repair in couples where a female factor has been completely ruled out or treated. Unfortunately, the two studies have opposing results, which leads to the continued controversy regarding the clinical utility of varicocele repair amongst some clinicians. However, both studies (Madgar *et al.*, 1995; Nieschlag *et al.*, 1998) observed significant improvement in semen parameters of patients undergoing varicocele repair as compared to controls. Fertility is clearly an important end-point but pregnancy is confounded by numerous variables that may be beyond the effect of a varicocele repair. For instance, one study (Nieschlag *et al.*, 1998) concluded that counselling had a significant positive effect upon pregnancy rates. In contrast, semen parameters are a more direct reflection of the patient's testicular function even though this is not an end-point that patients are greatly concerned about. Therefore, the adverse effect of varicoceles upon the testis appear to be at least partially reversible as demonstrated by improvement in semen parameters in all controlled studies and fertility in most.

Thus, there is significant evidence in the literature to support the thesis that varicoceles have an adverse effect upon the testis and that repair of a varicocele may reverse or prevent some of these adverse effects. Many of the adverse effects are incomplete such that men may initiate conception without ever realizing that their testicular function is partially compromised, for many men with a varicocele are fertile (Pinto *et al.*, 1994). However, co-existence of a varicocele with another factor that adversely affects fertility of either partner may be enough to prevent conception (Klaiber *et al.*, 1987; Peng *et al.*, 1990). Therefore, varicocele

repair should be considered in any man who has abnormal semen parameters, normal or treated spousal fertility and the absence of any other identifiable and/or correctable cause of male infertility.

Progressive effect of varicoceles

Many clinicians believe that varicoceles exert a progressive deleterious effect upon male fertility over time. Judging from the clinical evidence currently available, this issue can be divided on the basis of age: adolescents versus adults. There is a great deal of clinical data suggesting that a varicocele has a progressive deleterious effect upon the testes during adolescence. Prospective studies have shown that testicular volume either fails to increase or actually decreases in testes that are associated with varicoceles (Haans *et al.*, 1991; Aragona *et al.*, 1994; Sayfan *et al.*, 1997). Moreover, randomized prospective studies have documented catch-up growth after the varicocele is repaired (Okuyama *et al.*, 1988; Laven *et al.*, 1992; Yamamoto *et al.*, 1995b; Paduch and Niedzielski, 1997). Unfortunately, there are few data on the effect of varicoceles and varicocele repair upon semen parameters in this age group. Most clinicians have been reluctant to request semen specimens from their adolescent patients. In addition, normative data for semen parameters during early puberty are unavailable. Despite these impediments, two studies (Okuyama *et al.*, 1988; Yamamoto *et al.*, 1995b) have assessed semen parameters in a group of adolescents with varicoceles who were followed prospectively. Significant semen improvement was observed in both studies while in one (Okuyama *et al.*, 1988), a progressive decline of semen parameters was observed in the untreated group. These findings provide strong evidence supporting the hypothesis that varicoceles exert a progressive deleterious effect upon the testis during adolescence.

The question remains whether or not varicoceles exert a progressive deleterious effect during adulthood. In other words, will a man with a varicocele, who reaches young adulthood with normal semen parameters, become less fertile with time? Current dogma, which has been based upon limited evidence, is that varicoceles do exert a progressive deleterious effect upon fertility during adulthood. The evidence that has been used to support this hypothesis is the increased prevalence of varicoceles amongst men with secondary infertility as compared to men with primary infertility (Gorelick and Goldstein, 1993; Witt and Lipshultz, 1993) and a single study demonstrating a decline in sperm counts over time in men with varicoceles (Chehval and Purcell, 1992b). Primary infertility is defined as never being able to initiate conception, whereas secondary infertility is defined as having been able to father children in the past but currently having difficulty. The increased prevalence of varicoceles amongst men with secondary infertility suggests that this vascular lesion has a progressive rather than static effect upon male fertility. In other words, men were able to father children during adulthood but develop infertility over time. However, these studies did not address potential alternative explanations for their findings and both are potentially flawed. The observed increase in the prevalence of varicoceles may be due to either an absolute increase in the number of men with varicoceles who have secondary infertility or a relative increase due to a reduction of other etiologies that cause primary infertility. Another factor which may affect the interpretation of these studies is the fertility

potential of the spouse. Female fertility potential is greatly reduced with advancing age. A varicocele may produce secondary infertility without being a progressive lesion if the wife's fertility potential is impaired with time. A varicocele may reduce a man's fertility but the couple may conceive while the wife is fully fertile. As the female partner's fertility potential declines with age, the couple may later present with secondary infertility. In an effort to control for this factor, one study (Gorelick and Goldstein, 1993) excluded couples in which the wife was older than 40 years of age. Potential flaws in these studies are the small number of men with secondary infertility and the use of scrotal ultrasonography to diagnose varicoceles. Gorelick and Goldstein reported only 98 men with secondary infertility and the incidence of varicoceles in this group was extremely high, 81%, which suggests a possible referral bias. The study by Witt and Lipshultz (1993) reviewed the charts of only 510 patients. Moreover, the 50% prevalence of varicoceles amongst men with primary infertility in this study is significantly higher than the published average prevalence of varicoceles in infertile men, which may be due to their use of scrotal ultrasonography to diagnose varicoceles.

A third study (Jarow *et al.*, 1996a) on this subject did not demonstrate an increased prevalence of varicoceles amongst men with secondary infertility. In this multicentre study, more than 2000 men with infertility, of whom 741 had secondary infertility, were examined by the same physicians using the same criteria for the diagnosis of a clinical varicocele. With the exception of vasal agenesis, which represented only a small fraction of the patient population, a significant reduction in the prevalence of factors that are thought to cause primary infertility was not observed. Therefore, it is unlikely that the observed increased prevalence of varicoceles amongst men with secondary infertility in the other two studies was due to the absence of other factors causing primary infertility unless their patient population with primary infertility contained an unusually large number of men with vasal agenesis. In contrast to the other published reports, the prevalence of varicoceles amongst men with primary and secondary infertility was not significantly different in this study (Jarow *et al.*, 1996a). Exclusion of those men with spouses aged >40 years did not alter the results of this study. Thus, the evidence in the literature regarding the prevalence of varicoceles amongst men with secondary infertility is divided.

The other study that is frequently quoted as supporting evidence that varicoceles are progressive lesions during adulthood is a retrospective study of semen parameters amongst men with untreated varicoceles (Chehval and Purcell, 1992b). Chehval and Purcell observed deterioration in seminal parameters in 13 adult men with untreated varicoceles over time. These patients were the male partners of couples being evaluated for infertility that had been evaluated previously and were re-evaluated because of persistent infertility. Their varicoceles were not repaired initially because they had either normal or near normal semen parameters at baseline. Repeat semen testing, performed 1-8 years later because of continued infertility, revealed a significant decline in the average semen parameters. The average sperm count went from $90 \times 10^6/\text{ml}$ at baseline to $15 \times 10^6/\text{ml}$ at follow-up. This study suggests that varicoceles exert a significant and rapid deleterious effect over time during adulthood. However, there are significant concerns regarding the study design. The methods used by the authors to select patients for re-evaluation is highly biased.

In addition, a control group of infertile men without varicoceles should have been followed to determine whether the observed effect is specific to varicoceles or related to being infertile. The authors did not identify a similar population of men with untreated varicoceles whose wives eventually conceived to see if their semen parameters also declined.

There is only one prospective longitudinal study (Lund and Larsen, 1998) assessing semen quality of men with untreated varicoceles performed to date, and this study did not demonstrate a significant decline in semen parameters. Lund and Larsen evaluated 77 men, asymptomatic men with varicoceles and controls, over an 8 year period. Follow-up was obtained in 75% of the men, with an equal distribution amongst patients and controls. As observed in many other studies, the semen quality at baseline was significantly worse in men with varicoceles as compared to controls. However, this study did not demonstrate a significant deterioration of semen parameters over time in the men with untreated varicoceles. Interestingly, there was a decline in sperm count in the control group but the absolute values remained well within normal limits.

Thus, the evidence that is currently available strongly supports the conclusion that varicoceles do exert a progressive deleterious effect upon testicular function as reflected by both testicular volume and semen parameters during adolescence. In contrast, there is little compelling evidence available at this time to suggest that varicoceles have the same deleterious effect over time during adulthood; most of the current data suggest otherwise. However, it would still be prudent to monitor young men who have asymptomatic varicoceles until they have completed their reproductive goals. Based upon current literature, a yearly semen analysis would be sufficient as long as baseline semen parameters are well within normal limits.

Varicocele size

A topic of considerable debate over the recent past is whether or not varicocele size affects outcome of varicocele repair. This is of considerable importance since early reports suggested that varicocele size did not have an impact upon subsequent pregnancy rates (Dubin and Amelar, 1970; Fogh-Andersen *et al.*, 1975), leading to the conclusion that very small varicoceles (subclinical) should be identified and treated. A subclinical varicocele is defined as a varicocele that is not palpable on physical examination but detected by a radiological imaging study. The most commonly used imaging studies are scrotal ultrasonography, venography and thermography (World Health Organization, 1985a; McClure and Hricak, 1986; Yamaguchi *et al.*, 1989). As stated previously, clinical varicoceles are present in ~15% of the general population and up to 40% of men being evaluated for infertility. In contrast, studies have shown that subclinical varicoceles are much more common, being present in 44% of fertile men and ~60% of men attending infertility clinics (Kursh, 1987; Meacham *et al.*, 1994). Thus, the majority of subfertile men and many men in the general population would be candidates for varicocele repair if subclinical varicoceles were considered significant.

Dubin and Amelar reported a series of 111 men undergoing varicocele repair and observed that varicocele size did not have an impact upon either semen improvement or pregnancy rates (Dubin

and Amelar, 1970). Moreover, Fogh-Andersen and colleagues demonstrated improvement in semen parameters and fertility following internal spermatic vein ligation in 22 men without varicoceles (Fogh-Andersen *et al.*, 1975). The implication of this study is that either the presence of pathology is not relevant to subsequent improvement following a varicocele repair or that many of these patients had subclinical varicoceles that were not detected by routine physical examination. These two studies have served as the cornerstone for advocates of the detection and treatment of subclinical varicoceles. The initial development of a more 'objective' method to diagnose varicoceles using a Doppler stethoscope was intended to substantiate the clinical findings (Greenberg *et al.*, 1979). However, these diagnostic studies soon led to the detection of abnormalities that were not detectable by routine physical examination. Several of other radiological imaging modalities have been developed and their accuracy has been assessed in clinical practice (World Health Organization, 1985b; Petros *et al.*, 1991; Eskew *et al.*, 1993). Unfortunately, in the absence of a true 'gold standard' for the diagnosis of a subclinical varicocele, the accuracy of these diagnostic techniques can never be determined. Subsequent studies of the outcome of subclinical varicocele repair show conflicting results (Marsman, 1985; Bsath and Masabni, 1988; Yarborough *et al.*, 1989; McClure *et al.*, 1991; Dhabuwala *et al.*, 1992; Marsman and Schats, 1994; Jarow *et al.*, 1996b; Yamamoto *et al.*, 1996). However, the only randomized prospective study that was performed does not demonstrate any efficacy of subclinical varicocele repair (Yamamoto *et al.*, 1996).

There are two major issues that speak strongly against subclinical varicocele repair. The first issue is accuracy of diagnosis. As previously mentioned, a commonly accepted 'gold standard' for the diagnosis of a varicocele does not exist. The most commonly employed diagnostic techniques for subclinical varicoceles are venography, scrotal ultrasonography and thermography. The accuracy of these diagnostic studies is far from perfect. For instance, the correlation between venography and colour Doppler scrotal ultrasonography reveals an accuracy of ~60% when venography is used as the standard (Eskew *et al.*, 1993). This accuracy is only slightly better than if one had performed a coin toss to determine the diagnosis. Other studies assessing the diagnosis of subclinical varicoceles came to a similar conclusion (Netto Junior *et al.*, 1984; Petros *et al.*, 1991; Hoekstra and Witt, 1995). The second issue is that more current studies suggest that varicocele size does have an impact upon prognosis. Steckel and associates observed a direct relationship between varicocele size and seminal improvement following varicolectomy in 86 men (Steckel *et al.*, 1993). They found that men with large varicoceles tend to have significantly worse baseline semen parameters but much more improvement following varicocele repair as compared to men with small varicoceles. In an attempt to identify the appropriate venous size criteria for the ultrasonographic diagnosis of varicoceles, Jarow and colleagues also found that varicocele size had a major impact upon outcome (Jarow *et al.*, 1996b). The findings of this study strongly supported the conclusions of Steckel and associates that varicocele size had an inverse relationship with baseline semen parameters and a direct relationship with potential improvement. In other words, men with large varicoceles tend to have worse baseline semen parameters and they also tend to experience the

greatest improvement following varicocele repair. The patients with clinical varicoceles started out with a lower baseline total motile sperm count, smaller testicular volume, and higher serum FSH. Marks and co-workers had previously shown that all of these pre-operative factors would predict a poor outcome following varicocele repair (Marks *et al.*, 1986). Yet, despite the worse prognosis, the patients with a clinical varicocele experienced a significantly greater improvement in total motile sperm count post-operatively. The mean total motile sperm count of this group went from 13×10^6 to 39×10^6 /ejaculate with 67% experiencing an improvement of >50% from baseline. In contrast, only 41% of the patients with a subclinical varicocele experienced significant improvement in semen parameters and the mean total motile sperm count for the entire group was unchanged.

Thus, the current evidence in the literature supports the hypothesis that varicocele size does matter and that patients with large varicoceles are more likely to improve. Diagnosis and treatment of subclinical varicoceles is not recommended since the current evidence suggests that these patients are unlikely to benefit and, potentially more importantly, the accuracy of the diagnosis 'subclinical varicoceles' is highly questionable.

Conclusions

The varicocele is a common and relatively simple vascular lesion that has highly variable and individualized effects upon men. There is a great deal known about varicoceles but still much to learn and many controversies. It appears that some of these discrepancies are related to varicocele size as well as age of onset. Yet, the majority of men who have varicoceles are able to conceive without intervention. Based upon the current data available, several firm conclusions may be reached. First, there is very strong evidence to support the fact that, as observed for centuries, varicoceles exert a deleterious effect upon the testis and its function. This effect appears to be bilateral, even in men with unilateral varicoceles. Second, repair of a varicocele, whether as an adolescent to prevent damage and encourage growth or as an adult to improve fertility, does ameliorate some of the harmful effects of this vascular lesion. Third, there is convincing evidence that varicoceles exert a progressive deleterious effect during adolescence. However, the evidence that a varicocele has a progressive deleterious effect upon adults with normal semen parameters is not convincing. Finally, current evidence suggests that varicocele size does have prognostic value and that the relationship between varicocele size and seminal improvement is a direct one. Therefore, men with smaller varicoceles experience the least improvement. This fact, combined with the inaccuracies of diagnosis subclinical varicoceles, makes the detection and management of subclinical varicoceles a highly dubious enterprise.

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