

## Varicocele and Male Infertility: Evidence in the Era of Assisted Reproductive Technology

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### Abstract

**Purpose:** To evaluate the current literature on the varicocele treatment and impact on fertility.

**Materials and Methods:** Pertinent articles were identified through PubMed search on varicocele repair and male infertility.

**Discussion:** The proposed mechanisms of how varicocele results in impaired spermatogenesis and infertility include an altered or impaired testicular blood flow, increased scrotal temperature and oxidative stress as well as resulting sex hormone changes, reflux of adrenal hormones, and autoimmunity with anti-sperm antibody formation. The repair of varicocele as an infertility treatment is dependent on many factors such as the grade and size of the varicocele, unilateral or simultaneous bilateral repair, female partner's age, the period during which the couple as failed to conceive and quality of the semen.

**Summary:** Varicoceles can present in up to 40% of men presenting with infertility and published literature support the findings that varicocele adversely affect spermatogenesis. Surgical varicocelectomy is an effective treatment for improving the semen parameters in men and spontaneous pregnancy rate for couples with an infertile male partner who has low semen parameters and a palpable varicocele. Comparative studies favour the microsurgical subinguinal technique as the standard of care with highest rates of success and lowest rates of complications.

### Introduction

Varicocele is defined as dilatation of the pampiniform plexus of the spermatic cord and has long been thought to be associated with male infertility. It is estimated that 10-15% of men and adolescent boys have varicoceles [1], and in men with abnormal semen analysis, the prevalence of varicocele reached 25% [2]. In fact varicocele is the most commonly seen and correctable cause of male factor infertility [1].

The aetiology and pathophysiology of varicocele is complex and likely multifactorial. Contemporary literature suggests that this phenomenon is likely age-dependent, as the incidence in prepubertal boys is extremely rare and increases to about 15% in adolescent [3]. Primary varicocele involves defective venous valves and secondary varicoceles often are a result of external venous compression (e.g., retroperitoneal mass). Most varicoceles are left sided and proposed pathophysiologic mechanisms include anatomical insertion of the left testicular vein in to the renal vein as opposed to a more oblique inlet on the right side. Other proposed mechanism include defective valves, partial compression of the left renal vein between the aorta and superior mesenteric vein (nutcracker syndrome) or extrinsic pressure from retroperitoneal processes on the testicular vein [1].

Varicocele is often asymptomatic and if symptoms do occur, they may include testicular discomfort and presence of varicosities of the scrotal wall. The diagnosis of varicocele is predominantly made by clinical examination. Varicocele can be classified as (1) Grade 3 (visible and palpable at rest), (2) Grade 2 (palpable at rest, but no visible), (3) Grade 1 (palpable during valsalva maneuver but not otherwise), and (4) subclinical (only demonstrable on Valsalva maneuver on imaging studies such as colour-Doppler ultrasound). In general, there is no indication to routinely perform scrotal ultrasound or other imaging for subclinical varicocele (thermography, Doppler, scintigraphy or spermatic venography) as only palpable varicocele has been shown to be associated with infertility [4]. Nonetheless colour-Doppler ultrasound can be useful to assess underlying testicular abnormality such as parenchymal lesion and quantify degree of testicular hypotrophy.

### Pathophysiology of Varicocele and Male Infertility

Many studies have established the association between the presence of varicocele and abnormal semen parameters in infertile men. MacLeod was largely credited to first report that sperm in the majority of semen samples obtained from infertile men with varicocele were present at a lower count, decreased motility, and more frequently had abnormal morphologies compared to fertile men [5]. While varicocele has been implicated as a cause in 35-50% of men with primary infertility, it affects up to 80% of men with secondary infertility, suggesting that varicoceles can cause progressive decline in testicular function over time [6]. A study conducted by the World Health Organization found that of the 25.4% of infertile men with abnormal semen, it was often accompanied by decreased testicular volume, lower total sperm count, and a decline in Leydig cell function [2].

The proposed mechanisms of how varicocele results in impaired spermatogenesis and infertility include an altered or impaired testicular blood flow, increased scrotal temperature and oxidative stress as well as resulting sex hormone changes, reflux of adrenal hormones, and autoimmunity with anti-sperm antibody formation through potential breaches in blood-testis barrier [7]. A growing body of literature directly correlates an increase in reactive oxygen species and reduced sperm quality among infertile men with varicocele [8]. Studies in infertile men also showed higher DNA fragmentation, decreased mitochondrial

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activity in sperm, and reduced total antioxidant capacity of semen [9]. Allamaneni reported that semen reactive oxygen species levels correlated positively with the grade of the varicocele [10]. Regardless of specific mechanisms, it seems likely that the pathophysiology of varicocele is multifactorial and involves additional effects of inter-relatedly increase the detrimental effects on spermatogenesis.

## Varicocele Repair in the Era of Assisted Reproductive Technology: What is the Evidence?

A joint consensus statement between The Practice Committee of the American Society for Reproductive Medicine and The Male Infertility Best Practice Policy Committee of the American Urological Association [11] concluded that varicocelectomy should be offered to the male partner in couples attempting to conceive only when all of the following conditions were present: a palpable varicocele, documented couple infertility, a female partner with normal fertility or potentially correctable infertility, and a male partner with one or more abnormal semen parameters or test results showing abnormal sperm function. In addition, an adult male presenting with palpable varicocele and abnormal semen analyses is a candidate for varicocele repair even if he is not currently attempting to conceive but has a desire for future fertility. The committees also reported that varicocele treatment for infertility is not indicated in patients with normal semen parameters, even those presenting with testicular atrophy [11]. In contrast, testicular atrophy is the most widely accepted indication for varicocele repair in adolescent boys and should be offered to adolescents presenting with palpable varicocele and ipsilateral testicular growth retardation greater than 2 ml or two standard deviations from the mean of the normal testicular growth curve.

The repair of varicocele as an infertility treatment is dependent on many factors such as the grade and size of the varicocele, unilateral or simultaneous bilateral repair, female partner's age, the period during which the couple has failed to conceive and the quality of the semen. Current evidence supports the idea that varicocele size does matter and that repair of large varicoceles is more likely to improve seminal parameters than repair of smaller varicoceles [12]. Studies also supported that bilateral varicoceles repair compared to unilateral repair was associated with greater improvement in semen parameters and a higher spontaneous pregnancy rate [13,14]. This evidence would support that subfertility in men with abnormal semen analyses and bilateral palpable varicoceles is the result of an additive effect and therefore would justify simultaneous varicoceles repair, even if one is small. In addition, patients with higher sperm counts prior to repair showed significantly greater absolute improvement in semen parameters than those with more severe oligospermia [15]. Several factors are thought to predict the success of varicocele repair outcomes in infertile men and these include the presence of Y chromosome micro-deletion, high follicle stimulating hormone level, low testosterone level, significant testicular hypotrophy and severe oligospermia [16].

While varicocele can be treated by various surgical approaches (subinguinal vs. inguinal vs. retropubic) and techniques (open vs. laparoscopic vs. radiological embolization), microsurgical subinguinal varicocelectomy technique seems to emerge as the standard of care in terms of least recurrence and complications. Cayan et al. [17] concluded in a meta-analysis that microsurgical technique has a higher spontaneous pregnancy rate (41% vs. 30-38%) and lower postoperative recurrence (1% vs. 2-15%) and hydrocele formation (0.4% vs. 2-8%) compared to other techniques.

Meta-analysis by Marmar published in 2007 reported that surgical

varicocelectomy in infertile men with palpable lesions and at least one abnormal semen parameter improves the odds of spontaneous pregnancy rate in their female partners, compared with no or medical treatment for palpable varicocele (2.87; 95% Confidence Interval (CI) 1.33-6020]. However the number needed to treat were 5.7 (95% CI, 4.4-9.5) [18]. In contrast, the Cochrane review published in 2009 (with some debatable methodology) concluded that varicocele repair for otherwise unexplained infertility could not be recommended as the odd ratio favouring treatment over no treatment of only 1.1 (95% CI, 0.73-1.68] [19]. More recently Abdel-Meguid [20] reported that subfertile men who underwent subinguinal varicocelectomy compared to observation was associated with higher spontaneous pregnancy rate (32.9% vs. 13.9%; odds ratio 3.04, 95% CI, 1.33-6.95) and that in the treatment group within-arm analysis, the mean of all semen parameters improved significantly at 12 months follow up ( $p < 0.0001$ ) in a prospective, non-masked, parallel-group randomised controlled trial with a one-to-one concealed-to-random allocation that.

The advent of Intracytoplasmic Sperm Injection (ICSI) has transformed the landscape of assisted reproductive technology and relative pregnancy rates achieved by ICSI have resulted in a troubling decrease in efforts among IVF specialists for the need to correctly diagnose and/or to a certain degree treat various causes of male infertility. Cost analysis studies by Schegel [21] and Meng et al. [22] found that primary treatment with varicocelectomy was more cost effective than sperm retrieval/ICSI and that the average delivery rate reported after one ICSI attempt was similar to that after varicocele repair (28% vs. 30%). Furthermore, only the male partner need to undergo surgery and avoid issues associated with IVF therapy (e.g., cost, multiple gestations, birth defects and ovarian hyperstimulation). An important point to counsel a couple that pregnancies is not immediately achieved after varicocele repair and that the mean time for semen improvement and spontaneous pregnancy rate after surgery is approximately five to seven months [16].

## Conclusions

Varicoceles can present in up to 40% of men presenting with infertility and published literature support the findings that varicocele adversely affect spermatogenesis. Indeed surgical varicocelectomy is an effective treatment for improving the spontaneous pregnancy rate for couples with an infertile male partner who has low semen parameters and a palpable varicocele. Comparative studies favour the microsurgical subinguinal technique as the standard of care with highest rate of success and lowest rate of complications. However the degree to which varicocele repair improves pregnancy rates and the success of assisted reproductive technology remains controversial and further carefully randomized controlled trials are needed for more precise evaluation of true impact of varicocelectomy on fertility outcomes.

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