

Varicocele—A Dilemma for the Urologist Current Concepts

a report by

Marcello Cocuzza, MD, Edmund Sabanegh, MD and Ashok Agarwal, PhD

Reproductive Research Center, Glickman Urological Institute, Cleveland Clinic

Although varicocele repair is widely used as a treatment for male infertility, the effectiveness of varicocelectomy has been a focus of intense debate for nearly 50 years. A number of conflicting reports in the literature has resulted in divergent guidelines by various professional groups. The American Urological Association (AUA) and the American Society for Reproductive Medicine (ASRM) recommend treatment for clinical varicoceles when a male partner has abnormal semen parameters. The National Collaborating Center for Women's Health of 2005 suggests not offering surgery for men with varicocele as a fertility treatment, while the European Association of Urology (EUA) still considers it controversial.

There is significant evidence in the literature to support the theory that varicocele has a harmful effect on the testis and that varicocelectomy can prevent the progressive decline in testicular function, as well as reverse the damage. However, there are few adequately controlled prospective trials concerning the effect of varicocele repair on fertility.

The development of intracytoplasmic sperm injection (ICSI) as an effective therapy for cases of male infertility has become a valid means of overcoming multiple sperm deficiencies. ICSI has been suggested by some to represent the solution for all cases of male factor infertility, regardless of etiology. Even

men with potentially treatable causes of infertility might be treated with assisted reproductive techniques instead of specific therapy.

The following review discusses current concepts in varicoceles and summarizes the leading theories on the mechanisms for varicocele-induced testicular damage. It reviews existing literature on the efficacy of varicocelectomy for the treatment of infertility. It discusses the role of varicocelectomy in the management of varicoceles in the adolescent as well as in nonobstructive azoospermic patients. Finally, the authors critically review the cost-effectiveness of the surgical treatment of a varicocele compared with assisted reproductive techniques.

Varicocele and Male Infertility

Over the past decade, the association of varicocele with male subfertility has been repeatedly demonstrated and the beneficial effect of varicocele repair in infertile men with oligoasthenospermia has been reported.¹ Varicocele is implicated as a factor in 35–50% of men with primary infertility and up to 81% of men with secondary infertility.^{2,3} The higher incidence in secondary infertility implicates varicoceles in producing a progressive decline in testicular function over time.

An association of abnormal semen parameters in infertile patients with the presence of varicocele during physical examination has been reported by several studies. In 1965, MacLeod first reported that the majority of semen samples obtained from 200 infertile men with varicocele had decreased sperm count, decreased motility, and increased abnormal forms.⁴ A study conducted by the World Health Organization (WHO) on varicocele found its presence in 25.4% of infertile men with abnormal semen, noting that it is accompanied by decreased testicular volume, lower total sperm count, and a decline in Leydig cell secretion.⁵

Large numbers of uncontrolled studies have suggested that varicocele ligation can improve sperm count, motility, and morphology. Overall, varicocelectomy studies reported significant improvements in one or more semen parameters in 65% of men, and pregnancy rates of 40% in couples.⁶ However, the effectiveness of varicocele repair in terms of pregnancy rate improvement is a controversial matter in the literature due to the large number of poorly designed and uncontrolled studies.

Various mechanisms have been proposed for infertility in men with varicocele. The etiology remains to be proved, but suggested mechanisms include hypoxia and stasis, testicular venous hypertension, elevated testicular temperature, increase in spermatic vein catecholamine, and increased oxidative stress.^{7–12} However, the exact cause is still unknown.



Marcello Cocuzza, MD, is a Fellow in Andrology in the Glickman Urological Institute at the Cleveland Clinic. Since 2004, he has been a staff member in the Urology Department of Hospital das Clinicas, Sao Paulo, Brazil. His research interests are in the surgical treatment of male infertility and in unraveling the role of oxidants in sperm dysfunction.



Edmund S Sabanegh Jr, MD, is Chief of the Section of Male Infertility for the Glickman Urological Institute. His research interests include complex reconstructions for obstruction of the reproductive tract, testicular blood flow, varicoceles, and environmental influences on fertility. He heads one of the few Male Infertility Fellowship programs in the US, which combines basic research with extensive clinical experience.



Ashok Agarwal, PhD, is the Director of the Reproductive Research Center, and the Director of the Clinical Andrology Laboratory and Reproductive Tissue Bank at the Cleveland Clinic's Glickman Urological and Kidney Institute. Professor Agarwal is recognized internationally for his innovative research into the pathophysiology of male infertility.

Oxidative Stress and Varicocele

In the context of human reproduction, a balance normally exists between reactive oxygen species (ROS) production and antioxidant scavenging activities in the male reproductive system. Minimal amounts of ROS remain in the system since they are needed for the regulation of normal sperm functions such as sperm capacitation, the acrosome reaction, and sperm–oocyte fusion.¹³ The production of excessive amounts of ROS in semen can overwhelm the antioxidant defense mechanisms of spermatozoa and seminal plasma, causing oxidative stress. Recent studies report that increased ROS levels are detected in the semen of 25–40% of infertile men.^{14,15} Aitken et al. reported that men with elevated ROS levels in semen have a seven-fold reduction in conception rates compared with men with low ROS.¹⁶ Moreover, high levels of DNA damage and oxidative stress have been associated with a decrease in the fertilizing capacity of spermatozoa.¹⁷

The relationship between ROS and varicocele has been documented by our center.¹² Studies in subfertile men with varicocele demonstrate the existence of an excessive release of nitric oxide within dilated spermatic veins, which might be responsible for spermatozoa dysfunction.^{18,19} Seminal ROS levels show a positive correlation with varicocele grade. Men with varicocele grade 2 and 3 have significantly higher seminal ROS levels compared with men with varicocele grade 1.²⁰ A recent meta-analysis reported that oxidative stress parameters (such as ROS and lipid peroxidation) are significantly increased and antioxidant concentrations significantly decreased in varicocele patients compared with normal sperm donors.²¹ Mostafa et al. was the first to show that varicocelectomy reduces ROS levels and increases concentrations of antioxidants such as superoxide dismutase, catalase, glutathione peroxidase, and vitamin C of seminal plasma from infertile men.²²

DNA Damage and Varicocele

Excessive generation of ROS in the reproductive tract attacks not only the fluidity of the sperm plasma membrane, but also the integrity of DNA in the sperm nucleus. DNA bases are susceptible to oxidative damage, resulting in base modification, strand breaks, and chromatin cross-linking. Infertile men with varicoceles have high levels of spermatozoal DNA damage, which also appear to be related to increased levels of reactive oxygen species.²³ Chen et al. reported that patients with varicocele have increased 8-hydroxy-2'-deoxyguanosine, an indicator of oxidative DNA damage.²⁴ Zini and Libman reviewed the reports of 37 men who underwent microsurgical varicocelectomy and showed decreased sperm DNA denaturation six months after varicocelectomy compared with pre-operatively, suggesting a mechanism for semen parameter improvements noted post-ligation (27.7 versus 24.6%, respectively, $p < 0.05$).²⁵

Predicting Improvement in Semen Parameters and Pregnancy Rates Following Varicocelectomy

The etiology underlying infertility is uncertain in men whose seminal parameters do not significantly improve or whose partners do not achieve pregnancy following varicocele surgery. A key to resolving this problem is to identify patients who could benefit from treatment by evaluating variables of favorable prognosis. Fretz and Sandlow summarized these variables and they are shown in *Table 1*.

Recently, the impact of varicocele grade on the magnitude of improvement in semen quality after varicocele repair has been discussed. Early reports suggested that varicocele size had no relation to outcome following

varicocele repair in infertile men.^{26,27} These findings led to the conclusion that non-palpable varicoceles detected by radiological image studies should be candidates for treatment as well. The majority of infertile men and other males of the general population would be candidates for varicocele repair, as subclinical varicocele is detected in approximately 44% of fertile men and up to 60% of infertile patients.^{28,29} However, subsequent studies have suggested that subclinical varicocelectomy is of questionable benefit. While there are mild improvements in post-operative semen parameters, pregnancy rates were not improved with ligation of these subclinical varicoceles.^{30–33} This was also confirmed by the only randomized prospective study.³⁴ Additionally, surgical repair of subclinical varicoceles did not result in statistically significant differences in seminal parameters or pregnancy rate compared with treatments using clomiphene citrate.³⁵ The debate over repair for subclinical varicoceles can be resolved only by performing randomized trials with treated and untreated groups of patients. In the mean time, patients with subclinical varicocele should be aware that surgery is highly questionable and no longer recommended based on the existing literature.¹

Steckel et al. reported that men with grade III varicocele have lower motile sperm counts and show a greater relative improvement in semen quality after varicocelectomy than those with grades I and II varicoceles who present with higher mean sperm densities.³⁶ However, since large varicoceles are associated with the lowest pre-operative semen quality and thus compensate for greater initial testicular impairment, overall pregnancy rates are similar regardless of size.³⁰ The current evidence supports that varicocele size does matter and that infertile patients receiving varicocele repair for large varicoceles are more likely to show seminal parameter improvement than patients with smaller varicoceles.

Patients with higher pre-repair sperm counts have significantly greater absolute improvement in semen parameters than those with more severe oligospermia.⁶ Moreover, men who achieved a post-operative total motile sperm count greater than 20 million were more likely to initiate a pregnancy by less invasive techniques: natural and intrauterine insemination (IUI).³⁷

Marks et al. described that pre-ligation sperm motility of 60% or more is associated with an improved post-ligation pregnancy rate. Also, reduced presurgical testicular volume or elevated follicle-stimulating hormone (FSH) concentrations were identified as negative predictors for post-ligation outcome. The lack of testicular atrophy was found to indicate higher post-operative pregnancy rates, and testicular volume greater than 30ml was identified as an independent predictor of fertility after varicocelectomy.^{38,39} Varicocele repair is more likely to improve fertility in patients with serum FSH concentrations lower than 11.7mIU/ml or lower than 300ng/ml.^{38,39}

The gonadotropin response to exogenous gonadotropin-releasing hormone (GnRH) test has been suggested by some as a means to identify patients who would benefit from varicocele ligation. Atikeler et al. showed that a significant elevation in FSH (approximately 1.5–2.0 times baseline) and luteinizing hormone (LH) (approximately 2.0–2.5 times baseline) 30–60 minutes after an intranasal bolus of GnRH (100mg) was a predictor in identifying patients whose semen parameters would improve after varicocelectomy.⁴⁰ Similarly, Segenreich et al. reported that 81% of men with an exaggerated GnRH response had a post-operative improvement in their sperm variables, whereas only 19% of men lacking an exaggerated response showed improvement. Corresponding pregnancy rates at 18

Table 1: Pre-operative Predictors of Seminal Improvement after Varicocelectomy⁴⁷

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|---|
| High-grade varicocele (grade III) |
| Lack of testicular atrophy |
| Normal serum FSH |
| Total motility >60% |
| Total motile sperm count >5x10 ⁶ |
| Positive GnRH stimulation test |

FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone.

months in the two groups were 67.4 and 9.3%, respectively. The authors concluded that a positive pre-operative GnRH test is a good predictor of improvement in semen parameters and pregnancy after varicocele surgery.⁴¹

Y chromosome microdeletions are another factor that portends little or no improvement after varicocele ligation. The Y chromosome plays a critical role in the control of spermatogenesis. Y chromosome microdeletions can be detected in as many as 4–14.3% of oligospermic men and in up to 18% of azospermic men.^{41,42} Moro et al. reported that Y chromosome deletions were observed in seven out of 40 infertile patients (17.5%) presenting with severe oligospermia (fewer than 5x10⁶ sperm/ml), bilateral testicular volume loss, and varicocele. Interestingly, no deletions were found in 80 patients with varicocele and mild oligozoospermia (sperm count 10–20x10⁶/ml).⁴³ Pryor et al. examined the incidence of Y chromosome microdeletion in 200 consecutive infertile men and found that 3% of those with varicocele had microdeletions.⁴⁴ Cayan et al. reported results after varicocelectomy in five patients who had co-existing Y chromosome deletions and found no significant improvement in seminal parameters or pregnancy rates.⁴⁵ These findings suggest that men with poor seminal parameters and Y chromosome microdeletions might have an incidental varicocele for which surgical repair is unlikely to improve fertility.⁴⁶

These prognostic indicators can facilitate the identification of patients with a better prognosis for varicocele repair, or the choice of those couples more likely to be initial candidates for assisted reproductive techniques.

Varicocelectomy or Assisted Reproductive Technology—What Is Better?

In the era of intracytoplasmic sperm injection, the role of andrologists has been transformed. The relative pregnancy rates achieved by this modality have led to a troubling decrease in efforts to establish a correct diagnosis of infertility cause.

Although assisted reproduction technology (ART) provides an opportunity to families with infertility, the potential medical risks entailed by multiple-gestation pregnancies and the associated costs cannot go unnoticed. Therefore, couples considering assisted reproductive techniques should be aware of the risks of these procedures. Medical risks include ovarian hyperstimulation and multiple-gestations.^{48–50}

In addition to the safety concerns, which procedure is more cost-effective for infertile couples with male varicocele in this era of cost-containment awareness: ICSI or varicocele repair? Schlegel first reported a comparison of ICSI and varicocele repair using a ‘cost per delivery’ analysis and concluded that primary treatment with varicocelectomy was more cost-effective than sperm retrieval/ICSI, while providing comparable delivery rates.⁵¹ Total hospital delivery costs, as well as costs attributable to multiple gestations

and complications, were analyzed. The average US reported delivery rate after one attempt of ICSI was 28% compared with 30% found after varicocele repair. The average cost per delivery for varicocelectomy was \$26,268, whereas for ICSI it was estimated at \$89,091.

Recently, Meng et al. applied a decision-analyses model to compare the cost of pregnancy for varicocelectomy versus ART treatment in varicocele patients.⁵² Decision models are constructed with pre-defined assumptions and are used to estimate outcomes once several options for treatment are available. The authors concluded that initial varicocele repair was more cost-effective than ART treatment for infertile couples.

After varicocele repair, a couple can proceed with assisted reproduction if pregnancy is not achieved. Varicocele repair may allow some couples to proceed with IUI prior to proceeding with more advanced assisted reproductive techniques, since studies suggest that varicocelectomy improves the effectiveness of subsequent IUI.^{53,54}

While ICSI provides a viable alternative for the treatment of infertile couples with varicocele, current evidence supports that the treatment of varicocele is a more cost-effective therapy for infertility.^{51–53}

Managing Varicocele in Adolescents

Although varicocele is cited as one of the leading causes of male infertility, it is essential to recognize that varicocele does not typically begin in adulthood, but rather in the peri-pubertal period. Epidemiological studies reveal that varicocele is not generally present in children under 10 years of age, and its incidence gradually increases at the beginning of the second life decade.^{55,56} The incidence of varicocele in adolescents is approximately 15% by the late teenage years, a rate similar to the general population, and with the same distribution of grades. Varicocele incidence peaks at the age of 15 years and remains relatively stable thereafter.^{55,56}

Awareness of the potential damage associated with long-standing varicoceles has motivated urologists to become more conscientious in their pursuit of adolescent varicoceles. The decision of when to treat adolescents with varicocele is controversial, since 80% of adults with varicocele are fertile.⁵⁷ Routine surgery is inappropriate for all adolescents since it is not cost-effective and fertility will not necessarily be affected by the varicoceles. Non-selective surgical intervention would submit a large population of boys to unnecessary surgery. On the other hand, it is unacceptable to allow potentially irreversible testicular damage to manifest with infertility as adults. Adolescent varicoceles are often associated with testicular volume loss, endocrine abnormalities, and abnormal seminal parameters.⁵⁸ After varicocele diagnosis, patients should be evaluated for testicular volume and consistency. Varicocelectomy is indicated when a palpable varicocele is associated with ipsilateral testicular growth retardation greater than 2ml or two standard deviations compared with the normal testicular curve. Additionally, it should be considered in boys with bilateral varicoceles or a solitary testis, since testicular growth retardation may not be evident in this population. Physicians may discuss the possibility of seminal analysis for older adolescents to help with the decision to treat although few studies have evaluated the normality of seminal parameters in adolescents with varicocele, most likely because of ethical concerns related to the procurement of semen specimens in young boys.^{59,60} If seminal parameters are abnormal and high-grade varicocele is present, surgery should be

considered even with bilateral normal testicular volume.

As in adults, exaggerated GnRH response to stimulation has been detected in adolescents with varicocele.⁶¹ Adolescents with a palpable varicocele and abnormal gonadotropin stimulation test responses may benefit from varicocele surgery.⁶² In addition, in adolescents large varicoceles that are associated with debilitating ipsilateral testicular pain should be considered for repair.⁶³

A rapid catch-up growth of the affected testis after varicocelectomy has been consistently reported in 50–80% of adolescents and suggests that early intervention is effective as well as defensible.^{59,64–67} In addition, semen quality improvement has been demonstrated.^{68–70} Recently, in an uncontrolled study Salzhauer et al. showed high paternity rates among men who underwent a varicocele repair during adolescence.⁷¹

In some boys, a varicocele develops immediately before puberty when the testis is immature and vulnerable. Based on testicular size, evidence suggests that the time of development of a varicocele in relation to puberty may be the critical factor in the subsequent development of infertility.⁷² The recognition and treatment of an early-developing varicocele may help to reduce the infertility associated with this condition. In the absence of prospective controlled studies concerning the optimal management of asymptomatic varicocele in adolescents, parents should be made aware of the possibility of subsequent infertility.

Induction of Spermatogenesis after Varicocelectomy in Azoospermic Men

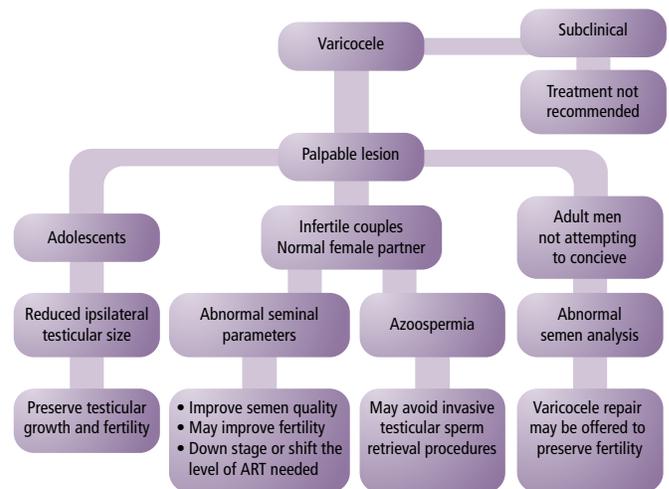
Nonobstructive azoospermia in association with a varicocele is estimated to range between 5 and 10% in adults.^{73–75} Tulloch, in 1955, reported the return of spermatogenesis and subsequent pregnancy after varicocele repair in an initially azoospermic patient, renewing attention on varicocele treatment.⁷⁶ After varicocele repair, motile sperm are found in the ejaculate of azoospermic men in 21–55% of the cases, although spontaneous pregnancies are rare.^{74,75,77} Varicocele repair in this population may avoid the need for subsequent testicular sperm retrieval procedures because they can provide sperm via ejaculation.

Even though an improvement in spermatogenesis is seen in up to half of the patients, assisted reproductive techniques will be necessary for the majority of these couples to initiate pregnancy.⁷⁸ Fertilizing ability and ICSI success rates are superior when fresh motile ejaculated sperm is used compared with sperm provided by testicular biopsy or microsurgical testicular sperm extraction.^{79,80}

Although azoospermic patients may exhibit an improvement in spermatogenesis after varicocelectomy, a gradual decline in spermatogenesis and return to azoospermia has been reported in up to 55.5% of the patients 12 months after surgery.⁷⁸ These patients may experience intermittent sperm production, and varicocele repair may have solely a temporary effect, resulting in the induction of spermatogenesis for a short period of time. Since these patients may not be able to maintain spermatogenesis, semen cryopreservation is strongly recommended following the initial improvement after surgery.

As mentioned previously, a high prevalence of Y chromosome microdeletions in azoospermic infertile men exists. Karyotype and Y

Figure 1: Algorithm of Indications and Benefits of Varicocele Repair



chromosome mapping is crucial in the evaluation of men with varicocele and azoospermia. These patients should be aware of chromosomal abnormalities so that they can obtain genetic counseling to stratify their risk of transmission to offspring.

Varicocele Treatment in the Light of Evidence-based Medicine

In this age of evidence-based medicine, it is interesting that few randomized controlled studies have been performed to clarify the cost-effective benefit of varicocelectomy. Reviews concerning efficacy of varicocelectomy in subfertile couples are heterogeneous and include studies with suboptimal methodology.⁸¹ Comparison among these reported trials is confounded by substantial differences in important factors such as varicocele size, infertility cause, seminal parameter criteria for study inclusion, concurrent female fertility factors, and short follow-up time after varicocelectomy.⁸²

The results of a systematic review by Evers and Collins in 2003 had a negative influence on the varicocele treatment recommendations of the EUA Working Group on Male Infertility.⁸³ Only randomized, controlled trials were included that addressed varicocele repair for male subfertility, and the conclusion was that surgery or radiological treatment of varicocele does not seem to be an effective treatment for male or unexplained subfertility.

A recent review challenged the meta-analysis by Evers and Collins, carrying out their own critical analysis of all available randomized, clinical trials.⁸¹ As the AUA and ASRM did not recommend varicocele repair in patients with normal semen analyses or subclinical varicoceles, five out of eight studies selected in the previous meta-analysis were excluded to allow a critical assessment of current treatment guidelines.^{34,35,84–86} Based on this review, Ficarra et al. concluded that the meta-analysis by Evans and Collins would support varicocele treatment in the context of only examining studies in the literature that were consistent with current guideline recommendations. It suggested supporting continuing varicocele treatment for improvement of fertility instead.⁸¹

The two most important randomized, controlled studies reported an

improvement in seminal parameters following varicocele repair, but they are discordant regarding pregnancy outcomes and maintain the controversy concerning varicocele treatment effects upon fertility.^{87,88}

Recently, our center tried to resolve this controversy by conducting a meta-analysis that examined the effect of varicocelectomy on semen parameters and pregnancy rates for infertile couples in which the male partner had abnormal semen parameters and clinical varicocele. We analyzed both randomized, controlled trials and observational studies. Although this data is not published yet, we concluded from our meta-analysis that surgical varicocelectomy is an effective treatment for improving semen parameters of infertile males with clinically palpable varicocele. Based on the data from current literature and contrary to previous meta-analyses, our study suggests that varicocelectomy does indeed have a beneficial effect on fertility status by improving the odds of spontaneous pregnancy in female partners.

Our results further support that the improvement in semen parameters achieved with varicocelectomy may help infertile couples achieve pregnancy spontaneously or with less invasive and inexpensive techniques such as IUI.

Conclusion

Varicocele remains a common finding in infertile men and is often the sole identifiable cause of infertility in couples. There is convincing evidence that

varicoceles produce a progressive harmful effect upon the testis resulting in the decline of seminal parameters. *Figure 1* summarizes the most common indications and the expected benefits from the varicocele repair.

The main goal of varicocelectomy is to preserve testicular function and initiate pregnancy in infertile couples. However, even when pregnancy is not achieved, improved seminal quality after surgery can obviate or downstage the need for assisted reproductive techniques. Identifying those individuals with varicocele who will present better benefit from varicocele treatment is always a challenge for andrologists.

Current data support the assertion that varicocelectomy is successful in reversing the harmful effects of varicocele upon testicular function in selected patients by improving seminal parameters in the majority of controlled studies. While the topic of varicocele treatment regarding pregnancy will remain controversial due to the limited number of randomized, controlled clinical trials, new meta-analysis supports improvements in pregnancy rates with varicocele ligation. Although ART can achieve rapid results, considering the higher expenses involved and potential safety issues—as well as the fear of transferring the unnecessary burden of invasive treatment onto healthy female partners—current literature indicates that evaluating and treating the specific male infertility cause is more cost-beneficial for infertile couples. ■

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