VARICOCELE IN INFERTILITY

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What is a VARICOCELE?

- Varicocele is a condition that involves the dilatation of the pampiniform plexus, which drains blood from the testicles.

- Normally, reverse blood flow is prevented by one-way valves.

- Defects in these valves or compression of the veins by adjacent structures can cause vessel dilatation.

- Approximately 90% of varicoceles are unilateral on the left side.
What is a VARICOCELE?

- Less frequently, bilateral varicoceles are present
- **Right-sided varicoceles are rare** and should raise suspicions of a retroperitoneal mass that is compromising venous return from the right testis [1, 2]


How to diagnose VARICOCELE?

- Clinical examination – bags of worms
- Confirmed by Duplex ultrasound

**AUA GUIDELINE**

**Recommendation:**
- Routine evaluation of infertile men with varicoceles should include a medical and reproductive history, physical examination and a minimum of two semen analyses
- Imaging studies are not indicated for the standard evaluation unless physical exam is inconclusive
The following classification of varicocele is useful in clinical practice:


<table>
<thead>
<tr>
<th>GRADE</th>
<th>PRESENTATION</th>
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<tbody>
<tr>
<td>Subclinical</td>
<td>not palpable or visible at rest or during Valsava manoeuvre, but can be shown by Doppler ultrasound</td>
</tr>
<tr>
<td>Grade 1</td>
<td>palpable during Valsava manoeuvre, but not otherwise</td>
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<tr>
<td>Grade 2</td>
<td>palpable at rest, but not visible</td>
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<tr>
<td>Grade 3</td>
<td>visible and palpable at rest</td>
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VARICOCELE in infertility

- Varicocele is a physical abnormality present in 11.7% of adult men and in 25.4% of men with abnormal semen analysis [3]

- Testicular temperature elevation, hypoxia, stasis, testicular venous hypertension, increase in spermatic vein catecholamines, increased oxidative stress and venous reflux appear to play an important role in varicocele-induced testicular dysfunction, however the exact pathophysiology of varicocele induced damage is not yet completely understood [4]

- Only palpable varicoceles have been documented to be associated with infertility

Varicocele has been implicated as a cause in 35–50% of patients with primary infertility and up to 81% of men with secondary infertility [5, 6]

High incidence in secondary infertility suggests that varicoceles cause progressive decline in testicular function over time

Varicocelectomy can reverse sperm DNA damage [7]

Although the ultimate goal of treating male factor infertility is to increase the pregnancy rate, varicocelectomy also seeks to maximize a couple’s fertility potential by improving sperm quality or avoiding a decline in testicular function

VARICOCELECTOMY - can surgery really help infertility?

- **2009 Cochrane review**: there is no evidence that treatment of varicocele improves a couples' chance of conception [8]

- **2011 meta-analysis of four RCTs of varicocelectomy in men with a clinical varicocele**: surgical correction is helpful in oligozoospermia (semen with a low concentration of sperm) and unexplained infertility [9]

- Although treatment of varicocele in infertile men may be effective, in adolescents there is a significant risk of overtreatment: most adolescents with a varicocele will have no problem achieving pregnancy later in life [10]

Recommendations:
• Varicocele treatment should be offered to the male partner of a couple attempting to conceive, when ALL of the following are present:
  1) a varicocele is palpable
  2) the couple has documented infertility
  3) the female has normal fertility or potentially correctable infertility
  4) the male partner has one or more abnormal semen parameters or sperm function test results
Recommendation:
• Adult men who have a palpable varicocele and abnormal semen analyses but are not currently attempting to conceive should also be offered varicocele repair
• Young men who have a varicocele and normal semen analyses should be followed with semen analyses every one to two years
• Adolescents who have a varicocele and objective evidence of reduced ipsilateral testicular size should be offered varicocele repair
• Adolescents who have a varicocele but normal ipsilateral testicular size should be offered follow up monitoring with annual objective measurements of testicular size and/or semen analyses
VARICOCELE - Management

AUA GUIDELINE

Recommendations:

• Varicocele repair may be considered as the primary treatment option when a man with a varicocele has suboptimal semen quality and a normal female partner

• IVF with or without ICSI may be considered the primary treatment option when there is an independent need for such techniques to treat a female factor, regardless of the presence of varicocele and suboptimal semen quality

* IVF (in vitro fertilisation): the eggs and sperm are mixed together in a dish and the sperm fertilises the egg ‘naturally’

* ICSI (intracytoplasmic sperm injection): a laboratory procedure where a single sperm is picked up with a fine glass needle and is injected directly into each egg
## EAU Guidelines

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
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</thead>
<tbody>
<tr>
<td>Varicocele treatment is recommended for adolescents with progressive failure of testicular development documented by serial clinical examination.</td>
<td>B</td>
</tr>
<tr>
<td>No evidence indicates benefit from varicocele treatment in infertile men who have normal semen analysis or in men with subclinical varicocele. In this situation, varicocele treatment cannot be recommended.</td>
<td>A</td>
</tr>
<tr>
<td>Varicocele repair should be considered in case of a clinical varicocele, oligospermia, infertility duration of ≥ 2 years and otherwise unexplained infertility in the couple.</td>
<td>A</td>
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## EAU Guidelines

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
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<tbody>
<tr>
<td>Current information supports the hypothesis that the presence of varicocele in some men is associated with progressive testicular damage from adolescence onwards and a consequent reduction in fertility.</td>
<td>2a</td>
</tr>
<tr>
<td>Although the treatment of varicocele in adolescents may be effective, there is a significant risk of overtreatment.</td>
<td>3</td>
</tr>
<tr>
<td>Varicocele repair may be effective in men with subnormal semen analysis, a clinical varicocele and otherwise unexplained infertility.</td>
<td>1a</td>
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VARICOCELE – How to repair?

There are two approaches to varicocele repair:
- surgery – open or laparoscopy
- percutaneous embolization

Surgical repair of a varicocele offers various surgical approaches:
- retroperitoneal
- inguinal
- subinguinal
- laparoscopy
VARICOCELE – Surgical repair

- Inguinal or subinguinal surgical repair employing loupes or an operating microscope for optical magnification

- Techniques using optical magnification maximize preservation of arterial and lymphatic vessels while reducing the risk of persistence or recurrence of varicocele

- Laparoscopy has been used for varicocele repair but this approach carries the risk of major intraperitoneal complications, such as injury to bowel, bladder and major blood vessels which may require laparotomy for correction
VARICOCELE – Complications of open surgical repair

- Infrequent and usually mild

- All approaches to varicocele surgery are associated with a small risk of:
  - wound infection
  - hydrocele
  - persistence or recurrence of varicocele
  - testicular atrophy (rare)
  - scrotal numbness (inguinal incision)
  - prolonged pain (inguinal incision)
## VARICOCELE – Complications

### Surgical Treatment of Varicocele

<table>
<thead>
<tr>
<th>Technique</th>
<th>Internal Spermatic Vein Ligation</th>
<th>External Spermatic Vein Ligation</th>
<th>Recurrence Rate</th>
<th>Hydrocele Formation Rate</th>
<th>Spontaneous Pregnancy Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retroperitoneal High-Ligation (Palomo)</td>
<td>Yes</td>
<td>No</td>
<td>7-35%</td>
<td>6-10%</td>
<td>25-55%</td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>Yes</td>
<td>No</td>
<td>2-7%</td>
<td>0-9%</td>
<td>14-42%</td>
</tr>
<tr>
<td>Embolization</td>
<td>Yes</td>
<td>No</td>
<td>2-24%</td>
<td>NR</td>
<td>20-40%</td>
</tr>
<tr>
<td>Macroscopic Inguinal (Ivanissevich)</td>
<td>Yes</td>
<td>Yes</td>
<td>0-37%</td>
<td>7%</td>
<td>34-39%</td>
</tr>
<tr>
<td>Microscopic Inguinal or Subinguinal</td>
<td>Yes</td>
<td>Yes</td>
<td>0-0.3%</td>
<td>0-1.6%</td>
<td>33-56%</td>
</tr>
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</table>

Estêves, 7
VARICOCELE – Percutaneous embolization

▶ Accomplished by percutaneous embolization of the refluxing internal spermatic vein(s)

▶ May be associated with less pain than occurs after the standard inguinal surgical approach, but availability of physicians with experience in interventional radiologic techniques is required

AUA GUIDELINE

Recommendations:
• The treating physician’s experience and expertise, together with the options available, should determine the choice of varicocele treatment
VARICOCELECTOMY – Follow up

AUA GUIDELINE

Recommendations:

• Persistence or recurrence of a varicocele may be treated by either surgical ligation or percutaneous embolization of the refluxing veins.
• After treatment of a varicocele, semen analysis should be done at approximately three-month intervals for at least one year or until pregnancy occurs.
STORY OF SUCCESS?

Repair of Varicocele
VARICOCELE – Story of success

- Surgical approach: eliminates over 90% of varicoceles
- Percutaneous embolization are variable and depend on the experience and skill of the interventional radiologist performing the procedure
- Most studies have reported that semen quality improves in a majority of patients following varicocele repair
- The fertility outcomes of varicocele repair have been described in numerous published studies
- A review of 12 controlled studies found a pregnancy rate of 33% in couples in which the male received varicocele treatment, as compared with 16% in untreated couples over one year
VARICOCELE – Story of success

Improvement in testosterone levels following varicocelectomy

Serum Testosterone Levels (ng/dL)

Preop

Postop

P<0.01


VARICOCELE – Story of success

Microsurgical Varicocelectomy – Semen Analysis

Fertility Index
(sperm conc.) x (% motility)/100

Grade I  Grade II  Grade III

Pre-op  Post-op

*Steckeland Goldstein. J. Urol., 149-769, 1993
There are only two well-designed, randomized, controlled studies using men with palpable varicoceles, abnormal semen parameters and normal spouses.

**STUDY 1:** showed no greater likelihood of pregnancy following varicocele repair, it did demonstrate significant improvement in testis volume and semen parameters compared to controls.

**STUDY 2:** using a crossover design, showed a statistically significant improvement in fertility following varicocele repair.

The conception rate in couples in which the male had undergone varicocele repair was 60% within one year following surgery as compared to only 10% in untreated control group.
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 [16].

In fact, varicocele treatment is not indicated in patients with subclinical varicoceles, since the improvements in seminal parameters or pregnancy rate are identical to those obtained by treatment with clomiphene citrate [17].

Patients with higher sperm counts prior to repair show significantly greater absolute improvement in semen parameters than those with more severe oligospermia [18].

In addition, men who achieved a postoperative total motile sperm count greater than 20 million were also more likely to achieve pregnancy using less invasive techniques, namely spontaneous pregnancy or intrauterine insemination [19].

Patients presenting with sperm motility of 60% or more before varicocele repair had better pregnancy rates after surgery.

On the other hand, reduced presurgical testicular volume and elevated FSH concentration predict negative post-surgical outcomes [20 21].

Azoospermia is defined as the complete absence of sperm from the ejaculate and is present in approximately 1% of all men and up to 15% of fertile men.

Testicular disorders leading to azoospermia are generally irreversible and are classified as non-obstructive azoospermia.

The prevalence of varicocele in men with azoospermia is estimated to range between 5% and 10%.
In 1955 Tulloch reported that varicocele repair in an azoospermic patient restored spermatogenesis and led to successful pregnancy, and this announcement renewed interest in varicocele treatment.

Although spontaneous pregnancy is rare, motile sperm are found in the ejaculate of azoospermic men in 21–55% of cases following varicocele repair.

Varicocele repair in this population may obviate the need for subsequent testicular sperm retrieval procedures, since sperm can be provided via ejaculation.
VARICOCELE – in azoospermic men

- Even though varicocele repair can improve spermatogenesis in up to 50% of azoospermic patients, assisted reproductive techniques will be necessary for the majority of these couples to initiate pregnancy.

- Gradual decline in spermatogenesis and return to azoospermia have been reported in up to 55.5% of patients one year after surgery.

- These patients may experience intermittent sperm production; in fact, the effects of varicocele repair may be only temporary, resulting in the induction of spermatogenesis for a short period of time.

- Semen cryopreservation is strongly recommended following initial improvement after surgery.
Varicocele remains the most common clinical finding in infertile males and is often the only identifiable cause in infertile couples, the most correctable cause of male infertility.

Although the exact pathophysiology remains unknown, there is convincing evidence that varicoceles have an increasingly harmful effect on testes over time, resulting in the decline of seminal parameters.

Current data suggest that varicocele repair is successful in reversing the harmful effects of varicocele on testicular function and in improving seminal parameters.

Current evidence indicates that microsurgical varicocelectomy is the most effective and least morbid method among the varicocelectomy techniques.
However, identifying infertile men with varicocele who will most benefit from varicocele ligation remains a challenge for andrologists.

The use of assisted reproductive techniques may lead rapidly to pregnancy, but the associated cost, health risks, and invasiveness of the procedures on healthy female partners make this treatment option less appealing.

More randomized, controlled trials are needed for more precise assessments of the impact of varicocelectomy on fertility outcomes.
The efficacy of varicocele treatment for increasing the pregnancy rate has remained controversial over the last decade because of the large number of poorly designed and uncontrolled studies. Nevertheless, current evidence supports the contention that varicocele treatment should be considered an initial choice for certain infertile couples because of its greater cost-effectiveness and lower surgery-related risks compared to ART.
So far only two randomized, prospective, controlled studies have addressed fertility outcomes in subfertile patients with clinical varicocele, abnormal seminal parameters, and no female factors. The first study compared interventional treatment (e.g., surgical repair or angiographic embolization) with counseling only for infertile couples. Although semen parameters improved significantly in the treated group, pregnancy rates did not differ between the two groups. However, half of the varicoceles in this study were small (grade I), and approximately 25% were treated with embolization rather than surgical ligation. Moreover, the study did not include microsurgical artery-sparing ligation techniques, and pregnancy rates were lower than reported by other authors. The second study uses the best design so far to determine the benefits of varicocele surgical repair; the authors use a cross-over design of surgery compared with observation. They observed a significant pregnancy rate improvement following varicocelectomy. Although both studies reported improvements in seminal quality after varicocele repair, the pregnancy outcomes were different between the two, so they failed to resolve the uncertainty concerning the effect of varicocele treatment on fertility.
Recently our center has tried to address this controversy by conducting two meta-analyses and including only randomized, controlled trials and observational studies.

The first examined the effect of varicocelectomy on semen parameters.\(^9\)

This analysis demonstrated that sperm concentration increased by 9.71 \times 10^6/mL (95% confidence interval (CI), 7.34–12.08, \(P < 0.00001\)), total motility increased by 9.92% (95% CI, 4.90–14.95, \(P = 0.0001\)), and sperm morphology according to WHO standards increased by 3.16% (95% CI, 0.72–5.60, \(P = 0.01\)) after varicocelectomy.

The authors concluded that surgical varicocelectomy was an effective treatment for improving semen parameters of infertile males with a clinically palpable varicocele.
The second meta-analysis evaluated pregnancy rates for infertile couples in which the male partner had abnormal semen parameters and clinical varicocele. Based on data from the current literature and contrary to previous meta-analyses, our study suggested that varicocelectomy did indeed improve fertility by increasing the likelihood of spontaneous pregnancy in female partners. The odds of spontaneous pregnancy after surgical varicocelectomy, compared to no medical treatment for palpable varicocele, were 2.87 (95% CI, 1.33–6.20, p = 0.007). The number needed to treat was 5.7 (95% CI, 4.1–9.5). These results further support the idea that the improvement in semen parameters following varicocelectomy may help infertile couples achieve pregnancy spontaneously or through the use of less invasive and inexpensive techniques, such as intrauterine insemination.


Elevated production of ROS in the reproductive tract disrupts not only the fluidity of the sperm plasma membrane, but also the integrity of DNA in the sperm nucleus. Infertile men with varicoceles have high levels of spermatozoal DNA damage. For example, Chen et al. reported that patients with varicocele showed increased levels of 8-hydroxy-2'-deoxyguanosine, an indicator of oxidative DNA damage. Excessive levels of DNA damage have been associated with a decrease in several fertility indices, including fertilization rate, embryo cleavage rate, implantation rate, pregnancy rate, and live birth rate. DNA damage can have significant clinical implications because in vitro fertilization using spermatozoa containing damaged DNA may lead to paternal transmission of defective genetic material with adverse consequences for embryonic development. This damage may be reversible: Zini and Libman recently reported that infertile men showed improved sperm DNA integrity six months after varicocele repair. These studies may help us understand the pathophysiology of varicoceles, and possibly lead to the development of improved diagnostic tools.
Biopsies of varicocele-affected testes show a decrease in E-cadherin and alpha-catenin at the Sertoli-Sertoli junction, and subsequent disruption of the blood-testis barrier, which can contribute to defects in sperm production. In addition, atomic force microscopy reveals structural and morphological alterations in the sperm neckpiece and flagella, as well as changes in head dimensions.

Oxidative stress due to an excess of reactive oxygen species (ROS), is now recognized as a major factor in infertility. Normally, the body contains a minimum amount of ROS remain, since they are needed for regulating normal sperm functions such as sperm capacitation, the acrosome reaction, and sperm-oocyte fusion. However, in 25–40% of infertile men, the semen has been found to produce excessive amounts of ROS. Men whose semen contains elevated ROS levels may have decreased fertility for both in vitro and in vivo procedures, and there may be negative effects on embryo development.

The association between semen ROS levels and varicocele has been well documented over the last few years. According to a new meta-analysis from our center, oxidative stress parameters are significantly increased in varicocele patients compared with normal sperm donors. Mitropoulos et al. evaluated peripheral blood samples in subfertile men with varicocele and compared them with blood samples from the dilated varicocele vein before ligation. The authors found elevated oxidative stress due to the release of nitric oxide synthase and xanthine oxidase within the dilated spermatic vein. This led to dramatic increases in the levels of nitric oxide, peroxynitrite, and S-nitrosothiols, all of which are biologically active. They suggested that peroxynitrite production from the reaction of nitric oxide and superoxide might be responsible for impaired sperm function in patients with varicocele. Allamaneni et al. reported that semen ROS levels correlated positively with varicocele grade. In addition, the authors showed that men with varicocele grade II or III had significantly higher semen ROS levels than men with varicocele grade I. Similarly, Koksal et al. evaluated levels of malondialdehyde in testicular biopsy specimens and found significantly higher levels of malondialdehyde in infertile men with grade III varicocele compared to men with grade I or II varicocele. These findings indicate that increased oxidative stress is associated with more severe varicocele. Surgical varicocelectomy has recently been shown to reduce seminal oxidative stress in infertile men.
Several treatments are available for varicocele (Table 4).

Current evidence indicates that microsurgical varicocelectomy is the most effective and least morbid method among the varicocelectomy techniques.