

The great debate: varicocele treatment and impact on fertility

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Introduction

- Varicoceles (abnormally dilated veins in the pampiniform plexus) → most commonly seen and correctable cause of male factor infertility
- Incidence :
 - 4.4%–22.6% in the **general population**
 - 21%–41% in men with **primary infertility**
 - 75%–81% in men with **secondary infertility**
- An abundance of evidence → surgical correction offers an improvement in a couple's chances of obtaining a pregnancy → spontaneously or ART.

- Studies → **extremely heterogeneous** in the parameters of the populations studied (initial grading of varicocele lesion, presence of infertility, age of patients treated, and age of their partners) → controversy.
- The practice guideline of both the American Urological Association and the American Society for Reproductive Medicine (ASRM):
 - correction of a varicocele should be offered to infertile men with palpable lesions and one or more abnormal semen parameters.
- However, the conclusion of the updated Cochrane review in 2009 that treatment of varicocele **does not improve** the chances of conception when present as the only proven explanation of infertility

- infertility couples → male factor : up to 50% → varicocele : most common finding
- Objective of this article:
 - provide an overview of the indications and choices for treatment
 - highlight points of controversy in the literature.
- Furthermore, this review may help improve counseling of patients before pursuing therapy as to anticipated expectations for improvements in fertility.

DIAGNOSIS

- the most used methods : physical examination and scrotal ultrasound.
- The condition is graded at the time of the initial physical examination from 1–3 (Dubin grading system)
 - grade 3: visible while the patient is standing
 - grade 2: is palpable without Valsalva maneuver
 - grade 1: is not able to be visualized and only palpable with Valsalva maneuver.
- **Significant interexaminer variability exists** → depending largely on the level of expertise.
- scrotal ultrasound: subclinical varicocele → at least the presence of dilated veins with diameter >3.0 mm with concomitant reversal of flow after Valsalva

PATHOPHYSIOLOGY

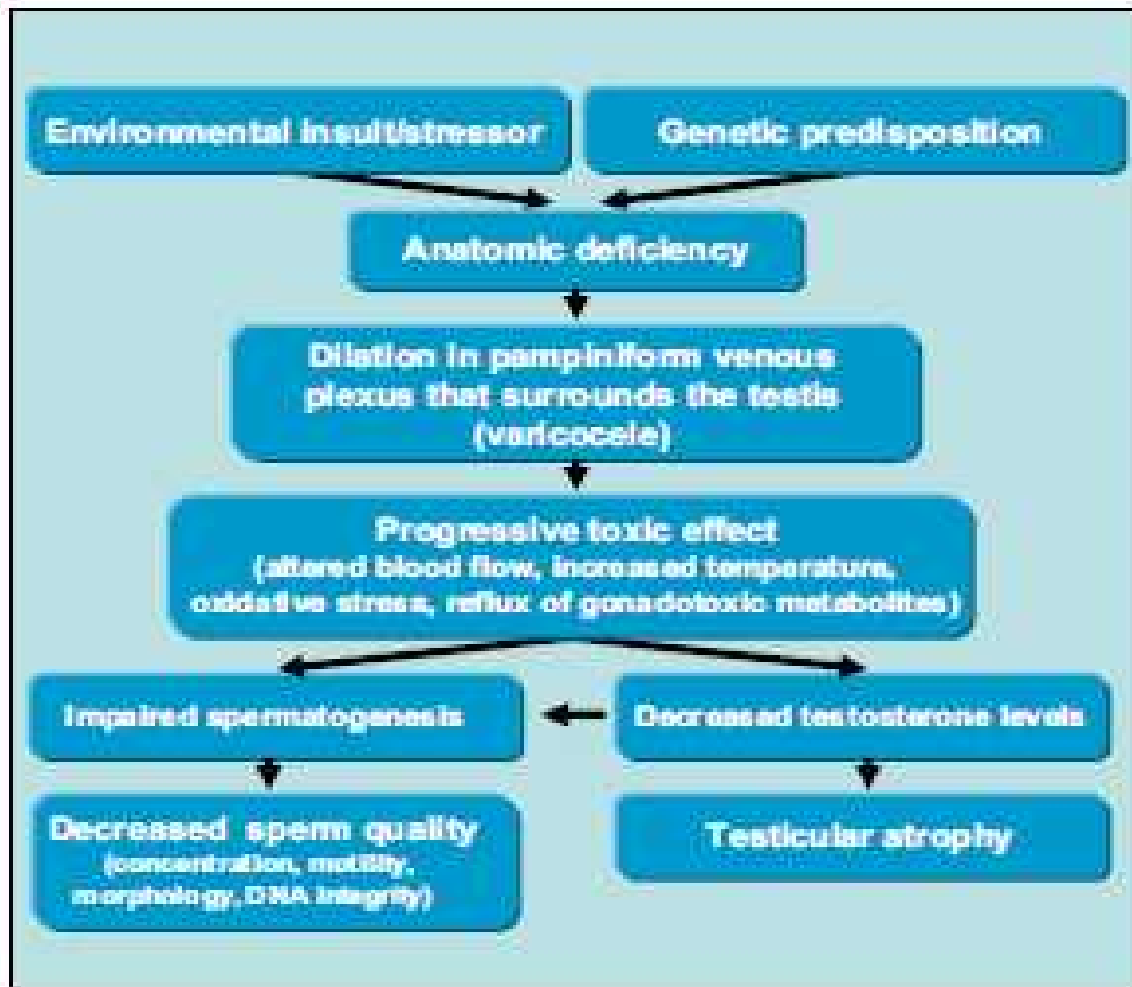
- The phenomenon is age dependent → incidence in prepubertal boys is extremely rare and increases to about 15% in adolescents
- a varicocele > 30 years have lower sperm concentrations, impaired Leydig cell function, and lower T concentrations
- Genetic factors and toxins may also serve as potential cofactors in the development and implications of a varicocele
- Most varicoceles are **left sided** (anatomical configuration) → a more vertical inlet of the internal spermatic vein to the renal vein as opposed to a more oblique inlet on the right

- Defective or missing venous valves also play an important role in the pathogenesis
- Histologic studies:
- Abdelrahim et al. : bilateral testicular biopsies from 30 varicocele patients taken both during varicocelectomies and postoperatively. (Compared with healthy control subjects)
 - preoperative biopsies: reduced spermatogenesis with maturation arrest, dead spermatogenic epithelium, and an increase in the volume of Leydig cells.
 - After treatment: **spermatogenesis improved** in 22 of the patients, who also showed regeneration of the epithelium.

- Other studies suggest that Sertoli cell dysfunction and hypospermatogenesis.
- Several studies suggest a mechanical mechanism of spermatozoa.
- Most of the studies have reported impaired scrotal temperature.
- In addition, some studies have cited as

FIGURE 1

Flow chart showing progression of varicocele and spectrum of effects that contribute to impaired fertility.



- Normal testicular temperatures: 2°C below core body temperature → increases in scrotal temperature : reductions in both sperm output and quality.
- Jung and Schuppe : men with varicocele and reduced sperm quality have significantly higher scrotal temperatures than men with normal sperm quality and the treatment of varicoceles reduced testicular temperature.
- Factors, such as sleeping posture, duration of sedentary posture, and exposure to high temperatures, are likely to increase the scrotal temperature further.

- Another possible explanation: increased production of reactive oxygen species (ROS).
- **Oxidative stress**, from increased testicular temperature → ROS and other gonadotoxic factors → reduced sperm function through oxidation of fatty acids in spermatozoa membranes or through direct DNA damage resulting in increased sperm DNA fragmentation
- after varicocele repair → Levels of biomarkers for oxidative stress have also been found to decrease
- This sperm DNA damage may be due to increased ROS and reduced total antioxidant capacity (TAC) of semen in men with varicocele

- **Imbalance in the hypothalamic-pituitary-gonadal axis and reduced T levels in the peripheral blood** (some patients with varicocele) → contributors to the observed diminished sperm production and quality.
- after varicocelectomy: improvements in sperm quality associated with a normalization of the endocrine axis and an increase in T levels
- An additional explanation for impaired spermatogenesis includes deficient sperm maturation or increased sperm apoptosis as a result of low T levels.

- Varicoceles have also been associated with possible breaches in the blood–testis barrier and subsequent antisperm antibody formation → BUT: evidence suggested **no correlation** with autoantibodies
- It seems likely that the pathophysiology of varicocele is **multifactorial** and involves additional effects that inter-relatedly increase the detrimental effects on spermatogenesis.

TECHNIQUES OF VARICOCELE REPAIR

- A variety of operative and nonoperative approaches have been advocated for varicocele repair, including
 - percutaneous radiologic techniques (embolization or sclerotherapy),
 - open surgical (inguinal, subinguinal, retroperitoneal approach),
 - Laparoscopic
 - microsurgical (inguinal or subinguinal) varicocelectomy.
- the procedure should leave intact the testicular arteries, lymphatics, and vas deferens

(Unilateral or Bilateral Repair)

- Several investigations have examined whether bilateral repair is similar or superior to one-sided repair.
- Kondoh et al. → a small case series of 27 men with bilateral varicoceles and 40 men with unilateral left-sided varicoceles → **less improvements in sperm density in the group with bilateral** when compared with the left-sided only group.
- 4 subsequent reports → support the contrary.
- Scherr and Goldstein : **significantly greater improvements** in motile sperm concentrations in those with **bilateral repair**.
- Libman et al. and Baazeem et al. noted significantly higher spontaneous pregnancy rates (PR) in bilateral repair

(Nonmicrosurgical Techniques for Spermatic Vein Ligation)

- In 1948, Palomop described the classic retroperitoneal high ligation.
- ligating the internal spermatic vein as it exits the inguinal canal and preserves the internal spermatic artery.
- Two modifications → the inguinal (Ivanissevich) or subinguinal approaches.
- The **subinguinal** technique has the benefit of **preserving muscle layers and the inguinal canal** → more technically challenging due to the greater number of internal spermatic veins and arteries below the external ring

(Radiointerventional Techniques)

- Interventional radiologists offer occlusion procedures (embolization, sclerotherapy) as minimally invasive outpatient options that have the advantage of venography to delineate anatomy more clearly.
- less invasive but **potential for failure** to ligate the varix
- the failure rate can vary from 4%–27%.
- Recurrence rates are to be higher.

(Microsurgical Approach)

- the preferred approach by most urologists → significant reductions noted in recurrence rates or other postoperative complications.

Complications

- **Hydrocele formation** was previously the most common complication reported after operative varicocele repair.
- microsurgical and radiointerventional techniques → incidence has **dramatically reduced**
- **Recurrences** after varicocele repair are the most variable complication in incidence and rates depend largely on the technique and the use of magnification: 0–35%
- **Testicular artery ligation or injury** is also a common complication of nonmicrosurgical varicocelectomy
- Because of the presence of other spermatic cord arteries, such as the vasal and cremasteric arteries, injury to the artery does not always result in atrophy.

Comparative Studies

- Most of studies involve prospective collection of data and randomization of subjects → few include a control (no treatment) group.
- Reports of operative experiences have noted **longer operative times with the microsurgical approach** in comparison with open and laparoscopic approaches
- Laparoscopy VS. sclerotherapy: higher postoperative complications (epididymitis, prolonged pain)
- microsurgery → higher rates of preserving the testicular artery and the lowest rates of recurrence and hydrocele formation
- Embolization and sclerotherapy → very little-to-no risk of hydrocele formation

- Improvements in semen parameters have been the main outcome of most studies focusing on men with infertility for at least 12 months as the target population.
- Three recent randomized trials comparing open, laparoscopic, and microsurgical :
 - improvements in concentration, motility, and/or morphology in comparison with preoperative evaluations,
 - did not demonstrate significant differences between techniques based on sperm parameters alone

TABLE 1

Rates of pregnancy and complications based on technique.

Technique	Artery preserved	Hydrocele (P = .001)	Recurrence (P = .001)	Potential for serious morbidity	Pregnancy rates (P = .001)
Retroperitoneal high ligation (Palomo), %	No	8	15	No	38
Macroscopic inguinal (Ivanissevich), %	No	7	3	No	36
Laparoscopic, %	Yes	3	4	Yes	30
Radiologic, %	Yes	0	12	No	38
Microsurgical, %	Yes	0.4	1	Yes	42

Note: Modified from data in Cayan et al., 2009 (74).

Will. Varicocele treatment and fertility. Fertil Steril 2011.

recurrences, postoperative hydroceles, or other complications.

- Agarwal et al. : RCTs and observational studies → more focused at infertility, abnormal sperm, and hydroceles.

- a direct parameter of sperm counts in semen
- significant difference in sperm count, motility, and morphology between high ligation and microsurgery (Table 2)

TABLE 2

Differences in postoperative semen analysis.

Technique	Sperm concentration	Average motility, %
High ligation	$12.03 \times 10^6/\text{mL}$	11.72
Microsurgery	$9.71 \times 10^6/\text{mL}$	9.92

Note: Modified from data in Agarwal et al., 2007 (75).

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VARICOCELE REPAIR AND EFFECT ON SEMEN ANALYSIS PROFILE

- Varicoceles have classically been described to induce a “stress pattern” that affects several parameters measurable simultaneously on semen analyses.
- Most studies focus on abnormalities in concentration, motility, and/or morphology.
- Each of these parameters individually has been examined for relative postoperative improvements after surgery, but also as independent prognostic factors of whether varicocele repair is a successful treatment strategy for male subfertility.

Asthenospermia

- 19% of subfertile men with a clinical varicocele will present with isolated abnormalities in sperm motility
- Boman et al. reported a retrospective review :
 - Varicocele repair → significant increases in total motile sperm count and spontaneous pregnancy (65% compared with 32%; $P < .01$).

Teratozoospermia

- Several investigators (retrospective data) : postoperative improvements in sperm morphology as well as teratozoospermia as primary indication for repair.
- Vazquez-Levin et al. : significant improvements in concentration and morphology.
- Seftel et al. : (microsurgical varicocelectomy) improvements in concentration and motility, but not in morphology.
- Kibar et al. : improvements in morphology but significant improvements in all sperm parameters in the oligospermic (5–20 million/mL) group.

Oligozoospermia

- Dubin and Amelar : a lesser percentage of improved semen quality in men with a sperm concentration less than 10 million/mL.
- Matkov et al., Kamal et al., and Fujisawa et al. : men with severe oligozoospermia (<5 million/mL) are less likely to see improvements in semen parameters.
- Kamal et al. : men with severe oligozoospermia have a much lower chance of spontaneous pregnancy (8% compared with 61% in those with >5 million/mL).
- Studies that examined men with low sperm counts in the less severe range show greater postoperative improvements

Severe Oligozoospermia/Nonobstructive Azoospermia

- Severe oligozoospermia (SO) and nonobstructive azoospermia (NOA) are conditions that **significantly reduce** a couple's chances at spontaneous pregnancy.
- Approximately 4%–13% of men with a palpable varicocele will present with azoospermia or severe oligoasthenospermia.
- Matthews et al.: patients after microsurgical varicocelectomy
 - return of motile sperm to the ejaculate postoperatively.
 - Mean total motile sperm count increased
 - testicular atrophy on initial examination had no prognostic value.

- Several other small cohort studies: experiences with varicocele repair in men with SO or NOA. →
 - Rates at which motile sperm are noted in postoperative ejaculates range from 21%–69%.
 - rates of subsequent spontaneous pregnancy range from 5.3%–19%.

Sperm DNA Damage

- Mancini et al.: no absolute change in semen TAC after surgical repair of varicocele.
- With the advent of new laboratory assessment tools to aid in the selection of higher quality sperm with less DNA fragmentation for use with ICSI, it will be interesting to determine whether varicocelectomy will be required in the future for specific patients, depending on subsequent treatment plans.

CLASSIFICATION OF VARICOCELE AND EFFECT OF REPAIR

TABLE 3

Summary of postoperative measurements after varicocele repair.

Type of varicocele (Ref)	Improvements in semen parameters			Improvements in spontaneous pregnancy rates
	Concentration	Motility	Morphology	
Subclinical				
Yamamoto et al. (110)	+	-	-	-
Unal et al. (111)	+	+	-	-
Grasso et al. (112)	+	-	-	-
Clinical				
Nilsson et al. (113)	-	-	-	-
Breznik et al. (114) ^a	-	-	Not assessed	-
Madgar et al. (88)	+	+	+	+
Nieschlag et al. (118)	+	-	-	-
Krause et al. (115)	-	-	-	-

Note: Data are limited to statistically significant differences from randomized controlled trials.

^a Study included subclinical and clinical varicoceles.

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- Marsman and Comhaire and Kunnen : analyses of patients who underwent embolization as treatment →
 - Similar postoperative improvements in semen parameters and PRs were noted in studies comparing men with subclinical and clinical varicoceles after surgical repair.
- Three RCTs examining varicocele repair for subclinical varicoceles showed modest postoperative improvements.
- Grasso et al., (RCT of 68 infertile men with subclinical varicocele) → no differences postoperative semen analyses or PRs between high ligation versus observation for 12 months.
- Thus, conclusive evidence in favor of repair of subclinical lesions is lacking.

Grade of Clinical Varicocele

- Given the observations that not all men benefit from varicocele repair, researchers have sought markers that would identify those men who benefit the most (e.g., greatest improvements in sperm parameters and/or improvement in fertility).
- Dubin and Amelar : grade of varicocele as a prognostic factor in 1970 and noted **no difference in degree of improvement** when comparing grade of varicocele and differences between preoperative and postoperative semen quality.

- 3 subsequent studies: significantly greater percentage of men with improvements in postoperative sperm parameters (density and/or motility) in men with larger varicoceles.
- Jarow et al. : prospective study: no correlation in postoperative improvements based on grading
- Regardless, if associated with abnormal semen parameters and infertility, grade of varicocele should not be a deterrent of varicocele repair.

Recurrent Varicocele

- With the overall low incidence of recurrence seen after a microsurgical approach, few studies have examined the best route of repair if a recurrence is noted
- Madjar et al. and Grober et al. : good surgical outcomes using the subinguinal approach.
- Madjar et al. used the **nonmicrosurgical technique** and noted marked improvement in size in 91% (21/23) of those undergoing **secondary repair**.

SURGICAL TREATMENT OF VARICOCELE AND SUCCESS OF ART

Intrauterine Insemination

- Marmar et al. : reported IUI as a possible treatment option for men with a history of a varicocele and refractory infertility.
- Daitch et al. studied 58 couples with varicocele-associated infertility (pregnancy rates per cycle):
 - 34 (underwent microsurgical repair) → 11.8%
 - 24 (not to undergo repair) → 6.3%
- **Odds of pregnancy were 4.4-fold higher** in the **surgically treated** group favoring varicocelectomy as a strategy to improve chances of pregnancy with assisted means.

In Vitro Fertilization and Intracytoplasmic Sperm Injection

- At least one small observational study examining infertile men with a history of previous failed fertilization with IVF indicates that **varicocelectomy could improve fertilization potential of sperm in a subsequent IVF cycle**
- There is debate on whether varicocele is correlated with **antisperm antibodies**, and whether surgical correction has an impact that may influence subsequent ART treatment.

- This question is worth answering considering its implications involve more than simply cost (chance of success, slight increase in risk of birth defects).
- Furthermore, well-designed studies are warranted to investigate whether surgery and ART have an additive relationship.

- Three cost analyses have been published that favor **varicocele repair as a more cost effective strategy.**
- Schlegel and Meng et al.: reported decision analyses that favor varicocele repair instead of ART. (cost per live delivery)
 - after varicocelectomy → \$26,268
 - after ICSI → \$89,091

CONCLUSION AND UPCOMING RESEARCH DIRECTIONS

- **Varicocele repair** is a reasonable consideration as the **primary treatment option** when a couple with documented infertility involves a man with
 - a palpable varicocele
 - suboptimal semen quality
 - female partner has a **normal evaluation**.
- **Bilateral repair** is warranted when varicoceles are noted on both sides, regardless of grade.
- Persistent or recurrent varicoceles may be treated by either surgical ligation or percutaneous embolization.

- Comparative studies favor the microsurgical approach as the technique with the highest rates of success and lowest rates of complications.
- However, approach to varicocele treatment should be based on the physician's experience and the additional options available.
- Assisted reproductive technologies may serve as a viable adjunct or alternative to surgery to improve chances of pregnancy.
- Currently, two clinical trials investigating the contemporary role of varicocele repair in the treatment of male factor infertility are registered with ClinicalTrials.gov.

- A multicenter randomized study based in Mount Sinai Hospital, Canada (NCT00961558) is evaluating the effect of surgical repair versus observation alone on spontaneous PRs in infertile couples.
- In addition, another multicenter randomized study sponsored by The Reproductive Medicine Network (NCT00767338) is evaluating the effect of microsurgical varicocelectomy versus IUI on live birth rates in couples affected by male factor infertility.
- With improvements in ART laboratory technology, future research efforts are warranted to delineate the benefit of varicocele repair in patients who will require subsequent IVF/ICSI.

Thanks for your attention!