Varicocele in the Adolescent and Adult: When Is A Repair Indicated?

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OBJECTIVES

1. Review the etiology and pathophysiology of varicoceles
2. Discuss current indications for repair of varicoceles in the adult
   • Fertility
   • Low Testosterone (Hypogonadism)
3. Evaluate the evidence supporting the various parameters included in the assessment of varicoceles in the adolescent
   • Testicular Size and Asymmetry
   • Ultrasonography
   • Semen Analysis
What is a Varicocele?

- Abnormal enlargement of the pampiniform venous plexus secondary to the retrograde flow of blood to the testicle
- Predominantly left sided
- Increased prevalence was observed in first-degree relatives (particularly brothers) of patients with known varicoceles


Etiology

Theories:
1. Incompetent venous valves
2. Difference in hydrostatic pressure between the left right testicular veins
3. Testicular vein compressed between SMA and aorta – “nutcracker effect”
4. Increased arterial blood flow to testis exceeds venous capacity


Image: CW Urology Chapter 1
Pathophysiology

- Hyperthermia – stasis of blood in the varicocele with resultant temperature increase may have negative effects on spermatogenesis

- Hypoxia – stasis of blood could affect partial oxygen pressure and metabolism in the testis

- Adrenal Reflux – reflux of blood down the testicular vein, leading to exposure of the testis to adrenal and renal metabolites that may contribute to testicular damage

- Free Radicals – resulting from conditions of hyperthermia and hypoxia associated with varicoceles lead to germ cell harm and testicular function impairment


Grading

- Grade I (only palpable on Valsalva maneuver)

- Grade II (palpable with no Valsalva maneuver)

- Grade III (visible with no need for palpation).

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Why is it important?

• 15% of men in the general population have a varicocele¹

• In adult men with primary infertility 40% have a varicocele

• In adult men with secondary infertility 81% have a varicocele²

• 15% of couples fail to conceive in 12 months
  • Male factors 20%
  • Both Male and Female Factors 30-40%

To complicate things…

• 80% of men with varicoceles are fertile

• Most studies use semen parameters as surrogate outcomes for fertility
  • Presence of varicocele cause abnormalities in semen parameters – reduced sperm count, motility and morphology

1. Sigman 2011. There is more than meets the eye with varicoceles: current and emerging concepts in pathophysiology, management and study design. Fertil Steril 96(6) 1281-2.

• Included 22 studies reporting on sperm concentration, 17 on total motility and 5 on progressive motility before and after varicocelectomy (all prospective)

Sperm Concentration

Varicocele Repair Favored


Sperm Motility

Progressive Sperm Motility

Varicocele Repair Favored

Does Varicocele Repair Improve Male Infertility? An Evidence-Based Perspective From a Randomized, Controlled Trial

Taha A. Abdel-Meguid, Ahmad Al-Sayyad, Abdulmalik Tayib, Hasan M. Farsi
Department of Urology, King Abdulaziz University Medical City, Jeddah, Saudi Arabia
Department of Urology, El-Minia University, El-Minia, Egypt

• Aim: To determine whether varicocele treatment is superior or inferior to no treatment in male infertility from an evidence-based perspective

• “Prospective, one-to-one concealed-to-randomization, controlled, parallel-group, non-blinded, open label fashion”


Study Design

• Primary outcome: determining spontaneous pregnancy rate during a 12-mo period after receiving allocated intervention

• Inclusion criteria:
  • Married, over-all healthy men 20-39 years of age
  • Infertility for > 1 yr of unprotected intercourse
  • Clinically palpable varicocele
  • At least one impaired semen parameter (sperm concentration, progressive sperm motility, <30% morphologically normal sperm)

• Exclusion
  • Subclinical or recurrent varicoceles, normal semen parameters, azoospermia, abnormal hormonal profile, significant medical disease, additional causes of infertility, smoking, occupational heat exposure, female partner >35 years of age, associated female factor infertility, unstable marriage

Study Design

- Patient had to willingly accept either immediate varicocelectomy (Tx Arm) or observation for 1 year with re-evaluation of management plan (Control Arm)
- Computer generated random allocation
- Neither investigators nor participants blinded to intervention after allocation
- Tx via subinguinal microsurgical varicocelectomy
- F/U semen analysis at 3, 6, 9 and 12 months with any pregnancy during that time also recorded

All 3 sperm parameters improved after varicocelectomy

Conclusion from authors: varicocelectomy incr odds of spontaneous pregnancy

<table>
<thead>
<tr>
<th>Table 3 - Pregnancy rates in both arms</th>
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<tr>
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<tr>
<td><strong>Within-arm analysis</strong></td>
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<tr>
<td>CA (n = 30 of 72)</td>
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<td>Age of patient, yr ± SD (65% CI)</td>
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<td>Pregnancy, % (95% CI)</td>
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<td>13.9 (7-24)</td>
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<td>22.5 (22-45)</td>
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<td>19 ± 6.8 (5.10 - 32.78)</td>
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<td>OR</td>
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<td>3.04 (1.33 - 6.95)</td>
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<td>NNT</td>
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<td>5.27 (1.55 - 8.95)</td>
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<td>TA (n = 24 of 73)</td>
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<td>Age of patient, yr ± SD (65% CI)</td>
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<td>26.1 ± 4.4</td>
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<td>1.11 (1.37 to 4.59)</td>
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CA = control arm; TA = treatment arm; D = mean difference; CI = confidence interval; OR = odds ratio; NNT = number needed to treat.


Other Notables

- Improvement in semen parameters also found in patients with repair due to testicular pain, discomfort or cosmesis (not infertility)

- Degree of sperm impairment associated with varicocele grade

- Most significant improvement in semen parameters occurs at 3 months

- Uncertain if this translates to the main goal → ability to achieve pregnancy

New Measures of Spermatic Function

Specialized sperm function tests in varicocele and the future of andrology laboratory

Ahmad Majzoub¹, Sandro C Esteves², Jaime Gosálvez³, Ashok Agarwal¹

• Sperm DNA Fragmentation Test

• Reactive Oxygen Species

Majzoub et al. Specialized sperm function tests in varicocele and the future of andrology laboratory. Asian J Andrology. 18:205-212

Sperm DNA Fragmentation Test

• ROS (as result of oxidative stress) can inflict damage to mitochondrial and nuclear DNA

• Results in base modification, strand breaks and chromatin cross-links

• May also trigger an apoptosis-like process affecting maturation

• Increased levels of sperm DNA fragmentation associated with infertility, poor assisted repro technology outcomes and miscarriage

Majzoub et al. Specialized sperm function tests in varicocele and the future of andrology laboratory. Asian J Andrology. 18:205-212
Sperm DNA Fragmentation Test

• Tests evaluate single and/or double breaks occurring at DNA strand

<table>
<thead>
<tr>
<th>Assay</th>
<th>Principle</th>
<th>How results are expressed</th>
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<tr>
<td>ISNT</td>
<td>Direct incorporation of DNA probes at the site of damage (free single or</td>
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<td>TUNEL</td>
<td>double strand DNA breaks)</td>
<td>Percentage of sperm with DNA damage represented</td>
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<td>SCSA</td>
<td>Susceptibility of DNA to denaturation with formation of ss DNA from native</td>
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<td>SCD test</td>
<td>DNA; Selective partial DNA denaturation after acid and/or lysis treatment,</td>
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<td>Comet</td>
<td>with formation of ss DNA from native ds or ss, in sperm with a damaged chromatin</td>
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<td>AG test</td>
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<td>Percentage of sperm with fragmented DNA (SCD, SCSA, AG)</td>
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<tr>
<td>AB</td>
<td>Direct incorporation of probes to nuclear proteins</td>
<td>Percentage of sperm with loose chromatin packing</td>
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<td>CMA3</td>
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Reactive Oxygen Species

• Increase ROS disrupts the lipid in the sperm cell membrane causing defects in sperm structure and function

• ROS detected by assays that directly or indirectly measure oxidative radicals

• Indirect – lipid peroxidation products (malondialdehyde), protein oxygenation products (carbonyl groups), oxidized DNA (8-OHdG)

• Direct – using chemiluminescence
Where does this all fit?

Summary

• The majority of patients with varicoceles are fertile

• In patients with a varicocele and worked up for infertility, varicocele repair improves semen parameters: sperm concentration, sperm motility and progressive sperm motility. It is unclear if this translates to increased pregnancy rates.

• New measures of spermatic function are available for patients with varicoceles. Where this best fits in the management algorithm remains to be seen.
Varicocele and Testosterone

- Leydig cells of the testis responsible for testosterone production

- Impaired testosterone production (and thus low serum T) + symptoms (ED, fatigue, decreased libido, difficulty concentrating) = hypogonadism

- Biochemically hypogonadal = serum total testosterone < 325 ng/dL

- Does varicocele repair improve testosterone level?


Varicocele as a risk factor for androgen deficiency and effect of repair

- Aim: To determine whether men with varicoceles have lower testosterone levels than those without and to ascertain if testosterone levels increase after varicocelectomy

- Case control study

Study Design

- Men 18-70 with clinically palpable varicoceles mostly referred for infertility evaluation
- All had subinguinal microsurgical varicocelectomy
- Comparison group: men presenting with vasectomy reversal with proven fertility (prior conception) and no varicocele on examination
- Serum T levels measured pre-op, taken between 8 am-10:30 am.
- Serum T repeated 3-12 months post-op for patients with varicocele repair

Results – Baseline Serum T

- 325 men with varicocele (mean age 36) included
- 510 men (mean age 43) with vasectomy reversal as comparison group
- Men with varicocele had significantly lower serum testosterone levels than comparison group
- Serum FSH, LH were within normal range for patients with varicocele

Results – Serum T pre & post surgery

- 200 men with varicocele post repair included in this analysis (125 lost to f/u)

- Serum T levels significantly greater post varicocele repair compared to pre-surgery levels


Results – Serum T pre & post surgery

- 30% of patients did NOT have any change in serum T levels

- Age, mean testicular volume, varicocele grade had no association or did not predict change in testosterone levels

Elevation of serum testosterone and free testosterone after embolization of the internal spermatic vein for the treatment of varicocele in infertile men

Yigal Gat¹, Michael Gornish², Alexander Belenky² and Gil N.Bachar²,³

• Serum testosterone measure pre- and post varicocele embolization
• N= 83 patients
• Mean serum T increased (348 ng/dL pre vs. 496 ng/dL post)

Summary

• Serum testosterone measurement prone to variation by multitude of factors not necessarily related to varicocele, thus making it difficult to determine appropriate baseline levels and response

• In patients with a varicocele and low serum T, varicocele repair may increase serum T levels

• It is unclear if improvement in serum T levels after varicocele repair translates to improving hypogonadal symptoms

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   • Testicular Size and Asymmetry
   • Ultrasonography
   • Semen Analysis
Adolescent Varicocele

• Varicoceles are uncommon in boys under 10 years of age

• In adolescence, the prevalence of varicoceles typically range from 10-15%

• Does early repair of varicoceles in this age group improve future fertility?

Testicular Asymmetry

• Testicular asymmetry classically accepted as potential indicator for long-term subfertility

• Threshold values for "significant" asymmetry range from 10%, 15% or 20% relative difference or an absolute differential of 2-3 cc testicular volume

• Abnormal semen parameters have been correlated with testicular volume differentials as low as 10%, and these findings are more dramatic when asymmetry is greater than 20%

Catch-up Growth

- Retrospective chart review of patients 18 years or younger presenting with varicocele from January 1993 to April 2003


Catch-up Growth

- Exclusion: scrotal pathology (e.g., Cryptorchidism), previous inguinal/scrotal surgery, endocrinopathy that might affect testicular size

- Interested in patients with no initial treatment and at least 3 f/u US

- Follow—up with serial US every 12 months

- 71 patients with no repair and 3 or more US
Catch-up Growth

- Of the 71 patients with 3 f/u U/S = 38 had >15% asymmetry
- 27 of 38 patients had eventual normalization of size (< 15% asymmetry)
- Recommend at least 2, preferably 3 f/u testis volume measurements 1 year apart prior to performing surgery


Important Considerations

- The methods to measure volume (orchidometer vs. ultrasound) are prone to error and still involves subjectivity (intra- and inter-recorder)
- Testicular asymmetry can occur normally during the adolescent years as the testes enlarge at different rates regardless to whether the patient has a varicocele or not
Corpse Flower - flowers every 80-150 years

Image from: The United States Botanic Garden. www.usbg.gov

Peak Retrograde Flow (PRF)

• Measurement of peak retrograde venous flow in spermatic cord via doppler color flow imaging (cm/sec)

• Patient performing Valsalva maneuver in supine position

• PRF emerging as predictor for progressive testicular asymmetry


Peak Retrograde Flow (PRF)

Retrospective review involving institution’s varicocele database

Aim: whether varicocele grade or duplex doppler US measurements of PRF could be used as predictors of persistent, progressive or new onset asymmetry


Asymmetry defined as 10% or more difference in volume

Patients divided into PRF of >40 cm/sec, 30-39 cm/sec, 20-29 cm/sec and <20 cm/sec

77 patients identified/ included in the study (age range 9-20 years)

Mean interval between two ultrasounds = 13 months

50 of 77 patients (65%) had 10% or greater asymmetry at the first ultrasound examination

At first exam, 68% had grade III varicocele and 32% had grade II varicocele

• Catch up growth rare in patients with greater than 20% initial asymmetry and a PRF of greater than 38 cm/second

Semen Analysis

Relationship of Varicocele Grade and Testicular Hypotrophy to Semen Parameters in Adolescents


From the Departments of Urology and Radiology (HJP), Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts

• Semen analysis performed on 57 Tanner stage V adolescent males with varicocele (age range 14-20)

• Examined relationship between varicocele grade or testicular volume differential and semen parameters

Semen Analysis

In a study by Moursey et al, 59 of 60 patients with a varicocele and less than 20% asymmetry managed conservatively were found to have normal semen analysis at age 18 (mean follow-up 79 months)\(^1\)

Others have described normalization of total motile sperm count in two-thirds of Tanner V boys with uncorrected varicocele\(^2\)

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Important Considerations

• Sperm morphology changes throughout the different stages in puberty

• We do not know what “normal” semen analysis is in an adolescent → this is graded against the WHO criteria for adults

• Range of normal for semen analysis is vast, thus arriving at a set point to decide for surgery would be very difficult

Summary

• Patients should be followed regularly with serial physical examination and assessment of testicular size as the bare minimum.

• There continues to be a lack of consensus on the threshold for testicular asymmetry (10%, 15% or 20%) that warrants varicocele intervention.

• Measurement of the PRF may be helpful in selecting which patients are likely to demonstrate catch-up growth versus those that may benefit from early intervention. Based on the data available, surgical intervention may be considered in patients with a PRF of greater than 38 cm/sec and concurrent testicular asymmetry greater than 20%.

• Semen analysis can be considered in those with consistently equivocal findings (ie. Persistent 10-15% testicular asymmetry), with the understanding of the limitations of the test in this demographic
THANK YOU

Dr. M. Nigro

Dr. L. Machan

Dr. A. MacNeily

Dr. K. Afshar

QUESTIONS?