

Varicocele and male infertility: an evidence based review

Ashok Agarwal, Ashok Agarwal,
Arch Med Sci 2009; 5, 1A: S20–S27

Presented by R1 孫怡虹

Advised by VS 蔡永杰



Varicocele

- An enigma in the Tx of male infertility
- Evidence (> 30 years)
 - Repair => Improved infertility
- =>Retrospective Controversy (Utility of Tx)
- Evaluation
 - History: Medical/Reproductive
 - Physical examination
 - Recumbent / Upright / Valsalva maneuver
 - Inconclusive => Imaging study
 - Semen analysis (at least 2x)



Incidence

- 20% in general population
- 40% in infertile population
- Varies according to age

2~19 yrs	2~6 yrs	7~10 yrs	11~14 yrs	15~19 yrs	>20 yrs	60 yrs
7.2%	0.79%	0.96%	7.8%	14.1%	10~25%	42.9%

- Inverse correlation with **BMI**
- Relationship with **hormonal abnormalities** (No prospective, randomized, controlled studies)



- Reason for Incidence remains unknown
- Infertility \Leftrightarrow Intratesticular temperature \Leftrightarrow Time
- Blood supply to the testis / Counter current heat exchange
 - \Rightarrow Cool intra-testicular temperature than body
 - \Rightarrow Disruption of this system
 - \rightarrow hyperthermia of the testes



Testicular blood flow

- L't side => a system with **higher resistance**
- **Small venules:** may persist or open during embryogenesis
- Testicular blood flow
 - Before puberty: remains low
 - Until adolescence: ↑, veins become clinically apparent
- This explains the appearance of most varicoceles around puberty



- Men with varicocele, Intense physical activity 2~4 h/day, 4~5 times/week, > 4 years have a ↓ in semen parameters
- First-degree relatives more frequently than the general population



Pathophysiology and typical testicular histological abnormalities

- Possible course of varicocele
- Obstruction or compression of the vein system
 - Absence or congenital incompetence of the **left spermatic vein valves**
 - Difficulties in the **venous return**



Pathophysiology and typical testicular histological abnormalities

- Several theories to explain the impact of varicocele on testicular function
 - None of them alone is able to elucidate the variable effects of varicocele in spermatogenesis and male infertility:
 - hyperthermia, hypoxia, ↓ in intratesticular and epididymal blood flow, intratesticular hormonal abnormalities, oxidative stress and renal and adrenal metabolite reflux



Varicocele as a cause of infertility

- Most common cause of male infertility (only weak evidence)
- WHO, observational study, Abnormal semen analysis of 9,034 men
 - 25.6% varicocele
 - Significant ↓ in the ipsilateral testicle volume (Does not occur in infertility without varicocele)



Varicocele diagnoses

- Gold standard: does not exist
- Most common method => **PE**:
 - Patient standing in a 25°C room temperature
 - sensitivity and specificity only 70%
 - “Clinical”
- Classified according to their size.
 - The larger (grade III): visually detected
 - Moderate(grade II): detected through palpation without the Valsalva maneuver
 - Smallest(grade I): PE with Valsalva maneuver



- **Clinical / subclinical**
 - **Radiological tests** are not able to differentiate
 - **Spermatic vein venography**: the most widely recognized method for the Dx of **pampiniform plexus vein reflux**
- **Color Doppler ultrasound**: > 90% sensitivity and specificity
- **Scrotal thermography and cintilography** have variable results



Clinical treatment for varicocele

- Medical, nonsurgical treatment
 - Few well-designed studies focusing on
- Carnitine + nonhormonal anti-inflammatory drugs
 - Clinical varicocele and infertility
 - for 6 months
 - => did not resolve the problem



Clomiphene citrate

- Subclinical varicocele,
 - did not improve **sperm concentration** and **motility** to the level that surgery does
 - did promote a significant improvement in **semen quality**
 - as well as in **pregnancy rates**
- lacks sufficient information to validate in patients with clinical varicocele



- Kallikrein (65 patients, 3 months)
 - 38 men: **statistical improvement** in sperm motility/morphology
- Menotropin (3 months before the varicocelectomy)
 - **Better** outcome compared to surgery alone
 - The sooner introducing, the better
- Vitamins and antioxidants
 - Data are insufficient



Subclinical varicocele

- Identified only with the help of Complementary tests beyond PE
- May be associated with male infertility
- **Scrotal Doppler ultrasound:**
 - Infertile men when the PE is inconclusive or for the detection of venous reflux
- The ideal treatment: undefined
- Varicocele treatment for infertility is not indicated



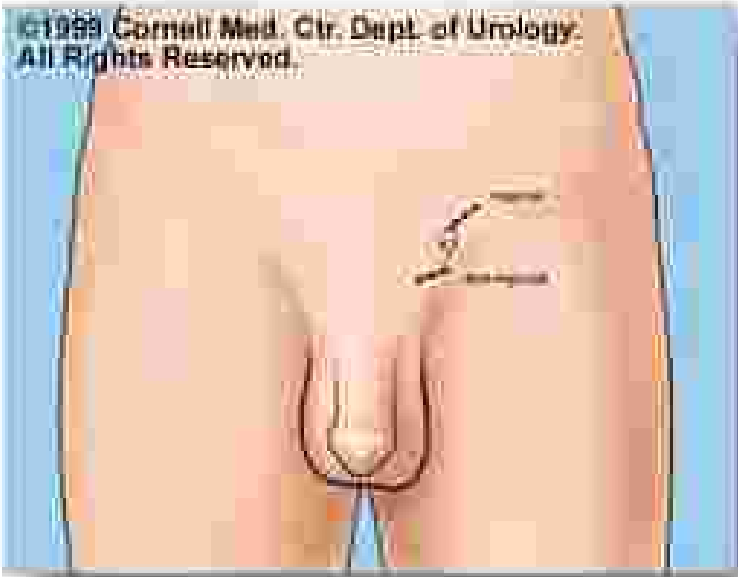
Surgery versus embolization

- Choice of treatment for varicocele
 - experience, expertise, the options available
- Only 2 methods are well-described
 - Surgical vein ligation
 - Percutaneous embolization
- 3 approaches:
 - Inguinal (groin)
 - Retroperitoneal (abdominal)
 - Infrainguinal/subinguinal (below the groin)

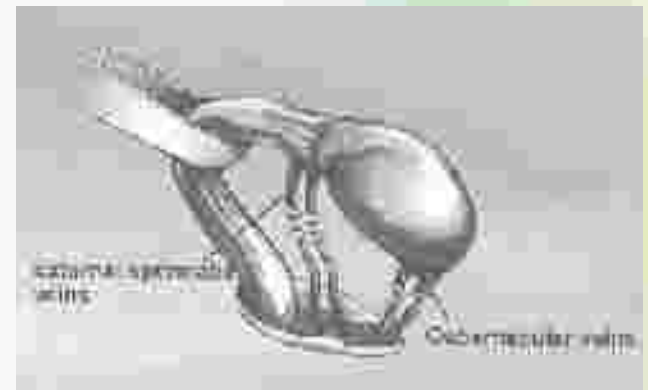
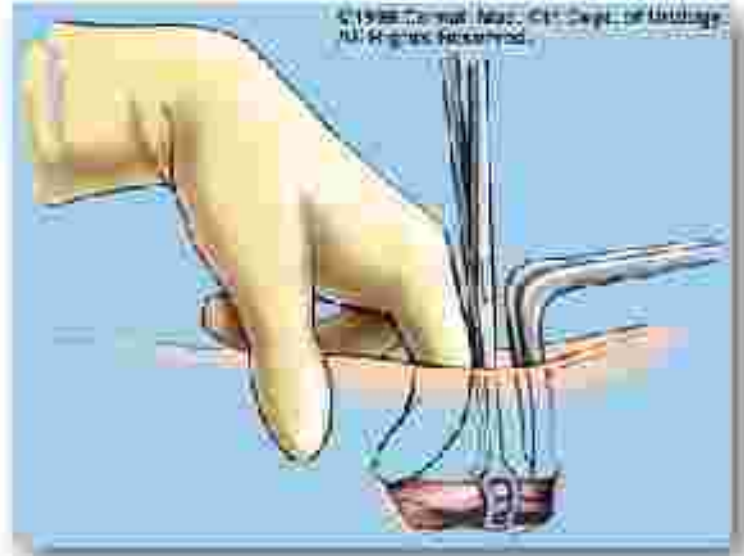


- Subinguinal microsurgical varicocelectomy with ligation and sclerosis Marmar et al.
- Modified the microsurgical technique with delivery of the testis in search of scrotal collaterals, including the gubernacular veins Goldstein et al.
- Percutaneous embolization:
 - occluding the internal spermatic vein
- None of these methods have been proven to be superior to the others in fertility improvement

©1999 Cornell Med. Ctr. Dept. of Urology.
All Rights Reserved.



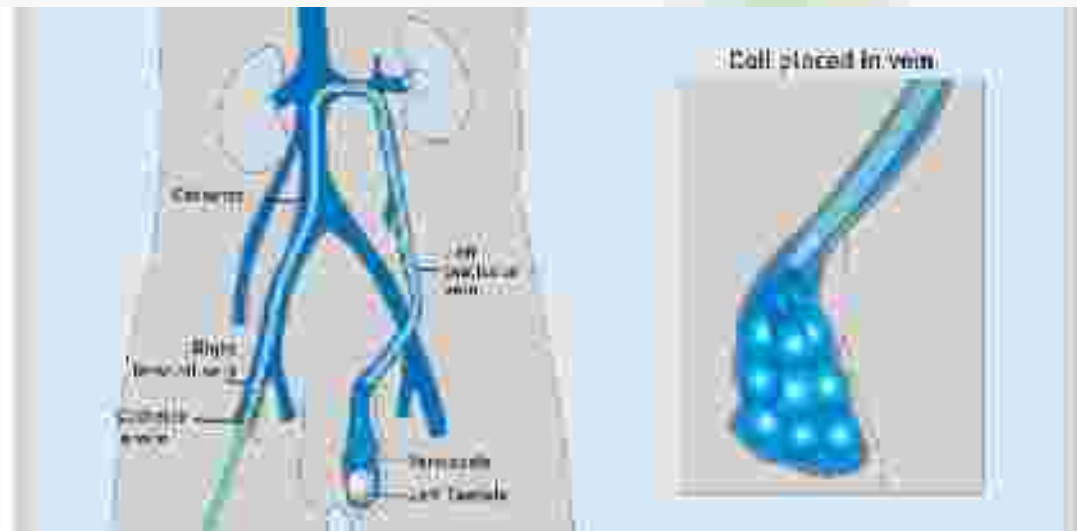
©1999 Cornell Med. Ctr. Dept. of Urology.
All Rights Reserved.



0125 - 3435 - 2516

Urological Sensitivity Effectiveness





www.ijerph.in

0121-2610-2611

Transparency Accountability Effectiveness



Differences in the complication and recurrence rates

- **Subinguinal varicocelectomy** with optical magnification,
 - ↑ **arterial and lymphatic vessel preservation**
 - Significantly ↓ risks of recurrence and postoperative complications in relation to LSC and surgeries without magnification
- Percutaneous embolization
 - Higher recurrence rates
 - Complications should be taken into account
- Patients with bilateral clinical varicocele should be submitted to a bilateral varicocelectomy

Azoospermia and varicocele

- Azoospermic patients
 - Palpable varicocele => Varicocele repair must be considered for all men
 - With germ cell aplasia in a single large testis biopsy => may have an improvement in semen quality following varicocelectomy
 - Surgical treatment of varicocele may promote spermatogenesis, avoiding the need to obtain sperm from the testicle for ART



Azoospermia and varicocele

- Possibility of relapse into azoospermia after an initial improvement in semen quality following varicocelectomy
 - Informed sperm cryopreservation



Varicocelectomy

- Management of couples with male factor infertility associated with a varicocele
 - Varicocele repair
 - Intrauterine insemination (IUI)
 - *in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI)*
- The decision as to which method to use is influenced by many factors



Varicocele repair opposed to IUI/ART

1. Improvement in semen parameters
 - Potential to **reverse** a pathological condition
 - Effect a **permanent** cure for infertility
2. Possibly greater cost-effectiveness
3. Failure to treat a varicocele (May result in a progressive decline in semen parameters)
4. Other considered factors
 - Age of the female partner
 - IVF/ICSI potential long-term health effects on the offspring



Semen quality following varicocelectomy

- Prognostic parameters for men with varicocele
 - Testicular size, varicocele grade, seminal parameters, hormonal levels
 - Impossible to conclude which are predictive
- Lack standardization
 - Selection methods, diagnostic techniques, forms of treatment, variables evaluated, adequate patients, prospective/randomized trials



Several literature

- Improved semen parameters & fertility following varicocelectomy
 - 50%, **semen quality** improves (1 randomized)
 - Natural pregnancy \uparrow 2.8 x (compared with no treatment or medical treatment)
- Surgery or embolization for varicocele in infertile men **does not** increase the chance of **natural pregnancy** (Clinical randomized)



- (Evers and Collins) Metaanalysis: 7x prospective, randomized trials, Varicocelectomy & pregnancy outcomes
 - Insufficient evidence to conclude: treatment of clinical varicocele improved the likelihood of conception for couples with male infertility
 - Routine treatment of the male partner of subfertile couples was **unadvisable**
 - Multiple questionable outcome, evaluation methods...



Controlled studies

- Majority, failed to use randomization
 - Men with palpable varicoceles
 - Men with abnormal semen analyses and/or Men with normal female partners
- Most : Improvement in fertility after varicocele Tx
- Few: varicocele Tx has little or no effect on fertility
- A review of 12 controlled studies: male had received varicocele treatment, compared with untreated
 - Pregnancy rate (1 yr) : > 33% / 16%



A Cochrane review

- Identified 5 randomized controlled trials
- Examined outcomes in couples with male factor infertility and varicoceles
- They did not show sufficient evidence regarding the treatment of varicoceles to warrant their repair
- No evaluation of the methods was performed. Use of embolization, high pregnancy rates in untreated couples (25% in a one-year period), and inherent selection bias in the study



Brief summary

- Although few randomized controlled trials show the benefit of treating varicocele-related infertility, many nonrandomized studies support this concept
- Based on a review of numerous studies, most of them **retrospective**, several conclusions were drawn



Brief summary

- Most participants showed improvement in postoperative sperm density and motility.
- Natural pregnancy rates varied, but the overall average was 37%, (a clearly higher figure than any reported for non-treatment)
- Although many of these studies suffer from the flaws of non-randomized trials, these results would be **difficult to explain on the basis of chance alone.**



Brief summary

- Certain circumstances, even Female factor infertility present
- Some men with nonobstructive azoospermia
 - Tx of varicocele before initiating ART
 - Restore at least low numbers of sperm to the ejaculate
 - Making IVF/ICSI possible without testicular sperm aspiration or extraction



Varicocele in the adolescent

- Varicocele grade
(As In adults, is related to testicular volume)
 - Grade I, minimal impact on testicular volume
 - Grade II, related to unilateral atrophy
 - Grade III, related to bilateral abnormalities
- Not related to the presence or gravity of testicular disproportion



-Testicular hypotrophy

- Caused by varicocele: 9%
- According to Tanner Kass classification

Tanner Stage	Left Testis	Right Testis
1	4.76 ±2.76 cm ³	5.20 ±3.86 cm ³
2	6.40 ±3.16 cm ³	7.08 ±3.89 cm ³
3	14.58 ±6.54 cm ³	14.77 ±6.1 cm ³
4	19.80 ±6.17 cm ³	20.45 ±6.79 cm ³
5	28.31 ±8.52 cm ³	30.25 ±9.64 cm ³

- **Criteria**, arbitrary (not compared with fertility in a long-term follow-up), include:
 - 1) Difference in testicular size, 10~25%
 - 2) Absolute difference between the testicles 2~3ml

-Scrotal pain

- Uncommon, incidence 2 ~ 4%
- Indications for varicocelectomy: No studies have been published



-Varicocele repairment (1)

- Higher Sperm motility ↑ after varicocelectomy (compared with adults)
- Affected testis size ↑: 50 ~ 90%
- Main challenge: establishing criteria for OP
 - The same techniques as in adults



-Varicocele repairment (2)

- Adolescents with Unilateral/bilateral varicoceles
 - First detection of testicular / semen abnormality
 - Bilateral normal testicular development / absence of symptoms
 - Evidence is lacking to support the benefits of surgical varicocele repair
 - Annual followed up testis size and/or S/A (earliest sign of varicocele-related testicular injury)



Benefits of surgery in ART

<i>Penson et al.</i>	Post varicocelectomy	Post IVF/ICSI
Probability of Live Birth	29.7%	25.4%
Multiple Gestation Rate	1% (twins)	39%
<i>Schlegel.</i>		
Cost	\$26,268	\$89,091



-Surgical treatment of varicocele

- Improving semen parameters →
 - ↑ total motile sperm count
 - Improved sperm morphology
 - ↓ oxidative stress → Improvement in the function of the male gamete
- Avoid the need for ART
- ↓ Tx complexity grade when ART is indicated
- In azoospermic patients
 - Promote spermatogenesis
 - Avoid the need to obtain sperm from the testicle



After varicocele treatment

1. Evaluate persistence or recurrence of the varicocele
 - **Internal spermatic venography** (identify the site of persistent venous reflux)
 - **Surgical ligation / percutaneous embolization** of the refluxing veins
1. Semen analysis (3-month intervals for at least 1 year or until pregnancy is achieved)
2. Infertility persists (If anatomically successful repair)
 - IUI or ART should be considered



Conclusions (1)

Varicocele treatment

- **Absence of definitive studies** on fertility outcomes
- **Conflicting evidence** from both randomized and nonrandomized trials
- **Clinical experience** still favors the surgical treatment of clinical varicoceles in men with infertility



Conclusions (2)

Varicocele treatment (Conc.)

- Should be considered as an option for appropriate infertile couples
 - Has been proven to **improve semen parameters** in most men
 - may possibly **improve fertility**
 - The **risks are small**
- Need randomized, properly controlled trials



Thank You For Your Attention

THE END



UNIVERSITY OF THE PHILIPPINES

Excellence, Accountability, Effectiveness

