The Role of the Urologist in the Era of IVF/ICSI

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Intracytoplastic Sperm Injection (ICSI)

- Revolutionized the treatment of male infertility (1993)
- Injection of a single sperm/egg
- Enabled men to be biologic fathers despite severe testicular damage or obstruction
### Assisted Reproductive Technology

<table>
<thead>
<tr>
<th>Year</th>
<th>Method</th>
<th>Description</th>
<th>Number of Sperm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1953</td>
<td>IUI (Intra-uterine Insemination)</td>
<td>3-5 million motile sperm</td>
<td></td>
</tr>
<tr>
<td>1978</td>
<td>IVF (In Vitro Fertilization)</td>
<td>75,000 motile sperm</td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td>ICSI (Intracytoplasmic Sperm Injection)</td>
<td>~20 motile sperm</td>
<td></td>
</tr>
</tbody>
</table>
ICSI Use in the United States

Year

1996

36.4%

2012

76.2%

Does male infertility inform about the general health of the male?

Male patients are being blocked from an evaluation and are being “detoured”

http://blog.thankfulfor.com/post/861441183/detours-welcome
Recommendation/Guidelines

- American Society for Reproductive Medicine (ASRM)
  - “Evaluation of both partners should begin at the same time.”

- National Institute for Health and Care Excellence (NICE)
  - England’s NHS advisory board
  - “Couples who experience problems in conceiving should be seen together ...”
What is the Role of the Urologist?

- Treat the affected male patient?
- Or assist in sperm retrieval?

The Urologist’s Role
Evaluation and Treatment of the Infertile Male

• To diagnose serious or life threatening conditions associated with infertility

• To identify and successfully treat reversible causes of infertility

• To define untreatable causes of testis failure and offer appropriate consultation and referral

• To perform sperm procurement procedures to enable IVF-ICSI
Incidence of Serious or Life-Threatening Medical Pathology

- N=1,236 patients (Baylor and Bowman Gray)
- 13 (1.1%) had serious underlying pathology
- Incidence of problems noted much greater than general population
  - Testicular tumors
  - Brain tumors
- No patient had a previous diagnosis of serious disease

Significant Medical Pathology Discovered During a Male Infertility Evaluation

- Retrospective study, 2 academic centers

- 33/536 (6%) patients had significant medical pathology

“There were no findings on just semen analysis or hormone testing that could identify all patients with significant medical pathology”

<table>
<thead>
<tr>
<th>Pathology</th>
<th># Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testis cancer</td>
<td>1</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1</td>
</tr>
<tr>
<td>Cystic Fibrosis Mutations</td>
<td>24</td>
</tr>
<tr>
<td>Karyotype abnormalities</td>
<td>3</td>
</tr>
</tbody>
</table>

Increased risk of Cancer in Infertile Men

- N= 22,562 (California cancer registry + 15 IVF centers in California)
- “Increased risk of high grade prostate cancer among infertile men”
  - Infertile men were 2.6 X more likely to be diagnosed with high grade prostate cancer
- “Increased risk of testicular germ cell cancer among infertile men”
  - Infertile men were 3 X more likely to be develop testicular cancer

Male Infertility and Morbidity/Mortality


Men with Impaired Semen Parameters Have Higher Mortality

• 11,935 infertile men, mean age 37 years
• 69 (0.58%) died during mean f/u 7.7 years

Mortality increases as quality of semen decreases

Increased Risk of Cancer Among Azoospermic Men

Methods

• Examined semen data from men entered into BCM andrology database from 1989-2009
• Linked with an administrative database for data regarding diagnosis, treatment, and identifying information
• Collated data then linked with Texas Cancer Registry

Eisenberg ML et al, Abstract 2289, 2013 AUA, San Diego, CA.
Men with azoospermia have an increased risk of subsequently developing all cancers, suggesting a common etiology between azoospermia and cancer development.
Medical Comorbidities Are More Common in Men with Impaired Semen Parameters

- 9,387 men, mean age 38 years
- Associated semen parameters with risk of comorbidities

<table>
<thead>
<tr>
<th>Condition</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>0.02</td>
</tr>
<tr>
<td>Genitourinary Disease</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Skin Disease</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.02</td>
</tr>
<tr>
<td>Non-ischemic Heart Disease</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Chronic Medical Conditions Are More Common in Men with Impaired Semen Parameters

- 13,027 infertile men, 23,860 men tested for fertility
- Mean ages 33 years in both groups
- Truven MarketScan Database 2001-2009
- Associated fertility status with comorbidities
- Associations stronger in men with longer follow-up

<table>
<thead>
<tr>
<th>Condition</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>1.3 (1.1-1.5)</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>1.5 (1.2-1.8)</td>
</tr>
<tr>
<td>Alcohol Abuse</td>
<td>1.5 (1.1-2.1)</td>
</tr>
<tr>
<td>Drug Abuse</td>
<td>1.7 (1.1-2.6)</td>
</tr>
</tbody>
</table>
Male Infertility and Hypogonadism

- Retrospective review of 310 + prospective evaluation of 229 male infertility patients; 225 controls
- Mean age ~35 years, range 18-50 years
- Sperm density <20 million/mL
- **Subgroups:**
  - Controls (Ctl)
  - Mild oligospermia (MO) → 10.1-20 million/mL
  - Severe oligospermia (SO) → 0.1-10 million/mL
  - Nonobstructive azoospermia (NOA)
- Hypogonadism = testosterone < 231 ng/dL

Hypogonadism is More Common in Infertile Men

Odds Ratio (OR) for Hypogonadism

10 (95% CI 5.1-22)

Ctl – Control
MO – mild oligospermia
SO – severe oligospermia
NOA – non-obstructive azoospermia

Male Infertility and Men's Health: What We Know

Male Infertility

Malignancy
- Genitourinary
- Blood / Immune
- Nervous System
- Endocrine

Chronic Conditions
- Genitourinary
- Endocrine
- Skin
- Cardiovascular

Mortality

Hypogonadism
The Urologist’s Role
Evaluation and Treatment of the Infertile Male

• To diagnose serious or life threatening conditions associated with infertility
• To identify and successfully treat reversible causes of infertility
• To define untreatable causes of testis failure and offer appropriate consultation and referral
• To perform sperm procurement procedures to enable IVF-ICSI
### Distribution of Final Diagnostic Categories Found in a Male Infertility Clinic

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>1535</td>
<td>32.6</td>
</tr>
<tr>
<td>Varicocele</td>
<td>1253</td>
<td>26.6</td>
</tr>
<tr>
<td>Obstruction</td>
<td>720</td>
<td>15.3</td>
</tr>
<tr>
<td>Normal female factor</td>
<td>503</td>
<td>10.7</td>
</tr>
<tr>
<td>Cryptorchidism</td>
<td>129</td>
<td>2.7</td>
</tr>
<tr>
<td>Immunologic</td>
<td>121</td>
<td>2.6</td>
</tr>
<tr>
<td>Ejaculatory failure</td>
<td>95</td>
<td>2.0</td>
</tr>
<tr>
<td>Endocrinologic</td>
<td>70</td>
<td>1.5</td>
</tr>
<tr>
<td>Drug/Radiation</td>
<td>64</td>
<td>1.4</td>
</tr>
<tr>
<td>Genetic</td>
<td>56</td>
<td>1.2</td>
</tr>
<tr>
<td>Testicular failure</td>
<td>52</td>
<td>1.1</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>32</td>
<td>0.7</td>
</tr>
<tr>
<td>Pyospermia</td>
<td>25</td>
<td>0.5</td>
</tr>
<tr>
<td>Cancer</td>
<td>20</td>
<td>0.4</td>
</tr>
<tr>
<td>Systemic disease</td>
<td>15</td>
<td>0.3</td>
</tr>
<tr>
<td>Infection</td>
<td>10</td>
<td>0.2</td>
</tr>
<tr>
<td>Torsion</td>
<td>5</td>
<td>0.1</td>
</tr>
<tr>
<td>Ultrastructural</td>
<td>5</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4710</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

Overview

• Pathophysiology of the varicocele effect

• Advantages of a varicocele repair in the “Era of IVF”

• Update on current techniques of varicocele repair

• Controversies on the safety of IVF-ICSI
### Incidence

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population</td>
<td>9,129</td>
<td>20(^1)</td>
</tr>
<tr>
<td>Infertile</td>
<td>2,131</td>
<td>40(^2)</td>
</tr>
</tbody>
</table>

Pathophysiology of a Varicocele

Mechanism of Effect

- Elevated testicular temperature
- Pressure effect
- Oxygen deprivation
- Retrograde toxins
Influence of Surgically Induced Varicocele on Testicular Blood Flow, Temperature and Histology in Adult Rates and Dogs

• Vx model: partial ligation of the left renal vein or destruction of a valve of left testicular vein

• Intra-testicular temperature was higher in both testes in the Vx model

  • Right: (34.8 vs 36.2 °C, p<0.01)
  • Left: (34.8 vs 35.8 °C, p<0.05)

Reduction in Testicular Temperature After Varicocelectomy in Infertile Men

- Measured scrotal surface temperature using electronic thermometer
- 119 Varicocele
- 45 control

<table>
<thead>
<tr>
<th>Side</th>
<th>Preop</th>
<th>Postop</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>34</td>
<td>↓33</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Bilateral</td>
<td>34</td>
<td>↓33</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Control</td>
<td>33.04</td>
<td>33</td>
<td>NS</td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>34.37</td>
<td>↓32.8</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Bilateral</td>
<td>34.34</td>
<td>↓33.5</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Control</td>
<td>32.86</td>
<td>32.86</td>
<td></td>
</tr>
<tr>
<td>P Value</td>
<td>0.01</td>
<td>NS</td>
<td></td>
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Leydig Cells
Germ Cells
Sertoli Cells
Pathophysiology
# Varicocele: Pathophysiology

## Effects of Increased Temperature on the Testes

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<th>Effect</th>
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<tr>
<td>Leydig</td>
<td>Decreased testosterone synthesis</td>
</tr>
<tr>
<td>Sertoli</td>
<td>Function and morphology altered</td>
</tr>
<tr>
<td>Germinal</td>
<td>Thermolabile cell membranes injured</td>
</tr>
<tr>
<td></td>
<td>Amino acid transport decreased</td>
</tr>
<tr>
<td></td>
<td>Protein biosynthesis decreased</td>
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Varicocele As a Risk Factor for Androgen Deficiency
Effect of Repair

- **Testosterone levels** in 325 men with palpable Vx were compared with 510 men without Vx
- Men with Vx had lower T levels (416 vs 469 ng/dL, p<0.001)
- 70% of patients showed improvement in T levels post-op

Varicocele As a Risk Factor for Androgen Deficiency

Effect of Repair

• Post-op testosterone levels increased significantly (358 → 454 ng/dL, \(p<0.001\))

• The significant improvement of T levels persists after adjusting for age, laterality and degree of Vx

## Varicocele: Pathophysiology

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Effect of Surgically Induced Varicocele on Sertoli Cell Function

Transferrin and ABP

• Evaluated the effect of surgically induced varicocele in rats compared to sham operated

• Recorded testicular blood flow and histo-chemical analysis of Sertoli Cell markers
  • Transferrin
  • Androgen binding protein (ABP)

Effect of Surgically Induced Varicocele on Sertoli Cell Function


![Graph showing the intensity of immunoreactivity for ABP* and Transferrin* in Control and Experimental Varicocele groups. The graph indicates a significant difference with a * P<0.05.]
## Varicocele: Pathophysiology

### Effects of Increased Temperature on the Testes

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<td></td>
<td>Protein biosynthesis decreased</td>
</tr>
</tbody>
</table>
Reactive Oxygen Species (ROS) and Total Antioxidant Capacity (TAC) Varicocele Patients vs. Controls

<table>
<thead>
<tr>
<th></th>
<th>Control patients* (n=17)</th>
<th>Incidental varicocele (n=15)</th>
<th>Infertile varicocele (n=21)</th>
<th>Control vs all varicocele P</th>
<th>Control vs varicocele Incidental P</th>
<th>Control vs varicocele Infertile P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>31.1 ± 2.1</td>
<td>29.9 ± 1.7</td>
<td>33.6 ± 1.0</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Log (ROS+1)</strong></td>
<td>1.30 ± 0.33</td>
<td>1.99 ± 0.26</td>
<td>2.1 ± 0.25</td>
<td>0.007</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>TAC = total Anti-oxidant</strong></td>
<td>1443.0 ± 105.0</td>
<td>939.0 ± 107.0</td>
<td>1186 ± 96.9</td>
<td>0.02</td>
<td>0.05</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Controls are normal donors without varicocele

The Advantages of a Varicocele Repair: Especially in Era of IVF
Impact of Spermatic Vein Ligation on the Male Factor in IVF-ET and Its Relation to Testosterone Levels Before and After Operation

- 22 infertile couples failed IVF
  - 12 combined infertility
  - 10 male factor only

- All male partners underwent Vx repair

<table>
<thead>
<tr>
<th></th>
<th>Pre Vx repair</th>
<th>Post Vx repair</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertilization Rate</td>
<td>9.4%</td>
<td>35.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cleavage Rate</td>
<td>66%</td>
<td>81.2%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pregnancy Rate</td>
<td>0</td>
<td>20%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Impact of Spermatic Vein Ligation on the Male Factor in IVF-ET and its Relation to T Levels Before and After Operation

- Plasma testosterone levels increased in 50% of men
- Improvement of testosterone levels enhanced outcomes:
  - Increased fertilization rate: 27.9 vs. 43.4%
  - Increased pregnancy rate: 18 vs. 64%

Clinical Outcome of ICSI in Infertile Men With Treated and Untreated Clinical Varicocele

• 242 infertile couples/men with clinical Vx
  • 162 untreated
  • 80 underwent microsurgical varicocelectomy
• Only first cycle ICSI was included
• No difference in baseline characteristics of the female partners

Clinical Outcome of ICSI in Infertile Men With Treated and Untreated Clinical Varicocele

- Statistical postop improvement
  - Sperm count (14 → 35M)
  - Motile sperm (6.7→15.4M)

- Improved clinical pregnancy rate
  - 48 vs 73%, p=0.04

- Improve live birth rate
  - 37 vs 51%, p=0.03

Varicocelectomy Improves Intrauterine Insemination Success Rates In Men With Varicocele

- 58 infertile couples (101 IUI cycles)
  - 24 men with untreated Vx (63 cycles)
  - 34 men with treated Vx (101 cycles)
- No difference found between the use of clomiphene or gonadotropins
- No difference in post-wash semen parameters between the 2 groups

Varicocelectomy Improves Intrauterine Insemination Success Rates In Men With Varicocele

<table>
<thead>
<tr>
<th>Rate</th>
<th>% Untreated</th>
<th>% Treated</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy/cycle</td>
<td>6.3</td>
<td>11.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Live birth/cycle</td>
<td>2.1</td>
<td>11.8</td>
<td>0.007</td>
</tr>
<tr>
<td>Live birth/couple</td>
<td>4.2</td>
<td>32.4</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Varicocele Repair Improves Sperm Ultra-morphology

- 75 men with varicocele – treated and untreated
- Treated $\rightarrow$ improvement in:
  - **Semen parameters** $\rightarrow$ density, motility, normal forms
  - **Ultramorphology** $\rightarrow$ acrosome agenesis, chromatin condensation, amorphous heads

Can Varicocelectomy Significantly Change The Way Couples Use Assisted Reproductive Technologies?

• Cohort of 540 infertile men with clinical Vx
• Divided into 4 groups based on total motile sperm count
  • < 1.5M (154 ICSI candidates)
  • 1.5-5M (79 IVF candidates)
  • 5-20M (151 IUI candidates)
  • >20M (156 Spontaneous pregnancy candidates)
• Female factors were excluded

Can Varicocelectomy Significantly Change The Way Couples Use Assisted Reproductive Technologies?

- 50% of men had >50% improvement in total motile sperm count post Vx repair
- 36.6% spontaneous pregnancy rate postop
- Post-op shift in ART candidacy
  - 31% ICSI → IVF, IUI or spontaneous pregnancy
  - 53% IVF → IUI or spontaneous pregnancy
  - 42% IUI → Spontaneous pregnancy

Current Techniques of Varicocele Repair
Sites of Surgical Incision

- Retroperitoneal
- Inguinal
- Subinguinal
Mini-inguinal Incision
Varicocele Repair
Common Vascular Pattern
Micro-tip Jacobson Clamp
Micro Doppler Probe
(With Disposable Tip)

Vascular Technology, Inc. (VTI)
VTI Micro Doppler Box
(Low Signal-to-Noise Ratio)
Veins are occluded with 3-0 silk sutures or hemoclips.
Sony 3-D Projection and Head Set
Varicocele Repair
Metanalysis

No. Studies: 22
No. Patients: 2,989
Improved Semen: 71%
Pregnancy: 37%

Outcomes of Varicocelectomy Treatment
An Updated Critical Analysis

• Meta-analysis 29 RT’s
• Overall pregnancy rate was 39.4%
• 72% studies showed improvements in semen quality

The Urologist’s Role
Evaluation and Treatment of the Infertile Male

- To diagnose serious or life threatening conditions associated with infertility
- To identify and successfully treat reversible causes of infertility
- To define untreatable causes of testis failure and offer appropriate consultation and referral
- To perform sperm procurement procedures to enable IVF-ICSI
IS ICSI SAFE?
Genetic Defects Transmitted to Offspring Conceived by ICSI

- Y Chromosome microdeletions
- Robertsonian translocations
- Ring chromosomes
- Autosomal trisomies
- Sex chromosome aneuploidies
- Inversions
- Diandric triploidy from fertilization by diploid sperm (69XXY)
- Renal agenesis
- Hypospadias?
Congenital Defect in Assisted Reproductive Technology Pregnancies

- 225 ART pregnancies
  - 88 IVF
  - 137 IVF + ICSI
- 13 congenital malformation (5.8%)
  - Control group (5884 pregnancies), malformation rate 2.7%
  - No difference between IVF vs. ICSI (5.8 vs. 5.7%)
- Most common malformations
  - Anencephaly (38.5%)
  - Limb abnormalities (23.1%)

A Review of the Belgium ICSI Experience: Major Risks

- Multiple pregnancies
- Increased major congenital malformations
- More de novo sex and autosomal chromosome abnormalities
- Increased risk of imprinting disorders
  - Angelman’s and Prader-Willi Syndromes
What About Counsyl and "23andMe"??

- One-time carrier screening → 100 Mendelian disorders
- Requires physician order
- "Next Generation" Fertility Testing:
  - Utilize known genes involved in male fertility to develop a screening panel
  - Incorporate future genes on a rolling basis
- Trait information → 50 traits
- Pharmacogenetics → predict response to drugs
- Ancestry data
Challenges to ICSI Safety Follow-up

- Many genetic defects due to ICSI may have similar phenotypes
- Techniques to identify new genetic abnormalities are improving
- Current data on ICSI safety may only be the “tip of the iceberg”
Conclusion

• Varicocele is a common cause of testicular dysfunction and can be easily corrected

• Varicocele-induced damage can affect Leydig cells, Sertoli cells as well as the germ cells

• Varicocele repair in the “Era of ICSI” is especially important
  • Offer patients less complicated forms of ART
  • Improve outcomes with IUI
  • Increase embryo quality with IVF/ICSI

• The safety of IVF/ICSI continues to be scientifically debated
Summary

- As ICSI increases, the role of the urologist in treating the infertile male will be more frequently challenged.
- Infertility as a metric of men’s health needs to be stressed to both patients as well as gynecologists.
- Urologists can still play a vital role in actually curing male infertility.
- IVF-ICSI must be viewed as the treatment of last resort and not as the only treatment with effective results.
Thank You

Texas Medical Center, Houston