Evaluation of Male Infertility

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Annual Refresher Course for the Family Physician
Infertility: Definition

- Within 6 months 50% of normal couples will conceive
- Within 12 months 80% will conceive (limit of normal)
- Within 2 years 85% will conceive
Infertility: The Problem

- 15% of couples attempting to conceive spontaneously will fail
- 10% of couples with 1 child will fail to conceive a second time
- Over $1 billion is spent per year
- The psychological costs are inestimable
The Care Void

Responsible Parties

Female 47%  
Male 33%  
Both 20%

By Specialty

Female 89%  
Male 11%
Male Infertility – The Specialty

- Evaluation and treatment of infertile couples
- Close relationship and collaboration with the reproductive endocrinology (IVF) team and lab
# Etiology

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Varicocele</td>
<td>37.4%</td>
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<tr>
<td>Idiopathic</td>
<td>25.4%</td>
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<tr>
<td>Testicular failure</td>
<td>9.4%</td>
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<tr>
<td>Obstruction</td>
<td>6.1%</td>
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<tr>
<td>Cryptorchidism</td>
<td>6.1%</td>
</tr>
<tr>
<td>Volume</td>
<td>4.7%</td>
</tr>
<tr>
<td>Agglutination</td>
<td>3.1%</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>2.8%</td>
</tr>
<tr>
<td>Viscosity</td>
<td>1.9%</td>
</tr>
<tr>
<td>Ejaculatory failure</td>
<td>1.2%</td>
</tr>
<tr>
<td>Endocrine</td>
<td>0.9%</td>
</tr>
<tr>
<td>High density</td>
<td>0.5%</td>
</tr>
<tr>
<td>Necrospermia</td>
<td>0.5%</td>
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Greenberg, Lipshultz, Wein 1978
Genetic Disorders

- May account for many of the idiopathic male infertility cases

- Genetic abnormalities may cause infertility by affecting sperm production or sperm transport
Genetic Factors Known to Be Related to Male Infertility

- Cystic fibrosis gene mutations associated with CBAVD
- Chromosomal abnormalities resulting in impaired testicular function
- Y-chromosome microdeletions associated with isolated spermatogenic impairment
Chromosomal Abnormalities

- Found in karyotypes of 10-15% of men with azoospermia and 5% of men with oligospermia, but <1% of normal men

- Kleinfelter syndrome (XXY):
  - Most common disorder associated with male infertility (14% of azoospermia cases)
  - Phenotype: gynecomastia, small firm testicles, azoospermia
  - Karyotype confirms diagnosis
  - 10% mosaic – 46,XY/47,XXY
  - Sperm can be found in 50% of mosaic KS
Cystic Fibrosis

- Almost all men with clinical cystic fibrosis have CBAVD
- About two thirds (up to 80%) of men with CBAVD but no other clinical signs of cystic fibrosis have mutations of the CFTR gene detectable by current laboratory tests
- CF gene located at chromosome 7; over 500 mutations reported
Microdeletions of the Y Chromosome

- Found in 10-15% of men with azoospermia or severe oligospermia
- AZF regions a, b, c (long arm of Y chromosome; Yq11)
- Micro-deletions in AZFc: better prognosis for sperm retrieval
- Assay available
The Purpose of the Male Evaluation

- Identify potentially correctable conditions
- Identify irreversible conditions amenable to assisted reproductive techniques using the sperm of the male partner
- Identify irreversible conditions not amenable to the above techniques but for which donor insemination or adoption are possible options
The Purpose of the Male Evaluation (Cont’d)

- Identify life- or health-threatening conditions that may underlie the infertility and require medical attention

- Identify genetic abnormalities that may affect the health of the offspring if assisted reproductive techniques are to be used
Initial Screening Evaluation for Male Infertility

- No pregnancy within 1 year of unprotected intercourse

- Before 1 year: known male or female risk factors for infertility (such as bilateral cryptorchidism and age over 35, respectively); or if male partner questions his fertility potential
Components of Initial Screening Evaluation

- Reproductive history

- Two properly performed semen analyses, preferably separated by at least one month
Sexual and Reproductive History

- Timing and frequency of intercourse
- Frequency of masturbation
- Lubricants
- Duration of infertility and previous fertility
- Childhood illnesses and developmental history
- Systemic medical illnesses and previous surgeries
- Sexual history: erectile function, libido, STDs
Childhood and Development

- Undescended testicles
- Testicular surgery: orchiopexy, hydrocele repair
- Herniorrhaphy
- Urinary bladder surgery
- Testicular torsion
- Testicular trauma
- Onset of puberty
Surgical History

- Orchiectomy (testis cancer, torsion)
- Retroperitoneal surgery
- Pelvic injury
- Pelvic, inguinal or scrotal surgery
- Herniorrhapsy
- Urinary bladder and prostate surgery
Infections

- Viral, febrile
- Mumps orchitis
- Sexually transmitted diseases: gonorrhea, chlamydia
- Tuberculosis
Gonadotoxins

- Chemicals (pesticides)
- Chemotherapeutics
- Cimetidine
- Sulfasalazine
- Nitrofurantoin
- Alcohol

- Cannabis
- Androgenic steroids
- Thermal exposure
- Radiation
- Nicotine
Full Evaluation

- **Positive initial screening evaluation.**

- **Components:**
  - Complete history
  - Physical exam
  - Semen analysis
  - Proceed according to findings
Physical Examination

- General examination
- Normal male habitus? Hair distribution? Gynecomastia?
- Emphasis on genitalia: size of penis, plaques, curvature, urethral meatus (hypospadias?), testicular size and consistency, vas deferens, epididymis, rectal examination (enlarged seminal vesicles? midline cyst?)
- Examine in upright position and valsalva for varicocele
Varicocele

- Present in 15% of normal men and in approximately 40% of men presenting with infertility
- The preponderance of experimental data from clinical and animal models shows that varicoceles have a deleterious effect on spermatogenesis
- Exact pathophysiology of varicocele-induced damage:
  - Not yet completely understood
  - Suggested mechanisms: elevated testicular temperature, venous reflux
Varicocele (Cont’d)

- Physical exam: upright position, valsalva
- Only palpable varicoceles have been documented to be associated with infertility!
- Scrotal ultrasonography:
  - Not indicated for detection of varicoceles in the standard evaluation of infertile men
  - May occasionally help to clarify an inconclusive physical examination of the scrotum
Semen Analysis
Semen Analysis

- Cornerstone of lab evaluation

- Abstain from sexual activity 2-3 days prior to semen collection

- Values outside normal range suggest male infertility factor and indicates the need for further evaluation, but men with variables outside normal limits may still be fertile
## Semen Analysis

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<tr>
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<th>WHO 1999</th>
<th>WHO 2010</th>
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<tbody>
<tr>
<td>Semen volume (ml)</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>Sperm concentration (million/ml)</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Sperm motility (%)</td>
<td>50</td>
<td>32</td>
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</table>
Semen Analysis

- No significant sperm agglutination
- No significant pyospermia
- No hyperviscosity
Postejaculatory Urinalysis (PEU)

- **Indication:** ejaculate volumes <1 ml  
  (exceptions: CBAVD, clinical hypogonadism)

- Positive PEU in patients with azoospermia or aspermia suggests retrograde ejaculation

- Other possible causes for low-volume or absent ejaculate: anejaculation, ejaculatory duct obstruction, hypogonadism, or CBAVD
Sperm Morphology
Kruger Strict Criteria (WHO, 1999)

- Sperm stained, 100-200 counted
- Normal sperm:
  - Smooth contour and normal head
  - Acrosome 40-70% of distal head
  - No abnormalities of neck, midpiece or tail
  - No cytoplasmic droplets of more than half of head
- Any single abnormality = entire sperm is abnormal
- Typically, thresholds of normality 4-14% range
Specialized Clinical Tests On Semen And Sperm

- Quantitation of leukocytes in the semen
- Antisperm antibodies (IgG, IgA)
- Sperm DNA fragmentation/integrity tests:
  - Various tests: SCSA, COMET, TUNEL
  - Conflicting IVF pregnancy results in couples with increased sperm DNA damage
  - Use in the evaluation and management of the infertile male - controversial
Specialized Tests (Cont’d)

- Not required for the standard diagnosis of male infertility

- May be useful for identifying a male factor that contributes to unexplained infertility

- May be useful for selecting therapy, such as assisted reproductive technology
Pituitary/Testis Axis
Endocrine Evaluation

- Minimum initial endocrine evaluation:
  - Serum FSH
  - Testosterone (total, morning sample)

- This evaluation should be performed:
  - Oligospermia (especially <10 million cells/ml)
  - Azoospermia
  - Impaired sexual function
  - Other clinical findings suggestive of a specific endocrinopathy
Further endocrine evaluation should be considered if the initial endocrine studies are abnormal.

Endocrine disorders are uncommon in men with normal semen variables.
Hypogonadotropichypogonadism

- Delayed onset/arrested pubertal development/azoospermic (may be oligospermic in mild cases)

- When acquired: screen for pituitary tumor (Prl, imaging)

- FSH, LH, testosterone low to non-detectable

- Treatment: hormonal replacement (HCG, rFSH)
Hyperprolactinemia

- Serum prolactin > 50 ng/dl
- Screen for macro/microadenomata
Genetic Screening

- CFTR (CF transmembrane conductance regulator) gene mutations screen: CBAVD; Female partner screen!

- Y-chromosome micro-deletion assay & karyotype: should be offered in severe oligospermia and non-obstructive azoospermia, especially prior to IVF/ICSI
Imaging

- TRUS
- Scrotal ultrasonography
Transrectal ultrasound examination of normal seminal vesicles.

A, Transverse view; B, Sagittal view.

B, bladder; ED, ejaculatory duct; SV, seminal vesicle; U, urethra.
Azoospermia

- **Pre-testicular (endocrine):** rare, possibly correctable

- **Testicular:** usually irreversible, with the exception of varicocele

- **Post-testicular (obstructive):** frequently correctable; ~40%
Obstructive Azoospermia

- Normal size testis
- Vas, epididymis present
- FSH, testosterone, prolactin normal
- Vas absent (CBAVD)
- Semen normovolemic (EV obstruction)
- Semen hypovolemic (EJD obstruction)
- Dilated seminal vesicles per TRUS (EJD obstruction)
Non-obstructive Azoospermia

- Testicles small or in the lower end of the normal size range
- Vas, epididymis present
- FSH high, testosterone normal or low