Urological management of male infertility

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**Definition**

- **Infertility** = “the inability of a sexually active, non-contracepting couple to achieve spontaneous pregnancy in one year”, World Health Organization (WHO)

- **Primary infertility** = the failure to conceive at any time in the past with any prior partner

- **Secondary infertility** = indicates a prior conception with the current or previous partner
About 15% of couples do not achieve pregnancy within one year and seek medical treatment for infertility!

1/8 couples encounter problems when attempting to conceive a first child

1/6 couples encounter problems when attempting to conceive a subsequent child

(EAU Guidelines on Male Infertility, 2013)
Simmons, 1956:
- 20% of infertility cases are related to purely male factor etiology ($\mathcal{M}$)
- 30% to 40% of cases involve both male and female factor pathology ($\mathcal{M} + \mathcal{F}$)

Recent studies => similar results

In 50% of involuntarily childless couples, a male-infertility-associated factor is found together with abnormal semen parameters
(EAU Guidelines on Male Infertility, 2013)
Why evaluate the infertile man in the era of Assisted Reproductive Technology (ART)?
Missing important pathology

1. 3 to 20 times higher incidence of testis cancer

2. 30 to 100 times higher incidence of genetic abnormalities (ex: Klinefelter’s syndrome (47XXY) in <1/600 men)
3. **Varicocele** $\rightarrow \downarrow$ **testosterone!!**

1. Libido $\downarrow$
2. Erectile function $\downarrow$
3. Osteopenia/Osteoporosis $\downarrow$
4. Energy levels $\downarrow$

Repairing varicocele improves or at least halts the decline of each of these factors!!!!

- DNA damage $\uparrow$
- ART outcomes $\downarrow$
Donor Sperm/Adoption

Surgical Sperm Retrieval for ICSI

(IVF)/(ICSI) with Ejaculated Sper

IUI = Intra-uterine insemination
IVF = “in vitro” fertilization
ICSI = intracytoplasmatic sperm injection

Natural Conception

“Upgrading” fertility status

(Goldstein, 2013 AUA Meeting)
ART use for male factor infertility in the United States has been estimated to cost almost $18 billion dollars in 1 year alone (Meacham et al, 2007).

Lowering costs can be achieved by addressing the specific cause of male factor infertility!!!
Male infertility evaluation sooner than 1 year if:

1. male infertility risk factors such as a history of bilateral cryptorchidism are known to be present
2. female infertility risk factors including advanced female age (older than 35 years) are suspected
3. the couple questions the male partner’s fertility potential.

(AUA, Male Infertility Best Practice Committee Report 2006a&b)
Risk factors (summary)

- Congenital or acquired urogenital abnormalities
- Malignancies
- Urogenital tract infections
- ↑ Scrotal temperature (e.g. consequence of varicocele)
- Endocrine disturbances
- Genetic abnormalities
- Immunological factors

30-40% of cases = IDIOPATHIC male infertility
Prognostic Factors

- Duration of infertility
- Primary or secondary infertility
- Result of semen analysis
- Age and fertility status of female partner
History ➔ Physical examination ➔ Semen Analysis ➔ Additional tests ➔ Final Diagnosis
History

- Detailed history → Questionnaire!
- Sexual History (frequency, type, duration, “timing”, contraception)
  (lubricants can significantly alter sperm motility!!!!)
- Evaluation of erectile function and ejaculation
Ocupation & Habits
Ocupation & Habits
Surgical History:

- Trauma/Testicular Torsion => Atrophy, ASA
- Retroperitoneal Lymphadenectomy => Anejaculation, retrograde ejaculation
- Hydrocele surgery => damage of the vas deferens/epididymis
- Hernia repair => Extrinsic stenosis of the vas deferens
- TUR-P, TUIP => retrograde ejaculation
Infection
- Post pubertary viral orchitis
- Sexually Transmitted Diseases (Chlamydia/Neisseria gonorrhea)
- UTI (e.g. prostatitis)
- Bilateral Epididymitis => Epididymal obstruction => AZOOSPERMIA

Chemo/Radiotherapy
- Restoration of spermatogenesis after 3-4 years depending on the degree of destruction of the stem cells (Costabile, 1993)
- Total Distruption => Permanent azoospermia.
Medical History

- Delayed puberty => hypogonadotropin hypogonadism + anosmia => Kallmann syndrome
- Precocious puberty => Congenital Adrenal Hyperplasia (CAH)
- Diabetes mellitus, Multiple sclerosis => decrease in erectile/ejaculation function
- **alfa blockers** (treatment of BPH & Hypertension) => retrograde ejaculation
- **5-ARI** (BPH) => low sperm volume, erectile and ejaculatory dysfunction
- **Antibiotics** (nitrofurantoin, erythromycin, tetracycline, gentamycin) => gonadotoxicity
- **Spironolactone**, ketoconazole, cimetidine => inhibits androgen production
- **Sulfasalazine** => reversible reductions in sperm concentration and motility (Toth, 1979)
Teamwork

UROLOGIST – GYNECOLOGIST!!

Involved in 2/3 of infertile couples

- Age >35
- Irregular menstrual cycles
- Endometriosis
- History of pelvic pathology
- Ovulatory dysfunction
History  →  Physical examination  →  Semen Analysis

Differential diagnosis  →  Additional tests

Final Diagnosis
Physical examination

- **General** – oriented toward identification of infertility associated anomalies

- **Secondary sexual characters**: (height, fat distribution, voice, hair, skin, smelling, breasts) => Klinefelter’s sd

- **Ginaecomastia** estrogen/androgen imbalance or prolactin excess

- **Situs inversus** => Kartagener’s sd. = immobile cilia => immobili spermatozoa
Genital examination

- Both standing and in supine position
- Warm exam Room
- Penis: hipopspadias, curvatures
- Testicle size (Orchidometer)
- Testicular consistence
- Palpation - vas deferens– CBAVD
  - epididymis=>hardened/sensible
- Varicocele – Valsalva maneuver
  - Subclinical = irrelevant in regard to fertility status
Diagnostic

History → Physical examination

Semen Analysis

Differential diagnosis

Additional tests

Final Diagnosis
Semen Analysis

- Spermatogenesis => cca 64 days cycle
- Epididymal transit = 5-10 days
  (Clermont and Heller, 1963; Franca et al, 2005; Misell et al, 2006)
- Beware recent history (3 luni):
  • Fever
  • Malaise
  • Drugs
  • Substance abuse
- Repeat examination at 3 months interval
Semen Collecting

- Preferably in the laboratory
- Most frequent = masturbation (ethical/religious issues)
- Specially designed collecting condom – needs transportation at body temperature!!!!
- Withdrawal methods” ➔ high risk of incomplete ejaculation
- 3-5 days of sexual abstinence
- No alcohol
- Post ejaculation urine specimen
- Report of any drug use
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lower reference limit (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semen volume (mL)</td>
<td>1.5 (1.4-1.7)</td>
</tr>
<tr>
<td>Total sperm number (10⁶/ejaculate)</td>
<td>39 (33-46)</td>
</tr>
<tr>
<td>Sperm concentration (10⁶/mL)</td>
<td>15 (12-16)</td>
</tr>
<tr>
<td>Total motility (PR + NP)</td>
<td>40 (38-42)</td>
</tr>
<tr>
<td>Progressive motility (PR, %)</td>
<td>32 (31-34)</td>
</tr>
<tr>
<td>Vitality (live spermatozoa, %)</td>
<td>58 (55-63)</td>
</tr>
<tr>
<td>Sperm morphology (normal forms, %)</td>
<td>40 (30-40)</td>
</tr>
<tr>
<td>Other consensus threshold values</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>&gt; 7.2</td>
</tr>
<tr>
<td>Peroxidase-positive leukocytes (10⁶/mL)</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>Optional investigations</td>
<td></td>
</tr>
<tr>
<td>MAR test (motile spermatozoa with bound particles, %)</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>Immunobead test (motile spermatozoa with bound beads, %)</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>Seminal zinc (μmol/ejaculate)</td>
<td>&gt; 2.4</td>
</tr>
<tr>
<td>Seminal fructose (μmol/ejaculate)</td>
<td>&gt; 13</td>
</tr>
<tr>
<td>Seminal neutral glucosidase (mU/ejaculate)</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>No</td>
<td>All parameters are normal</td>
</tr>
<tr>
<td>----</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Oligospermia</td>
<td>$&lt;15 \times 10^6$ spermatozoa/ ml.</td>
</tr>
<tr>
<td>Asthenospermia</td>
<td>$&lt;50%$ spermatozoa with forward progression</td>
</tr>
<tr>
<td>Teratospermia</td>
<td>$&lt;30%$ spermatozoa with normal morphology</td>
</tr>
<tr>
<td>Oligoasthenoteratospermia (OAT)</td>
<td>All of the above</td>
</tr>
<tr>
<td>Azoospermia</td>
<td>No spermatozoa in the ejaculate</td>
</tr>
<tr>
<td>Aspermia</td>
<td>No ejaculate seminal</td>
</tr>
</tbody>
</table>
Parameter combination (Number, Motility, Morphology)

![Graph showing the relationship between the number of abnormal parameters and the chance of infertility.](image)

Guzick et al, NEJM345:1388, 2001
Factors influencing semen analysis results

- Certain drugs such as cimetidine, male or female hormones such as testosterone and estrogen, chemotherapy drugs;
- Coffee, alcohol, cocaine, marijuana, tobacco
- The semen sample is kept too cold or warm;
- Exposure to radiation or chemical agents such as pesticides and spermicides;
- Prolonged abstinence.
- Genital tract infections
Diagnostic

History → Physical examination

Semen Analysis

Differential diagnosis → Additional tests

Final Diagnosis
Low ejaculate volume

- Drugs
- Retroperitoneal or bladder neck surgery
- Ejaculatory duct obstruction
- Diabetes mellitus
- Spinal cord injury
- Psychologic disturbances
- Idiopathic
- Incomplete collection
Differential

Azoospermia

- Hypogonadotrophic hypogonadism
  - Kallman syndrome
  - Pituitary tumor
- Spermatogenic abnormalities
- Chromosomal abnormalities
- Y-Chromosome microdeletions
- Gonadotoxins
- Varicocele
- Viral orchitis
- Torsion
- Idiopathic
- Ductal obstruction
Differential

- Asthenospermia
  - Spermatozoal structural defects
  - Prolonged abstinence
  - Idiopathic
  - Genital tract infection
  - ASA
  - Varicocele
  - Partial Obstruction
Oligoasthenoteratospermia (OAT)

- Varicocele
- Criptorchidism
- Idiopathic
- Drugs, Heat, Toxins
- Systemic infection
- Endocrinopathy
Normal Sperm Analysis BUT Infertile

- Gynaecological pathology
- Abnormal coital habits
- Acrosomal defects
- ASA
- Unexplained
Diagnostic

History → Physical examination → Semen Analysis

Differential diagnosis → Additional tests

Final Diagnosis
Aditional Tests

- **Hormones (FSH, Testosterone, TSH)**
  - When concentration less than $10^6$/ml
- **Anti Sperm Antibodies**
- **Sperm culture**
- **Reactive Oxygen Species**
- **Genetic testing**
  - Non obstructive azoospermia
  - kariotype, $Y$ chromosome microdeletion
Purpose: identify retrograde ejaculation

Indications:
- Low volume semen or absent ejaculate

Technique:
- Void => collect semen sample => void into second container

Results:
- High number of spermatozoa in urine = ejaculare retrogradă
- Low number of spermatozoa = common findings
DNA fragmentation Assays

- Normal <30% (High is bad!!!!)
- Associated with recurrent miscarriages
- Not routinely indicated
- Interpretation
  - High fragmentation => nécessită tratarea cauzei:
    - Stop smoking
    - Treat Varicocele
    - Give antioxidants (limited data)

- ICSI
Scrotal US

- Not routinely indicated
- Physical exam difficult (adipose tissue, retractile scrotum)
- Scrotal mass

TRUS

- Low volume ejaculate

!!!! IF FINDINGS WILL CHANGE TREATMENT OPTIONS
Infertility Classifications

- Pre-testicular
  - Hormone deficiency

- Testicular
  - Impaired Sperm Production
    - Genetic
    - Varicocele

- Post-testicular
  - Obstruction
  - Anti-sperm antibodies
  - Infection
## Distribution of Etiology of Male Infertility

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varicocele</td>
<td>603</td>
<td>42.2</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>324</td>
<td>22.7</td>
</tr>
<tr>
<td>Obstruction</td>
<td>205</td>
<td>14.3</td>
</tr>
<tr>
<td>Normal/Female factor</td>
<td>119</td>
<td>7.9</td>
</tr>
<tr>
<td>Criptorhidism</td>
<td>49</td>
<td>3.4</td>
</tr>
<tr>
<td>Immunologic</td>
<td>27</td>
<td>2.6</td>
</tr>
<tr>
<td>Ejaculatory Disfunction</td>
<td>18</td>
<td>1.3</td>
</tr>
<tr>
<td>Testicular Failure</td>
<td>18</td>
<td>1.3</td>
</tr>
<tr>
<td>Drug/Radiation</td>
<td>16</td>
<td>1.1</td>
</tr>
<tr>
<td>Endocrinopathy</td>
<td>16</td>
<td>1.1</td>
</tr>
<tr>
<td>Others (all 1%)</td>
<td>31</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Management

• If the cause of the infertility is known, specific therapy may be instituted => results are often quite good

• If the cause of the infertility is not known, treatment options include ART and empirical therapy

• All medication used is “off label”

• “If a little is good, more must be better”

Mark Sigman, Medical Therapy of Male Infertility, AUA, 2013
Medical Management

1. Preventive – smoking
   – alcohol
   – occupational hazards
   – environmental hazards

2. Curative –
   a. hormone replacement or manipulations
   b. erectile dysfunction and immunological abnormalities
   c. Male Accessory Gland Infections (MAGI)
   d. sperm nutrients
   e. sperm motility enhancers
   f. miscellaneous – acupuncture, ayurvedic preparations.
Surgical Management

1. Diagnostic –
   - vasography (rarely needed)
   - testicular biopsy

2. Therapeutic –
   a. definitive – varicocele
      - vasal obstruction
      - epididymal obstruction
      - ejaculatory duct obstruction
      - erectile dysfunction
   b. Adjunctive – to aid in Assisted Reproduction Techniques (ART)
Varicocele-Definition

- “…veins (that) swollen and twisted over the testicle, which becomes smaller than its fellow”
  (Celsus 1st Century A.D.)

- “Abnormal dilation of the veins of the pampiniform plexus”
  (Howard. Fertil Steril, 1984)
Incidence of Varicocele

Men with Secondary Infertility: 80%
Men with Primary Infertility: 35%
All men: 15%

Varicoceles are graded by size:

- Small grade I varicoceles => detectable only during the Valsalva maneuver;
- Moderate size grade II varicoceles => can be palpated without Valsalva;
- Large grade III varicoceles, which are visible through the scrotal skin (classically described as feeling like a “bag of worms”)

- Right-angle insertion of the left gonadal vein into the renal => turbulent flow
- Almost 90% presenting on the left side alone.
A varicocele can be felt and sometimes be seen as a tortuous mass on the surface of the scrotum. A varicocele is made up of veins that contain inadequate valves.
What causes abnormal semen?

- Changes in temperature gradient
- Blood stagnation in testes and epididymis causing hypoxic changes in tissues
- Retrograde flow of toxic metabolites from adrenals or kidneys
- Alteration in testicular hormonal status
- Intratesticular hyperperfusion-induced testicular damage
Impaired Testicular Function

- Arrest of testicular growth (perceived in adolescence)
- Deranged semen parameters
- Leydig’s cell dysfunction
- Histological changes like tubular thickening
- Interstitial fibrosis and maturation arrests of sperms
“preventing future infertility underscores the importance of using a varicocelectomy technique that minimizes the risk of complications and recurrence.”  (Campbell-Walsh Urology, 2012)
Varicoceles cause a progressive decline in fertility

Prior fertility in men with varicocele does not predict resistance to varicocele-induced impairment of spermatogenesis

Men and adolescents with large varicoceles may benefit from prophylactic varicocelectomy to prevent future infertility and testosterone deficiency
Obstruction to ejaculatory ducts and vas are common conditions causing azoospermia.

It was originally performed by open surgery / now an operating microscope.

The various surgeries available are:
- vasovasostomy
- vasoepididymostomy
- crossed trans-septal vasovasostomy
Joining the ends of vas deferens to restore its anatomic continuity.

Restoration of fertility
- After vasectomy
- After severing of continuity of vas following juvenile hernia repair.

Vasal obstruction = 26.7% of subfertile patients with history of hernia repair (Matsuda, 1992)

Vasovasostomy can be performed by side to side or end to end anastamoses
Orchiopexy in adults

- Associated with a high incidence of infertility even when unilateral
- Leydig cell function in undescended testis can be retained
- Bilateral undescended testes repair can induce spermatogenesis and allow pregnancy (Shin et al, 1997).
- A solitary cryptorchid testis, placed in scrotum => enough testosterone to obviate the need for hormone replacement
- Needs regular self examination and yearly ultrasound
# Surgical Techniques for Sperm Retrieval

- **CBAVD**
- **Bilateral partial aplasia of VD**
- **FAILED SURGERY**
- **Surgically unreconstructable**

<table>
<thead>
<tr>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MESA (microsurgical epididymal sperm aspiration)</strong></td>
<td>Requires anesthesia and microsurgical skills.</td>
</tr>
<tr>
<td>Microsurgical procedure allows lower complication rate.</td>
<td>Not indicated for nonobstructive azoospermia.</td>
</tr>
<tr>
<td>Epididymal sperm has better motility than testicular sperm.</td>
<td>Complications include hematoma, pain, and vascular injury to testes and epididymis.</td>
</tr>
<tr>
<td>Large number of sperm can be harvested for cryopreservation of multiple vials in a single procedure.</td>
<td>Variable success in obtaining sperm.</td>
</tr>
<tr>
<td><strong>PESA (percutaneous epididymal sperm aspiration)</strong></td>
<td>Small quantity of sperm obtained than with MESA.</td>
</tr>
<tr>
<td>No microsurgical skill required.</td>
<td>Not indicated in nonobstructive azoospermia.</td>
</tr>
<tr>
<td>Local anesthesia.</td>
<td>Immature or immotile testicular sperm.</td>
</tr>
<tr>
<td>Epididymal sperm has better motility than testicular sperm.</td>
<td>Small quantity of sperm obtained.</td>
</tr>
<tr>
<td><strong>TESA (testicular sperm aspiration)</strong></td>
<td>Poor results in nonobstructive azoospermia.</td>
</tr>
<tr>
<td>No microsurgical skill required.</td>
<td>Complications include hematoma, pain, and vascular injury to testes and epididymis.</td>
</tr>
<tr>
<td>Local anesthesia.</td>
<td>Requires anesthesia and microsurgical skills.</td>
</tr>
<tr>
<td>Can be used for obstructive azoospermia.</td>
<td><strong>TESE (testicular sperm extraction)</strong></td>
</tr>
<tr>
<td>Low complication rate if performed microsurgically.</td>
<td>Preferred technique for nonobstructive azoospermia.</td>
</tr>
</tbody>
</table>
Microsurgical Epididymal Sperm Aspiration (MESA)
Employing ICSI, ongoing pregnancy or delivery rates exceeding 60% have been achieved with this technique using either fresh or cryopreserved epididymal sperm (Schlegel et al, 1995; Nudell et al, 1998).
Percutaneous Epididymal Sperm Aspiration (PESA)
Percutaneous Epididymal Sperm Aspiration (PESA)

- Less reliable than the open retrieval
- Sperm obtained is sometimes inadequate for cryopreservation.
- Reported pregnancy rates are half those achieved with open techniques.
1. Open testicular sperm largest member of sperm
2. Percutaneous core biopsy; same 14-gauge biopsy gun used for prostate biopsy
3. Percutaneous aspiration (testicular sperm aspiration—TESA)
   - high-suction glass syringe and a 23-gauge needle.
   - least invasive but requires 10 to 20 passes to obtain an adequate yield
micro TESE

- Identification of an area in the tunica albuginea free of blood vessels
- Tubules with spermatogenesis are of considerably larger diameter than tubules composed of Sertoli cells only
- Can only be observed under the operating microscope