Male infertility

Introduction

- **Definition:** infertility is defined as the inability to conceive after one year of intercourse without contraception (WHO). 15% of couples cannot have children within the first year of trying. In 40% of cases, the problem is solely male, in 40% solely female, and in 20% both.

- **Starting a fertility study:** should begin after 1 year of intercourse without contraception or sooner if there is any risk pathology in the ♂ (e.g. bilateral cryptorchidism) or in the ♀ (e.g. >35 years of age). The ♂ and ♀ should be studied simultaneously.

- **Woman’s age:** a key factor. Compared with a 25-year old woman, the fertility potential with assisted reproduction for a 35-year old ♀ is 50%, falling to 25% at 38 and 5% at 40.

Anamnesis

- **Personal history:** age of testicular descent and onset of puberty, general medical and surgical history, medications, smoking, drug or alcohol use, exposure to occupational or environmental toxins, heat or radiation, orchitis, STDs. Prepubescent mumps or postpubescent mumps without orchitis do not interfere with fertility. A febrile illness within the previous 6 m may induce oligospermia or azoospermia.

<table>
<thead>
<tr>
<th>Drugs that cause infertility</th>
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<tbody>
<tr>
<td>Valproic acid</td>
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<tr>
<td>Allopurinol</td>
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<tr>
<td>Ca-channel blocker</td>
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<tr>
<td>Hormones: androgen, antiandrogen, progestogens, LHRH agonists</td>
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</tbody>
</table>

- **Family history:** brothers who are infertile or who have testicular atrophy, hypogonadism, cryptorchidism, or dysraphias.

- **Reproductive history of the couple:** duration of primary or secondary infertility, miscarriages/children with current or previous partners.

- **Sexual history:** contraceptive methods, sexual practices, frequency of intercourse, use of lubricants.

Physical examination

- **General:** distribution of body hair, secondary sexual characteristics, height, breasts, and lower/upper limbs proportion.

- **Neurological:** visual field, anosmia, sphincter tone, and deep tendon reflexes.

- **Genitals:** penis and meatus, testicles, epididymis, vas deferens, prostate and seminal vesicles, presence of varicocele.

Baseline male infertility study

In addition to the medical history and physical exam, the following tests are recommended:

- **CBC and general blood biochemistry.**

- **Urinalysis.**

- **Hormonal evaluation:** FSH, LH, total and free testosterone.

- **Repeated spermiogram:** at least 2 separate spermiograms should be performed 1-3 weeks apart. If the 1st is normal, the 2nd is unnecessary. The semen should be collected by masturbation in a sterile container after 3-5 days of sexual abstinence. The sample should be taken to the laboratory within 30 m. In 2010, the WHO published new reference values for semen, taking as the lower limit the 5th percentile of men with proven fertility within 12 months from initiating unprotected intercourse.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>WHO reference values 1999</th>
<th>WHO reference values 2010</th>
<th>Disturbance¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>&gt;2 mL</td>
<td>&gt;1.5 mL</td>
<td>aspermia²</td>
</tr>
<tr>
<td>Seminal pH</td>
<td>≥7.2</td>
<td>≥7.2</td>
<td>hypospermia²</td>
</tr>
<tr>
<td>Sperm count</td>
<td>20-250 mill/mL</td>
<td>&gt;15 mill/mL</td>
<td>azoospermia³</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cryptozoospermia³</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>oligozoospermia³</td>
</tr>
<tr>
<td>Total number</td>
<td>&gt;40 mill</td>
<td>&gt;39 mill</td>
<td>oligozoospermia⁴</td>
</tr>
<tr>
<td>Motility</td>
<td>&gt;50% grade a+ b</td>
<td>&gt;32% PR (a+b)</td>
<td>asthenozoospermia⁵</td>
</tr>
<tr>
<td></td>
<td>&gt;25% grade a</td>
<td>&gt;40% PR+NP (a+b+c)</td>
<td>necrozoospermia⁵</td>
</tr>
<tr>
<td>Vitality</td>
<td>&gt;75% live</td>
<td>&gt;58% live</td>
<td>necrozoospermia⁵</td>
</tr>
<tr>
<td>Round cells</td>
<td>&lt;5 mill/mL perox +</td>
<td>&lt;1 mill/mL perox +</td>
<td>pyospermia⁵</td>
</tr>
<tr>
<td>Morphology</td>
<td>≥15% normal</td>
<td>&gt;4% normal</td>
<td>teratozoospermia⁷</td>
</tr>
<tr>
<td>Agglutination⁸</td>
<td>-/+ /+++ /+++</td>
<td>grades 1-4</td>
<td></td>
</tr>
<tr>
<td>Immunobead test⁸</td>
<td>&lt;50%</td>
<td>&lt;50%</td>
<td></td>
</tr>
<tr>
<td>MAR test⁸</td>
<td>&lt;50%</td>
<td>&lt;50%</td>
<td></td>
</tr>
<tr>
<td>Zinc⁰</td>
<td>≥2.4 µmol/ ejaculate</td>
<td>≥2.4 µmol/ ejaculate</td>
<td></td>
</tr>
<tr>
<td>Fructose⁰</td>
<td>≥13 µmol/ ejaculate</td>
<td>≥13 µmol/ ejaculate</td>
<td></td>
</tr>
<tr>
<td>Citrates⁰</td>
<td>≤50 µmol/ ejaculate</td>
<td>≤50 µmol/ ejaculate</td>
<td></td>
</tr>
<tr>
<td>α-glucosidase⁹</td>
<td>≥20 mU/ ejaculate</td>
<td>≥20 mU/ ejaculate</td>
<td></td>
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</table>

1. **Correct terminology**: the suffix “-spermia” should be used to denote changes in the ejaculate (e.g. hemospermia) and “-zoospermia” for changes in the sperm (e.g. asthenozoospermia is correct, not asthenoospermia). **Normozoospermia** refers to the total number (or concentration) of sperm with normal motility and morphology.

2. **Asgpermia** is the absence of semen emission (may or may not be retrograde ejaculation).

3. When sperm concentration is 0 mill/mL, but sample sperm are found after centrifugation, this is referred to as **cryptozoospermia**.

4. **Oligozoospermia** may refer to a concentration or total number of sperm (preferably the latter). Polizoospermia (>250 mill/mL) as a cause of infertility is controversial; the WHO does not consider it as such in their 2010 guidelines.

5. In 1999, the WHO classified **motility** as rapid progressive (a), slow progressive (b), nonprogressive (c), and immotile sperm (d). In 2010, the WHO classified progressive motility (PR) to include categories a+b from 1999, nonprogressive (NP – previously category c), and immotile sperm (IM – previously category d). The term **asthenozoospermia** refers to a decrease in PR (<32%). **Necrozoospermia** refers to a high percentage of immotile sperm (IM) and a low percentage of live sperm.

6. The round cell count, includes leukocytes, epithelial urinary tract cells, prostatic cells, and immature sperm cells. **Peroxidase** only stains leukocytes, allowing identification of **pyospermia** (or leukospermia or leukocytospermia).

7. In 1992, the WHO defined **teratozoospermia** as semen with <30% normal morphology, but in 1999, they adopted the strict morphological criteria of **Kruger** and lowered the number to <15%. The new WHO values from 2010 lower this number to <4%, in accordance with **Kruger** criteria.

8. **Agglutination** suggests an immunological factor, but is not sufficient for diagnosis. In 1999, the WHO recommended a semiquantitative scale from – (no agglutination) to +++ (severe). In 2010, it was gradated further to 1 (<10%), 2 (10-50%), 3 (>50%, some free), and 4 (100%). Both the **immunobead test (IBT)** and the **MAR test (mixed antiglobulin reaction)** determine the presence of IgA (the most clinically important) and IgG in seminal plasma. An immunological factor is considered present when >50% of the sperm are attached to particles.

9. **Fructose** is excreted to the seminal plasma by the seminal vesicles, **citrates** and **zinc** by the prostate, and **neutral α-glucosidase** by the epididymis. In both ejaculatory duct obstruction and bilateral agenesis of the vas deferens there is azoospermia with hypospermia, ↓ pH, ↓ fructose, ↑ citrates, and ↑ zinc. In epididymal or more distal obstruction there is azoospermia with ↓ of α-glucosidase.
**Advanced study**

Based on the findings in the baseline study, the following tests may be performed:

- **Urine culture:** if there is pyuria or bacteriuria, or a clinical suspicion of infection.
- **Four-glass test:** if there is a clinical suspicion of prostatitis or pyospermia. The four-glass test may be simplified to the 1st portion of the urine stream + semen culture.
- **Study of post-orgasm urine:** in cases of aspermia (absence of ejaculate) or hypospermia, to rule out retrograde ejaculation. Alkalization of the urine with oral administration of 2 g of sodium bicarbonate the night before and the morning of sample collection is recommended.
- **STD blood tests (HIV, HBV, HCV, and syphilis):** indicated when considering assisted reproduction techniques due to the special handling of the samples in the laboratory and the risk of vertical transmission. IVF is possible with sperm washing techniques for viruses.
- **Postcoital test:** if the MAR or immunobead test >50% or the spermiogram is normal. Its validity and interpretation are controversial.
- **TMS (total motile sperm):** after processing of the sperm, the fraction with progressive motility (PR) is selected and the total motile sperm count is performed. With >3-5 mill TMS, AIH/IUI can be carried out; if lower, IVF/ICSI must be performed.
- **Other hormones:**
  - *Prolactin*: if there is a history of taking dopaminergic drugs or changes in vision, smell, or headaches.
  - *Estradiol*: if there is gynecomastia or possible resistance to androgens (high testosterone and LH with submasculinization).
  - *ACTH, TSH, GH*: in cases of ↓ testosterone or ↑ PRL to complete the pituitary gland study.
  - *Inhibin B*: in oligozoospermia <10 mill/mL and azoospermia. In oligozoospermia, low levels indicate established testicular damage with little chance of responding to treatment. In azoospermia, low levels of inhibin B confirm a primary testicular origin while normal levels of inhibin B predict a high probability of successful TESE.
- **Genetic studies:** if changes are detected, proper genetic counseling is necessary (information about the risks of transmitting the abnormality).
  - *Karyotype*: indicated in oligozoospermia <10 mill/mL or when there is a family history of repeated miscarriages or mental retardation. The most frequently found chromosomal abnormality is Klinefelter syndrome (XXY).
  - *Y chromosome microdeletions*: indicated in oligozoospermia <5 mill/mL. In AZFc microdeletion or distal AZFb microdeletion, TESE can be attempted after proper genetic counseling (risk of transmitting infertility to male children). In AZFa microdeletions and complete or proximal AZFb microdeletions, sperm cannot be recovered.
  - *Mutations in the CFTR gene (cystic fibrosis transmembrane conductance regulator)*: indicated in ♂ with uni/bilateral agenesis of the vas deferens, other abnormalities of the seminal tract, or azoospermia with hypospermia. If the ♂ is CFTR mutation carrier, the ♀ must be studied. If both are carriers, 25% of the children will have the disease, 50% will be carriers, and 25% will be healthy.
  - *FISH*: detects aneuploidy in sperm. A very high number can cause genetic defects in embryos, with a low capacity for implantation and a high rate of miscarriages. In these cases, a pre-implantation diagnosis may be indicated.
  - *DNA fragmentation*: can be determined by means of TUNEL, SCD or SCSA. High fragmentation levels ↓ the fertilizing potential of sperm. One of the major causes of DNA fragmentation is oxidative stress caused by alcohol, smoking, environmental or occupational toxins, drugs, systemic or urogenital infections, varicocele, systemic diseases, etc.
- **Imaging studies:**
  - *Scrotal ultrasound*: if a testicular tumor or other scrotal pathologies are suspected. Searching for a subclinical (non-palpable) varicocele is not justified.
  - *Transrectal ultrasound*: if agenesis of the vas deferens or ejaculatory duct obstruction is suspected (azoospermia with hypospermia, low fructose, high citrates, and low pH).
  - *MRI of the sella turcica*: in cases of hyperprolactinemia or LH and FSH deficiency.
Azoospermia
The cause may be obstructive (excretory azoospermia) or primary testicular failure (non-obstructive or secretory azoospermia). Diagnostic-therapeutic management depends on:

- **Increased FSH or low inhibin B**: indicates testicular failure. May be secondary to:
  - Anorchia, gonadal dysgenesis, cryptorchidism, Klinefelter’s S, or other genetic diseases.
  - Germ cell aplasia (Sertoli cell-only syndrome) congenital or acquired (e.g. RT or CHTH).
  - Maturation arrest (FSH and inhibin B levels are correlated to the number of spermatogonia; in such cases, hormone levels are usually normal).
  - Systemic diseases.
  - Orchitis, torsion, testicular tumor, varicocele.
  - Idiopathic.

Testicular sperm extraction (TESE) should be attempted to obtain spermatozoa for intracytoplasmic injection (ICSI). In nonobstructive azoospermia, the chances of success are approx. 60%. If TESE fails, donor sperm or adoption are the only options. In the same surgical procedure a sample should be taken in Bouin’s fluid for histological analysis.

- **Decreased FSH**: indicates hypogonadotropic hypogonadism.
  - An LH-RH test can distinguish between a hypothalamic or pituitary cause.
  - Testosterone replacement therapy can restore hormonal – but not spermatoc – function in these patients. To recover spermatogenesis, an FSH substitute such as HMG or pure FSH + an LH substitute such as HCG must be administered in 120-day cycles. If spermatogenesis is restored, cryopreservation of semen should be carried out.

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name*</th>
<th>Dose</th>
<th>Duration</th>
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<tbody>
<tr>
<td>FSH/LH (HMG)</td>
<td>MENOPUR 75+75 IU</td>
<td>75-150 IU im/48 h</td>
<td>3 months</td>
</tr>
<tr>
<td>Follicitropin β</td>
<td>GONAL F 75 IU</td>
<td>75-150 IU im or s 3 times/week</td>
<td>3 months</td>
</tr>
<tr>
<td>HCG</td>
<td>PROFASI 500 and 1000 IU solution</td>
<td>500-1000 IU im/48 h</td>
<td>3 months</td>
</tr>
</tbody>
</table>

- **Normal FSH and inhibin B**: do not rule out primary testicular failure (e.g. maturation arrest). As such, it is impossible to distinguish a priori between primary testicular failure and obstructive problems. The following must be taken into account:
  - **Seminal volume <1 ml and acid pH**: semen fructose and citrate levels should be measured. Low fructose and high citrates indicate distal obstruction of the seminal tract. In this case, the vas deferens should be palpated:
    - If one (unilateral agenesis) or both (bilateral agenesis) vas deferens cannot be palpated: the CFTR gene mutation study should be carried out on the patient; if he is found to be a carrier, also on the partner. TESE should be offered.
    - If both vas deferens can be palpated: it may be an obstruction of the ejaculatory ducts. A transrectal ultrasound must be performed to detect dilation of the seminal ducts or a urethra cyst.
      - If there is a cyst or seminal duct dilation: TUR of the veru or cyst. After the TUR, semen must be frozen due to the high reobstruction rate.
      - If there is no cyst or dilation: TESE should be offered.
  - Normal seminal volume and pH: in the past, a diagnostic testicular biopsy would have been performed. Currently, a biopsy is justified only if accompanied by TESE and cryopreservation in the same procedure or if it is carried out in the context of another surgery (e.g. varicocelectomy) and there is no assisted reproduction laboratory. The histology may show:
    - Maturation arrest or other changes: in this case the only option is TESE for ICSI. If sperm cannot be obtained, donor sperm or adoption are the only options.
    - Preserved spermatogenesis: in this case there is probably an obstruction of the vas deferens or epididymis and sperm can be recovered from the testicle (TESE) for ICSI. If feasible, deferentography + microsurgical reconstruction can be offered by an experienced surgeon.
Azoospermia

- normal FSH and INHB
  - Seminal volume <1 mL
  - Acidic pH
  - Fructose ↓
  - Citrates ↑

  - yes
  - no

  - Palpable vas deferens
    - no
    - yes

  - Transrectal ultrasound
    - normal
    - not normal

  - Utricle cyst or dilation seminal vesicles
    - TUR

  - TESE + histological analysis
    - Tubular alteration and failure to obtain spermatozoa
    - Normal spermiogenesis; normal spermatozoa obtained
    - Tubular alteration and spermatozoa obtained

  - Seminal duct exploration
    - Surgery possible
    - Not possible

  - ICSI
Oligoasthenoteratozoospermia (OAT)

- Etiological treatment: when a cause has been identified.
  - **Hypogonadotropic hypogonadism**: see section on azoospermia with ↓ FSH.
  - **Hyperprolactinemia**: treatment of the cause (pituitary tumor) or administration of bromocriptine/cabergoline.

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<thead>
<tr>
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<th>Dose</th>
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<tbody>
<tr>
<td><strong>Bromocriptine</strong></td>
<td>PARLODEL 2.5 and 5 mg tablets</td>
<td>Initial 1.25 mg/d; increase depending on prolactine levels (max 7.5 mg/d)</td>
<td>3 months</td>
</tr>
<tr>
<td><strong>Cabergoline</strong></td>
<td>DOSTINEX 0.5 mg tablets</td>
<td>Initial 0.5 mg/1-2 times week; increase depending on prolactine levels (max 4.5 mg/week)</td>
<td>3 months</td>
</tr>
</tbody>
</table>

- **Varicocele**: causes testicular damage. Indications for surgery:
  - **Prepubescents**: if testicular size is ↓.
  - **Adolescents**: if spermiogram is abnormal or testicular size is ↓.
  - **Adults**: indiscriminate surgery of all varicoceles has not been shown to ↑ the rate of pregnancies. However, it appears to be beneficial if restricted to adults who meet all the following criteria:
    - Proven infertility (>12 months).
    - Palpable grade II-III varicocele (excluding subclinical and grade I varicocele).
    - Altered spermiogram, but with a sperm count >2 M/ml.
    - Couple with normal results in the fertility study and ≤36 years of age.

- **Urinary infection/prostatitis**: treatment can improve semen quality, but has not been shown to ↑ number of pregnancies. Gram-negative organisms in the urine should be treated with a short (3-5 days) course of antibiotics (e.g. Cefuroxime); in prostatitis, a longer course (6 weeks) of Ciprofloxin is indicated. Other pathogens (mycoplasms and ureaplasms) can be treated with a single dose of Azitromycin for both ♂ and ♀; if that fails, a 10-day course of Doxycycline is used. Antioxidants (see dosages below) and NSAIDs can be added.

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<thead>
<tr>
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<th>Dose</th>
<th>Duration</th>
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<tbody>
<tr>
<td><strong>Cefuroxime</strong></td>
<td>CEFTIN 500 mg tablets</td>
<td>500 mg/12 h</td>
<td>3-5 d</td>
</tr>
<tr>
<td><strong>Ciprofloxin</strong></td>
<td>CIPRO 500 mg tablets</td>
<td>1 tablet/12 h</td>
<td>6 weeks</td>
</tr>
<tr>
<td><strong>Azithromycin</strong></td>
<td>ZITHROMAX 0.5-1 g powder</td>
<td>1 g sd ♂ and ♀</td>
<td>1 d</td>
</tr>
<tr>
<td><strong>Doxycycline</strong></td>
<td>VIBRAMYCIN 100 mg capsules</td>
<td>1 comp/12 h ♂ and ♀</td>
<td>10 d</td>
</tr>
</tbody>
</table>

- **Pyospermia with ♂ culture**: antioxidant (see dosages below) and NSAID therapy.

- **Empirical treatment**: in idiopathic OAT (30-40% of cases) or if there is no treatable cause. Oxidative stress (free radicals) fragments spermatic DNA and ↓ fertilizing ability of spermatozoa. The hormonal disruption caused by an estrogenic environment (food, pollution, etc.) reduces spermatogenesis. To combat these factors, the following treatments should be administered in combination for at least 3 m, followed by TMS count:
  - **Healthy habits, elimination of toxins**: good hygiene, healthy diet, elimination of smoking, alcohol, drugs, occupational toxins, medicines, excess heat on the scrotum, stress.
  - **Antioxidants**:

<table>
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<tr>
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<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamin E</strong> + <strong>Vitamin C</strong></td>
<td>VITAMIN E 400 mg caps + REDOXON 1 g tablets</td>
<td>1 caps/12 h + 1 tablets/24 h</td>
<td>3 months</td>
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- **Antiestrogens**:

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<th>Dose</th>
<th>Duration</th>
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<tbody>
<tr>
<td><strong>Tamoxifen</strong></td>
<td>NOLVADEX 20 mg tablets</td>
<td>1 tab/24 h for 25 d and 5 d rest repeat this cycle three times</td>
<td>3 months</td>
</tr>
</tbody>
</table>
**Assisted reproduction**: if the aforementioned treatments fail. The woman’s age is the most important predictive variable with regard to the success of assisted reproductive techniques (compared with a 25-year-old ♀, fertility drops to 50% by age 35, to 25% at 38, and to ≤5% at 40).

- **AIH-IUI**: indicated if TMS >3 mill PR and normal morphology >4%.
- **IVF/ICSI**: indicated if TMS <3 mill PR, if normal morphology ≤4%, if AIH not possible, if failure of prior AIHs, or if MAR test/immunobead test >80% (severe immune factor).