Male reproduction and reproductive disorders.

Elisabeth Carlsen
The Fertility Clinic
Rigshospitalet
Copenhagen

NILS January 2015
Disposition

- Anatomy and physiology
- Spermatogenesis
- Reproductive hormones
- Semen analysis
- Male infertility
- Work up for male infertility
Male reproductive system
Cross-section of the testis
Spermatogonia

Sertoli cells

Primary spermatocytes

Secondary spermatocytes

Spermatid

Sertoli cells

Spermatogonia
Spermatogenesis

The process where the mature spermatozoa is formed achieving:

- 23 chromosomes by meiotic division and exchange of genes between homologues chromosomes (crossing over)
- the right shape to fertilize the ovum (spermiogenesis).
6. week

Puberty

- gonocyte enters the gonad
- spermatagonium
- mitotic division of diploid spermatogonia
- primary spermatocyte
- secondary spermatocyte
- round spermatids
- Elongation
- elongated spermatids (spermatoza)
Hypothalamic-pituitary-gonadal axis

Hypothalamus

GnRH

Pituitary

LH
FSH

Testosterone

Leydig cells
Sertoli cells

Testis

Inhibin B
Inhibin subunits

α  βA  βB

Inhibin A

Inhibin B
Regulation of Inhibin B production by germinal cells in the adult man

Sertoli cell

FSH

Inhibin B

α subunit

βB

pachytene spermatocytes?
spermatids?
specific germinal cells
Markers of spermatogenesis

- **Fertile men**
- **Infertile men**
Cut-off values for semen parameters
WHO laboratory manual (2010)

- Volume 1,5 ml
- Sperm concentration 15 mill/ml
- Total sperm count 39 mill
- Motile 40%
- Progressive motile 32%
- Morphology 4% (strict criteria)
- Vitality 58% viable
Definitions

- Azoospermia: no sperm cells in the ejaculate
- Oligozoospermia: <15 mill/ml in the ejaculate
- Astenozoospermia: > 40% immotile sperm cells
- Teratozoospermia: < 4% morphologically normal sperm cells
Intra-individual variations in semen quality

• Evaluation of monthly semen samples during 17 months form 27 men (median age 24,4 y)

• Intra-individual variation:
  • Sperm concentration 61,9%
  • % immotile sperm cells 30,7%
  • % normal sperm cells 10.4%
Effect of duration of abstinence on sperm concentration

20% increase/day (for the first 4 days)
### Effect of fever on semen quality

<table>
<thead>
<tr>
<th></th>
<th>Fever during mitotic proliferation (day -80 to -57)</th>
<th>Fever during meiotic division (day -56 to -33)</th>
<th>Fever during spermiogenesis (day -32 to -9)</th>
<th>Fever during sperm maturation (day -8 to 0)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sperm concentration</strong></td>
<td>5.5 (-21.7; 42.0) p=0.726</td>
<td>-32.6 (-49.9; -9.2) p=0.010</td>
<td>-35.0 (-50.5; -14.6) p=0.002</td>
<td>-0.3 (-38.7; 51.9) p=0.877</td>
</tr>
<tr>
<td><strong>% normal spermatozoa</strong></td>
<td>-2.8 (-7.5; 2.2) p=0.269</td>
<td>-4.3 (-9.0; 0.6) p=0.084</td>
<td>-7.4 (-11.6; -3.0) p=0.001</td>
<td>-1.4 (-8.7; 6.6) p=0.730</td>
</tr>
<tr>
<td><strong>% immotile spermatozoa</strong></td>
<td>2.7 (-10.5; 17.9) p=0.702</td>
<td>-6.4 (-18.7; 7.7) p=0.355</td>
<td>20.4 (6.0; 36.8) p=0.004</td>
<td>2.0 (-17.5; 26.1) p=0.856</td>
</tr>
</tbody>
</table>

% and 95% confidence interval
Intra-individual variation in semen parameters: effect of multiple semen samples
GUESS YOUR SPERM COUNT

WIN
Male infertility causes

- Compromised spermatogenesis
- Obstruction
- Ejaculatory dysfunction
- Other causes
Compromised sperm production

- Hormonal problems
  - Defect in GnRH release (Kallmann’s syndrome)
  - Pituitary tumors or hemochromatosis
- Testicular dysfunction
  - Idiopathic
  - associated with cryptorchidism
- Genetic disorders
- Acquired disorders
  - Trauma/orchitis
  - Torsion of the testis
- Exogenous factors
Testicular dysgenesis syndrome (TDS)

- Reduced semen quality
  - Compromised sperm production
  - Spermatogenic arrest
  - Sertoli cell only syndrome
- Cryptorchidism
- Cancer testis/ Carcinoma in situ testis (CIS)
- Hypospadia

Skakkebæk 2001
Testicular Dysgenesis Syndrome

Environmental factors
*i.e. hormone-disturbing chemicals*

Testicular Dysgenesis

- Disturbed Sertoli cell function
- Reduced Leydig cell function
- Abnormal germ cell differentiation
- Reduced semen quality

- CIS
  - Testis cancer

Genetic defects
*incl. 45,X/46,XY and point mutations*

- Reduced Leydig cell function
- Androgen insufficiency

- Hypospadias
- Cryptorchidism

Genetic disorders

- Klinefelter Syndrome (47, XXY)
- Chromosomal translocations
- Androgen receptor gen mutations
- Y chromosome microdeletions
Klinefelter syndrome (47,XXY)

- 0.2% of newborn boys
- 11% of men with non-obstructive azoospermia
- small testes < 5 ml and often azoospermia
- Decreased virilisation
- hypergonadotrophic hypogonadism
Autosomal translocations

- 0.5-1% of men with oligo-azoospermia
- Robertsonian/reciprocal
- Balanced/unbalanced embryos
- PGD (preimplantation gene diagnostic)
Y chromosome microdeletions

- **Frequency:**
  - *10% of men with non-obstructive azoospermia and 6% of men with severe oligozoospermia* (ESHRE Capri Workshop Group, Hum Reprod Update 2007)

- **Localization:**
  - 3 AZF regions on Yq: AZFa, AZFb and AZFc
  - Newer modifications of the original classification including b2/b4 and gr/gr
A Functional Map of the Y Chromosome
(from Lahn & Page 1997, Science 278:675)

Note: contrary to this figure, an X-homologue of RBM has recently been described (Nat Gen July 1999)
Exogenous causes

- Irradiation of the testis
- Medicine
  - Salazopyrine
  - Cytotoxic drugs
  - Anabolic steroids
Obstructions of sperm ducts

- Previous genital infections
  - Chlamydia, gonorrhea
- Urogenital surgery
  - Vasectomy, reconstructive surgery
- Congenital aplasia of sperm ducts
  - Cystic fibrosis or cystic fibrosis gen mutations
CFTR-mutation  
(cystic fibrosis transmembrane conductance regulator)

- Absent development of seminal duct (vas deferens) and seminal vesicle
- Azoospermia and a small semen volume
- Fertility treatment ICSI/TESA
- Female carrier?
Ejaculatory dysfunction

- Retrograde ejaculation
  - Neuropathy in diabetes
  - Previous prostatic surgery and other pelvic surgery
- Anejaculation
  - Neuropathy
  - Spinal cord injury
Andrological examination

• Clinical examination
  • history
  • objective examination
  • ultrasound scan of the testis

• Laboratory tests
  • semen samples
  • hormone analyses
  • genetic analyses

• Diagnostic testicular biopsy in certain cases
• History
  • Previous maldescensus
  • Infections/surgery
  • Previous conceptions
  • Symptoms
  • Medication

• Objective examination
  • Testicular size
  • Ducts and epididymis
  • Ultrasound scan
Laboratory tests

- **Semen analysis**
  - Urine analysis for retrograde ejaculation
  - Diagnostic swim-up or gradient centrifugation

- **Hormone analysis**
  - Inhibin B / FSH
  - LH
  - Testosterone

- **Genetic analysis**
  - Karyotype
  - Y chromosome microdeletion analysis
Genetic tests

• Routine tests in azoospermia and severe oligozoospermia and whenever ICSI is indicated:
  • Karyotype
  • Y chromosome microdeletion test
• When indicated
  • CFTR mutation analysis
Treatment of male infertility

- Elimination of environmental and lifestyle factors
- Medical treatment
- Surgical treatment
- Assisted reproduction
2 semen samples

Azoo-or severe oligozoospermia
- Andrological examination
  - ICSI or ICSI/TESA
  - Donor insemination

Mild to moderate oligozoospermia
- Diagnostic sperm test
  - If ≥2 mill/ml: 3-6 inseminations depending on female factor
  - If <2 mill/ml
  - ICSI
  - IVF