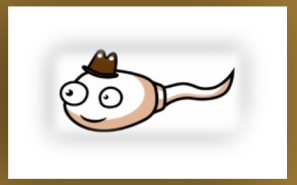
# Clinical investigation of the **Infertile Male**

**Hooman Sadri MD, PhD**

**Stuart Howards MD**



Wake Forest® School of Medicine

Jan 22nd 2020

# Disclosures

Drs. Sadri and Howards have *no financial disclosures or conflicts of interest* to report relevant to this presentation.

# Learning objectives

After this presentation, the learner should be able to:

- Explain indications for a male infertility workup.
- List commonly used tests to assess the infertile male patient.
- Identify indications for more complex laboratory and diagnostic testing.

# Case 1 (Medical History)

- A couple has been visiting the(a) urologist for primary infertility for two years. The husband is 32 years old and without urological complaints.

- There is no history of urogenital infection. He was operated for unilateral cryptorchidism at the age of seven. Sexual function is normal; ejaculations are antegrade. He takes no medications, does not smoke, and occasionally consumes a limited amount of alcoholic.

- His partner is 30 years old, has no gynecological history, and has a menstrual cycle of 26–28 days.

# Case 1 (Physical examination)

- Physical examination reveals a small 6ml testis on the right and a 12 ml testis on the left, both without palpable abnormality.

- Further physical characteristics are normal; his body mass index (BMI) is 28.

# Case 1 (Laboratory Evaluation)

- Semen analysis (S/A) shows a total count of 3.2 million spermatozoa (reference value >40 million) with 4% forward motility (reference value>40% A + B motile spermatozoa) and 1% normal forms (reference value >4% normal spermatozoa/strict criteria).

(FSH) is 12 IU/L (reference value 2–7), testosterone is 317 ng/dl (reference value 240–950).

# Case 1 (Scrotal Ultrasound)

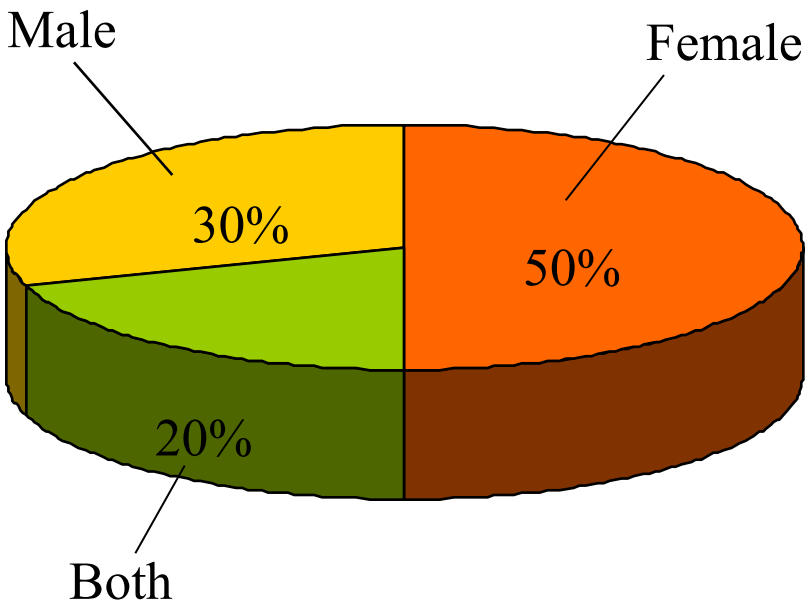
- Scrotal ultrasound shows an inhomogeneous testis on the right side with a cluster of microcalcifications in the lower pole. The left testis appears normal and homogeneous.

- The epididymis has a normal appearance on both sides. A grade 1 varicocele is found on the left side (a scrotal venous diameter during Valsalva maneuver of 3.2 mm; no reflux).

# Case 1 (Discussion)

- On the basis of the fertility investigations, the male is diagnosed with primary infertility due to testicular insufficiency (small testis, high FSH).
- The findings on ultrasound in the atrophic right testis need monthly self examination by patient and annual scrotal US.
- The varicocele can be considered an infertility-associated factor. Although, there is a chance of a substantial sperm improvement of 40% to 50% after varicocele treatment, there is uncertainty in the literature if varicocele repair will also increase the chance of conception.
- Alternatively, the couple can be candidates for assisted reproduction such as IVF. Genetic evaluation is indicated before assisted reproduction is performed.

# Clinical Male Infertility: Evaluation




- 85% of couples conceive with in 1 yr.
- No conception after 1 yr of unprotected sex is defined as possible infertility
- 50% of infertility involves male factor.
- The couple elects to initiate an infertility evaluation

Importantly, medical conditions present as infertility in **1-5%** of cases:

- Diabetes mellitus
- Prolactinoma
- Testis cancer
- Neurological disease
- Retroperitoneal tumor
- Cystic fibrosis
- Genetic syndromes

# Infertility: Prevalence

- **7 million couples in U.S. experince infertility[1]**
- **1.2 million women/year make new office visit to MD for infertility[1]**
- **20% of partners (240,000 men) receive a medical evaluation for infertility[1]**
- **An estimated 370,000-860,000 men not evaluated at time of infertility evaluation[2]**

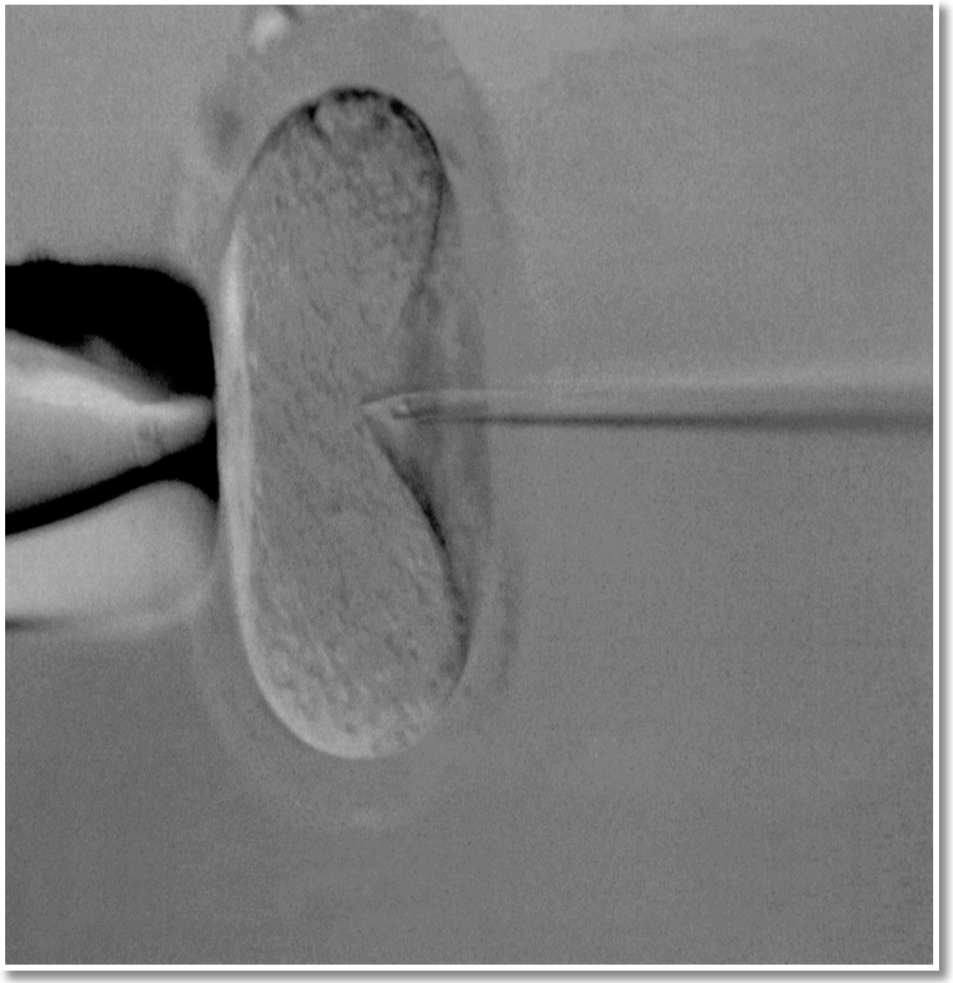

1. American Society of Reproductive Medicine, 1998.
2. Eisenberg, M. Frequency of the Male Infertility Evaluation, J. Urology, March 2013

# Where are the Men?

- Men frequently feel that “women are the usual cause of infertility”
- Many urologists are not well trained to treat male infertility and are reluctant to get involved
- Urologists have taken a “back seat” to media and public perception of IVF/ICSI as a safe cure-all for male factor infertility

# Intracytoplasmic Sperm Injection (ICSI)

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



# Assisted Reproductive Technology

**IUI**

5 million motile sperm

Intra-uterine Insemination

**IVF**

75,000 motile sperm

In Vitro Fertilization

**ICSI**

~20 motile sperm

**Intracytoplasmic Sperm Injection**

# Infertility: Evaluation

- **Indication for evaluation:**
  - **Failure to achieve pregnancy after 1 year of unprotected intercourse**
    - **85% conceive after 1 year, 92% after 2 years**
- **Indications for early evaluation:**
  - **The presence of Infertility risk factors, a female is > 35 years old, or if the couple request it.**
- **Minimum male evaluation:**
  - **H&P**
  - **At least one semen analysis**

1. American Society of Reproductive Medicine, 2012.

# Prognostic Factors

– Duration of infertility
– Primary or secondary infertility
– Results of semen analysis
– Age and fertility status of the female partner:

The fertility of a woman aged 35 years is only 50% of the fertility potential of a woman aged 25 years. By the age of 38, this has reduced to only 25%, and over the age of 40 it is less than 5%. Female age is the most important single variable influencing outcome in assisted reproduction.

# Clinical Male Infertility: History

- **Sexual History**:

Prior pregnancies

Timing of intercourse (every other day around ovulation best)

Lubricants. Vegetable oils

- **PMHx/PSHx:**

Cancer, fevers, systemic illness, ED

Childhood: mumps after puberty; bladder, orchidopexy (for torsion/UDT); hypo- or epispadias; trauma; epididymitis, varicocele

Adult surgery: TUIP, TURP, RPLND, spermatocele, hernia

Exposures: chemotherapy, XRT, environmental/occupational

- **Medications**

Antiandrogens, steroids, estrogens, alpha blockers, beta blockers, Ca+ channel blockers, antipsychotics, cimetidine, sulfasalazine, sulfa antibiotics

- **Habits**

EToH (>2 q d); tobacco; cocaine; anabolic steroids(?marijuana)

# Clinical Male Infertility: Exposures

Ionizing radiation (?pilots, ?cell phones)

Chronic heat (cooks, welders, ?laptops, hot tubs)

Aniline dyes

Heavy metals (lead, mercury, cadmium)

Pesticides
1. DBCP-Dibromochloropropane
2. DDT
3. Kepone

Industrial toxins ("smelly solvents")
1. Dioxin (paper)
2. PCB, bisphenol A
3. Cl-hydrocarbons
4. N-nitroso (rubber)
5. Paints
6. Benzene

# Significant abnormalities on physical examination

General

- Obesity (body mass index, waist circumference)
- Signs of hypermasculinity (anabolic steroids)
- Abnormality or absence of hair distribution
- Gynecomastia
- Stature (normal, eunuchoid, undervirilization)
- Signs of pulmonary disease

Penis/urethra

- Penile and urethral abnormalities (phimosis, meatal stenosis, hypospadia, epispadia, urethral fibrosis/stricture)

Scrotum

- Absence or atrophy of the testes
- Cryptorchidism
- Abnormal testicular volume and/or consistency
- Varicocele

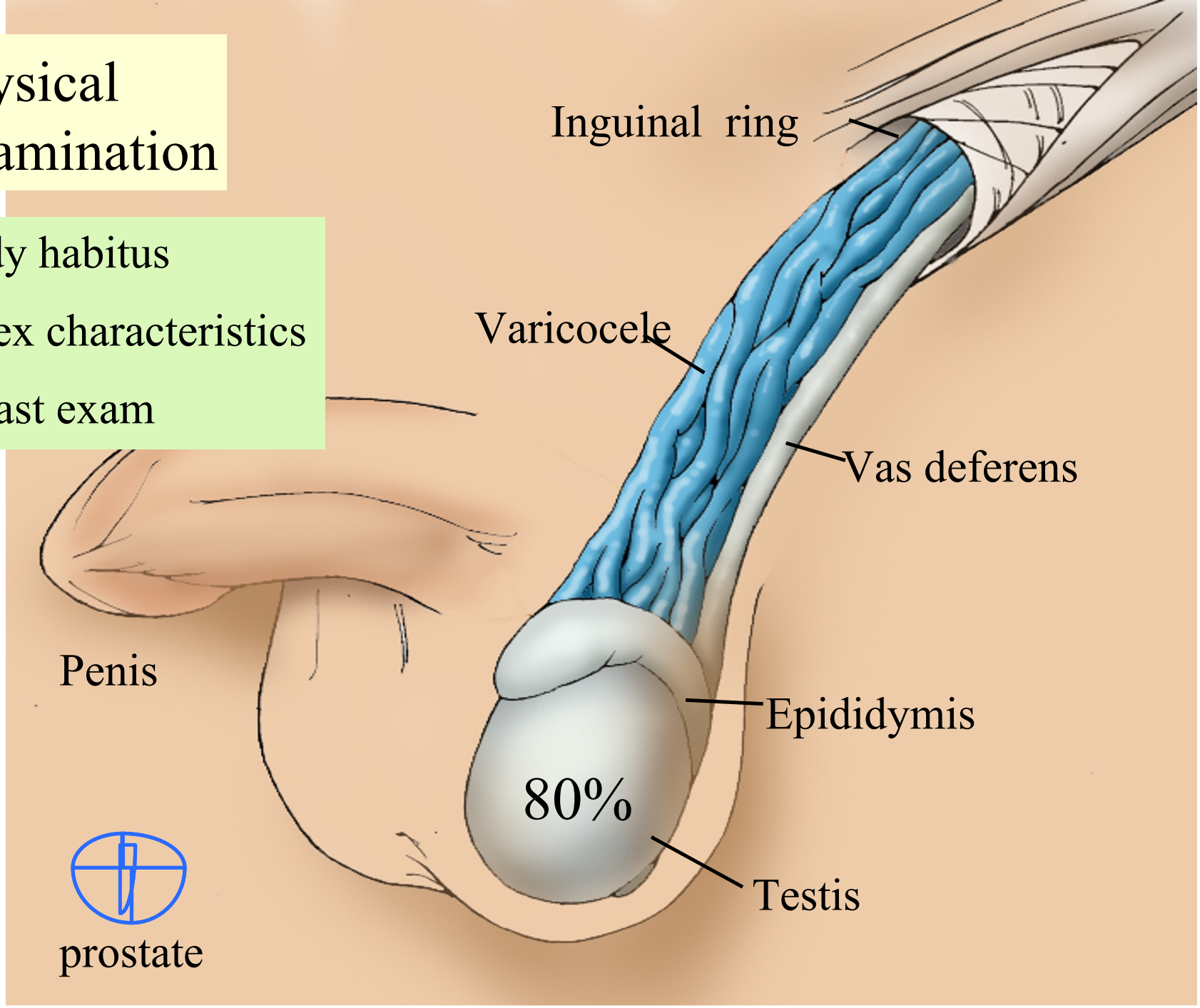
Rectal examination (if indicated)

# Physical Examination

Body habitus

$2^0$ sex characteristics

Breast exam



# Physical Examination: Varicocele

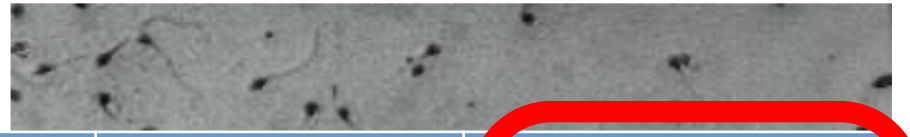
- 15% of all men
- 35% of primarily infertile men
- 60-80% of secondarily infertile men
- Reason for infertility:?hypoxia;hyperthermia?

| | |
|---|---|
| **Subclinical** | Not detected on physical exam; found by radiologic or other imaging study. |
| **Grade I** | Only palpable during or after Valsalva maneuver on physical exam |
| **Grade II** | Palpable on routine physical exam without Valsalva maneuver. |
| **Grade III** | Visible to the eye and palpable on physical exam. |

***Repair Clinical Varicocele Only***

# Semen Analysis

- **WHO minimally acceptable criteria (2010)**



- Vol. > 1.5 ml

| | WHO 1999 | WHO 2010 |
|---|---|---|
| Volume (mL) | 2.0 | 1.5 |
| Sperm Concentration (M/mL) | 20 | 15 |
| Total sperm count (M/ejaculate) | 40 | 39 |
| Total Motility (%) | 50 | 40 |
| Strict Morphology (% normal) | N/A | 4 |

- [illegible]%
  - **< 1 million wbc/cc**

# Assisted Reproductive Technology

**IUI**

5 million motile sperm

Intra-uterine Insemination

**IVF**

75,000 motile sperm

In Vitro Fertilization

**ICSI**

~20 motile sperm

**Intracytoplasmic Sperm Injection**

# Frequent Scrotal Ultrasonography Abnormalities

*Abnormalities of the testis*

Small size

Inhomogeneous parenchyma (dysgenesis)

Testicular cysts

Microcalcifications (5%) (Fig. 1)

Dilatation of the rete testis (Fig. 2)

Intratesticular varicocele

Inflammation (orchitis) (Fig. 3)

Tumors (0.5–1%)

Hypoechoic lesions (Fig. 4)

*Abnormalities of the epididymis*

Dilatation (Fig. 5)

Epididymal cysts/spermatocele

Inflammation (epididymitis)

*Other abnormalities*

Varicocele (Fig. 6)

Absence of the vas deferens

# Semen Analysis Findings from Infertile Men

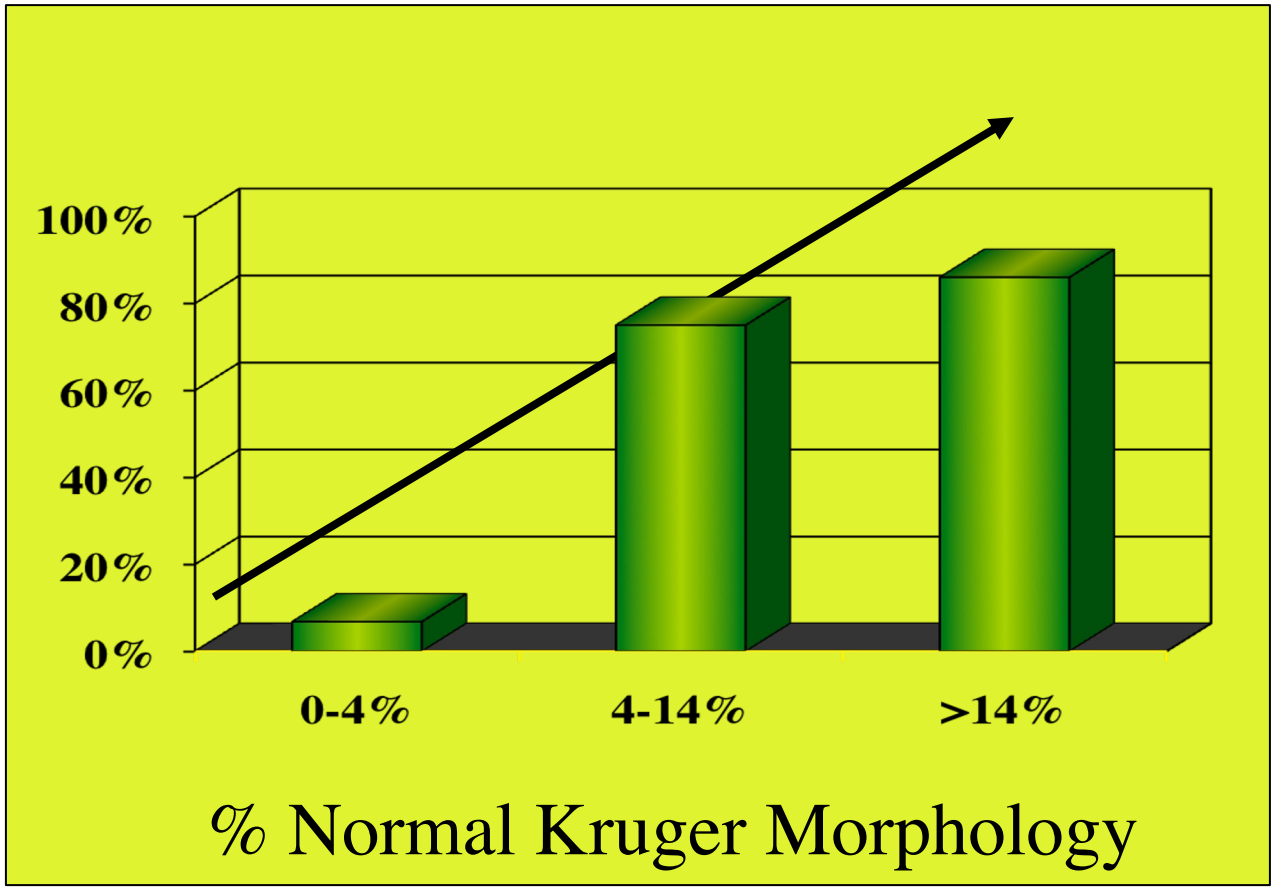
| | | |
|---|---|---|
| All normal | | 24% |
| Isolated abnormal | | 52% |
| Low motility | **36%** | |
| Low count | 2% | |
| Volume | 3% | |
| Morphology | 11% | |
| Multiple defects | | 19% |
| No sperm | | 5% |
| | | 100% |

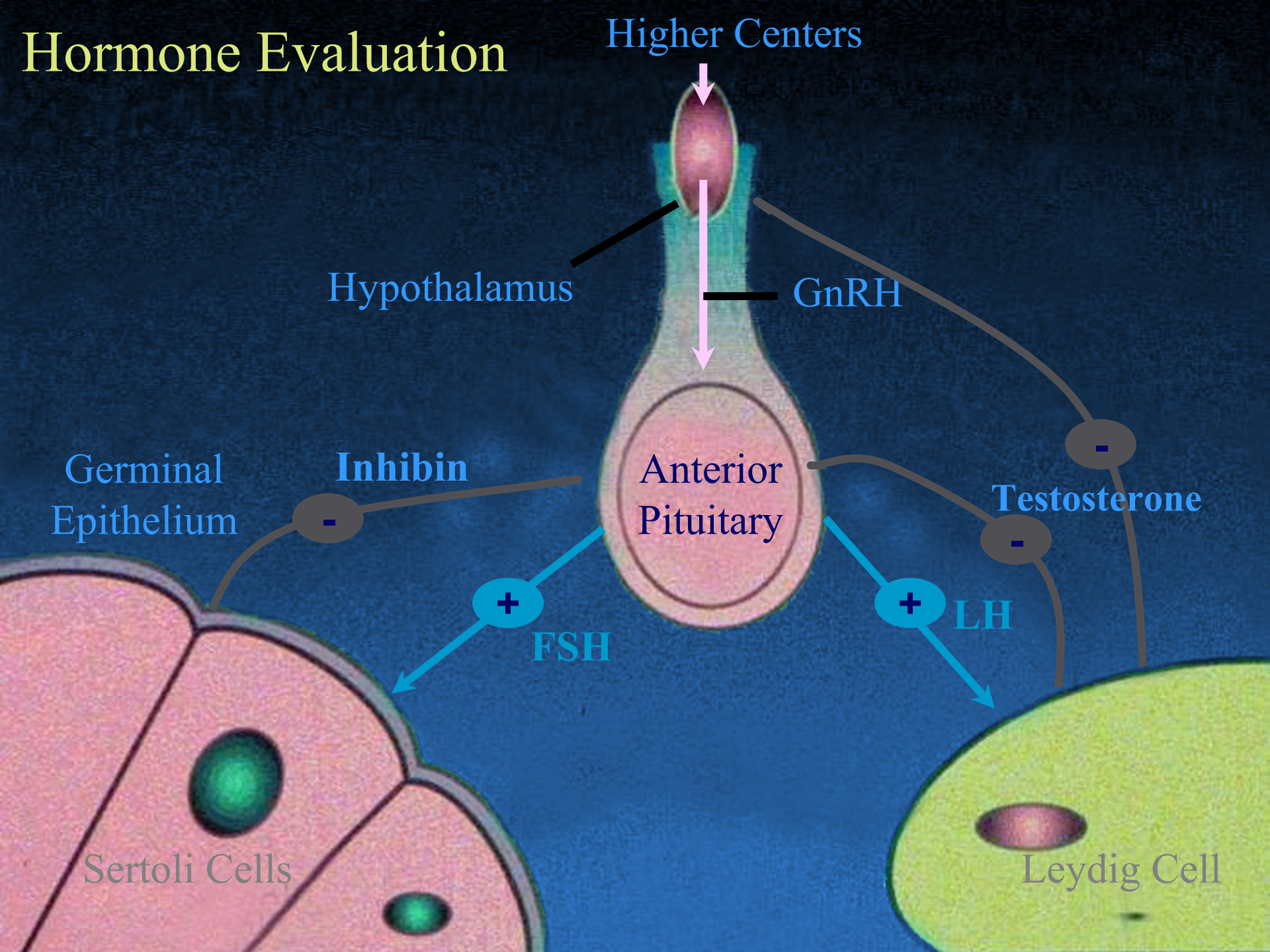
Sigman, Lipshultz, Howards. Infertility in the Male. 3rd Ed. 1997

# What is Sperm Morphology?

% Egg Fertil.

@IVF




Hormone Evaluation
Higher Centers
Hypothalamus
GnRH
Germinal Epithelium
Inhibin
Anterior Pituitary
Testosterone
FSH
LH
Sertoli Cells
Leydig Cell

# Clinical Male Infertility: When to Order Hormones?

- Sperm density <10 x $10^{6}$ sperm/mL
- Evidence of impaired sexual function (low libido, impotence)
- Findings of an endocrinopathy (thyroid)
- Before starting medical treatment

Sigman M, Jarow JP. Urology, 50: 659, 1997

Jarow JP et al. J. Urol. 167: 2138, 2002

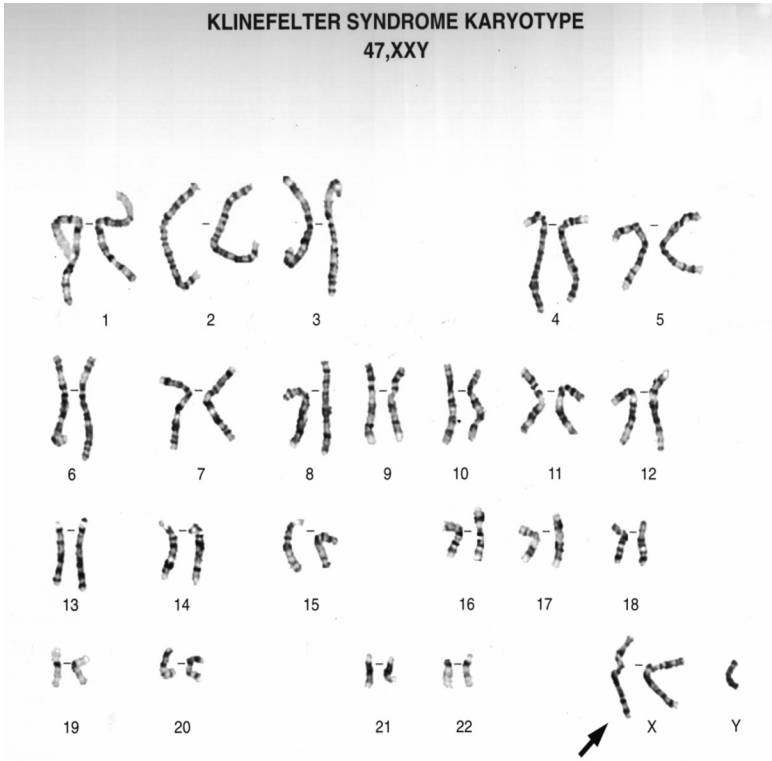
# Male Infertility Evaluation: Adjunctive Tests

| Test | Indication |
|---|---|
| Fructose | Low volume, azo |
| Post-Ejac Urinalysis | Low volume |
| IgA, IgG Antibody | Antisperm antibodies |
| Peroxidase, Entz stain | Elevated round cells |
| Sperm Chromatin Structure | Unexplained infertility |
| Scrotal Doppl. Ultrasound | Diffic.exam,varicocele, mass |
| TRUS | Low vol. ejac; abnl prostate |
| CT Scan/MRI | Isolated R varicocele |

Jarow JP et al. J. Urol. 167: 2138, 2002

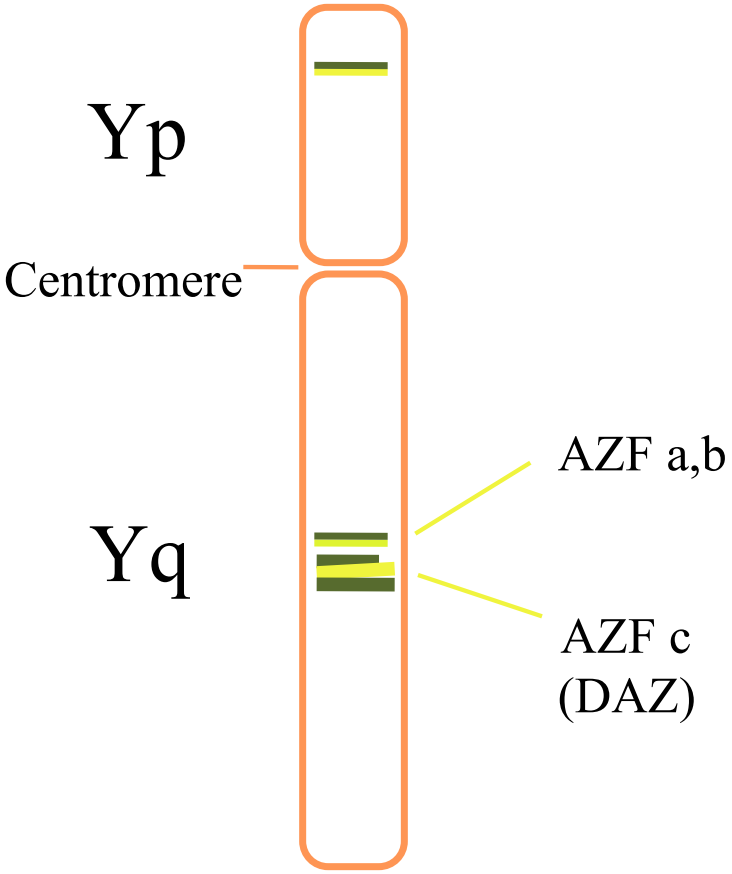
# Genetic Evaluation: The Karyotype

- Chromosomal duplications, loss, inversions, translocations.
- **2-5%** of oligospermic men
- **10-15%** of azoospermic men
- Can have health issues (47, XXY & breast cancer).
- Passed to offspring.
- Other treatments unlikely to work.
- In XX sex-reversed male, no sperm.
- In 47, XXY: **50%** have sperm.




Blood test-47, XXY karyotype

# Genetic Evaluation: Y Chromosome Microdeletions percents seem high




- Gene regions **(AZF a, b, c)** on the long arm of Y chromosome
- **6-8%** of oligospermic men
- **13-15%** of azoospermic men
- No health issues
- Passed to offspring with ICSI
- Other treatments unlikely to work
- If **AZFa or b** deleted, predicts no sperm in ejaculate or testis.

Reijo et al. Nat. Gen. 10: 383, 1995

Reijo et al. Lancet. 347: 1290, 1996

Pryor et al. NEJM. 336: 576, 1997

# When to do Genetic Testing?

| Situation | Y Delet. | Karyotype | Cyst. Fibr |
|---|---|---|---|
| Sperm <5 million/mL | X | X | |
| No sperm/testis failure | X | X | |
| Exam-absent vas deferens | | | X |
| Other syndromes | Whatever fits! | | |

# Testicular biopsy

| Score | Histological criteria |
|---|---|
| 10 | Full spermatogenesis (Fig. 10) |
| 9 | Slightly impaired spermatogenesis, many late spermatids, disorganized epithelium |
| 8 | Less than five spermatozoa per tubule, few late spermatids |
| 7 | No spermatozoa, no late spermatids, many early spermatids |
| 6 | No spermatozoa, no late spermatids, few early spermatids |
| 5 | No spermatozoa or spermatids, many spermatocytes |
| 4 | No spermatozoa or spermatids, few spermatocytes |
| 3 | Spermatogonia only |
| 2 | No germinal cells, Sertoli cells only |
| 1 | No seminiferous epithelium |

# Normal Spermatogenesis

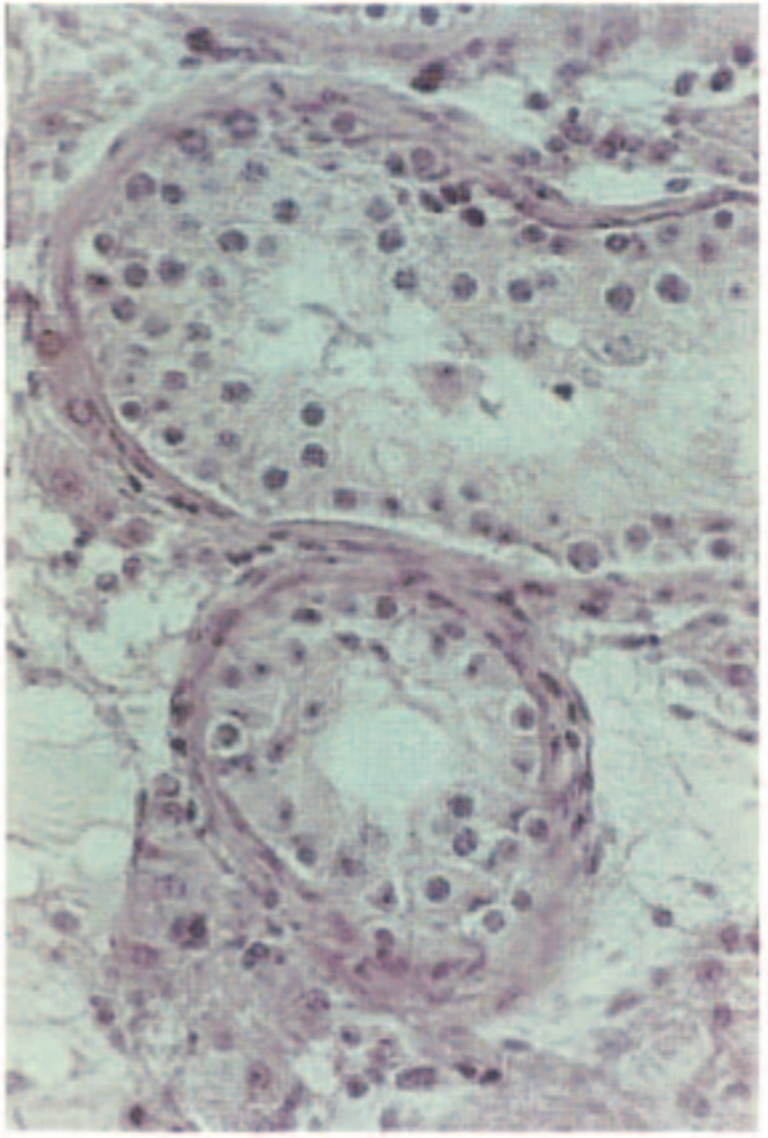
| Score | Histological criteria |
|---|---|
| 10 | Full spermatogenesis (Fig. 10) |
| 9 | Slightly impaired spermatogenesis, many late spermatids, disorganized epithelium |
| 8 | Less than five spermatozoa per tubule, few late spermatids |
| 7 | No spermatozoa, no late spermatids, many early spermatids |
| 6 | No spermatozoa, no late spermatids, few early spermatids |
| 5 | No spermatozoa or spermatids, many spermatocytes |
| 4 | No spermatozoa or spermatids, few spermatocytes |
| 3 | Spermatogonia only |
| 2 | No germinal cells, Sertoli cells only |
| 1 | No seminiferous epithelium |

# Hypo spermatogenesis

| Score | Histological criteria |
|---|---|
| 10 | Full spermatogenesis (Fig. 10) |
| 9 | Slightly impaired spermatogenesis, many late spermatids, disorganized epithelium |
| 8 | Less than five spermatozoa per tubule, few late spermatids |
| 7 | No spermatozoa, no late spermatids, many early spermatids |
| 6 | No spermatozoa, no late spermatids, few early spermatids |
| 5 | No spermatozoa or spermatids, many spermatocytes |
| 4 | No spermatozoa or spermatids, few spermatocytes |
| 3 | Spermatogonia only |
| 2 | No germinal cells, Sertoli cells only |
| 1 | No seminiferous epithelium |

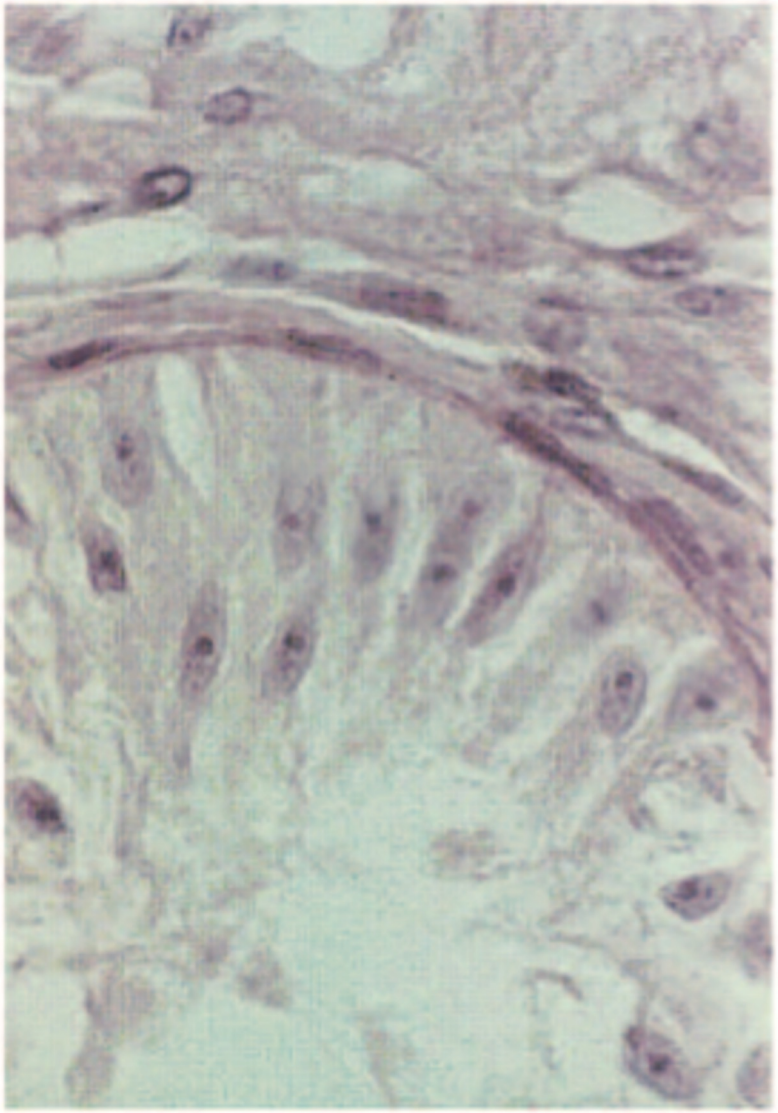
# Maturation Arrest

| Score | Histological criteria |
|---|---|
| 10 | Full spermatogenesis (Fig. 10) |
| 9 | Slightly impaired spermatogenesis, many late spermatids, disorganized epithelium |
| 8 | Less than five spermatozoa per tubule, few late spermatids |
| 7 | No spermatozoa, no late spermatids, many early spermatids |
| 6 | No spermatozoa, no late spermatids, few early spermatids |
| 5 | No spermatozoa or spermatids, many spermatocytes |
| 4 | No spermatozoa or spermatids, few spermatocytes |
| 3 | Spermatogonia only |
| 2 | No germinal cells, Sertoli cells only |
| 1 | No seminiferous epithelium |



# Sertoli Cell Only Syndrome (Germ Cell Aplasia)

| Score | Histological criteria |
|---|---|
| 10 | Full spermatogenesis (Fig. 10) |
| 9 | Slightly impaired spermatogenesis, many late spermatids, disorganized epithelium |
| 8 | Less than five spermatozoa per tubule, few late spermatids |
| 7 | No spermatozoa, no late spermatids, many early spermatids |
| 6 | No spermatozoa, no late spermatids, few early spermatids |
| 5 | No spermatozoa or spermatids, many spermatocytes |
| 4 | No spermatozoa or spermatids, few spermatocytes |
| 3 | Spermatogonia only |
| 2 | No germinal cells, Sertoli cells only |
| 1 | No seminiferous epithelium |



# Male Fertility: A Barometer for Men's Health

# FUTURE SESSIONS

- Session One: Clinical investigation of the infertile male
- **Session Two: Genetic causes of male infertility and their impact on future generations**
- **Session Three: Medical Treatments for Male Infertility**
- **Session Four: Surgical Treatments and Assisted Reproductive Technology (ART) for Male Infertility**
- **Session Five: Ejaculatory disorders**
- **Session Six: Clinical investigation and laboratory analyses in male hypogonadism**
- **Session Seven: Testosterone deficiency syndrome, , Androgen replacement—indications and principles**
- **Session Eight: Female-to-Male Transsexualism**