Subfertility / Male Infertility

Background, Definition:

Infertility = “failure to conceive following 1 year of unprotected intercourse if under 35 years of age or six months if over 35”.

- 10-15% couples affected

Etiology:

— Couples:

- 16% Tubal and pelvic pathology
- 21 % Male problems
- 29% Ovulatory dysfunction
- 18% Unexplaine
- 7% Endometriosis,2%Cervical,3%Uterine,4%Multiple

For a woman with a normal menstrual cycle of 28 days, ovulation occurs around day 14. The average survival time of the oocyte is around 24 hours, while after ejaculation sperm may survive for up to 7 days in the female reproductive tract.

* Normal couple: 25-30% chance of pregnancy per ovulatory cycle

- Primary -Couple has never conceived
- Secondary -couple has had at least one prior conception

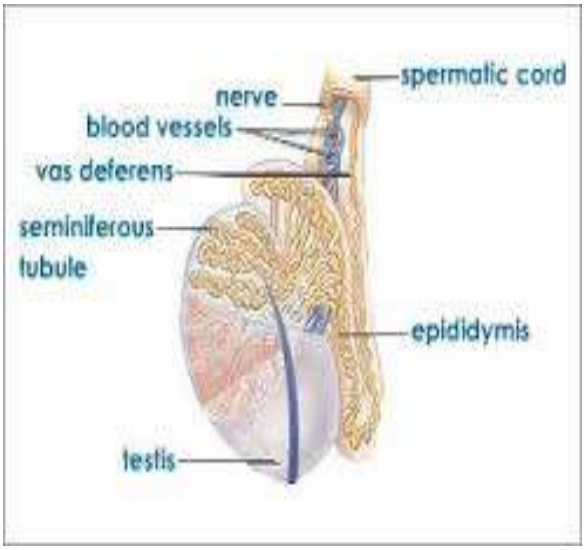
Time of Exposure	**% Pregnant**
3 months	60%
6 months	70%
1 year	85%
18 months	90%

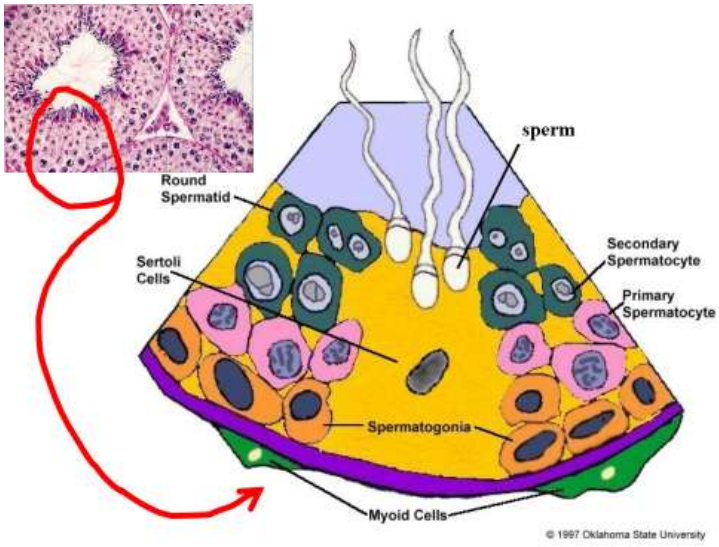
Causes

- Male
- Female
- Combined
- Unexplained

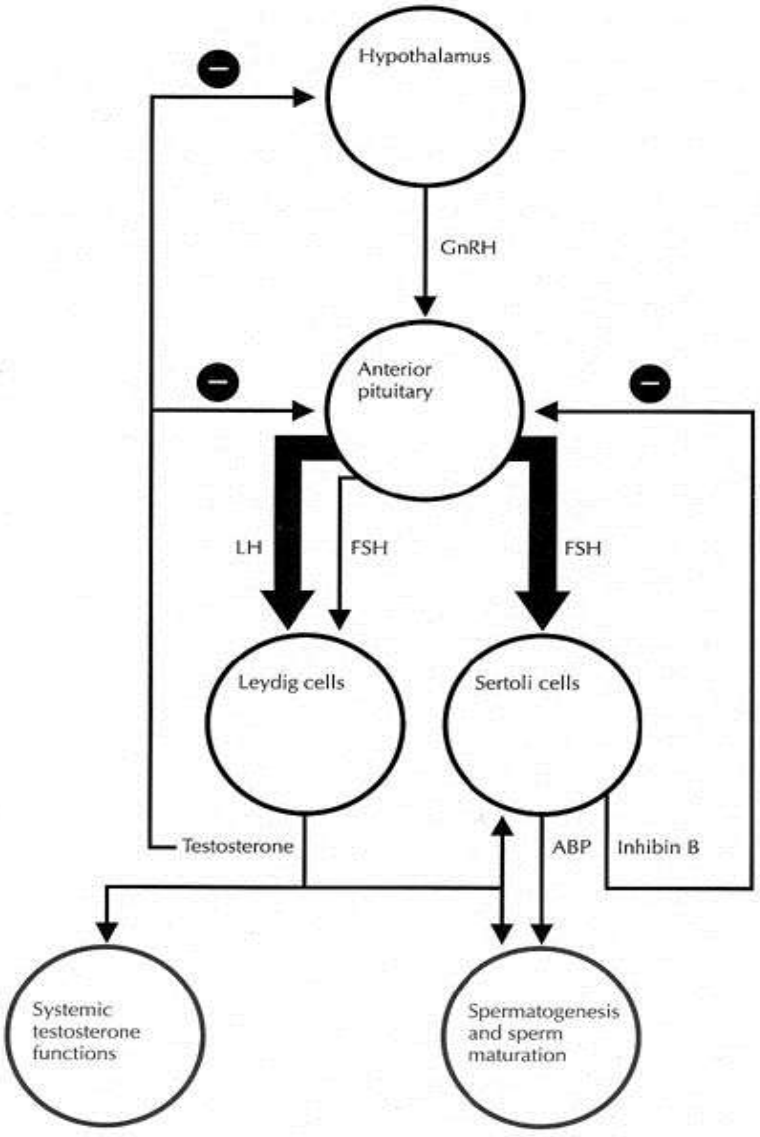
Male Infertility

Anatomy of the testis





Hypothalamic-Pituitary-Gonadal Axis



— **Hypothalamus**

- Congenital abnormalities of hypothalamus
  - — e.g. Kallman's syndrome
- Starvation, stress or severe illness
- Tumors (craniopharyngioma, metastatic tumor)
- Head injury
- Inflammation (sarcoidosis)
- Infection (tuberculosis)
- XRT
- Drugs: marijuana,

— **Pituitary**

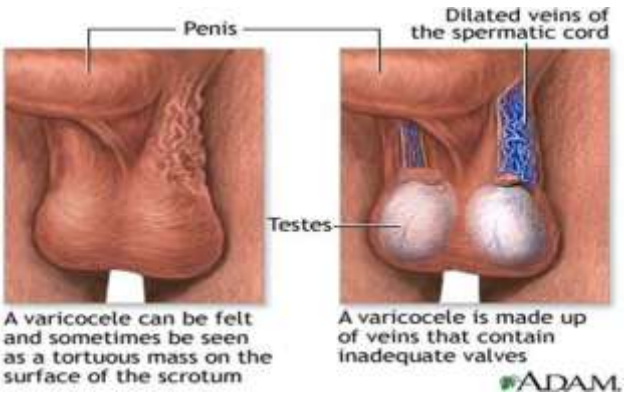
- Endocrine: thyroid, prolactin
- Tumors
- Inflammation: sarcoidosis, meningitis
- Infiltration
- Infarction
- Trauma/XRT
- Drugs: anabolic steroids

— **Testis:**

- Congenital: Klinefelters (XXY), developmental disorders
- Disorders of gonadal steroidgenesis
- Infection: chlamydia, prostatitis, mumps orchitis
- Autoimmune
- Cryptorchidism
- Tumors; chemo/XRT
- Drugs / alcohol
- Vascular: testicular torsion

— **Temperature**

- Rise in scrotal temperature
- Occupation
- Varicocoele



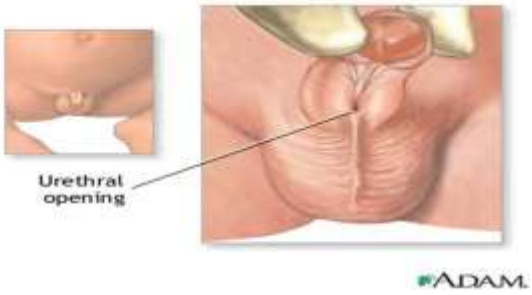
Post testicular causes:

Impotence/Ejaculation

A-Neurogenic: medications (α-blockers, methyldopa)

B-Endocrine: diabetes

- Congenital: absence vas deferens (CF)
- Genetic: cystic fibrosis
- Primary ciliary dyskinesia: Kartagener syndrome
- Hypospadia
- Vasectomy



Investigations:

— semen analysis

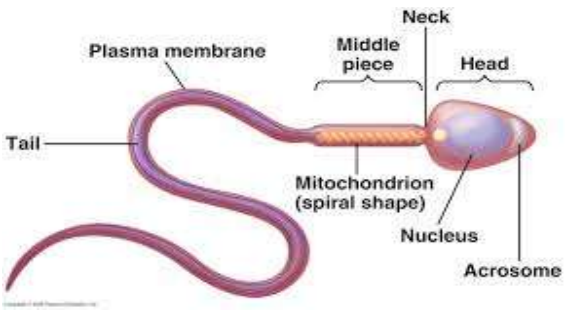
- Abstain 2-7 days prior
- At least 2 samples over different period of time

— If abnormal:

- Blood work: FSH, LH, TSH, testosterone, PRL
- Testicular U/S
- Chromosomal analysis

Semen

also known as *seminal fluid*, is an organic fluid that may contain spermatozoa. It is secreted by the gonads (testis and accessory sex glans). Seminal fluid contains several components besides spermatozoa: proteolytic and other enzymes as well as fructose are elements of seminal fluid which promote the survival of spermatozoa, and provide a medium through which they can move or "swim".



Macroscopical characteristics:

Liquefaction time:

Liquefaction time is a natural change in the consistency of semen from a semi liquid to a liquid. Immediate coagulation is due to a clot formation from seminal vesicles material, followed by gradual liquefaction over the next 5-20 minutes due to enzymatic process involving the prostatic secretion. In evaluation of liquefaction, ejaculate is placed in an incubator at 37°C and allowed to be liquefied. Liquefaction time more than 60 minutes or no liquefaction longer is pathologic showing lack of prostatic enzyme or inadequate prostate function .

Semen viscosity:

Normal semen has a viscous texture. Increase in viscosity may occur due to hypofunction of seminal vesicles. High viscosity may affect sperm motility and concentration. Increase in viscosity may reduce the success of intrauterine insemination (IUI) and *in vitro* fertilization (IVF) .

Appearance of the ejaculate:

A normal ejaculate has a homogenous grey-opalescent appearance.A whitish colour may indicate high sperm numbers or presence of leukocytes a yellowish appearance and purulent smell indicate infections. A reddish-brown colour indicates the presence of red blood cells (hemospermia) .

Semen volume:

The lower reference limit for semen volume is 1.5 ml (WHO 2010). A small volume may also be due to loss of part of the specimen, retrograde ejaculation, abnormality or infection of accessory sex glands, or ejaculatory duct obstruction. An extremely high volume may indicate inflammation or urine contamination and is associated with lower conception rates .

Semen pH:

The pH of semen reflects the balance between the pH values of the different accessory gland secretions, mainly the alkaline seminal vesicular secretion and the acidic prostatic secretion. A lower threshold value is 7.2

Microscopic characteristics

- Agglutination
- Agglutination of spermatozoa means that motile spermatozoa stick to each other, head to head, midpiece to midpiece, tail to tail, or mixed, e.g. midpiece to tail. The adherence of either immotile or motile spermatozoa to mucus threads, to cells other than spermatozoa, or to debris is not considered agglutination and should not be recorded as such. The presence of agglutination is suggestive of, but not sufficient evidence to prove the existence of an immunological factor of fertility.

When agglutination is observed, semen cultures and antibody assessment should be performed .

The major types of agglutination (WHO 2010):

- grade 1: isolated <10 spermatozoa per agglutinate, many free spermatozoa.
- grade 2: moderate 10–50 spermatozoa per agglutinate, free spermatozoa.
- grade 3: large agglutinates of >50 spermatozoa, some spermatozoa still free.
- grade 4: gross all spermatozoa agglutinated and agglutinates interconnected.

Sperm count and concentration

According to WHO2010, the lower reference limit for sperm concentration is 15×10^6 spermatozoa per ml and the lower reference limit for total sperm number is 39×10^6 spermatozoa per ejaculate. A sperm concentration of less than this value is regarded as abnormal .

Sperm motility

The percentage of motile spermatozoa and their progressiveness usually give a good indication on sperm quality and are important in predicting men fertility . Several studies have demonstrated the correlation of motility with the fertilization rate *in vivo* and *in vitro* .

- Categories of sperm movement (WHO 2010):

A simple system for grading motility is recommended that distinguishes spermatozoa with progressive or non-progressive motility from those that are immotile. The motility of each spermatozoon is graded as follows:

- Progressive motility (PR): spermatozoa moving actively, either linearly or in a large circle, regardless of speed.
- Non-progressive motility (NP): all other patterns of motility with an absence of progression, e.g. swimming in small circles, the flagellar force hardly displacing the head, or when only a flagellar beat can be observed.
- Immotility (IM): no movement ().

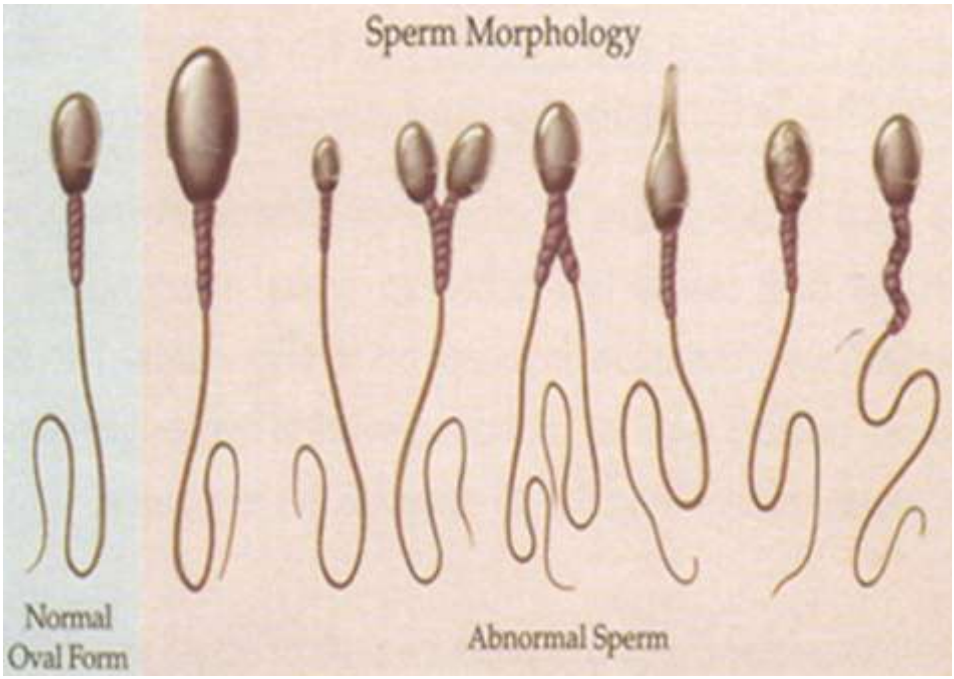
Lower reference limit (WHO 2010):

- The lower reference limit for total motility (PR + NP) is 40%.
- The lower reference limit for progressive motility (PR) is 32%.

Sperm morphology

Many authors have gone as far as to argue that sperm morphology is a reflection of sperm functional competence and Sperm morphology assessment has been considered a valuable and stable method for predicting the *in vivo* and *in vitro* sperm fertilizing ability .

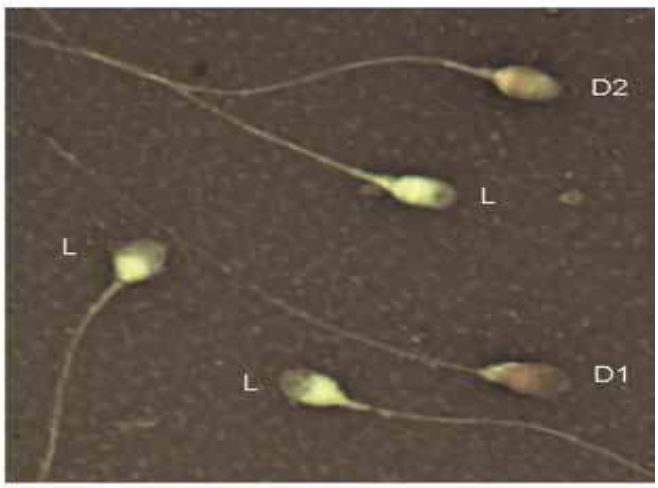
Abnormalities of spermatozoa can be classified into head abnormality, neck/midpiece abnormality, tail abnormality, or the presence of cytoplasmic residue. These abnormalities can occur as a single defect or in a combination of two, three or all four abnormalities simultaneously. The reference value for normal sperm morphology determined by Kruger is >14% WHO1999 vs. 2010 the WHO reference values for normal sperm morphology is >4% .



Sperm vitality

It is especially important for samples with less than about 40% progressively motile spermatozoa. The lower reference limit for vitality (membrane-intact spermatozoa) is 58 %(WHO 2010).

Nowadays, there are several standard tests available for the assessment of the vitality of spermatozoa . One of these tests is based on the principle that dead spermatozoa take up the supravital red stain of eosin-Y, whereas living cells, regardless of their motility stage, will be unstained This assay reflects sperm membrane integrity, particularly the head region which takes up the red stain immediately



Round cell count (cells other than spermatozoa)

The existence of round cells in human ejaculates is common. These can be immature germ cells or somatic cells including epithelial cells of the post-testicular tract and leucocytes . Epithelial cells are indicative of poor collection when present in high numbers . Leukocytes are the most significant non sperm cellular elements in the semen and are a frequent finding in patients who have unexplained infertility. A threshold for classification of leukocytospermia as high as 1×10^6/ml .The semen sample with **<**5 round cells/ HPF was considered normal .

Endocrine Tests

The endocrine assessment of an infertile man includes measurements of serum testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), and perhaps other tests:

- *Serum Testosterone*
- Measurement of a morning serum total testosterone is usually sufficient. In men with borderline values, the measurement should be repeated and measurement of serum-free testosterone may be helpful.
- *Serum Luteinizing Hormone and Follicle-Stimulating Hormone*
- When the serum testosterone concentration is low, high serum FSH and LH concentrations indicate primary hypogonadism and values that are low or normal indicate secondary hypogonadism.

Other Hormones

- Serum prolactin should be measured in any man with a low serum testosterone concentration and normal to low serum LH concentration. Although inhibin assays are not widely available outside of research laboratories, low serum inhibin concentrations may be an even more sensitive test of primary testicular dysfunction than high serum FSH concentrations, provided the assay is specific for inhibin B.

TERMINOLOGY

- Oligozoospermia; sperm conc. less than 15×10^6 spermatozoa per ml
- Teratozoospermia; normal sperm morphology is <4% kruger strict criteria
- Asthenozoospermia; total motility (PR + NP) < 40% or progressive motility (PR) < 32%.
- Azoospermia; no sperm in ejaculate
- Aspermia; no semen

Tx / Interventions:

— Treat underlying causes

— Intrauterine Insemination (IUI)

— Intracytoplasmic Sperm Injection (ICSI)

Treatment of male infertility involves the couple.

- Specific endocrine treatment is available for men whose infertility results from hypogonadotropic hypogonadism. Hypogonadotropic hypogonadism due to hyperprolactinemia can often be corrected and fertility restored by lowering the serum prolactin concentration. If the hyperprolactinemia results from a medication, as is often the case, that medication should be discontinued, if possible. The hyperprolactinemia is caused by a lactotroph adenoma. It should be treated with a dopamine agonist, such as cabergoline or bromocriptine. The process of spermatogenesis normally takes 3 months. As a result, restoration of a normal sperm count usually does not occur for at least 3 and sometimes 6 months or more after the serum prolactin and testosterone concentrations have returned to normal.
- In some patients, who have a lactotroph macroadenoma, the hypogonadotropic hypogonadism appears to be the result of permanent damage to the gonadotroph cells by the mass effect of the adenoma. Gonadotropin treatment should be instituted for these patients.
- *Gonadotropin therapy:* Treatment is initiated with human chorionic gonadotropin (hCG), 1,500–2,000 IU three times per week subcutaneously or intramuscularly for at least 6 months. hCG has the biologic activity of LH. The hCG dose should be adjusted upward according to symptoms of hypogonadism, serum testosterone concentrations, and semen parameters.
- Some patients with acquired hypogonadotropic states can be stimulated with hCG alone to produce sufficient sperm. If after 6–9 months the patient remains azoospermic or severely oligospermic, then human menopausal gonadotropin (hMG) or recombinant FSH should be added.
- • *Pulsatile GnRH treatment:* Pulsatile subcutaneous or intravenous treatment with GnRH has also been successfully used to treat gonadotropin deficient patients. GnRH has to be delivered in pulses using a portable pump with an attached catheter and needle for many months or years; most patients find it inconvenient to use GnRH therapy for so long.

Genital infection

- Infertile men rarely present with symptoms or signs of acute genital infections or prostatitis, but they are sometimes diagnosed as having infections of the urogenital tract by the presence of increased leukocytes in the semen. Despite the absence of symptoms, we typically treat patients who have leukospermia, even if the culture is negative, with at least a 10-day course of antibiotics such as erythromycin or trimethoprim-sulfamethoxazole. A second course of therapy is usually given if leukocytes persist in the semen after antibiotics.

Sperm Autoimmunity

- Continuous or intermittent high doses of prednisone (from 40 mg/ day to 80 mg/day) for up to 6 months have been shown in placebo-controlled trials to improve cumulative pregnancy significantly in partners of men with sperm autoantibodies.
- However, many patients cannot tolerate this regimen because of the adverse effects of high-dose corticosteroid therapy. As a result, most couples prefer to try an assisted reproductive technique, such as ICSI, as primary treatment for sperm autoimmunity.

Empirical Therapy

- Many treatments have been used empirically for male infertility, including clomiphene citrate and other hormones and vitamins.
- Aromatase inhibitors may improve sperm concentrations in men with severe oligozoospermia or azoospermia prior to sperm retrieval for ICSI.

To be continued,,,