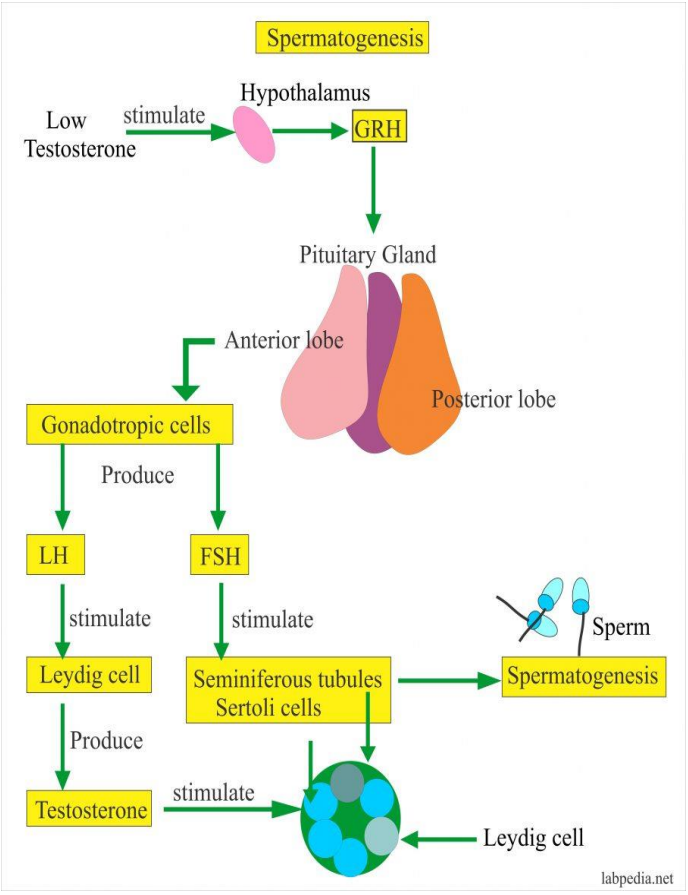
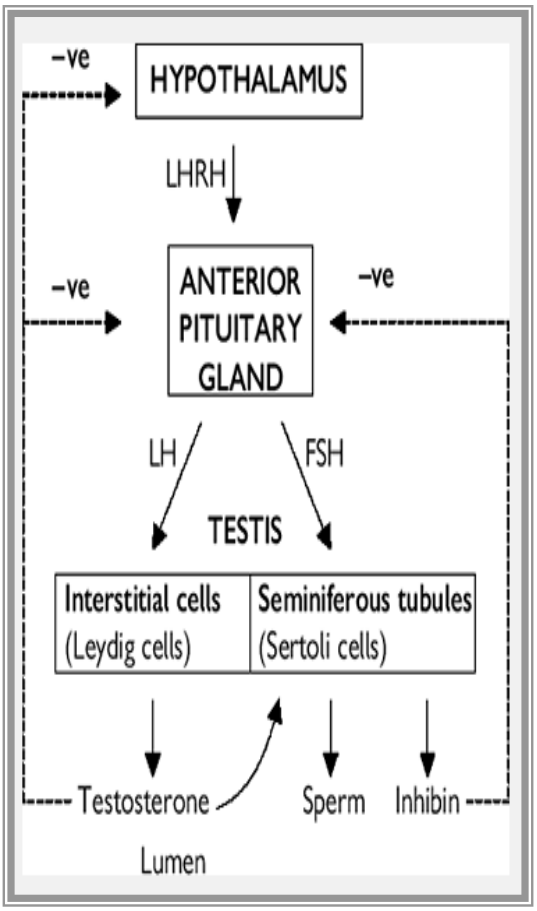
## *Hypothalamic & pituitary & testicular axis*

- The hypothalamus secretes luteinizing hormone-releasing hormone (LHRH), also known as gonadotrophin-releasing hormone (GnRH). This causes pulsatile release of anterior pituitary gonadotrophins, called follicle stimulating hormone (FSH) and luteinizing hormone (LH), which act on the testis.
- FSH stimulates the seminiferous tubules to secrete inhibin and produce sperm; LH acts on Leydig cells to produce testosterone.
- *Testosterone* is secreted by the interstitial Leydig cells, which lie adjacent to the seminiferous tubules in the testis. It promotes development of the male reproductive system and secondary sexual characteristics.

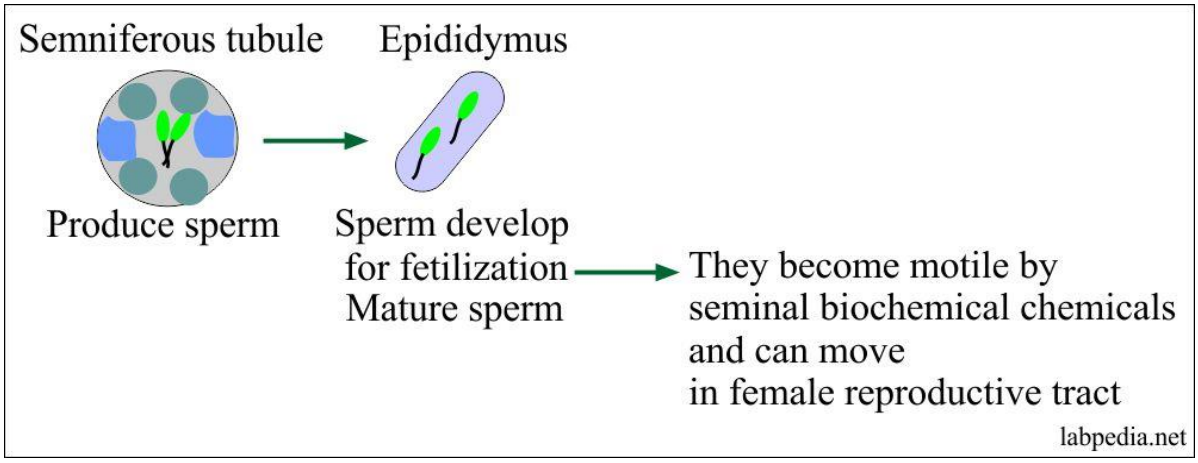



- *In primary gonadal failure:*
  - *FSH is raised.*
  - *LH is raised.*
- *In secondary gonadal failure:*
  - *FSH is decreased.*
  - *LH is decreased.*

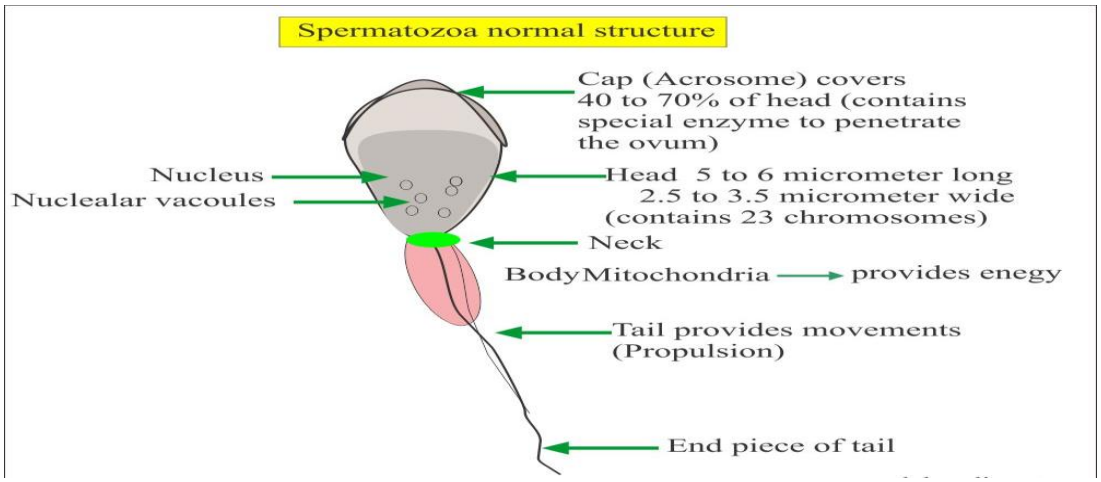
## *Spermatogenesis*

- Seminiferous tubules are lined with Sertoli cells, which surround developing germ cells (spermatogonium) and provide nutrients and stimulating factors, as well as secreting androgen-binding factor and inhibin .
- Primordial germ cells divide to form primary spermatocytes. These undergo a first meiotic division to create secondary spermatocytes (46 chromosomes), followed by a second meiotic division to form spermatids (23 chromosomes). Finally, these differentiate into spermatozoa.
- This process takes about 74 days. The non-motile spermatozoa leave the seminiferous tubules and pass to the epididymis, for storage and maturation (until ejaculation).
- Spermatozoa that are not released are reabsorbed by phagocytosis.




## *Mature sperm*

- have a head, middle piece, and tail. The head is composed of a nucleus covered by an acrosome cap, containing vesicles filled with lytic enzymes.
- The middle piece contains mitochondria and contractile filaments, which extend into the tail to aid motility.
- After deposition at the cervix, sperm penetrate cervical mucus and travel through the uterus to the site of fertilization in the fallopian tube.



## Environmental and lifestyle effect on male fertility:

- Overexposure to certain environmental elements such as heat, toxins and chemicals can reduce sperm production or sperm function. Specific causes include:

1. **Industrial chemical & Heavy metal exposure**: Extended exposure to benzenes, pesticides, painting materials and lead may contribute to low sperm counts.
2. **Radiation or X-rays.**
3. **Overheating the testicles**. Elevated temperatures impair sperm production and function. Sitting for long periods, wearing tight clothing or working on a laptop computer.
4. **Drug use.**
   - Anabolic steroids taken to stimulate muscle strength and growth can cause the testicles to shrink and sperm production to decrease.
   - cocaine or marijuana may temporarily reduce the number and quality of your sperm as well.
5. **Alcohol use.** Drinking alcohol can lower testosterone levels, cause erectile dysfunction and decrease sperm production. Liver disease caused by excessive drinking also may lead to fertility problems.
6. **Tobacco smoking**. Men who smoke may have a lower sperm count than do those who don't smoke.
7. **Emotional stress.** Stress can interfere with certain hormones needed to produce sperm. Severe or prolonged emotional stress, including problems with fertility, can affect your sperm count.
8. **Depression.** depression in men may cause sexual dysfunction due to reduced libido, erectile dysfunction, or delayed or inhibited ejaculation.
9. **Weight**. Obesity can impair fertility in several ways, including directly impacting sperm themselves as well as by causing hormone changes that reduce male fertility.

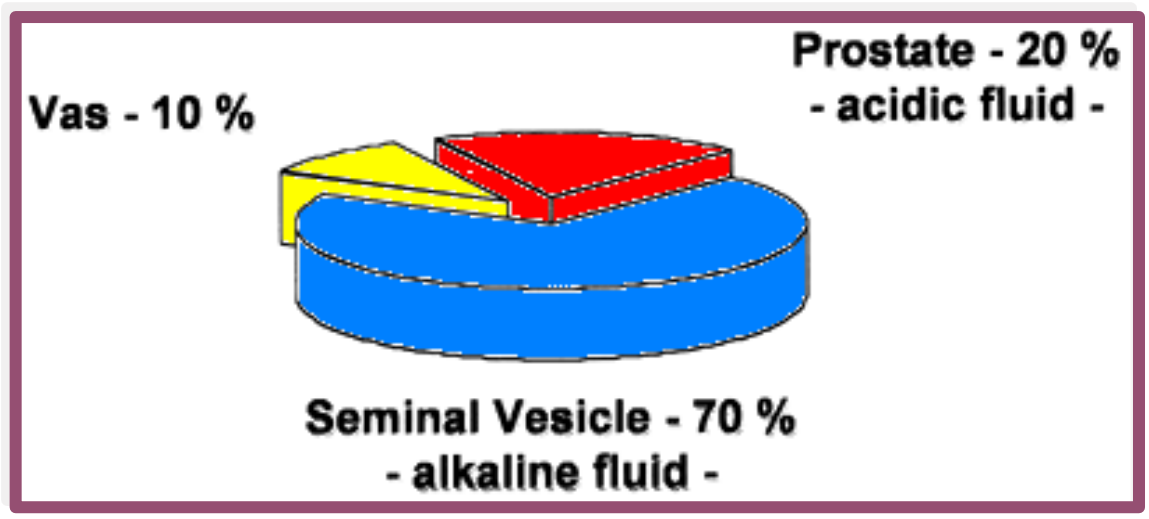
## Seminal fluid

### Source of semen

1. Testes
2. Epididymis (sperms mature here, storage site)
3. Vas deferens (also storage site)
4. Seminal Vesicle (nutritive fluid secreted during ejaculation)
5. Prostate
6. Bulbourethral glands of Cooper Produces

### Contents of semen

1. citric acid
2. proteolytic enzymes
3. zinc Mucous
4. PSA.
5. Spermatozoa
6. choline (energy source for sperms)
7. Carnitine
8. Fructose




## Normal Pattern of Semen Analysis

- This is preferred if the sample is collected by the patient in the lab.
- Masturbation is preferred and the entire collected semen should be submitted.
- 2 to 3 days of sexual abstinence is preferred.
- The analysis should be done immediately when the semen is liquefied.
- Should be examined within 4 hours
- Wait till liquefaction is complete for the examination.
- Don't use the condoms particularly with spermicide.
- 2 or 3 samples examined over a period of several weeks for more accuracy.

## Seminal fluid analysis (SFA)

Accepted volume is 1.5 to 5 ml.
pH Normal >=7.2 (Seminal vesicle secretion is basic)
Rapidly progressive – moving fast and forward in a straight line
Slowly progressive – Crooked, curved, slow forward movement

| Semen volume | More than 1.5 cc |
|---|---|
| Sperm concentration | ≥ 20 million / mL |
| Total no. of spermatozoa | ≥ 40 million / ejaculate |
| Motility | ≥ 50% with progressive motility or 25% with rapid motility within 60 min after ejaculation |
| Morphology | ≥ 14% of normal shape and form* |
| Leukocytes | < 1 million / mL |

- Based on experience, concentration and progressive motility are the most important sperm parameters in predicting the likelihood of pregnancy via coitus, only those sperms with rapid progressive motility are capable of fertilizing ovum

**Aspermia** (azoospermia) : When there is no sperm.
**Oligospermia**: when the count is < 15 million/mL.
**Asthenospermia** is low sperm motility.
**Teratozoospermia** is an increase in the percentage of abnormal sperm
**Oligoasthenoteratozoospermia (OAT).**
**Necrospermia** Normal count of the sperm but are non-motile.
**Hematospermia**: when there are abundant RBCs.


# INFERTILITY

**Infertility** is defined as the failure to conceive despite one year of regular unprotected intercourse.

## EPIDEMIOLOGY

- 25% of couples don't achieve pregnancy within one year, 15% of them seek medical treatment.
- 20% of infertility cases are due to male factors
- 40 of infertility cases are due to female factors
- 40% of them due to both male & female factors.
- Fertility rates are at their peak in men & women at age 24 years, beyond that age, they decline in both sexes.
- 25-35% of infertility couples will conceive at some time by intercourse alone.

## Goals of evaluation of infertile men

1. Identification of reversible disorders.
2. Identification of irreversible conditions.
3. Identification of chromosomal & genetic abnormalities that may affect the offspring. (lower pregnancy rates and live births)
4. Identification of idiopathic cases.

## Prognostic factors

1. Duration of infertility.
2. Primary or secondary infertility.
3. Results of seminal fluid analysis (SFA).
4. Age & fertility state of female partner.

## *Pretesticular Deficiency:*

- As a less common etiology than other causes of male infertility, hypogonadotropic hypogonadism (HH) is caused by insufficient GnRH or FSH and LH secretion.
- These insufficiencies result in deficient androgen secretion and spermatogenesis.
- Hypogonadotropic hypogonadism can arise from:

1. congenital GnRH deficiency.
2. Hemochromatosis.
3. genetic disorders, pituitary
4. hypothalamic tumors.
5. hormonal abnormalities, or medications (*anabolic steroids, spironolactone*).

## II-testicular factors

A. Congenital failure can manifest as anorchia, testicular dysgenesis, cryptorchidism, or genetic abnormalities (*Y-chromosomes, Klinefelter syndromes*).

B. Acquired testicular failure:

1. *Varicocele*
2. *idiopathic.*
3. *trauma.*
4. *mumps.*
5. *radiation.*
6. *tobacco smoking.*
7. *chemotherapy*

## *III-post testicular causes:*

1. *vas deferens obstruction, absence of vas deferens (e.g. cystic fibrosis).*
2. *Infections' prostatitis.*
3. *Retrograde ejaculation e.g D.M.*
4. *Ejaculatory duct obstruction.*
5. *Hypospadias.*
6. *Impotence.*

- In approximately 30% to 40% of men who are infertile, no male infertility factor can be identified.These men frequently have no previous history of infertility, unremarkable physical examination, and normal endocrine laboratory evaluation.
- Semen analysis reveals a decreased number of spermatozoa, reduced sperm motility, and many abnormal forms of sperm.
- These findings commonly occur together and are termed *oligo-astheno-teratozoospermia* or *OAT syndrome*.
- Idiopathic male infertility can be attributed to environmental pollution, reactive oxygen species, or genetic abnormalities.

## Evaluation of infertile male

1. **History.**
2. **Physical examination.**
3. **SFA.**
4. Adjunctive laboratory investigations.
5. Radiologic investigations.
6. Testicular biopsy.

## History

| Medical history |
|---|
| Fevers |
| Systemic illness—diabetes, cancer, infection |
| Genetic diseases—cystic fibrosis, Klinefelter syndrome |
| **Surgical history** |
| Orchidopexy, cryptorchidism |
| Herniorraphy |
| Trauma, torsion |
| Pelvic, bladder, or retroperitoneal surgery |
| Transurethral resection for prostatism |
| Pubertal onset |
| **Fertility history** |
| Previous pregnancies (present and with other partners) |
| Duration of infertility |
| Previous infertility treatments |
| Female evaluation |
| **Sexual history** |
| Erections |
| Timing and frequency |
| Lubricants |

| Family history |
|---|
| Cryptorchidism |
| Midline defects (Kartagener syndrome) |
| Hypospadias |
| Exposure to diethylstilbestrol |
| Other rare syndromes—prune belly, etc. |
| **Medication history** |
| Nitrofurantoin |
| Cimetidine |
| Sulfasalazine |
| Spironolactone |
| Alpha blockers |
| **Social history** |
| Ethanol |
| Smoking/tobacco |
| Cocaine |
| Anabolic steroids |
| **Occupational history** |
| Exposure to ionizing radiation |
| Chronic heat exposure (saunas) |
| Aniline dyes |
| Pesticides |
| Heavy metals (lead) |

## Physical examination

1. Abnormal secondary sexual characters.
2. Gynecomastia.
3. Genital examination:

- Penis
- Scrotum(Testicular size, varicocele).
- Spermatic cord.
- DRE.

## Adjunctive laboratory tests

## Semen culture

- For pyospermia (3-23% of infertility case).
- Immature germ cells vs. leukocytes??
- <u>Indications</u>:

1.History of genital infection.
2.Presence of $>10^6$ WBC/ml.

## Semen fructose

- Indicated in seminal fluid with low ejaculate volume, acidic PH & no sperms.
- Absent in seminal vesicle agenesis or obstruction.

## Post ejaculate urinalysis

- Indicated in low ejaculate volume for suspected retrograde ejaculation.

## Hormonal tests

- Less than 3% of infertile men have hormonal etiology.
- Used to evaluate the hypothalamus-pituitary-gonadal axis.
- Testosterone, LH, FSH &prolactin are the main hormones.
- Indications of hormonal evaluation:
  1. Sperm density< 10x10^6/ml
  2. Impaired sexual function.
  3. Findings suggestive of a specific endocrinopathy.

## Antisperm antibody (ASA) test

## Sperm function tests: Sperm-cervical mucus interaction

## Chromatin/DNA integrity testing.

## Genetic (chromosomal) tests

- Indicated in azoospermia or severe oligospermia.
- 5.8%of infertile men have genetic defects.
- The defects are either:
  - Numerical (e.g., Klinefelter syndrome).
  - Structural (e.g., CFTRG mutations).
- The defects are in the sex chromosomes or autosomes.
- Y chromosomes microdeletions (AZFc is the most common).

## Ultrasonography (US)

1. Scrotal US: for varicocele or testicular tumors.
2. Transrectal U.S.(T.R.U.S.)

- To assess the prostate, seminal vesicles, ejaculatory duct &vas.
- Indicated in azospermia with suspected ejaculatory duct obstruction.

## Testicular biopsy

1. Diagnostic (to differentiate obstructive from non-obstructive azoospermia in patient with normal testicular size & normal FSH level).
2. Therapeutic (to harvest sperms for IVF or for cryopreservation).

## Treatment of male infertility

- It is better to improve male/female fertility & to allow natural conception
- If this is not successful, assisted reproductive techniques(ART) are used.
- Types:
  1. Medical Rx.
  2. Surgical Rx.
  3. Assisted reproductive technologies (ART).

## Medical Rx.

1. **Life style modifications.**
2. **Hormonal Rx.**
   - **a.** Gonadotropins(LH/FSH)
     *Used for hypogonadotrophic hypogonadism.
     * Formulae: HCG, HMG or recombinent FSH.
   - b. GnRH : uesed only for hypogonadotrophic hypogonadism with intact pituitary function.
   - c. Testosterone Rx. :different formulae are used to induce virilisation in pt. with primary or secondary testicular failure.

excess testosterone is a male contraceptive.

3. **Antiprolactinaemic drugs**: For hyperprolactinemia.
4. **Treatment of thyroid disorders**
5. **Corticosteroids**: used for immunologic infertility( it accounts for 10% of infertility cases), It achieves pregnancy rate = 30-40%.
6. **Treatment of pyospermia**: Proper antibiotics, Antioxidants, Frequent ejaculation.
7. **Empirical medical Rx.**
   *for idiopathic infertility (25% of *infertility cases).
   *Includes→ clomiphene citrate, tamoxifen.
8. **Rx. of ejaculatory dysfunction:** Retrograde ejaculation (RGE).
9. **Rx. of erectile dysfunction.**
10. **Other drugs: Vit C, antioxidants , zinc, arginine& L-carnitine.**

## Surgical treatment

1. Varicocele Rx.
2. Rx. Of ejaculatory duct obstruction.
3. Surgical Rx. Of pituitary tumors.
4. Rx. Of anatomic ,congenital causes of male infertility: Hypospadias repair.

## Varicocele:

- Abnormally dilated testicular veins within the spermatic cord.
- Clinical vs. subclinical varicocele.
- Affects 15%of normal adolescents vs. 20-40% of infertile men.
- 90% left sided-10% bilateral.
- The most common surgically correctable cause of infertility.

MULTIFACTORIAL

- Raised Hydrostatic pressure.
- Raised Testicular temperature.
- Reflux of renal &adrenal metabolites from renal vein.

ALL→ reduced testicular size, sperm motility & count → infertility.

- Diagnosed: *clinically
- Treatment surgical
- This Rx. Improve seminal parameters in 70% of pt. & improve conception rate in 50% of couples.

## Assisted reproductive technologies(ART)

1. Intrauterine insemination(IUI).
2. In vitro fertilization(IVF).
3. Intracytoplasmic sperm injection(ICSI).

### 1. Intrauterine insemination (IUI)

### 2. In vitro fertilization (IVF).

⇒ It includes harvesting the oocyte & sperm in order to incubate them for fertilization then transferring the embryo to the uterine cavity.

⇒ Pregnancy rate: 20-30% per cycle.

⇒ Costly.

Indications:

1. Failed medical or surgical Rx. or IUI.
2. Severe oligospermia.
3. Azoospermia (obstructive or non-obstructive).
4. CBAVD.
5. Cryopreserved sperms.

### 3. Intracytoplasmic sperm injection (ICSI)

⇒ A special micromanipulation of the sperm into the cytoplasm of a harvested oocyte.

⇒ Useful in severe oligosprmia, azospermia & ultrasructural sperms defects.

⇒ Conception rate: 50% per cycle.

⇒ The risks associated with IVF-ICSI include ovarian hyperstimulation syndrome, multiple gestation, perinatal complications, and genetic disorders.

MOST COUPLES PREFER, NATURAL FOODS, NATURAL FIBERS, AND NATURALLY CONCEIVED BABIES

*Thank you*
*2021-2022*