DRUGS USED IN

MALE INFERTILITY

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ILOs

By the end of this lecture you will be able to:

- Define male infertility
- Recognize regulations contributing to male fertility & dysregulations leading to infertility
- Classify hormonal & non-hormonal therapies used in male infertility whether being empirical or specific.
- Expand on the mechanism of action, indications, preparations, side effects, contraindications & interactions of most hormonal therapies
- Highlight some potentialities of non-hormonal therapies

MALE INFERTILITY

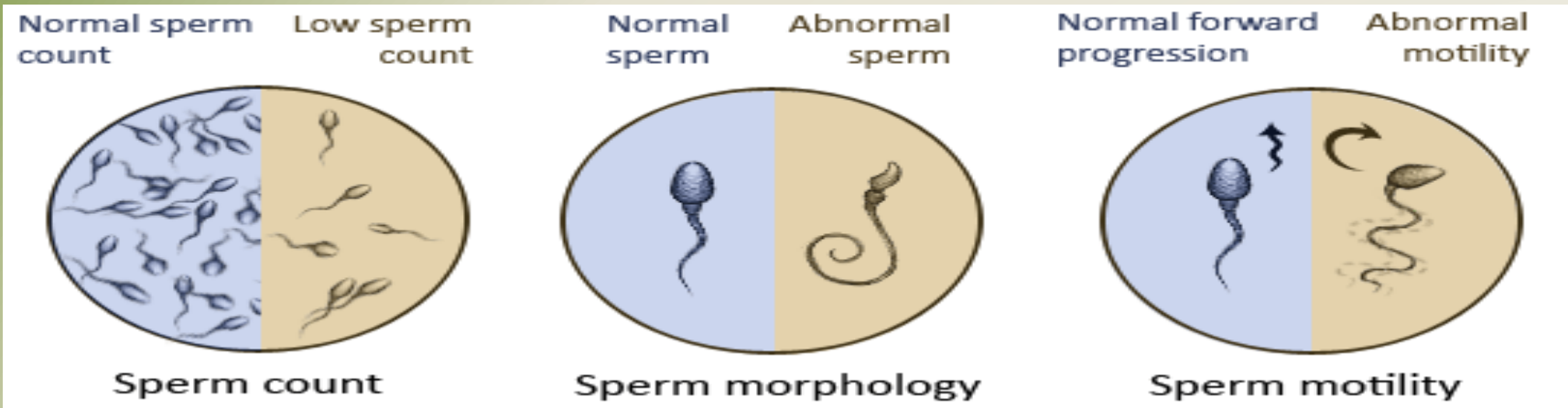
Definition

Inability of a male to achieve conception in a fertile woman after one year of frequent unprotected intercourse.

Prevalence

Infertility has traditionally been thought of as a woman's problem. However, about one out of every three cases of infertility is due to the man alone

INFERTILITY vs IMPOTENCE – What is the difference?

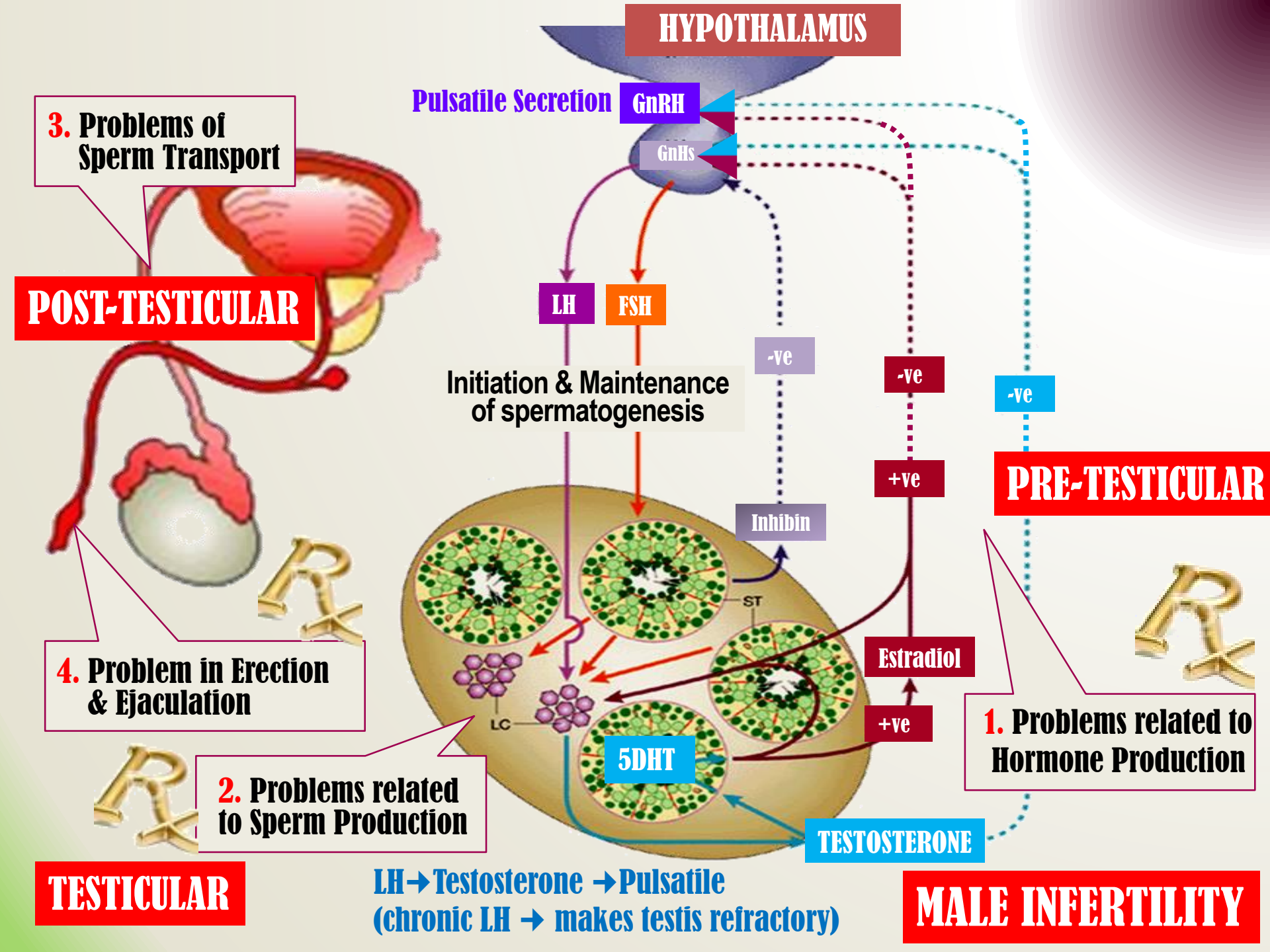


In male infertility, the semen analysis is abnormal:

- **Count is low (oligospermia)**
- **Sperms are absent in the ejaculate (azoospermia)**
- **Sperm motility is seriously affected (asthenospermia).**
- **Sperms are totally immobile or dead (necrospermia)**

Causes of Male Infertility

1. **Idiopathic** (causes unknown).
2. **Pre- testicular causes** (poor hormonal support & poor general health) including:
   Hypogonadism; Drugs; alcohol; Tobacco; Strenuous riding (bicycle & horse riding); Medications (chemotherapy; anabolic steroids).
3. **Testicular causes** (testes produce semen of low quantity and/or poor quality): Age; Malaria; Testicular cancer; Idiopathic (unexplained sperm deficiencies).
4. **Post- testicular causes** (conditions that affect male genital system after sperm production):
   Vas deferens obstruction; Infection, e.g. prostatitis, T.B; Ejaculatory duct obstruction; Impotence.


HYPOTHALAMUS
Pulsatile Secretion
GnRH
GnHs
LH
FSH
-ve
-ve
-ve
+ve
+ve
Inhibin
Initiation & Maintenance of spermatogenesis
Estradiol
5DHT
TESTOSTERONE
ST
LC
3. Problems of Sperm Transport
POST-TESTICULAR
4. Problem in Erection & Ejaculation
2. Problems related to Sperm Production
TESTICULAR
PRE-TESTICULAR
1. Problems related to Hormone Production
LH→Testosterone →Pulsatile
(chronic LH → makes testis refractory)
MALE INFERTILITY

DRUG TREATMENT OF MALE INFERTILITY

Needs 3 ms. before semen quality changes

HORMONAL THERAPY

SPECIFIC

Hyperprolactinaemia → *DA_2 Agonists*
Hypothyroidism → *Thyroxine*
Congenital Adrenal Hyperplasia →
Glucocorticoids excess

EMPERICAL

- **Idiopathic** → *Androgens, Antiestrogen, GnH(FSH)*
- **Euogonadotrophic Hypogonadism** →
  (↓T only) Antiestrogens (SERMs & Aromatase Is)
- **Hypogonadotrophic hypogonadism** → 2ndry
  Hypogonadism (Hypothalamo-Pituitary)
  (↓T & ↓ FSH / LH)
  Pulsatile GnRH, hCG, hMG, Androgens, Clomiphene

NON-HORMONAL THERAPY

EMPERICAL

- *Kallikrein*
- *Antioxidants; e.g.vit E, vit.c*
- *Zinc Supplements*
- *Folic acid*
- *L-Carnitine*

SPECIFIC

Erectile Dysfunction → *PDE 5 inhibitors,e.g. sildenafil (viagra) , vardenafil (levitra) , tadalafil (cialis)*
Premature Ejaculation → *SSRIs (e.g. prozac)*
Infection of testes, prostate &UT → *Antibiotics*

- **Hypergonadotrophic Hypogonadism** (Testicular dysfunction) → 1ry Hypogonadism (↓T &↑LH) *Assisted Reproduction (no treatment)*

Drugs Used in the Treatment of Male infertility

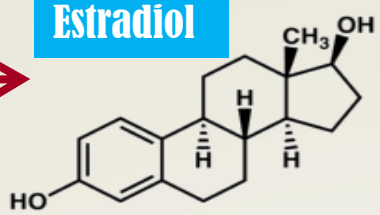
1. Testosterone and synthetic androgens
2. Anti-estrogens
   - SERMs-clomifen, tamoxifen
   - Aromatase inhibitors
     Anastrazole
3. GnRH
4. GnH together with hcG
5. Non- hormonal therapy

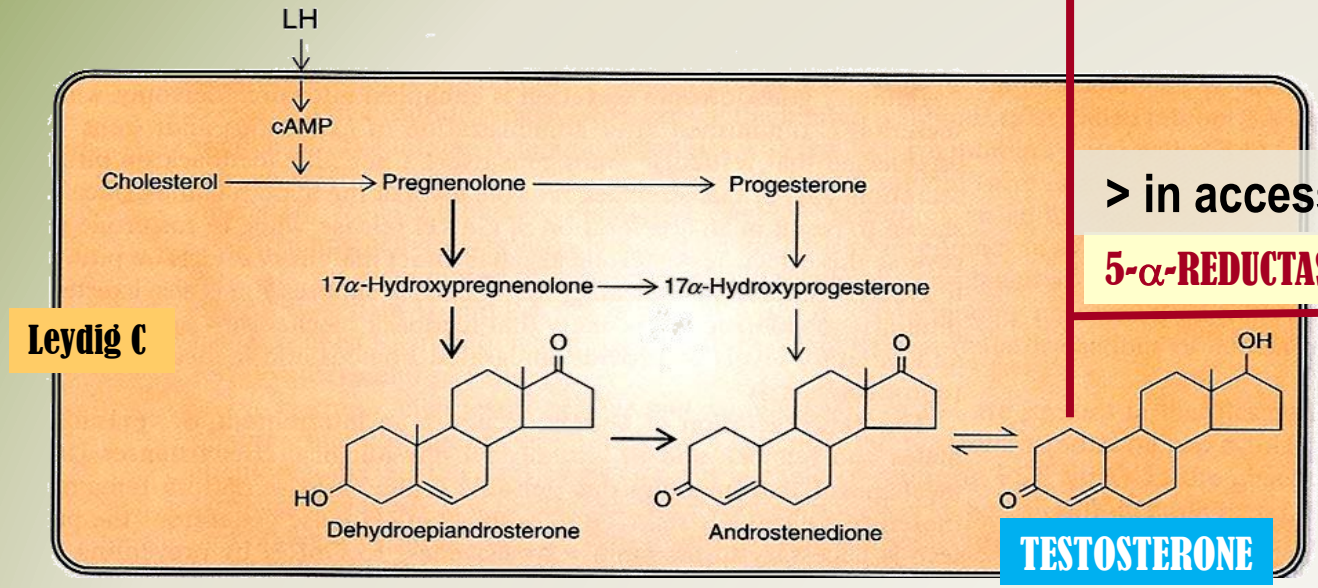
1.Testesterone

> in brain, bone, liver, adipose t.

AROMATASE

Estradiol

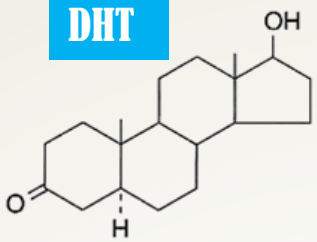




> in accessory sex organs

5-α-REDUCTASE

DHT



Principle male sex hormone produced in testis(> 95%), small amount in adrenals. It follows a circadian pattern➔↑in early morning & ↓in evening

Mechanism of action of testosterone

A. (prostate, seminal vesicles converted by α-reductase to DHT

B. Bones and Brain
Testesterone is metabolized to estradiol by c-p450 aromatase.

Bones: estradiol accelerates maturation of cartilage into bone leading to closure of the epiphyses & conclusion of growth.

Brain: estradiol serves as the most important feedback signal to the hypothalamus(esp. affecting LH secretion).

Pharmacological effects of Testesterone

Testesterone has virilizing and anabolic effects

Virilizing effects
- Gonadotropin regulation
- Spermatogenesis
- Sexual dysfunction
- Sexual restoration and development

Protein anabolic effects
- Increased bone density
- Increased muscle mass
- Increased red blood cell mass

← Testosterone & Synthetic Androgens

←Anabolic Steroids
Not used in infertility

Kinetics of Testesterone

Ineffective orally(inactivated by 1st pass met.)➔ **I.M or S.C.**

Skin patch & gels…. are also available

- Binds to Sex Hormone Binding Globulin [SHBG]
- t1/2 = 10 –20 min
- Inactivated in the liver.; 90% of metabolites ➔excreted in urine.
- Disadvantages: Rapidly absorbed, rapidly metabolized (Short duration of action).

Synthetic Androgens

- Less rapidly metabolized & more lipid soluble ► increasing its duration of action.

<u>Derived from Testosterone</u>

- Esters; proprionate, enanthate, cypionate ➔in oil for **IM**; every 2-3 weeks
- Other derivatives as Fluoxymesterone, Methyltestosterone, Danazol ➔ given **Orally;** daily

<u>Derived from DHT;</u> Mesterolone ➔ given **Orally;** daily

Adverse effects of Androgens

- Excess androgens (if taken > 6 wks) can cause impotence, decreased spermatogenesis & gynecomastia.
- Alteration in serum lipid profile: ↓HDL & ↑LDL, hence, ↑risk of premature coronary heart disease.
- Salt & water retention leading to edema.
- Hepatic dysfunction; ↑ AST levels, ↑alkaline phosphatase, ↑ bilirubin & cholestatic jaundice.
- Hepatic carcinoma (long term use)
- Behavioral changes; physiologic dependence, ↑ aggressiveness, psychotic symptoms
- Polycythemia (increase # of RBC) → ↑risk of clotting.
- Premature closing of epiphysis of the long bones.
- Reduction of testicular size

INDICATIONS

As Testesterone Replacement Therapy(TRT)

- Therapy for androgen deficiency in adult male infertility.
- In delayed puberty with hypogonadism
  ➔ give androgen slow & spaced for fear of premature fusion of epiphyses ➔ short stature.

Testesterone

Contraindications

- Male patients with cancer of breast or prostate
- Severe renal & cardiac disease → predispose to edema
- Psychiatric disorders
- Hypercoagulable states
- Polycythemia

Interactions

+ corticosteroids → oedema

+ warfarin → ↓metabolism → ↑ bleeding

+ insulin or oral hypoglycemics → hypoglycemia

+ propranolol → ↑ propranolol clearance → ↓efficacy

Mesterolone

More **safely** given in ↓ testosterone or in 2ndry hypogonadism.

Why ???

1. Not aromatized into estrogens →no –ve of GnHs → encourages natural testosterone production→ spermatogenesis is enhanced
2. Unlike other oral synthetic androgens it is not hepatotoxic.

2. Antiestrogens

Because estrogens → –ve feedback on hypothalamus →↓ GnRH pulse frequency & pituitary responsiveness to GnRH , so antiestrogens →↑ Gn RH & improve its pituitary response.

2.a. SERMs — Tamoxifen, Clomiphene

Tamoxifen

Clomiphene

Both drugs can induce libido & bad temper in men

2.b. Aromatase Inhibitors — Anastrozole

Blocks conversion of testosterone to estrogen within the hypothalamus

- All are used for inducing spermatogenesis in oligozoospermia (count is low)
- Given as daily dose over a period of 1–6 months.
- Best to improve sperm count & motility with good pregnancy rates

3. GnRH

Used in hypothalamic dysfunction➔androgenization & spermatogenesis
Given as Pulsatile GnRH therapy (4-8 ug subcut every 2 hours) using a portable pump.
Exogenous excess of GnRH ➔ down-regulation of pituitary GnRH receptors & ↓ LH responsiveness.

ADRs: Headache, depression, generalized weakness, pain , gynecomastia and osteoporosis.

4. GnHs

Used in 2ndry hypogonadism (FSH or both FSH or LH absent) ➔↑ spermatogenesis
GnHs replacement must be combined; hCG (IM.➔2 ms.) followed by hCG + hMG (IM. ➔6 -12 ms).

ADRs: Headache, local swelling (injection site), nausea, flushing, depression, gynecomastia, precocious puberty.

5.Non-HORMONAL THERAPY

Sometimes is very promising, to improve sperm quality and quantity.

Antioxidants Protect sperm from oxidative damage (e.g. vit E,C)

KALLIKREIN

Has proteolytic activity, cleaving kininogen to kinins➔ important for sperm motility.

FOLIC ACID

Plays a role in RNA and DNA synthesis during spermatogenesis & has antioxidant properties.

ZINC

Plays an important role in testicular development, sperm production & sperm motility.

L-CARNITINE

Is important for sperm maturation.

DRUGS USED IN MALE INFERTILITY

GOOD LUCK