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

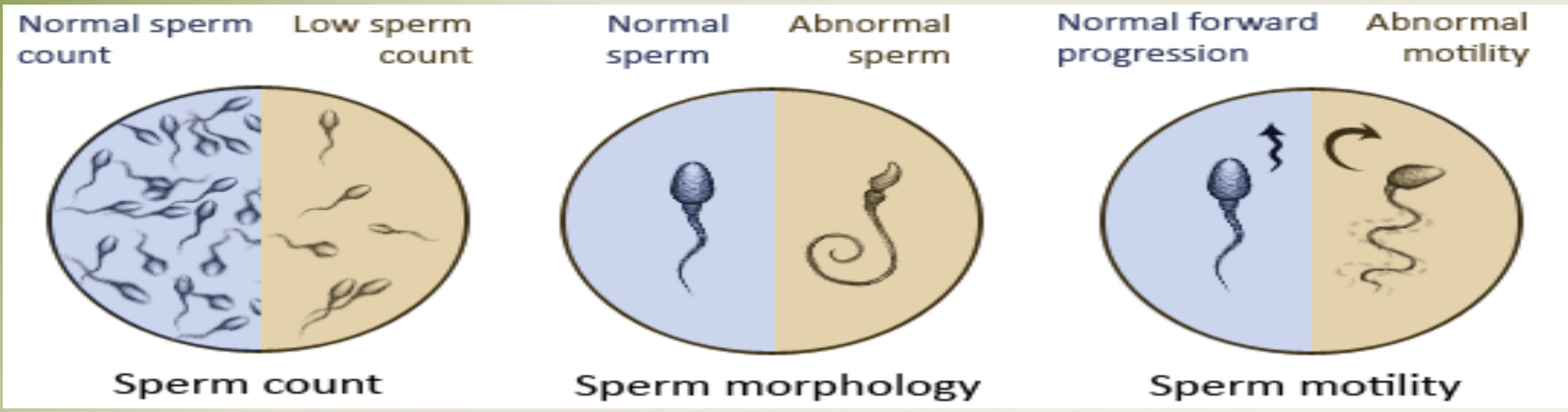
Definition

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?

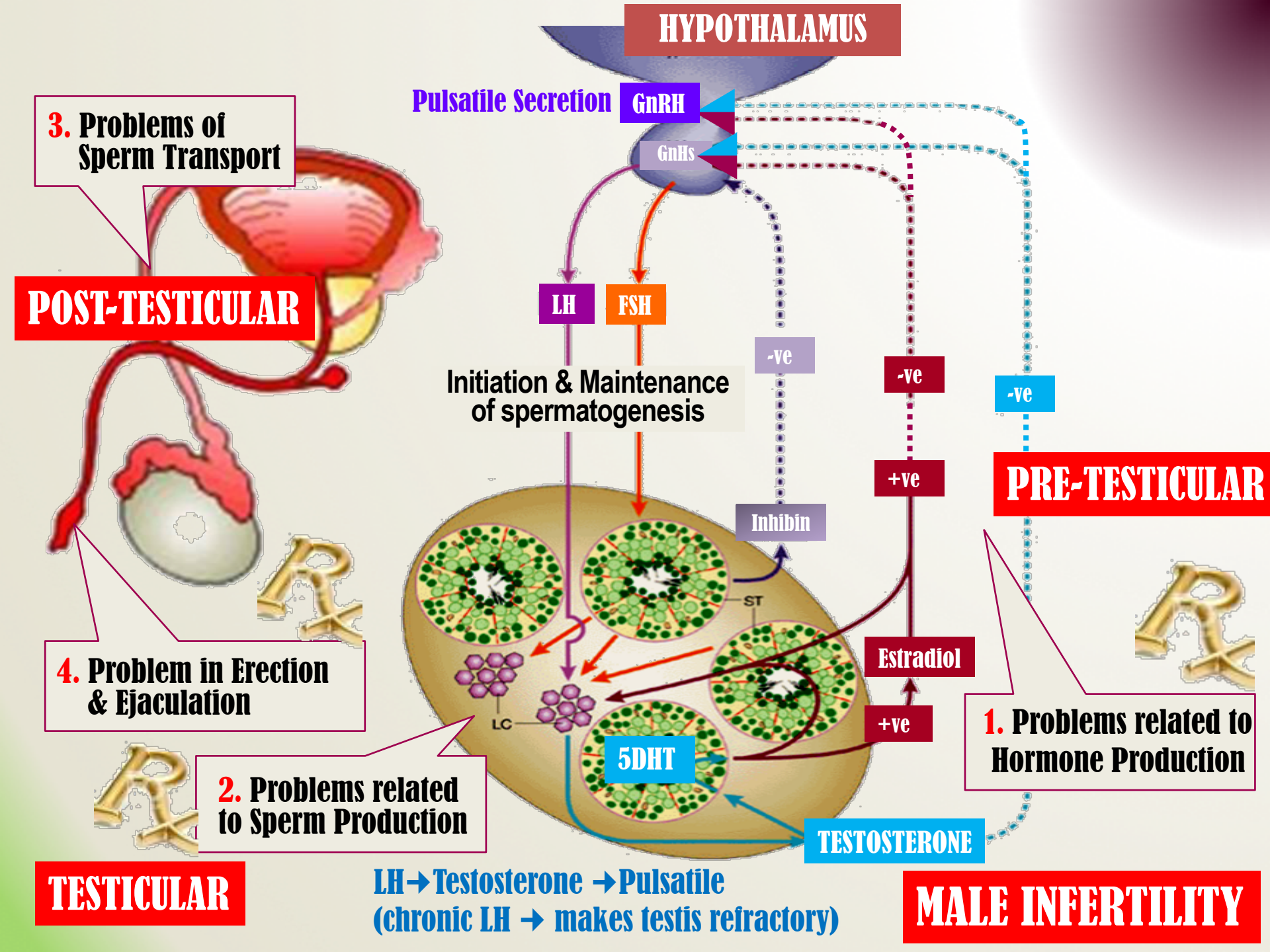


In male infertility, the semen analysis is abnormal:

- **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
Estradiol
Initiation & Maintenance of spermatogenesis
ST
LC
5DHT
TESTOSTERONE
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*

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

NON-HORMONAL THERAPY

EMPERICAL

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

SPECIFIC

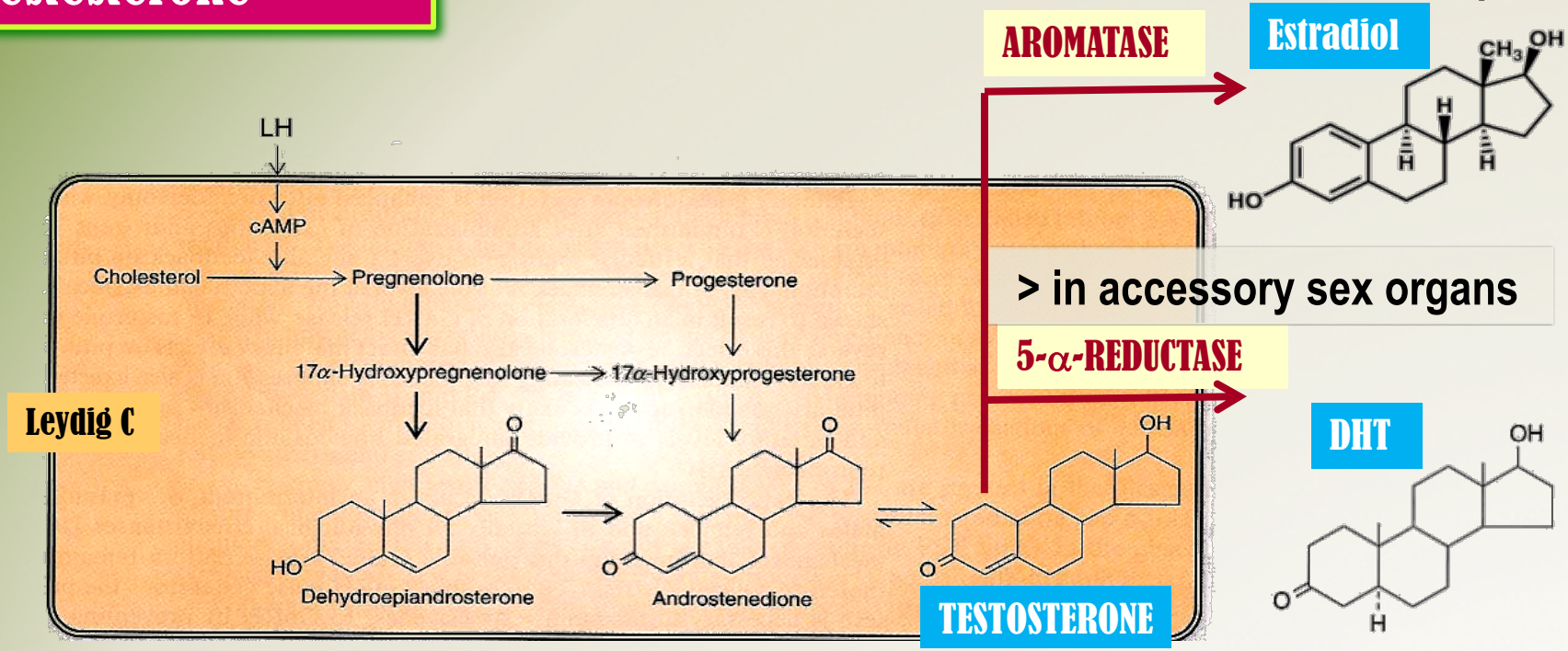
Erectile Dysfunction → *PDE 5 inhibitors,e.g. sildenafil (viagra) , vardenafil (levitra) , tadalafil (cialis)*
Premature Ejaculation → *SSRIs (e.g. prozac)*
Infection of testes, prostate &UT → *Antibiotics*

Drugs Used in the Treatment of Male infertility

1. Testosterone and synthetic androgens
2. Anti-estrogens
   - SERMs-clomiphene, tamoxifen
   - Aromatase inhibitors:

     Anastrazole
3. GnRH
4. GnH together with hcG
5. Non- hormonal therapy

1.Testesterone



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

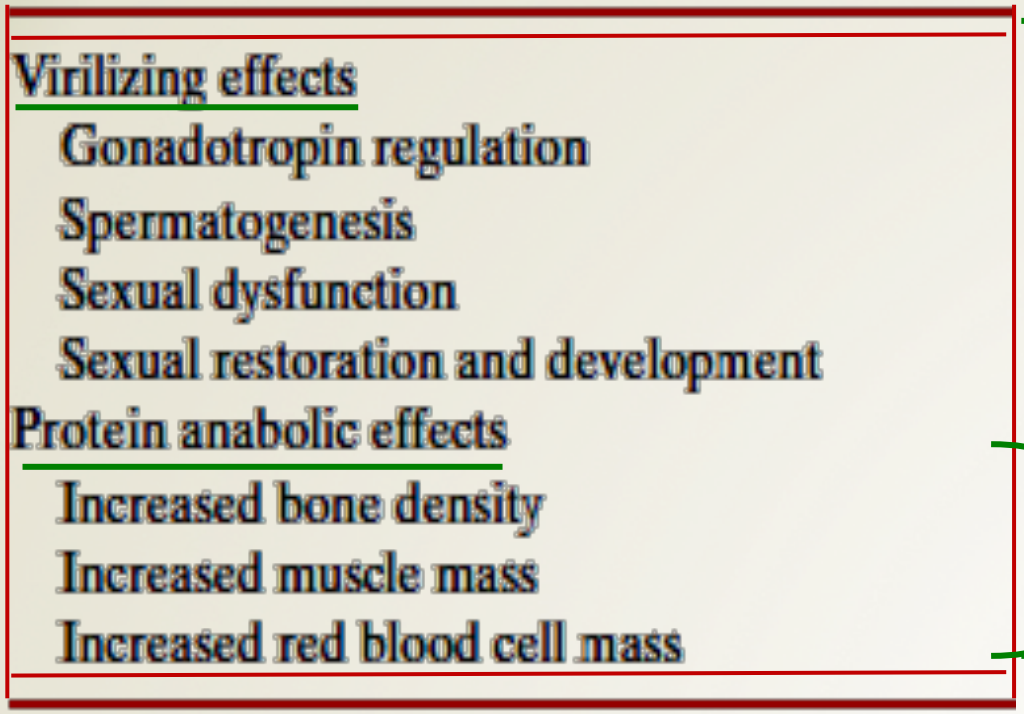
B. Bones and Brain
Testesterone is metabolized to estradiol by c-p450 aromatase.

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



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.

Contraindications

Testesterone

- 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.