DRUGS USED IN

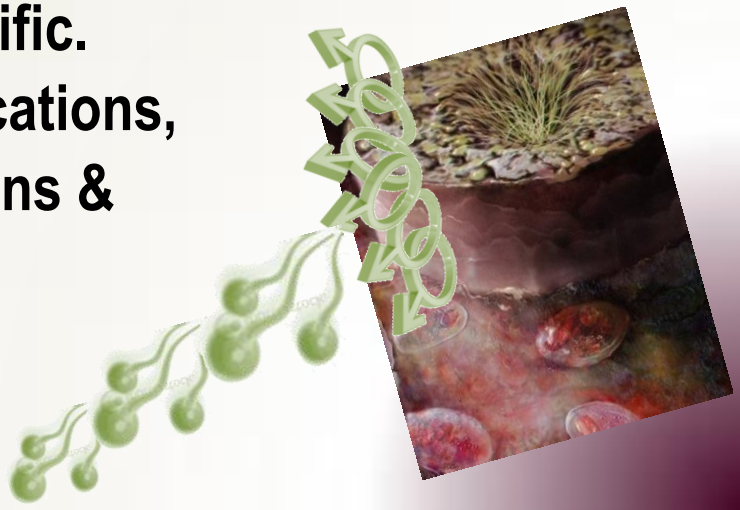
MALE INFERTILITY

DRUGS USED IN MALE INFERTILITY

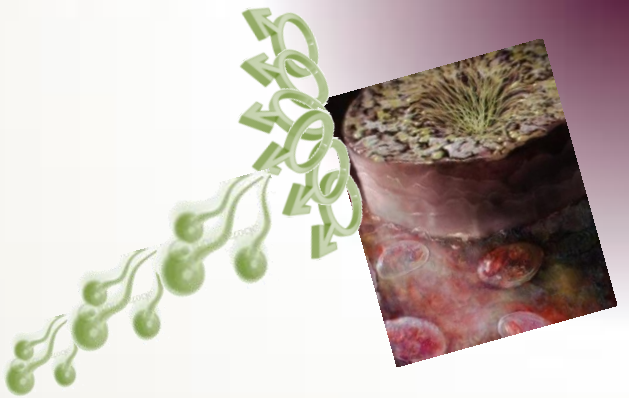
ILOs

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 emperical non-hormonal therapies



MALE INFERTILITY

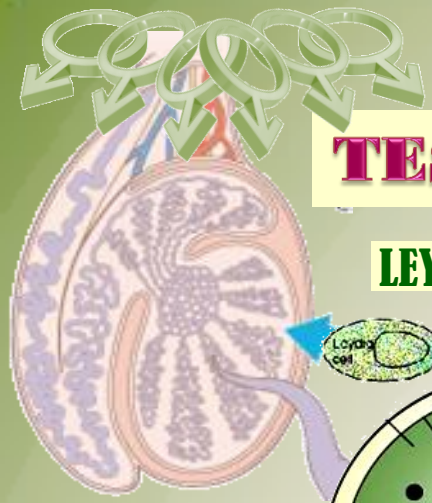


Definition

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

Prevalence

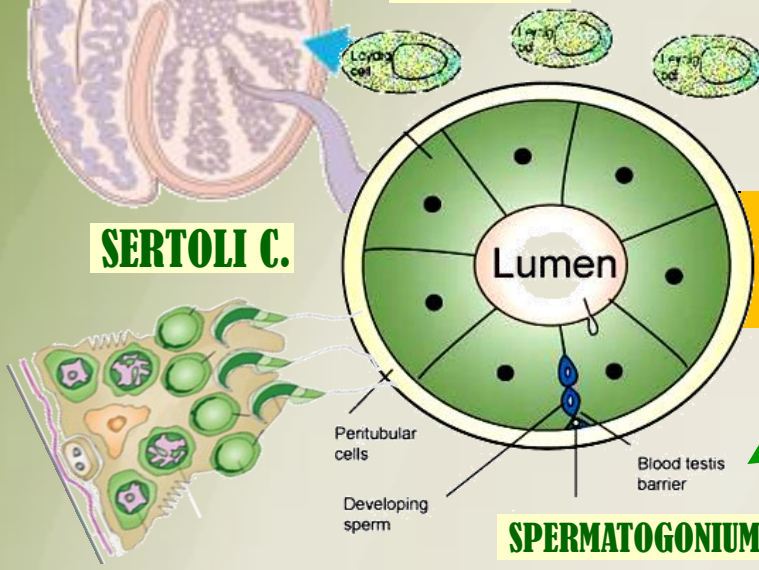
Approximately 15-20% of all cohabiting couples are infertile
In up to ± 50% of such cases, males are responsible



TESTIS → A Seminiferous Tubule
→ Site of SPERMATOGENESIS

LEYDIG C. → **TESTOSTERONE**

SERTOLI C.



Spermato cytogenesis

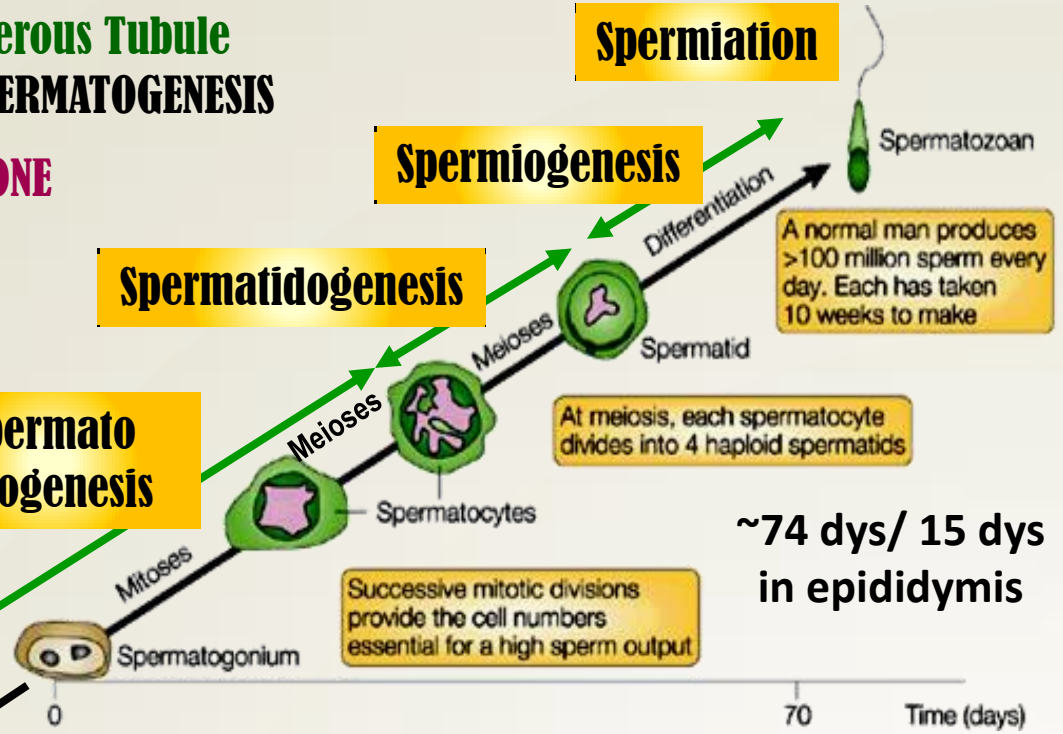
SPERMATOGONIUM

Mature Sperm / No motility / Sterile

Spermiation

Spermiogenesis

Spermatidogenesis



~74 dys/ 15 dys in epididymis

Nests → the **GERM CELLS**

- Communicate in a paracrine fashion
- Separate them from rest of body by the blood-testicular barrier
- Converts **Testosterone** to **Dihydrotestosterone [DHT]** & **Estradiol** to direct spermatogenesis
- Secret androgen-binding-proteins **[ABP]** → concentrate & ↑ testosterone in seminiferous tubules to stimulate spermiogenesis

Testosterone Secretion & Spermatogenesis Are Coupled

LEYDIG C. → **TESTOSTERONE** → **SERTOLI C.**

LH ↑ **PITUITARY** ↑ **FSH**

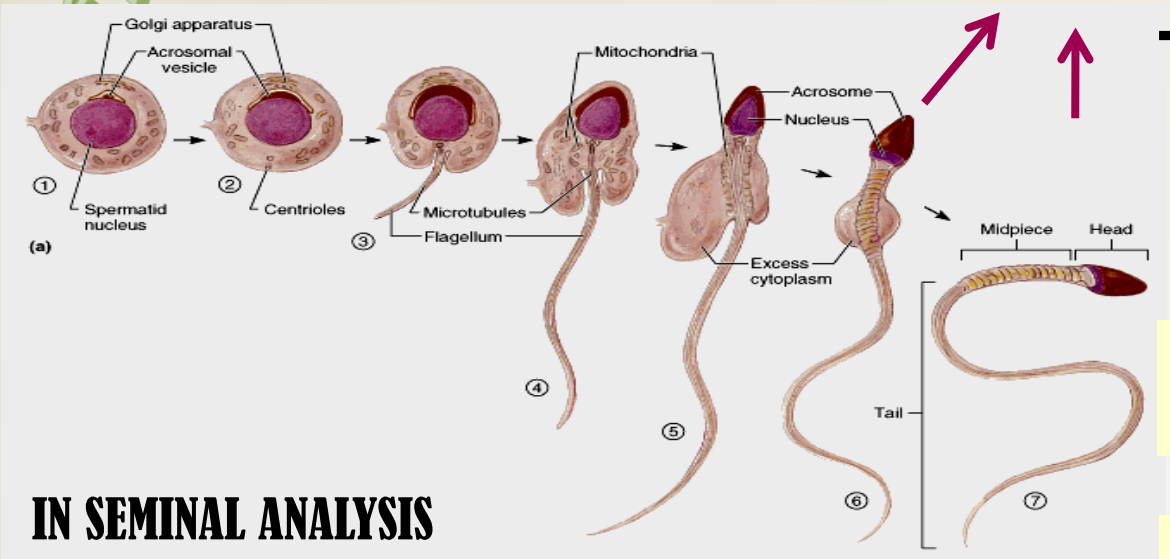
↑ **GnRH**

↑ **HYPOTHALAMUS**

Steps from Spermatid to Spermatozoan

Proceed ➔Seminiferous ducts➔Rete testis ➔ Efferent ductules➔Epididymis

DHT > Testosterone + Estradiol + other paracrine/autocrine



[Develop Motility & Fertilizing ability Protection+Storage] Till Ejaculation

Prostatic & seminal secretions add to sperm functions

IN SEMINAL ANALYSIS

Alteration in sperm quantity

Low (oligospermia) or non (azoospermia)

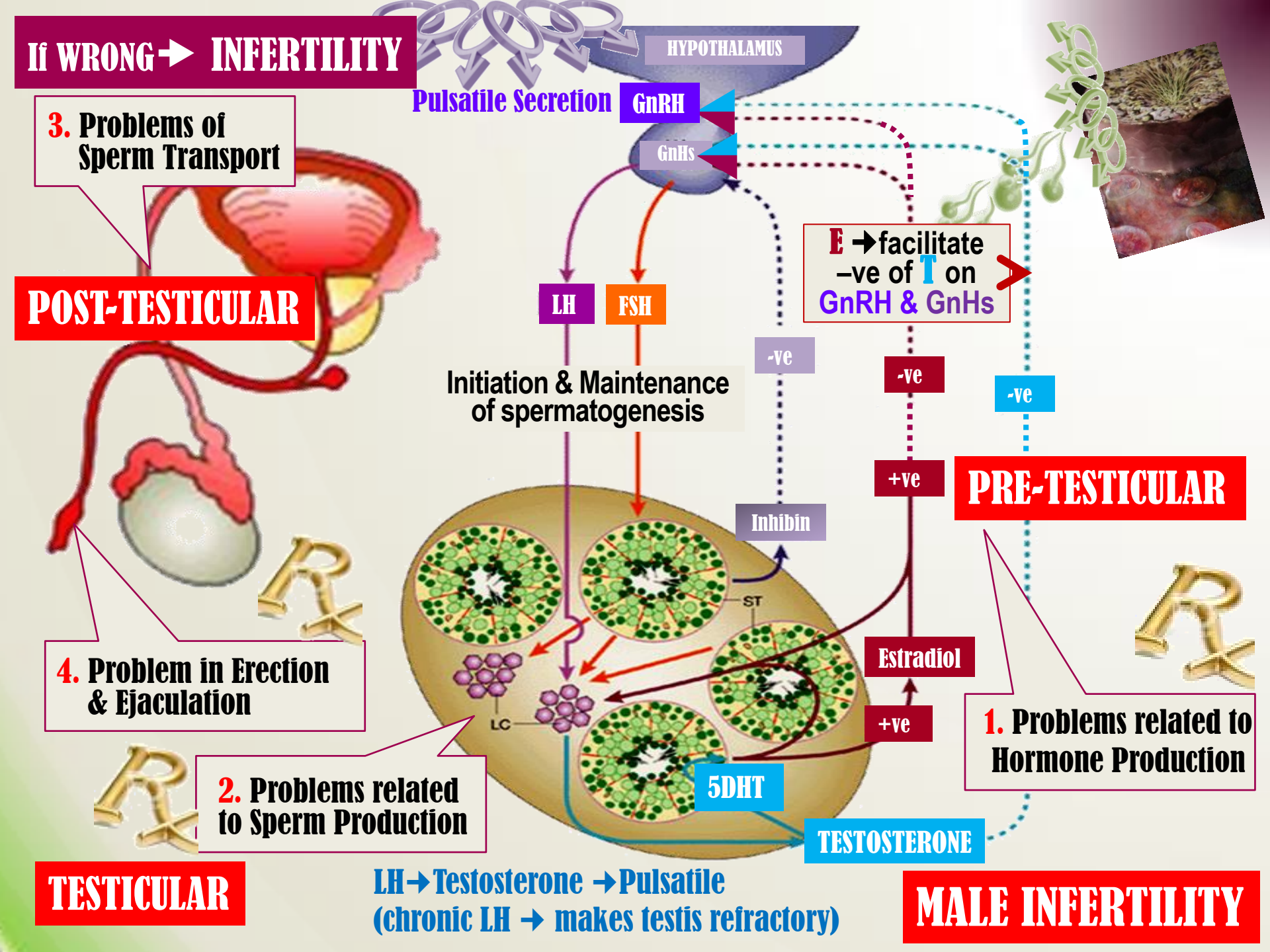
Alteration in sperm quality

Low motility (asthenospermia) or dead (necrospermia)

Alteration in both

If something went WRONG➔ INFERTILITY

If WRONG → 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*

IMPERICAL

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

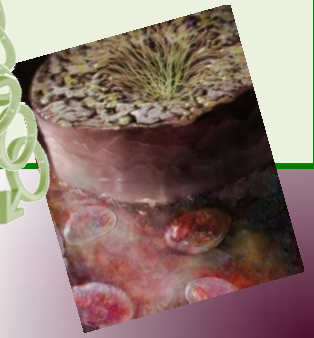
NON-HORMONAL THERAPY

IMPERICAL

Erectile Dysfunction → *PDE 5 Is, Alprostadil, Apomorphine…*
Premature Ejaculation → *SSRIs*
Retrograde Ejaculation → *αAD agonists*
Leukocytospermia → *Antibiotics*

SPECIFIC

- *Pentoxiphylline*
- *Kallikrins*
- *Antioxidants; Vit E, C/ N-A Cystiene*
- *Zinc Supplements*
- *Folic a.*
- *L-Carnitine*

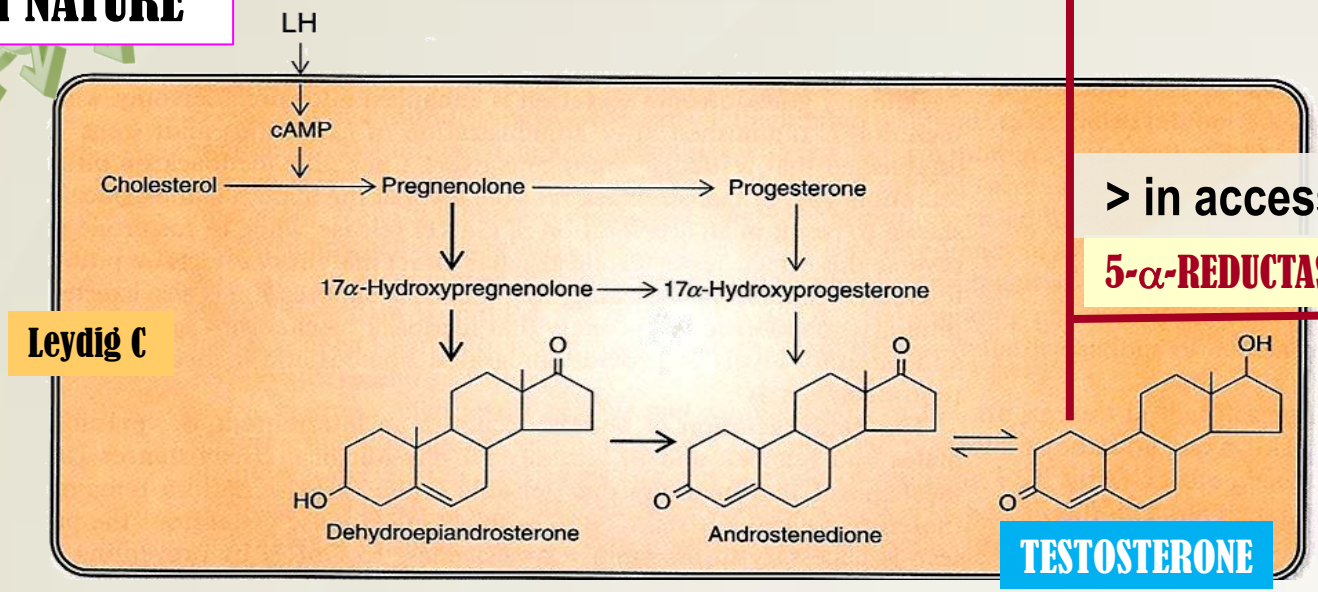


- **Hypergonadotrophic Hypogonadism →** Pry Hypogonadism (↓T &↑LH) *Assisted Reproduction*

HORMONAL THERAPY

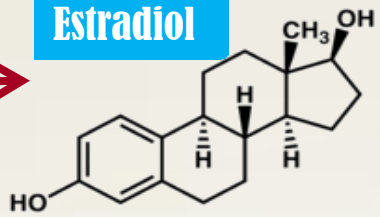
1. ANDROGENS

In NATURE



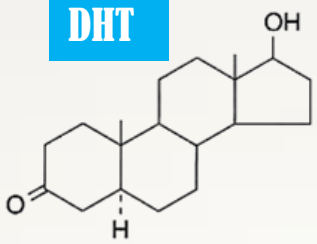
> in brain, bone, liver, adipose t.

AROMATASE → Estradiol



> in accessory sex organs

5-α-REDUCTASE → DHT



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

As Therapy

1. Testosterone

2. Synthetic Androgens;

Derived from Testosterone

Esters; proprionate, enanthate, cypionate

Or derivatives as Fluoxymesterone, Methyltestosterone, Danazol

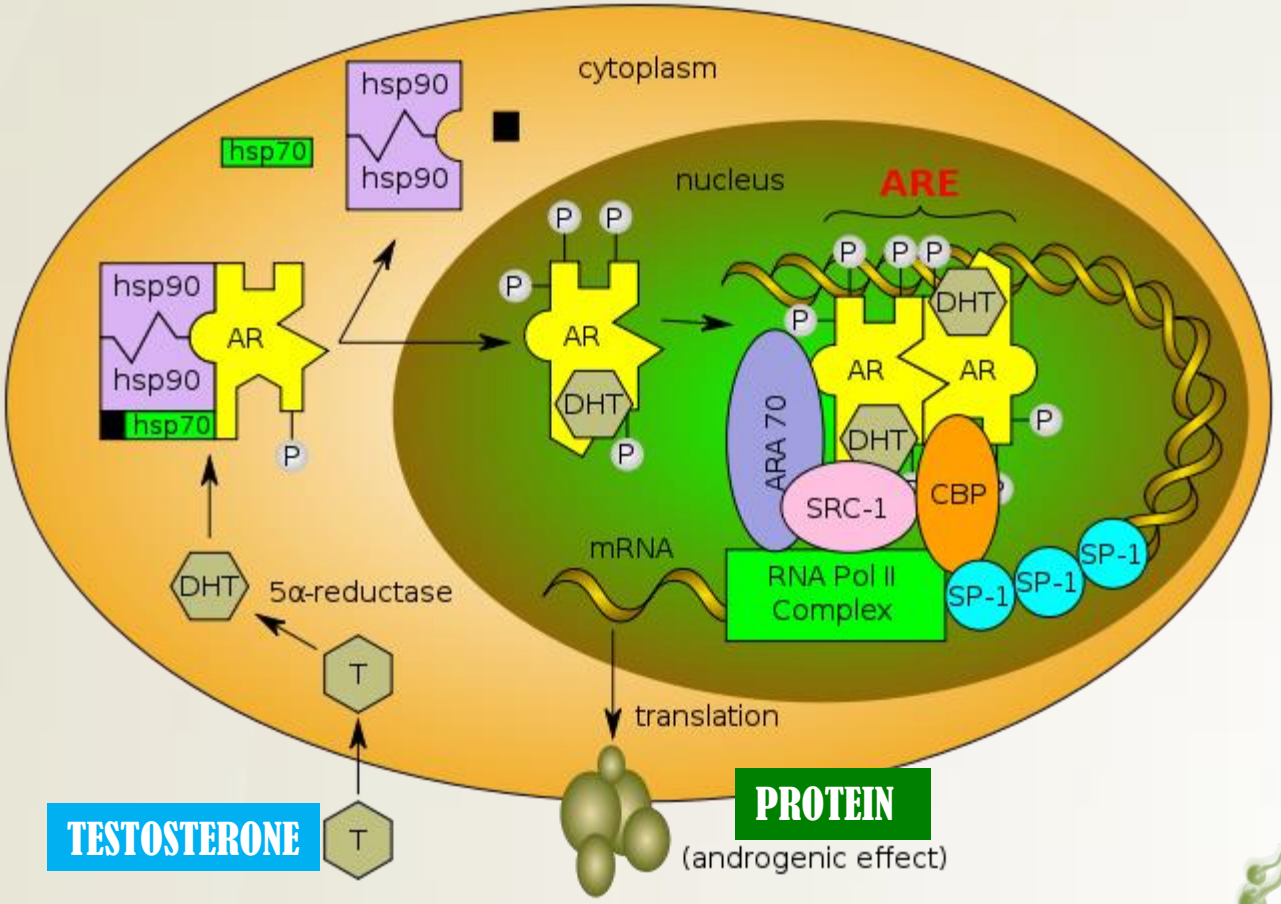
Derived from DHT; Mesterolone

What does testosterone do ?

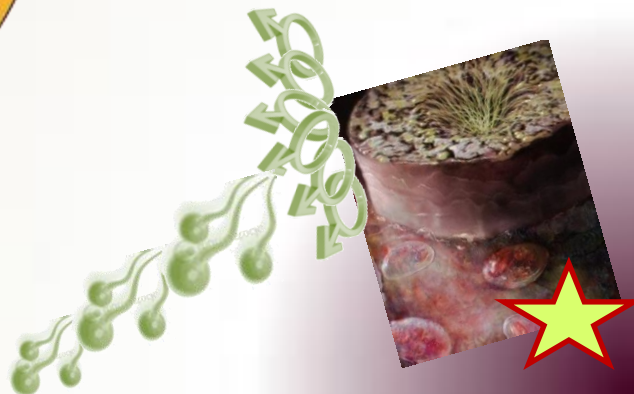
A. It or its DHT metabolite bind to Androgen Receptors [AR]

Like all other steroid hormones they act on;

1. Cytosolic ➔ GENOMIC Action ➔ mediates cell growth & differentation in AR responsive tissues; reproductive, those of 2ndry male sex characters, muscles …

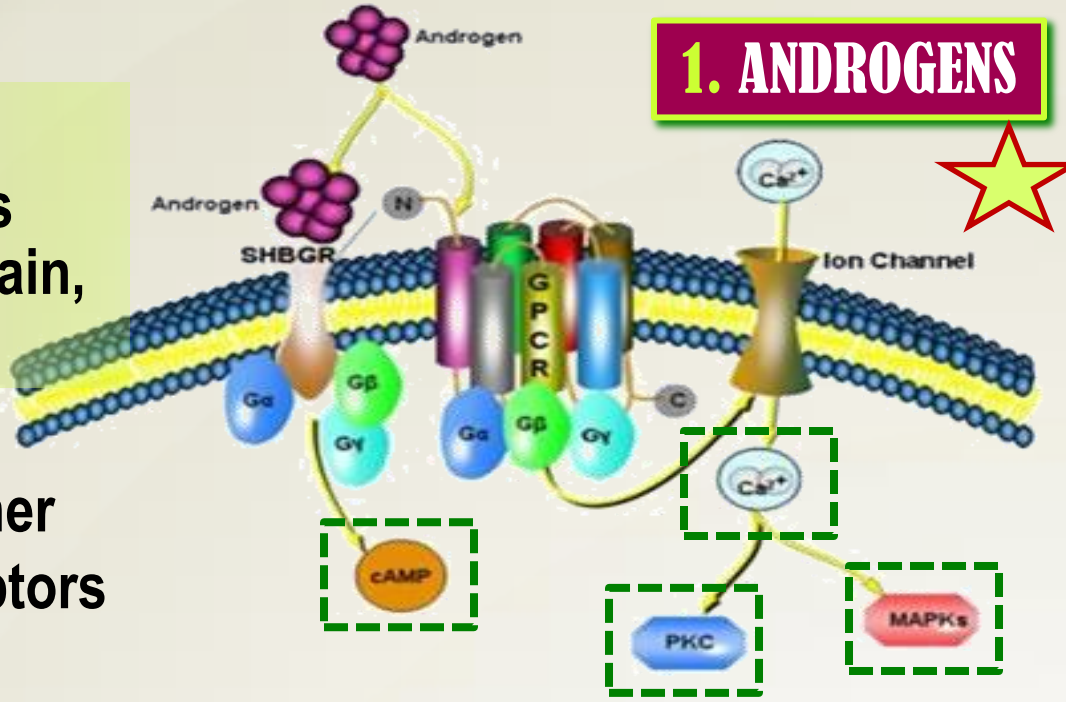


- Binding & Activation
- Nuclear translocation
- Dimerization on SRE
- Gene Transcription
- mRNA Translation
- New Protein Formation



1. ANDROGENS

2. Membranous ➔ NON-GENOMIC Action ➔ mediates rapid responses ➔ on some brain, CVS, T cells functions

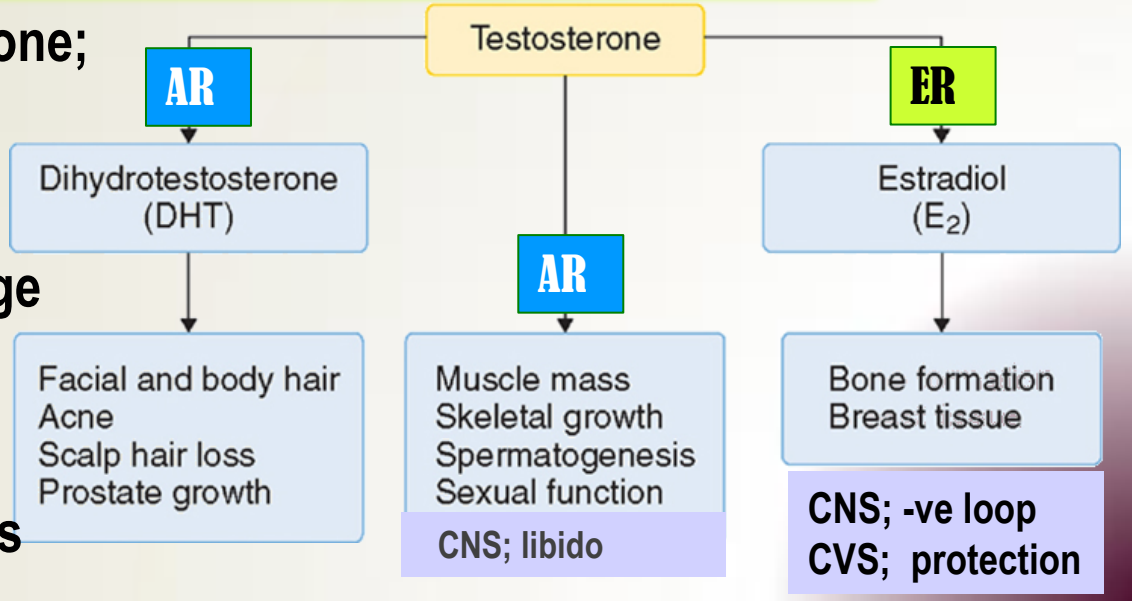


Like all other steroid receptors

B. It aromatize to estradiol and binds to Estrogen Receptors [ER]

Estradiol rather than testosterone;

1. Responsible for feedback inhibition on hypothalamus (specially –ve LH secretion)
2. Induce maturation of cartilage ➔ leading to closure of epiphyses & conclusion of growth.
3. Some CVS protective actions



1. ANDROGENS

ACTIONS

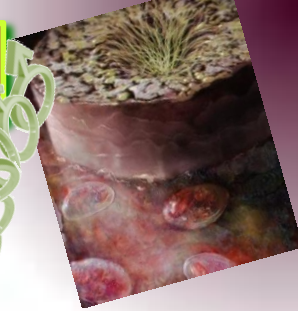
ACTIONS DIVIDED INTO

- 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

1. ANDROGENS



Kinetics

- Binds to SHBG
- t1/2 = 10 –20 min
- Inactivated in the liver.; 90% of metabolites ➔excreted in urine.
- Synthetic androgens ➔ less rapidly metabolized & some are excreted unchanged in urine

Administration

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

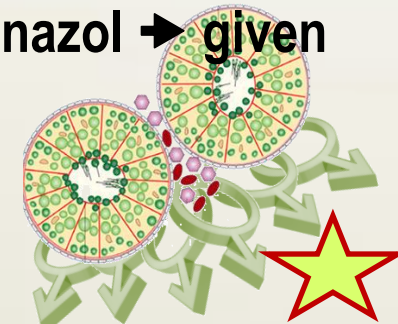
Skin patch (genital & no genital) & gels…. are also available

Synthetic Androgens

Derived from Testosterone

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

Derived from DHT; Mesterolone ➔ given **Orally;** daily



INDICATIONS

In adult Male Infertility

1. Low dose oral (methyltestosterone 10-50 mg/day)or(fluoxymesterone 5-20 mg/day) may improve epididymal function & ↑ sperm motility

2. High dose exogenous testosterone given then abruptly stopped will
1st → ↑ systemic T levels → -ve feedback → ↓ LH & ↓ endogenous testosterone production → ↓ spermatogenesis.
2nd → **TESTOSTERONE REBOUND** → ↑ spermatogenesis after stoppage .
The success rate is very low . Hazards are high → many men become azoospermic for prolonged periods after. Now this is best avoided

As Androgen Replacement Therapy

- In delayed puberty with hypogonadism
  → give androgen slow & spaced for fear of premature fusion of epiphyses → short stature

1. ANDROGENS

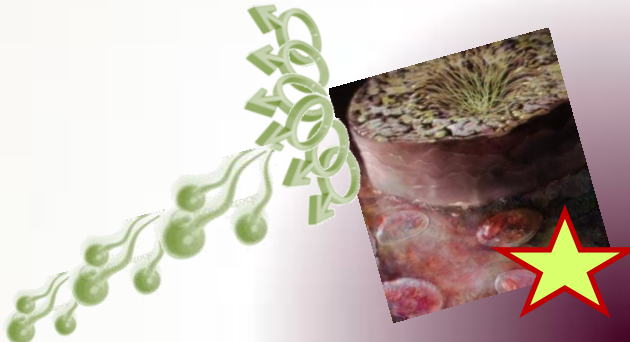
ADRs

Specific In Males

1. Prostatic hyperplasia → carcinoma specially in elder (give low dose)
2. 2ndry Gn H suppression ; azoospermia, impotence, gynecomastia (if taken > 6 wks).
3. Short stature due to premature closure of epiphysis (before 18 years)

General

1. Behavioral changes; physiologic dependence,↑ aggressiveness, psychotic symptoms
2. Alteration in serum lipid profile: ↓HDL & ↑LDL; ↑risk of ACS
3. Salt & water retention
4. Hepatic dysfunction;↑ AST levels,↑alkaline phosphatase, ↑ bilirubin & cholestatic jaundice.
   Most oral preparations are hepatotoxic → adenomas & carcinomas
5. Polycythemia



1. ANDROGENS

Contraindications

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

Interactions

- All forms + corticosteroids ➔ oedema
- All forms + warfarin ➔ ↓metabolism ➔ ↑ bleeding
- Synthetic Androgens + insulin or oral hypoglycemics ➔ hypoglycemia
- Testosterone + propranolol ➔ ↑ propranolol clearance ➔ ↓efficacy

Mesterolone ➔ oral synthetic androgen derived from DHT is more **safely** given if ↓ testosterone or in 2ndry hypogonadism. **Why???**

1. Not aromatised into estrogens/ no binding to estrogen receptors➔no –ve of GnHs ➔ encourages natural testosterone production+↓ SHBG from attaching to it ➔ spermatogenesis is enhanced
2. Unlike almost all other orals synthetic androgens it is not hepatotoxic; not -alkylated but methylated ➔ less hepatic complications

2. GnRH

LEUPROLIN **GOSERELIN**

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

ADRs: Headache, depression, generalized weakness, pain & gynecomastia osteoporosis, neurological symptoms.
Prostate cancer (on long term), yet can be prevented with the simultaneous use of antiandrogens for 2-4 weeks

3. GnHs

PREGNYL hCG **MENOTROPIN** hMG

Used in 2ndry hypogonadism (FSH or both FSH or LH absent) ➔↑ spermatogenesis
GnHs replacement must be combined; hCG (3 x 2000 U/w. IM.➔2 ms.) followed by hCG + hMG (3x 75 to 3 x 150 U /w. IM. ➔6 -12 ms). rhFSH alone ➔ little efficacy

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

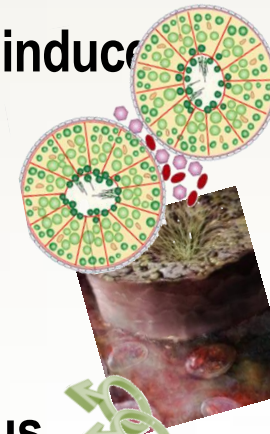
4. Antiestrogens

Because estrogens → –ve feedback on hypothalamus →↓ GnRH pulse frequency & pituitary responsiveness to GnRH , so antiestrogens → used, with the rationale that absence of such feedback inhibition→↑ Gn RH & improve its pituitary response…..

4.a. SERMs Tamoxifen, Clomiphene

Tamoxifen→↑ Gn RH, but has its own estrogen agonistic property → feminizing side effects.

Clomiphene→ has less estrogenic agonistic property. Yet both drugs can induce libido & bad temper in men



4.b. Aromatase Inhibitors Anastrozole

Blocks conversion of testosterone to estrogen within the hypothalamus

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

Non-HORMONAL THERAPY

Sometimes it is very promising, to improve sperm quality > quantity.

ANTIOXIDANTS Protect sperm from oxidative damage

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

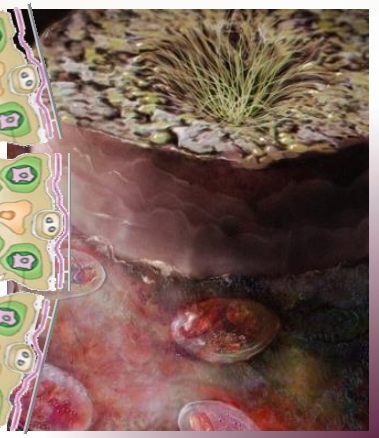
Plays an important role in testicular development, spermatogenesis & sperm motility.

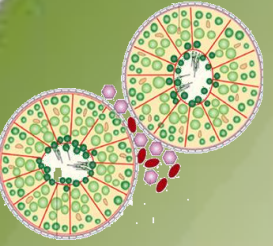
L-CARNITINE

Is highly concentrated in the epididymis & is important for sperm metabolism & maturation

DRUGS USED IN MALE INFERTILITY

GOOD LUCK





Cell type	Chromosome	Chromatide	Process
Spermatogonium	diploid/46	2N	**SPERMATOCYTOGENESIS** (mitosis)
P^{ry} Spermatocyte	diploid/46	4N	**SPERMATOCYTOGENESIS** (miosis1)
2^{ndry} Spermatocyte	haploid/23	2N	**SPERMATIDOGENESIS** (miosis2); Till formation of spermatid
Spermatid	haploid/23	1N	**SPERMIOGENESIS;** Till formation of mature spermatozoan
Spermatozoan	haploid/23	1N	**SPERMIATION;** deliveryr free in seminiferous tubules