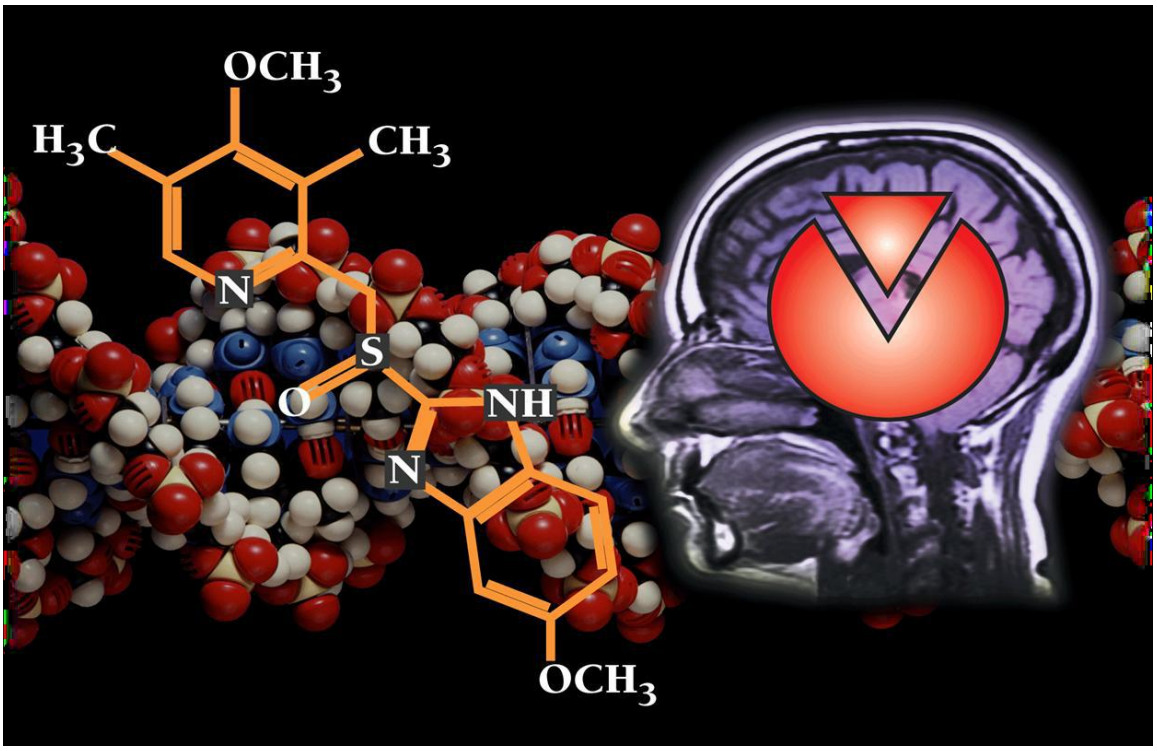
King Saud University
College Of Medicine
Pharmacology Team 430
Endocrine Block

06- Drugs used in male infertility



Note: Text in green is additional info. Text in red is important

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Introduction:

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 couples** are infertile.

Males are responsible In up to 50% of such cases (7.5-10%)

INFERTILITY vs IMPOTENCE – What is the difference?

Male infertility is due to low sperm production, misshapen or immobile sperm, or blockages that prevent the delivery of sperm.

Impotence (erectile dysfunction) occurs when a man can no longer get or keep an erection firm enough for sexual intercourse.

Male infertility means the semen analysis is abnormal:

• Count is low (oligospermia)

• Sperms are absent in the ejaculate (azoospermia)

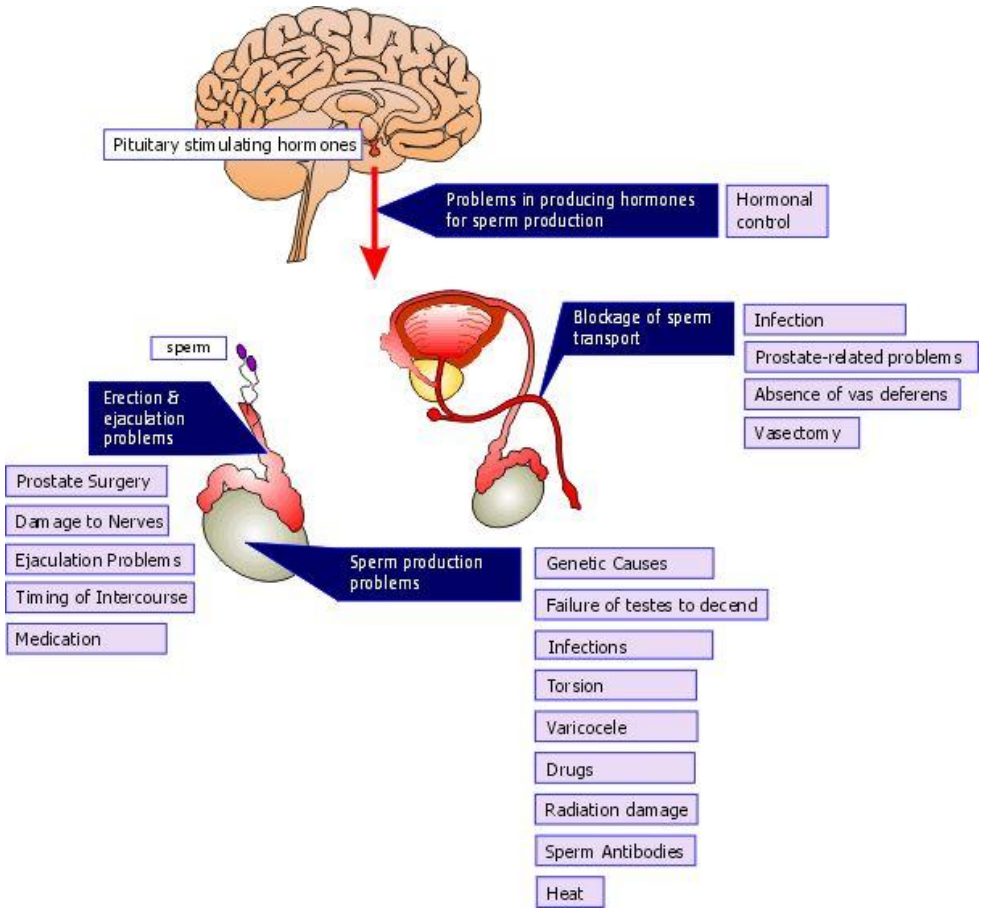
• Sperm motility is seriously affected (asthenospermia).

• Sperms are totally immobile or dead (necrospermia)

Causes of Male Infertility:

The known causes of male infertility can be subdivided into four areas:

- Hormonal problems (pre-testicular)
- Sperm production problems (Testicular: Most Common of known causes): disruption of the production of sperm within the testis or the production of antibodies against sperm, which block their function.
- Blockage of sperm transport (Post testicular) namely in the epididymis and vas deferens
- Erection and ejaculation problems.



Causes of infertility:

- Idiopathic
- Infection, e.g. Prostatitis, TB, etc.
- Sexually transmitted diseases
- Injury, e.g., Testicular trauma, Irradiation.
- Tobacco, ALCOHOL.
- Thermal Stress- Tight fitting clothes & prolonged period of sitting, sauna, strenuous riding (bicycle riding, horse riding).
- Spinal cord injury.
- Prolactin- secreting tumor of the pituitary gland.
- Hypogonadotrophic hypogonadism.
- Ejaculatory duct obstruction.
- Testicular cancer.
- Medications- chemotherapy, anabolic steroids & nitrofurantoin.

DRUG TREATMENT OF MALE INFERTILITY:

It takes 3 months to see any change any sperm analysis

Male infertility treatment is aimed, primarily, to the etiologic agent going along with partner treatment (if is required). Treatment can be broadly classified as:

A. HORMONAL THERAPY:

SPECIFIC

EMPERICAL

B. NON-HORMONAL THERAPY:

EMPERICAL

SPECIFIC

HORMONAL THERAPY

SPECIFIC:

• **Hyperprolactinaemia** ➔DA2- Agonists (the elevated serum prolactin level causes hypogonadism because it interferes with the normal pulsatile release of GnRH.). Dopamine inhibits Prolactin secreation.

• **Hypothyroidism**➔ Thyroxine Hyper and hypothyroidism can alter spermatogenesis. Changes affect both pituitary and testicular function with alterations in the secretion of releasing hormones and increased conversion of androgens to estrogens.

• **Congenital Adrenal Hyperplasia** ➔ Glucocorticoids (Genetic steroidogenic enzyme defects can cause failure of any one of the chemical conversions involved in the production of testosterone together with cortisol and aldosterone. Corticosteroids are also necessary for the metabolic background for spermatogenesis)

Empirical:

1. **Euogonadotrophic Hypogonadism** (functioning pituitary hormones but deficient testosterone secreation)➔ **(Testosterone only)**
2. **Antiestrogens : SERMs & Aromatase inhibitors**
3. **Idiopathic ➔Androgens, Antiestrogen, GnH (FSH)**
4. **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 –not imp"u will not be asked about them"-:

Erectile Dysfunction ➔*PDE 5 Is, Alprostadil, Apomorphine…*

Premature Ejaculation➔ *SSRIs*

Retrograde Ejaculation ➔ *aAD agonists*

Leukocytospermia ➔*Antibiotics*

HORMONAL THERAPY:

1. ANDROGENS

In Nature:

Principle male sex hormone produced in testis (> 95%), small amount in adrenals.

It follows a circadian pattern➔ ↑in early morning & ↓in evening

In therapy

A. Natural Testosterone

B. Synthetic Androgens:

Derived from Testosterone

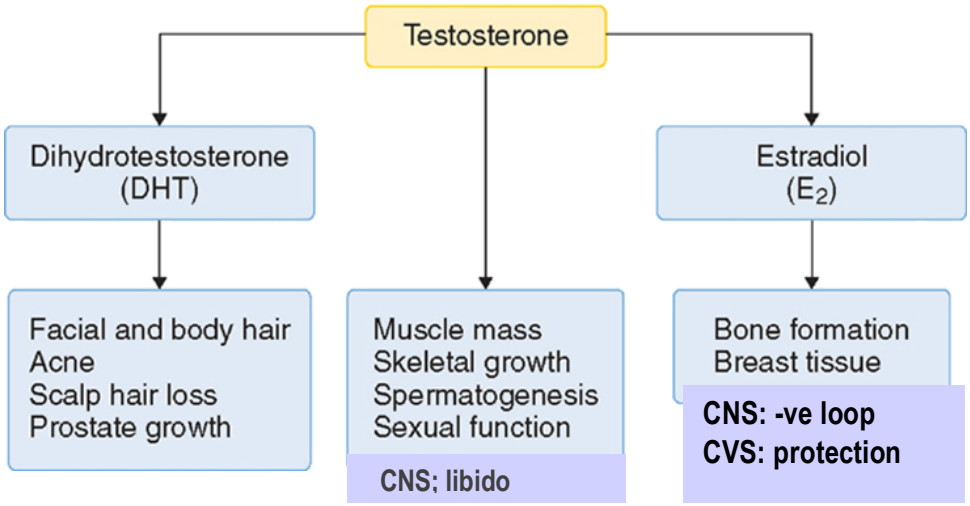
Esters; proprionate, enanthate, cypionate

Or derivatives as Fluoxymesterone, Methyltestosterone, Danazol

Derived from DHT; Mesterolone

Mechanism of action of testosterone:

Testosterone's Mechanism of action is based on A) binding of **Testosterone** and its metabolite **DHT** to their receptors (which has genomic and non-genemoic):



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

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

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

In **prostrate, seminal vesicles & skin** converted by **α-reductase** to DHT

B) **The aromatization of** testosterone to estrogen and then binding to the estrogen receptor: Estradiol rather than testosterone:

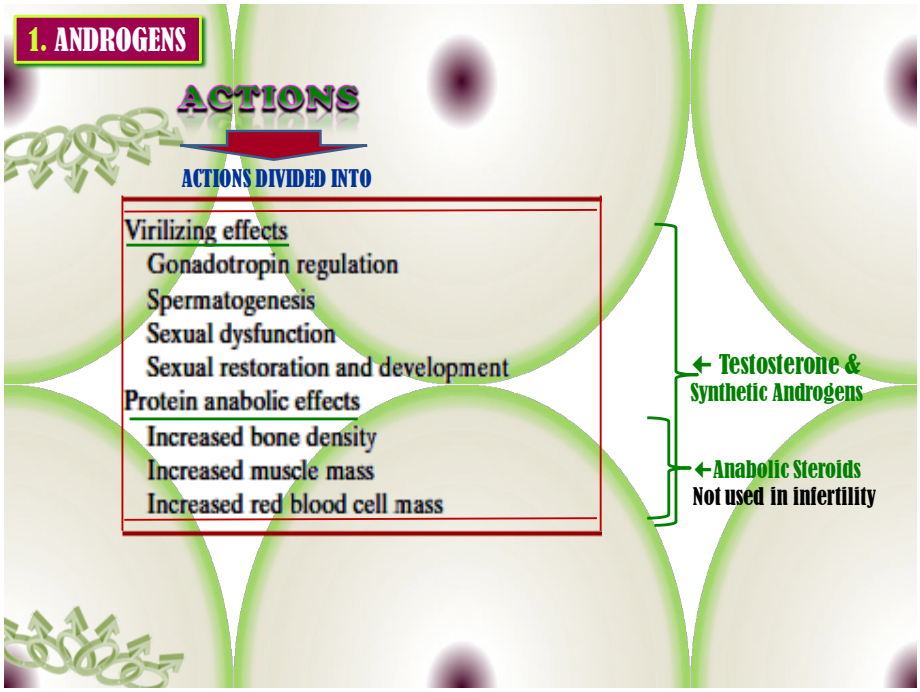
Testesterone is metabolized to estradiol **by Cytochrome -p450 aromatase**, mediates actions in bones and some brain areas.

1.Responsible for feedback inhibition on hypothalamus (especially –ve LH secretion)

2. Induce maturation of cartilage ➔ leading to closure of epiphyses & conclusion of growth.

3. Some CVS protective actions

Actions of Testosterone:



Kinetics of Testosterone:

- Binds to **Sex Hormone Binding Globulin [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 of Testosterone:

- Regular Testosterone is ineffective orally (inactivated by 1st pass met.)→ so it is given by I.M or S.C. Skin patch (genitial and non-genitial) & even gels are also available
- Esters: proprionate, enanthate, cypionate (SIP-e-o-nate) → in oil for IM; every 2-3 weeks
- Other derivatives as Fluoxymesterone [floo-ox-ee-MESS-teh-rone], Methyltestosterone, Danazol [DAH-nah-zole] → given Orally; daily
- Derived from DHT; **Mesterolone** → given Orally; daily (doesn't have 1 rst pass met.)

INDICATIONS:

A. In 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

B. As androgen replacement therapy:

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

Adverse effects of Androgens :

1. Specific In Females:

Masculinization with acne, growth of facial hair, deepening of the voice, and excessive muscle development. Menstrual irregularities may also occur. *Testosterone* should not be used by pregnant women because of possible virilization of the female fetus and undermusculinization of a male fetus.

2. Specific In Males:

1. Prostatic hyperplasia ➔ carcinoma specially in elder (give low dose)

2. 2ndry GnH(gonadotrophs) suppression; azoospermia (Sperms are absent in the ejaculate), impotence, gynecomastia (if taken > 6 wks).

3. Short stature due to premature closure of epiphysis (before 18 years)

3. General Effects:

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 → risk of clotting

Contraindications:

- Male patients with cancer of 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:

Mesterlone is an **oral synthetic androgen** derived **from DHT.**

It is more safely given if ↓ testosterone or in 2ndry hypogonadism. Why???

1. Not aromatised into estrogens/ no binding to estrogen receptors→no –ve on 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 :

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 :

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

A-SERMs:

Tamoxifen➔↑ GnRH, 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

B. Aromatase Inhibitors: *anastrozole* [an-AS-troe-zole]

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 is very promising, to improve sperm quality and 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 & are important for sperm metabolism & maturation

Summery

• ANDROGENS follow a circadian pattern➔ ↑in early morning & ↓in evening

• Androgens In prostate,seminal vesicles&skin converted by α-reductase to DHT and In Bones: premature closure of the epiphyses .

• ANDROGEN can be givin In delayed puberty with hypogonadism give androgen slow & spaced for fear of premature fusion of epiphyses

• Androgens can cause :

- Masculinization effects In Females , impotence,decreased spermatogenesis & gynecomastia in male

- Alteration in serum lipid profile: ¤HDL & £LDL

- Edema → contraindicated in Severe renal & cardiac disease

- Hepatic dysfunction.

- Behavioral changes → it's contraindicated in Psychiatric disorders

- Polycythemia ➔ it contraindicated in Hypercoagulable states and Polycythemia

- It's contraindicated in Male patients with cancer of breast or prostate

Androgens Interactions:

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

• Mesterolone is Synthetic Androgens used in 2ndry hypogonadism, derived from DHT given Orally (doesn't have 1 rst pass met.)

1. Not aromatised into estrogens (no feminization) + binds to estrogen receptors➔no –ve of GnHs ➔ spermatogenesis is enhanced

2. not hepatotoxic.

• GnHs and GRHs are Used in hypothalamic dysfunction(secondary hypogonadisim) ➔androgenization & spermatogenesis:

• Clomiphene Is Antiestrogens (SERMs) can induce libido & bad temper in men

• Anastrozole is Aromatase Inhibitors it Blocks conversion of testosterone to estrogen within the hypothalamus and Has good pregnancy rates

• NON-HORMONAL THERAPY are also used as treatment of infertility as :

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