PT 431 Team Pharmacology

Reproductive Block

Lecture 8

Drugs used in male infertility

Done by :

Walaa Al-shehri

Omar Al Omar

MALE INFERTILITY:

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%)

The germ cells (spermatocytes) Separate them from rest of body by the blood-testicular barrier

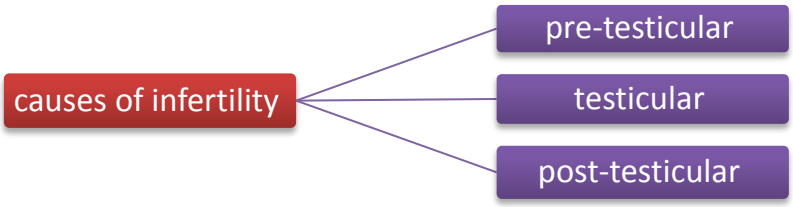
Converts Testosterone **to** Dihydrotestosterone [DHT] **&** Estradiol **to direct spermatogenesis**

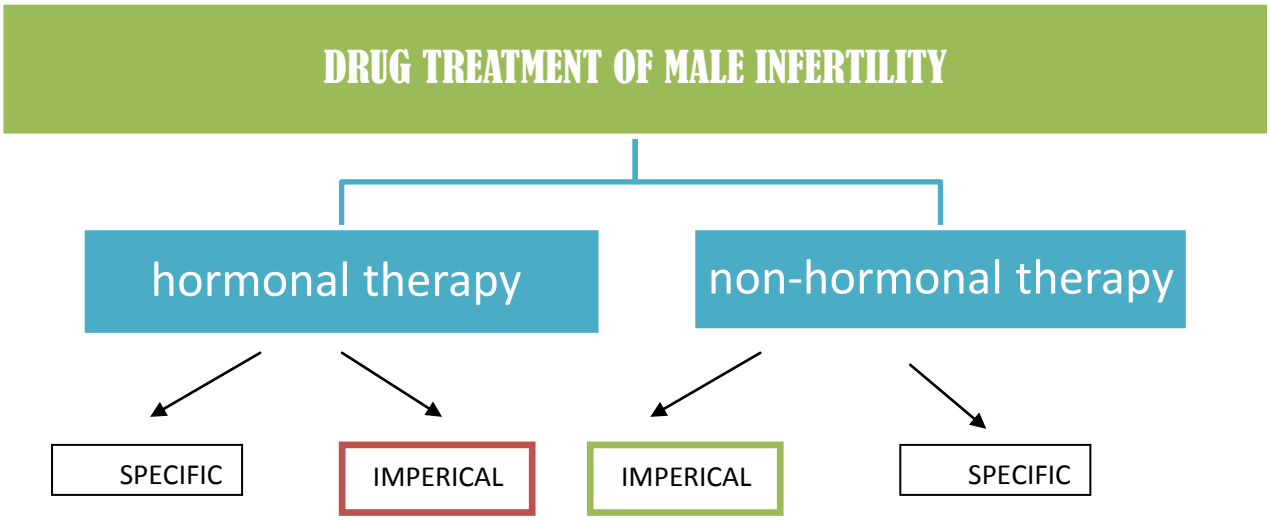
Secret androgen-binding-proteins [ABP] ➔ concentrate & ↑ testosterone in seminiferous tubules to stimulate spermiogenesis

~74 dys/ 15 dys in epididymis the become mature sperm so when I give the treatment I will take months to give the effect .

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





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

Pentoxiphylline

Kallikrins

Antioxidants; Vit E, C/ N-A Cystiene

Zinc Supplements

Folic a.

L-Carnitine

Improve quality not quantity

Hypergonadotrophic Hypogonadism ➔ **P^{ry} Hypogonadism (↓T &↑LH) *Assisted Reproduction*** difficult to treat problem in the testis

Action of testosterone:

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

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

1. ANDROGENS

Kinetics:

Short 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(for long half life): **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:

1-Low dose oral may improve epididymal function & ↑ sperm motility (quality)

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 (reactivate the hypothalamus to produce high amount of LH+FSH and finally increase testosterone)

As Androgen Replacement Therapy

In delayed puberty with hypogonadism give androgen slow & spaced for fear of premature fusion of epiphyses ➔ short stature (to avoid that give it gradually and small dose and with space)

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 (steroid)
4. Hepatic dysfunction; ↑ AST levels, ↑alkaline phosphatase, ↑ bilirubin & cholestatic jaundice. (like all steroid)

   Most oral preparations are hepatotoxic → adenomas & carcinomas
5. Polycythemia (increase RBCs COUNT)

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(best oral preparation):

➔ 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

GnRH(LEUPROLIN, GOSERELIN):

Used in : Given as Pulsatile GnRH therapy

ADRs: activate pituitary so, release other hormones cause Headache, depression, generalized weakness, pain & gynecomastia osteoporosis(estrogen) , neurological symptoms.

Prostate cancer(bcuz testosterone) (on long term), yet can be prevented with the simultaneous use of antiandrogens for 2-4 weeks

GnHs: PREGNYL hCG , MENOTROPIN hMG

LH from placenta (pregnyl)

FSH urine of menopause woman (menotropin)

Used in 2ndry hypogonadism given combine in sequential form

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

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

1-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

2-Aromatase Inhibitors (Anastrozole)

Blocks conversion of testosterone to estrogen within the hypothalamus

Best to improve sperm count & motility with good pregnancy rates

Non-HORMONAL THERAPY

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

ANTIOXIDANTS: especially if the problem with motility

KALLIKREIN: decrease viscosity of secretion in ejaculatory duct improve the motility

FOLIC ACID: Plays a role in RNA and DNA synthesis during spermatogenesis & has antioxidant properties (if there are sperms not fully develop)

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 (fuel for the sperm)

Summary

• 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

Questions

1- Which one of the following synthetic androgens is derived from DHT and is not hepatotoxic:

a-Danazole
b-fluoxymesterone
c-Mesterolone
d-Methyl testosterone

2- Why androgen must be administrated slowly and over a long interval for the treatment of delayed puberty with hypogonadism:

a-Delay development of polycythemia
b-Delay increasein alkaline phosphatase
c-prevent premature fusion of epiphysis

Answers : C,C