GONADAL HORMONES & INHIBITORS(PART-II)

Dr. Nada Mohammed Abd El-Latif

Lecturer of Clinical Pharmacology

Nada Mohammed Abd El-latif Hamada

MD,PhD

❑ **CONTACT:**

Email: dr_nadamohammed2015@yahoo.com

Tel: 01069430885

III. Androgens and anabolic steroids

➢ Preparations:

- Natural androgens: androsterone and testosterone
- Synthetic androgens: testosterone propionate.
- Anabolic steroids: nandrolone and stanazol.

➢ Mechanism of action

- Like the estrogens and progestins, androgens bind to a specific nuclear receptor in a target cell.
- Testosterone itself is the active ligand in muscle and liver, But in other tissues it must be metabolized to derivatives, such as DHT (dihydrotestosterone). For example, after diffusing into the cells of the prostate, seminal vesicles, epididymis, and skin, testosterone is converted by 5α-reductase to DHT, which binds to the receptor.

➢ Uses of androgens and anabolic steroids:

1) Males with primary hypogonadism or secondary hypogonadism (androgens)
2) Chronic wasting associated with human immunodeficiency virus or cancer. (anabolic steroids)
3) Illicit use by athletes: to increase muscle bulk and strength. (anabolic steroids)

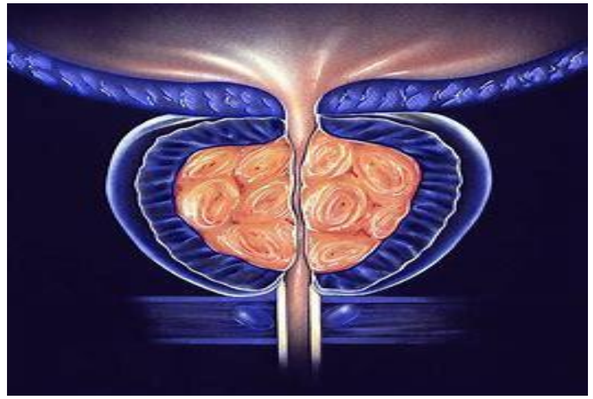
➢ Adverse effects

1) Reduction in spermatogenesis after stopping.
2) Virilizing effects in females.
3) Precocious puberty and premature closure of epiphysis in children.
4) Cholestatic jaundice.

➢ Contraindications

1) Prostatic tumors (benign and malignant).
2) Liver diseases
3) Children.

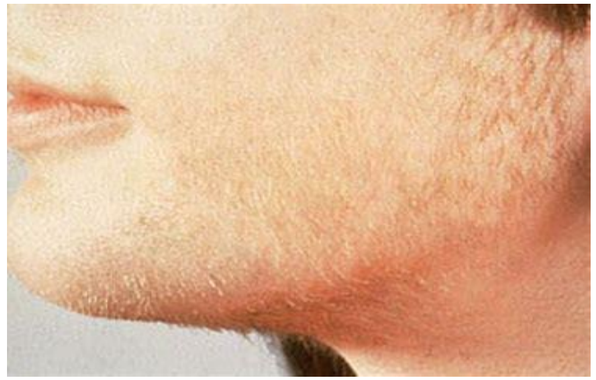
Antiandrogens



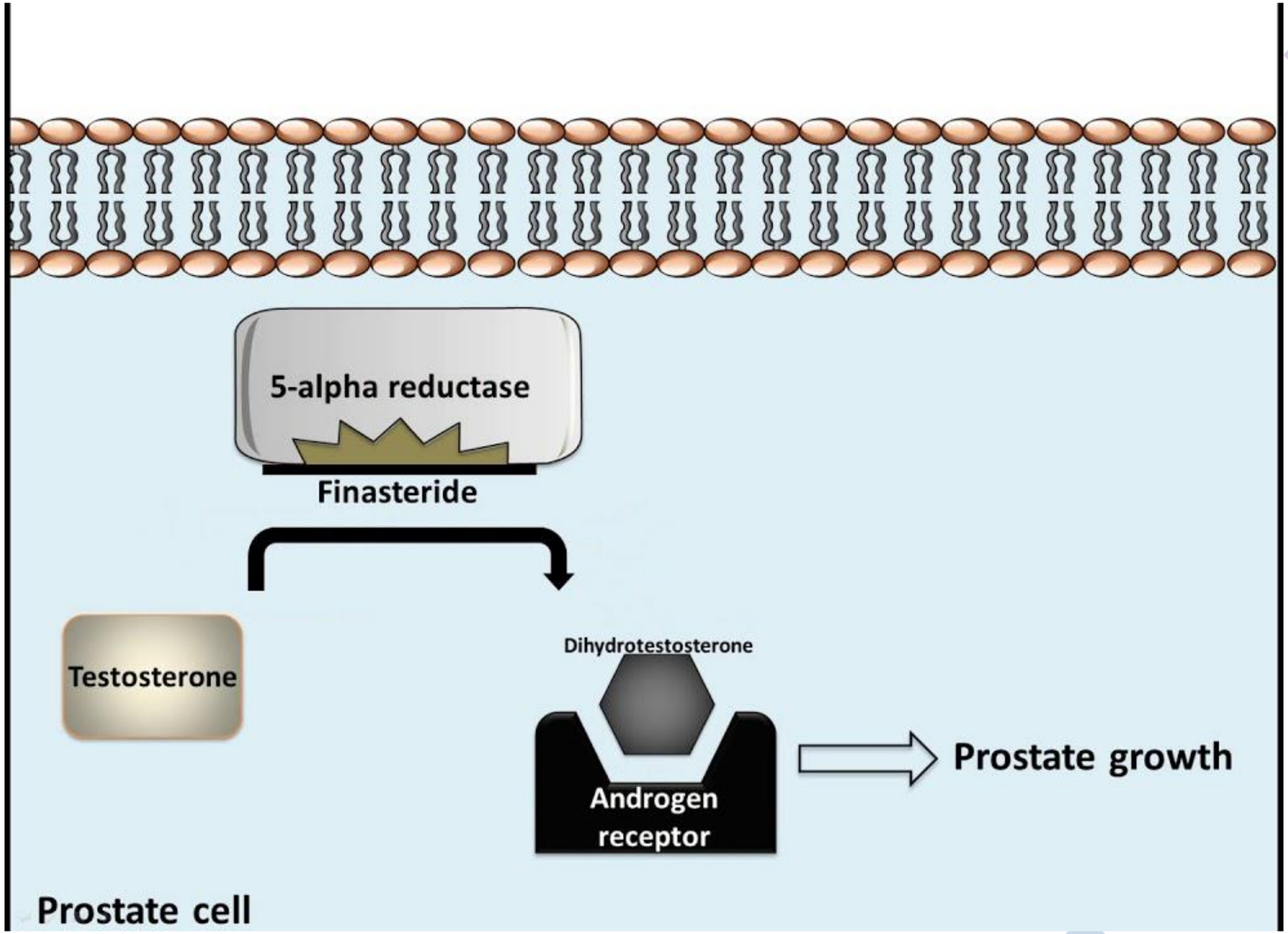
❑ 5 α-reductase inhibitors:

- Example: Finasteride
- It inhibits 5 α-reductase enzyme responsible for conversion of testosterone into the active form dihydrotestosterone (DHT).

➢ **Uses:**



1) Treatment of benign prostatic hyperplasia.
2) Treatment of male baldness.
3) Treatment of hirsutism in females.


5-alpha reductase
Finasteride
Testosterone
Dihydrotestosterone
Androgen receptor
Prostate growth
Prostate cell

❑ Testosterone receptor blockers:

❖ **Cyproterone acetate:**

- is a competitive blocker of testosterone receptors.
- Used in male hypersexuality, and hirsutism in females.

❖ **Flutamide:**

- is a competitive blocker of testosterone receptors.
- Used in cancer prostate.

❖ **Spironolactone**:

- is a competitive blocker of both aldosterone and testosterone receptors. Used in hirsutism in females.

Q.1 True or False:

A. Anabolic steroids are abused by body-builders at clinical doses.

B. Cyproterone acetate promotes spermatogenesis.

C. Nandrolone reduces muscle mass.

E. Dihydrotestosterone has marked antianabolic activity.

Q.2 A 60-year-old man is found to have a prostate lump and an elevated prostate-specific antigen (PSA) blood test. Magnetic resonance imaging suggests several enlarged lymph nodes in the lower abdomen, and an x-ray reveals 2 radiolucent lesions in the bony pelvis. This patient is likely to be treated with which of the following drugs?

(A) Anastrozole

(B) Desogestrel

(C) Flutamide

(D) Methyltestosterone

(E) Oxandrolone

Summary and wrap up

- **Estrogens** have many preparations natural like estradiol , semisynthetic like Ethinyl estradiol and synthetic like diethyl stilbosterol. They are responsible for many physiological effects in female and can be used for contraception and ovarian failure.
- **Anti-estrogens** like clomiphene used to stimulate ovulation. SERMs are oestrogen receptor modulators that act agonist at sites & antagonist at others. Tamoxifen used to treat breast cancer with positive estrogen receptor while raloxifene used to treat osteoporosis. Many complications associated with SERMs like increase endometrial cancer and thrombotic complications incidence. Aromatase inhibitors are a new class of oral estrogen synthesis inhibitors. They are used for treatment of postmenopausal women with estrogen-receptor positive breast cancer.

Summary and wrap up

- **Progesterone** and progestins have many preparations natural like **progesterone** and synthetic like **medroxy progesterone acetate**. Used in contraceptive pills , dysfunctional uterine bleeding. Its antagonist **mifepristone** used with misoprostol in medical abortion.
- **Androgens** have many preparations natural like **testosterone** and synthetic like **testosterone propionate**. Can be used Males with primary hypogonadism or secondary hypogonadism
- Anabolic steroids can be used in chronic wasting conditions and to increase muscle bulk by athletes.
- **Antiandrogens** may act by preventing synthesis like **finasteride** or by blocking androgen receptors like **flutamide**. Can be used in benign prostatic hyperplasia and in prostate cancer.

Drugs In Pregnancy

Drugs In Pregnancy

Taking medications during pregnancy is Necessary :

- for fetal health and development e.g., Vitamins and nutritional supplements
- To treat mother's health problem e.g., hypertension

✓ All drugs pass across the placenta to some extent, and therefore some exposure will occur

Drug passage of the placental barrier

Factors regulating passage of the drugs to the fetus:

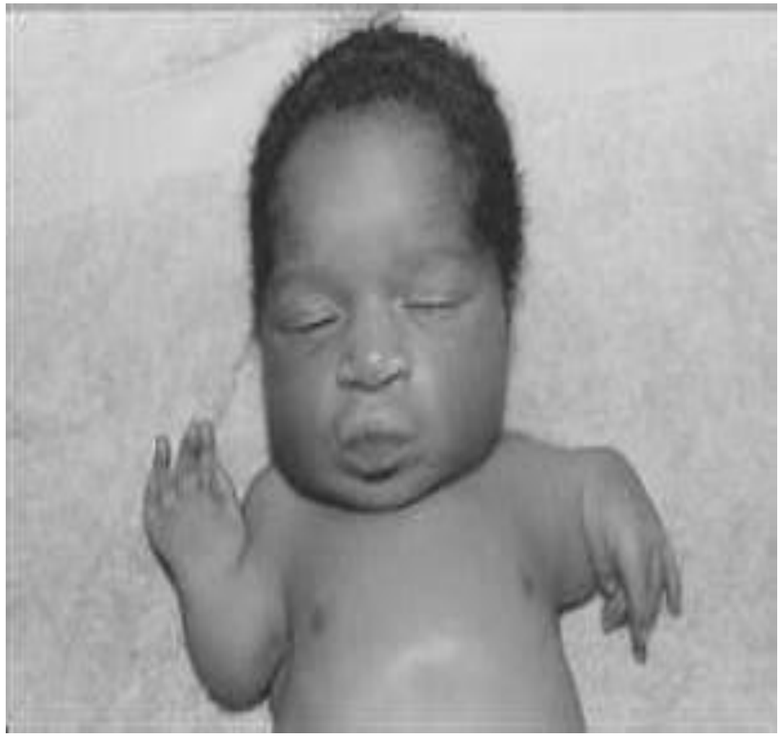
- **Drug size** : Most drugs with a MW
- **Lipid solubility**: the lipophilic drugs have more chance to cross placenta
- Binding to the maternal **plasma proteins**

Drugs In Pregnancy

There are two major considerations regarding drugs in pregnancy:

- The effects that the drugs have on the pregnancy.
- The effects that the pregnancy has on the drugs.

Examples of drugs with teratogenic effect



Thalidomide-induced Phocomelia

Hare lip ---phenytoin

Antiseizure drugs, valproic acid

How does drug affect pregnancy?

Teratogenicity: Defects that could happen to a developing fetus after exposure to a teratogen, which is most commonly a drug.

Types :

- Physical malformations e.g., Cleft lip
- Functional defects e.g., impaired intellectual development

Mechanism of teratogenicity

- **Before implantation:** (0-14 day):
  - The effect is all-or-none

- **Early pregnancy:** (3-10 weeks):
  - It is the most dangerous period because it is period of organogenesis.

- **Late pregnancy:**
  - Gross anatomical abnormalities are less liable to occur.
  - Functional defects rather than anatomical abnormalities.

FDA(Food &drug administration)- Pregnancy categories of drugs

▪ The FDA(American Committe) has established five drug categories (A,B, C,D & X) to indicate the potential of causing birth defects.

Pregnancy category	Definition
A	▪ Drug proved to be safe in animal and human ▪ e.g. Folic acid.
B	▪ Animal studies have shown a fetal risk, but adequate studies in human have not shown a risk to the fetus. ▪ e. g. paracetamol and penicillin

Pregnancy category	Definition
C	▪ Animal studies have shown a risk to the fetus but there are no adequate studies in humans ▪ e.g. Antihistamines
D	▪ There is evidence of fetal risk, but benefits are thought to outweigh the risks. ▪ e.g. lithium (anti-mania).
X	▪ Studies in animals or humans demonstrate fetal abnormalities. ▪ contra-indicated (should not be used) in pregnancy. ▪ e.g. thalidomide.

How does pregnancy affect drugs?

➢ Absorption

Drug absorption may decrease in a pregnant woman due to:

- Decreased gastric acidity
- Reduces gastric and small intestine motility.

➢ Distribution

- 50% Increase in plasma volume and body water:

Water soluble drugs are distributed and “diluted” more than in the non-pregnant state → adjustment of drug dose may be needed

- The capacity of the protein to bind drugs in the maternal system decreases.

How does pregnancy affect drugs?

➢ Metabolism

• Some microsomal enzymes(Cytochrome P450) activity increased→ increase metabolism of certain drugs

• Other enzymes of Cytochrome P450 activity may decreased → decrease metabolism of certain drugs

➢ Excretion

• The renal blood flow and GFR increase up to 50% →The kidneys may excrete drugs more rapidly

General advices to decrease the risk of teratogenicity

- Avoid all drugs if possible, including social drugs (e.g., smoking, alcohol, caffeine)
- Avoid drugs in the first trimester
- Choose drugs of proven safety or least toxicity
- Use short courses and the smallest doses.

❖ The risk/benefit ratio must be considered when drugs are used in pregnancy

Q.3 Thalidomide-induced phocomelia that belongs to Pregnancy

Category :

A. A

B. D

C. X

D. C

E. B

Q.4 The most dangerous period of pregnancy for drug adverse effect:

A. 0-14 day

B. 11-20 weeks

C. 3-10 weeks

D. 21-30 weeks

E. 31-40 weeks

References

- Lippincott's illustrated review: Pharmacology, 7th edition 2020

- USMLE Step 1 Lecture Notes 2018-Pharmacology (Dec 5,2017)_(1506221173)_ (Kaplan Publishing)

THANK YOU