



# **Gonadal Hormones & Inhibitors**

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# **Estrogens**

## **Estradiol**

- It is the most potent estrogen produced and secreted by the ovary.

## **Ethinyl Estradiol**

- Synthetic estrogens, such as undergo less first-pass metabolism than naturally-occurring steroids and, thus, are effective when administered orally at lower doses.

## **Tamoxifen and Raloxifene**

- Selective estrogen receptor modulators, Nonsteroidal compounds bind to estrogen receptors and give either estrogenic or antiestrogenic effects on target tissues.

# Mechanism of Action of sex Hormone

- Sex hormone-bind to globulin or albumin in the plasma, it dissociate from their binding sites & diffuse across the cell membrane and bind to specific nuclearreceptor proteins.
- The activated steroid-receptor complex interacts with nuclear chromatin to initiate hormone-specific RNA synthesis.
- This results in the synthesis of specific proteins that mediate a number of physiologic functions.
- Estrogen also increased formation and release of nitric oxide and prostacyclin in endothelial cells, this mediated dilation of coronary arteries .

## **Estrogens Used in:**

1. Contraception
2. Postmenopausal hormone therapy
3. Primary hypogonadism
4. Osteoporosis

# Postmenopausal Hormone Therapy

- Estrogen therapy is used in menopausal women who have (hot flashes, postmenopausal atrophy, and to reduce the risk of osteoporosis).
  - For women who not have hysterectomy, the combination of progestin with the estrogen therapy recommended, (to decrease the risk of endometrial carcinoma associated with estrogen alone).
  - For women with hysterectomy, estrogen therapy alone recommended (because progestins alters the HDL/LDL ratio).

## **Primary Hypogonadism**

- Estrogen usually in combination with progestins, is stimulate development of secondary sex characteristics in young women (11-13) years of age with hypogonadism.



# **Pharmacokinetics of Natural Estrogens**

1. Taken orally
2. Readily absorbed through the GIT, skin and mucous membranes.
3. Quickly distributed when administered IM.
4. Estradiol is rapidly metabolized by the microsomal enzymes of the liver.

# Pharmacokinetics of Synthetic Estrogen Analogs

## Ethinyl Estradiol

## Mestranol

- Well absorbed after oral administration or through the skin or mucous membranes.
- Metabolized more slowly than the natural estrogens.
- They have a prolonged action
- Higher potency than natural estrogens.
- Mestranol is quickly oxidized to ethinyl estradiol



## **Adverse Effects**

- Nausea and vomiting are (most common)
- Postmenopausal uterine bleeding  
,thromboembolic problems, myocardial infarction &endometrial cancer.
- Diethylstilbestrol cause cervical or vaginal adenocarcinoma (rare) observed among the daughters of women who took the drug during early pregnancy.

## OSTEOPOROSIS

- Estrogen decreases the resorption of bone but has no effect on bone formation.
- Estrogen decreases the frequency of hip fracture. [Note: Dietary calcium (1200 mg daily) and weight-bearing exercise also slow loss of bone.]
- Treatment with estrogens must begin within two or three years of menopause and earlier if possible.



## VASOMOTOR

- Estrogen treatment reestablishes feedback on hypothalamic control of norepinephrine secretion, leading to decreased frequency of "hot flashes."

## UROGENITAL TRACT

- Estrogen treatment reverses postmenopausal atrophy of the vulva, vagina, urethra, and trigone of the bladder.

Benefits associated with postmenopausal estrogen replacement.

# Selective Estrogen Receptor Modulators

**Tamoxifene**

**Raloxifene**

**Clomiphene**

- Compounds that interact at estrogen receptors display selective agonism or antagonism according to the tissue type.
- Tamoxifene is an estrogen antagonist in breast cancer tissue but can cause endometrial hyperplasia by acting as a partial agonist in the uterus.
- Used in the palliative treatment of advanced breast cancer in postmenopausal women.

# **Adverse Effects of Tamoxifen**

1. Hot flashes
2. Nausea and vomiting.
3. Menstrual irregularities and vaginal bleeding (due to its estrogenic activity in the endometrium)
4. Hyperplasia and malignancies (with long term used)

# Clomiphene

- Acting as a partial estrogen agonist and interfering with the negative feedback of estrogens on the hypothalamus and pituitary
- Clomiphene increases the secretion of GnRH and gonadotropins, leading to a stimulation of ovulation.
- used in infertility with anovulatory cycles.

# Progesterone

- Produced in response to luteinizing hormone (LH) by:
  - Females (secreted by the corpus luteum primarily during the second half of the menstrual cycle, and by the placenta)
  - Males (secreted by the testes).
- It is also synthesized by the adrenal cortex in both sexes.
- In females, progesterone promotes the development of a secretory endometrium that can accommodate implantation of a newly forming embryo.
- The high levels of progesterone that are released during the second half of the menstrual cycle (the luteal phase) inhibit the production of gonadotropin and further ovulation.



- If conception takes place, progesterone continues to be secreted, maintaining the endometrium in a favorable state for the continuation of the pregnancy and reducing uterine contractions.
- If conception does not take place, the release of progesterone from the corpus luteum ceases abruptly. This decline stimulates the onset of menstruation.

## **Mechanism of Action of Progestins**

1. Increase in hepatic glycogen probably through an insulin-mediated mechanism
2. Compete with aldosterone at the mineralocorticoid receptor (Decrease in  $\text{Na}^+$  reabsorption in the kidney)
3. Increase in body temperature
4. Decrease in some plasma amino acids
5. Increase in excretion of urinary nitrogen.

# **The clinical Uses of Progestins**

1. Hormonal deficiency
2. Contraception
3. Dysfunctional uterine bleeding.
4. Dysmenorrhea.
5. Suppression of postpartum lactation
6. Endometriosis.
7. Endometrial carcinomas.

# **Synthetic Progestins**

**Medroxyprogesterone Acetate**

**Hydroxyprogesterone Acetate**

**Norethindrone**

**Norgestrel**

- Synthetic progestins used in contraception are more stable to first-pass metabolism (lower doses when administered orally).
- Norethindrone and norgestrel are sometimes called the nortestosterone progestins (because of their structural similarity to the androgen & have some androgenic activity).

## Pharmacokinetics of Progestins

- Short half-life
- Completely metabolized by the liver.
- The hydroxyprogesterone & medroxyprogesterone derivatives are injected intramuscularly and have a duration of action of 1-2 weeks and 1-3 months, respectively. The other progestins last from one to three days.

# **Adverse Effects of Progestins**

1. Edema
2. Depression
3. Increase the ratio of LDL to HDL cholesterol
4. Thrombophlebitis
5. Pulmonary embolism
6. Acne, hirsutism
7. weight gain



# **Anti-progesterons & Progesteron Recerptor Modulators: Uses Of Anti-progestins and Progesterone-receptor Modulators:**

- Termination of pregnancy (Mifepristone).
- Preventing conception
- Induce labor
- Uterine leiomyomas and endometriosis.

# Mifepristone

- Progestin antagonist with partial agonist activity
- Potent antiglucocorticoid.
- Administration of this drug to females early in pregnancy results, in most cases in abortion of the fetus due to the interference with progesterone and the decline in human chorionic gonadotropin.
- Adverse effects are uterine bleeding & the possibility of an incomplete abortion.

# Androgens

- Steroids that have anabolic and/or masculinizing effects in both males and females.
- The most important androgen in humans, is testosterone, it is synthesized by the testes, the secretion is controlled by GnRH from the hypothalamus, which stimulates anterior pituitary to secrete FSH and LH
- It is also synthesized (smaller amount) in the ovary of the female and by the adrenal gland.

# Androgens

- Danazol
- Fluoxymesterone
- Nandrolone
- Stanozolol
- Testosterone cypionate

## **The androgens are Required for**

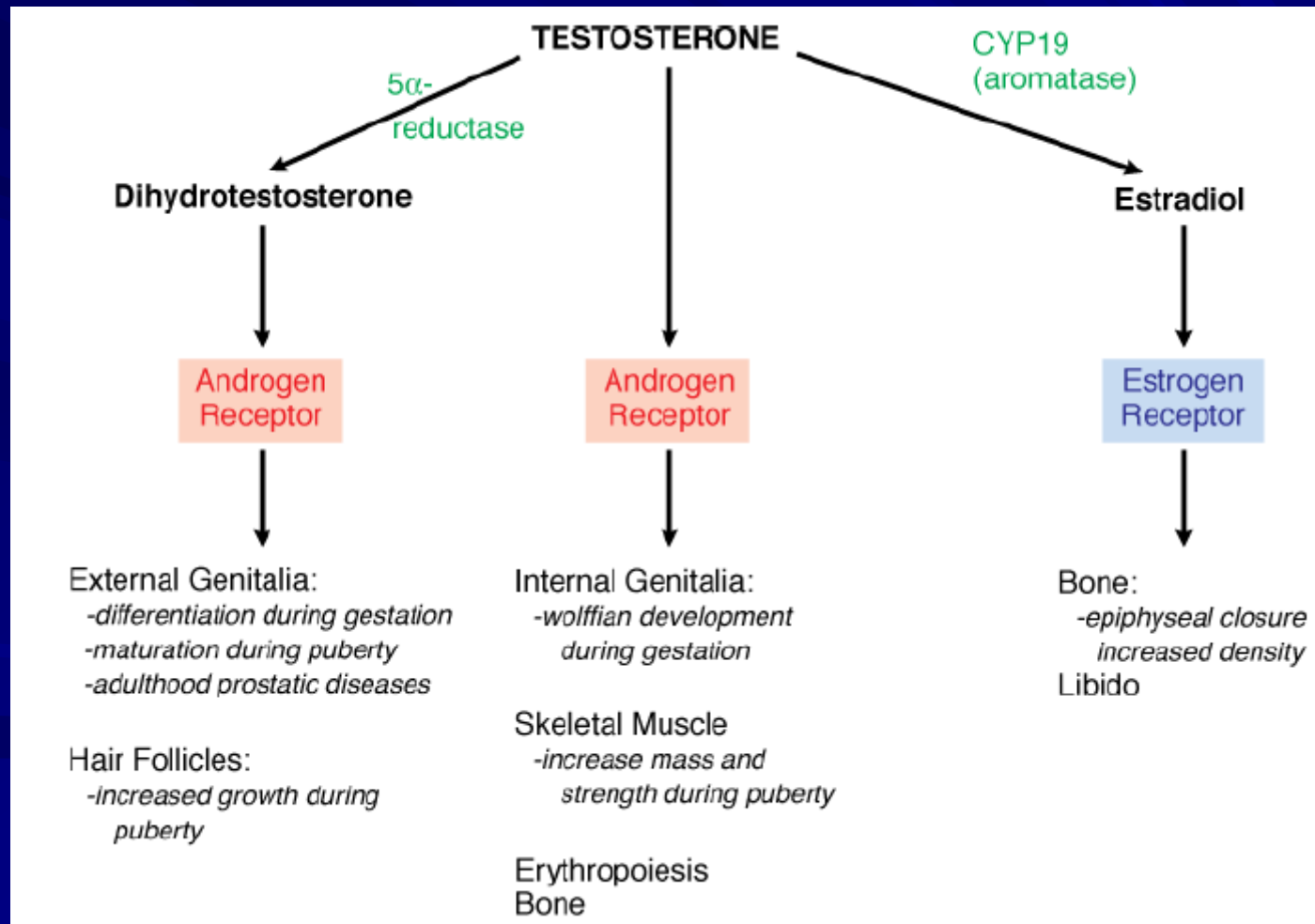
1. Normal maturation in the male
2. Sperm production
3. Increased synthesis of muscle proteins and hemoglobin
4. Decreased bone resorption

## Mechanism of Action of Androgens

- Bind to a specific nuclear receptor in a target cell.
- Testosterone is active ligand in muscle and liver but in other tissues it must be metabolized to derivatives **DHT**
- After diffusing into the cells of the prostate, seminal vesicles and skin, testosterone is converted to **DHT**, which binds to the receptor.



# Direct effects of testosterone and indirect effects mediated by dihydrotestosterone or estradiol.



## Therapeutic Uses

- 1. Androgenic Effects:** Androgenic steroids are used for males with inadequate androgen secretion.
- 2. Anabolic Effects:** to treat senile osteoporosis and severe burns, to speed recovery from surgery or chronic debilitating diseases, and to counteract the catabolic effects of externally administered adrenal cortical hormones
- 3. Growth:** promote skeletal growth in prepubertal boys with pituitary dwarfism (in conjunction with other hormones)

4. **Endometriosis:** Danazol inhibits several of the enzymes in the hormone synthetic pathway but has no effect on the aromatase.
5. **Unapproved Use:** Androgenic steroids are used to increase lean body mass, muscle strength in athletes and body builders.

# Pharmacokinetics

- Testosterone is ineffective orally because of first-pass metabolism.
- Testosterone and its C17-esters are administered intramuscularly, C17-esters have longer duration of action.
- Transdermal patches, topical gels and buccal tablets also available.

## **Adverse Effects**

- 1. In females:** masculinization, with acne, growth of facial hair, deepening of the voice and excessive muscle development & Menstrual irregularities. Testosterone should not be used by pregnant women because of possible virilization of the female fetus.
- 2. In Males:** cause priapism (persistent erection of the penis), impotence, decreased spermatogenesis gynecomastia and stimulate growth of the prostate.

3. **In Children:** Androgens can cause abnormal sexual maturation and growth disturbances resulting from premature closing of the epiphyseal plates.
4. **General Effects:** Androgens increase the LDL/HDL ratio & increase risk for coronary heart disease, fluid retention leading to edema.



**5. In Athletes:** Use of anabolic steroids, (for example, DHEA, nandrolone, or stanozolol by athletes can cause premature closing of the epiphysis of the long bones, reduction of testicular size, hepatic abnormalities, increased psychotic episodes

## **Antiandrogens**

- Interfering with the synthesis of androgens  
**or**
- Blocking their receptors.

### **Ketoconazole**

Inhibits steroid synthesis (by inhibiting cytochrome P450 enzymes)

### **Finasteride**

Inhibits 5- $\alpha$ -reductase. The resulting decrease in formation of DHT in the prostate leads to a reduction in prostate size in benign prostatic hypertrophy

# **Competitive Inhibitors of Androgens (Blocking their receptors)**

## **Cyproterone Acetate**

For the treatment of hirsutism in females

## **Flutamide**

For the treatment of prostatic carcinoma in males

## **Bicalutamide and Nilutamide**

For the treatment of metastatic prostate cancer