Pharmacology - 2

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Gonadal Hormones & Inhibitors

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LEARNING OUTCOMES:

After completing studying this chapter, the student should be able to:

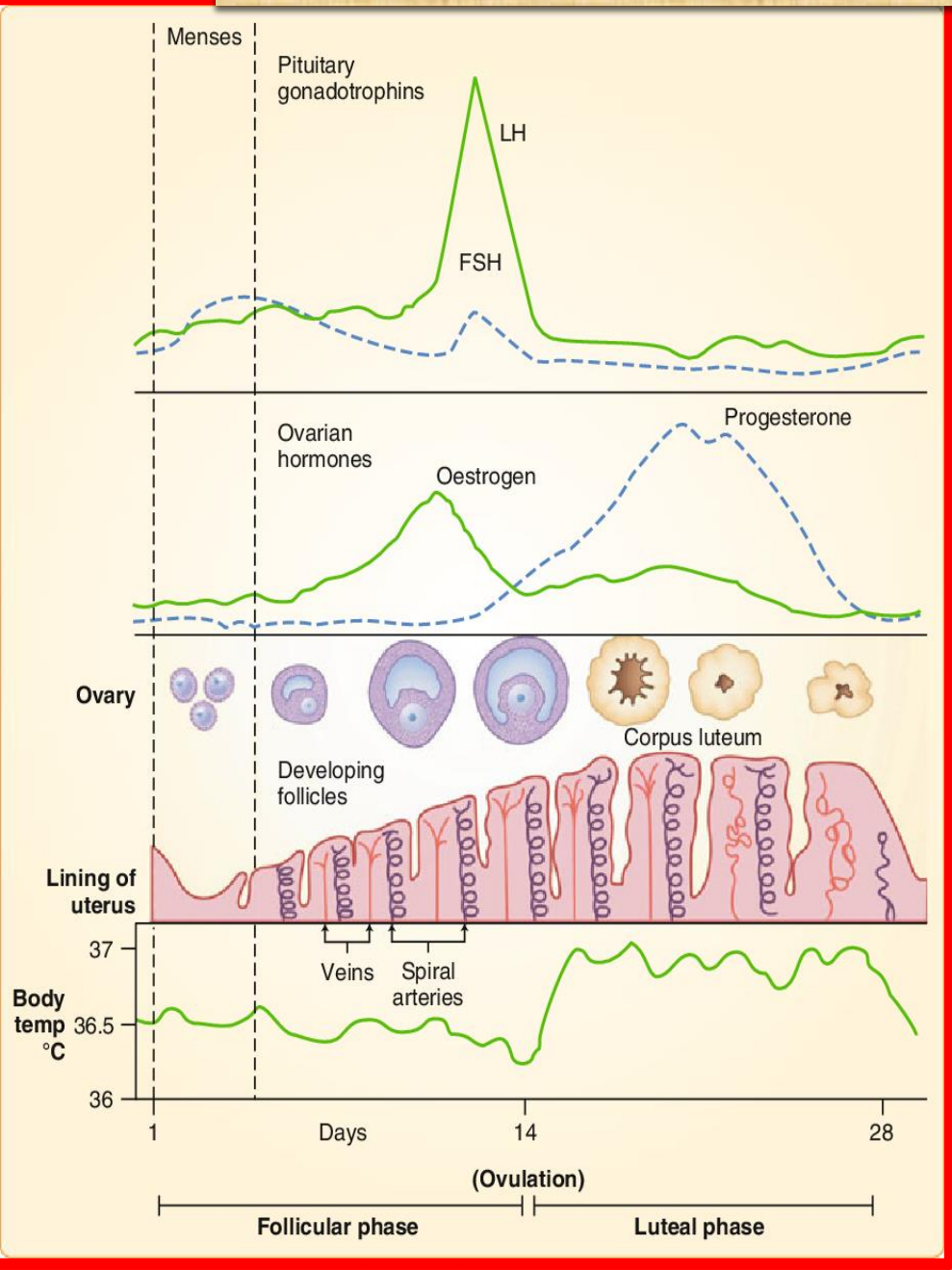
- Classify the studied drugs according to their pharmacological effects.
- Illustrate the mechanism of action of these drugs and hence deduce the possible indications and side effects related to them.
- List drugs used as contraceptives.
- Justifications of the clinical uses of some of these drugs in certain diseases, and explaining the contraindications or/and aspects of inappropriateness of certain clinical cases treatment.
- Specify the various pharmacokinetic and pharmacodynamic remarkable parameters of the studied drugs.

- Estrogens and androgens are sex hormones produced by the gonads.
- These hormones are necessary for conception, embryonic maturation, and development of primary and secondary sexual characteristics at puberty.
- The sex hormones are used therapeutically for {1}contraception, {2}management of menopausal symptoms, and{3} replacement therapy in hormone deficiency.
- Several antagonists are effective in the treatment or prevention of hormone responsive cancers.
- Sex hormones are synthesized from the precursor, cholesterol, in a series of steps that includes **shortening** of the hydrocarbon side chain and **hydroxylation** of the steroid nucleus.
- **Aromatization** is the last step in estrogen synthesis.

Highlights of the menstrual cycle:

- **GnRH** stimulates the release of **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)** from the pituitary gland.
- At the beginning of each cycle, a variable number of follicles each containing an ovum, begin to enlarge in response to FSH.
- After 5 or 6 days, one follicle, called the dominant follicle, begins to develop more rapidly.
- Under the influence of LH, the dominant follicle synthesizes and release estrogens at an increasing rate.
- The estrogens appear to inhibit FSH release and may lead to regression of the smaller, less mature follicles.
- Just before midcycle, estrogen reaches a peak, and progesterone is secreted. These changes result in a brief release of LH and FSH which stimulate ovulation.

Gonadal hormones & inhibitors



- **Corpus luteum** is formed and starts to secrete estrogen and progesterone for the remainder of the cycle.
- If pregnancy does **not** occur, corpus luteum starts to degenerate.
- The endometrium, proliferated during the follicular phase, is shed in the process of menstruation.

ESTROGENS:

- **Estradiol** is the most potent estrogen produced and secreted by the ovary.
- It is the principal estrogen in premenopausal women.
- **Estrone** is a metabolite of estradiol that has approximately one-third the estrogenic potency of estradiol.
- Estrone is the primary circulating estrogen after menopause.
- Synthetic estrogens, such as **ethinyl estradiol** undergo less first-pass metabolism than do naturally occurring hormones and, thus, are effective when administered orally at lower doses.

Therapeutic uses:

- Estrogens are most frequently used for contraception and postmenopausal hormone therapy (HT).
- In the past, estrogens were widely used for prevention of osteoporosis; however, due to risks associated with estrogen therapy, current guidelines recommend use of other therapies, such as bisphosphonate [e.g. risedronate and alendronate].

1. POSTMENOPAUSAL HORMONAL THERAPY (HT):

❖ The primary indication for estrogen therapy in postmenopausal women is menopausal symptoms, such as hot flashes {a sudden feeling of warmth that spreads over the body}, vaginal atrophy and dryness, insomnia and urinary urgency.

- A common oral preparation used for the treatment of menopausal symptoms is conjugated equine estrogens (obtained from urine of pregnant mares).
- Transdermal preparations of estradiol are also effective in treating menopausal symptoms.
- For women with an intact uterus, a progestogen is always included with the estrogen therapy, because the combination reduces the risk of endometrial carcinoma associated with estrogen alone.
- Women who have undergone a hysterectomy may use estrogen alone.
- The potency of estrogen used in HT is substantially less than that of estrogens used in contraception, which means less pronounced side effects in the former case.

- Use of HT has been associated with an increased risk of **cardiovascular** events and **breast cancer**.
- Many changes in coagulation factors have been reported.
- Increased plasminogen {the inactive precursor of plasmin, a potent serine protease involved in the dissolution of fibrin blood clots} levels and decreased platelet adhesiveness have also been found.
- HT should be prescribed at the lowest effective dose for the shortest possible time to relieve menopausal symptoms.
- Women who **only** have urogenital symptoms, such as vaginal atrophy, should be treated with **vaginal** rather than systemic estrogen to minimize the risks of use.
- **Estrogens** induce the synthesis of progesterone receptors.

2. CONTRACEPTION:

- The combination of an estrogen and progestogen provides effective contraception via the oral, transdermal, or vaginal route.

3. REPLACEMENT THERAPY:

In combination with progesterone:

A. To stimulate development of secondary sex characteristics in young women with primary hypogonadism.

B. For women who have hormonal deficiencies due to surgical menopause {where ovaries were surgically removed} or premature ovarian failure.

Pharmacokinetics:

Naturally occurring estrogens:

- They are readily absorbed through the GIT, skin, and mucous membranes.
- Oral estradiol is rapidly metabolized (and partially inactivated) by the microsomal enzymes of the liver.
- Micronized estradiol has better bioavailability.
- Although estradiol is subject to first-pass metabolism, it is still effective when taken orally.

Synthetic estrogens:

- These compounds, such as ethinyl estradiol and estradiol valerate are well absorbed after oral administration.
- Estradiol valerate is a prodrug of estradiol which is rapidly cleaved to estradiol and valeric acid.

- The synthetic estrogens are **fat soluble**, stored in adipose tissue, and slowly released.
- These compounds have a **prolonged** action **and a higher potency** {longer half-life} compared to the natural estrogens because they are **metabolized more slowly** than the natural hormones, with **less first-pass metabolism**.

❑ Metabolism:

- Bioavailability of estradiol after **oral** administration is **low** due to first-pass metabolism.
- To reduce first-pass metabolism, estradiol may be administered via a **transdermal patch**, **topical formulation** (gel or spray), **intravaginal preparation** (tablet, cream, or ring), or **injection**.
- Following oral administration, estradiol is metabolized to **estrone** and **estriol** [a weak and a minor estrogen].

Gonadal hormones & inhibitors

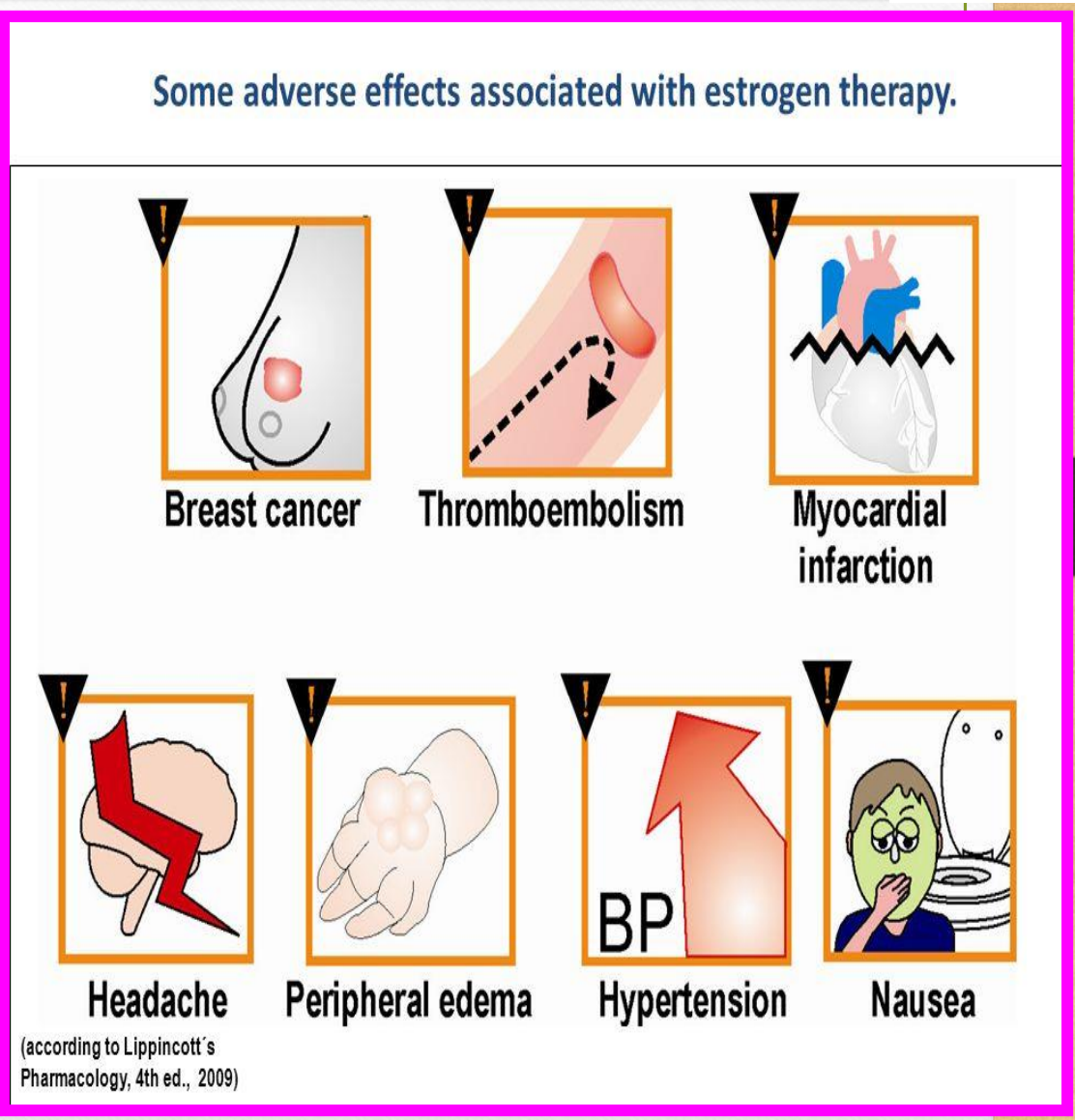
Adverse effects:

The most common:

- Nausea.
- Breast tenderness.

Increased risk of:

- Thromboembolic events.
- Myocardial infarction.
- Breast and endometrial cancer.



Selective Estrogen Receptor Modulators:

- Are a class of estrogen-related compounds that display selective agonism or antagonism for estrogen receptors depending on the tissue type.
- This category includes tamoxifen, raloxifene, bazedoxifene, clomiphene, and ospemifene.

Mechanism of action:

- Tamoxifen and raloxifene compete with estrogen for binding to the estrogen receptor in breast tissue.
- Normal breast growth is stimulated by estrogens. Therefore, some hormone-responsive breast tumors regress following treatment with these agents.
- In addition, **raloxifene** acts as an estrogen agonist in bone, leading to decreased bone resorption, increased bone density, and decreased vertebral fractures.

- Unlike estrogen and tamoxifen, **raloxifene** does ***not*** stimulate growth of the endometrium and, therefore, does not predispose {lead} to endometrial cancer.

- Like raloxifene, **bazedoxifene** antagonizes the action of estrogen on the uterus. The drug reduces the risk of endometrial hyperplasia with estrogen use.

- **Clomiphene** acts as a partial estrogen agonist and interferes with the negative feedback of estrogens on the hypothalamus.

- This effect increases the secretion of gonadotropin-releasing hormone and gonadotropins {FSH and LH}, thereby leading to **stimulation of ovulation**.

Therapeutic uses:

- Tamoxifen is currently used in the treatment of metastatic breast cancer, or as adjuvant therapy following mastectomy or radiation for breast cancer.
- Both tamoxifen and raloxifene can be used as prophylactic therapy to reduce the risk of breast cancer in high-risk patients.
- Raloxifene is also approved for the prevention and treatment of osteoporosis in postmenopausal women.
- Clomiphene is used in the treatment of infertility.
- Ospemifene is indicated for the treatment of dyspareunia (painful sexual intercourse) related to menopause (dryness).
- Bazedoxifene in combination with conjugated estrogens (mixtures) is indicated for the treatment of menopausal symptoms in women with an intact uterus {note: bazedoxifene antagonizes the action of estrogen on the uterus}.

Pharmacokinetics:

- Selective estrogen receptor modulators are rapidly absorbed after oral administration.
- **Tamoxifen** is extensively metabolized by cytochrome P450 system, including the formation of active metabolites.
- Patients with a genetic polymorphism in CYP2D6 may produce less active metabolite, resulting in diminished activity of tamoxifen (idiosyncrasy).
- **Raloxifene** is rapidly converted to glucuronide conjugates through first-pass metabolism.
- These agents undergo enterohepatic cycling, and the primary route of excretion is through the **bile** into feces.

ADVERSE EFFECTS:

Tamoxifen:

- Hot flashes and nausea.
- Endometrial hyperplasia and malignancies (due to estrogenic agonistic activity).
- Many drug interactions (due to the metabolism by CYTp450).
- Tamoxifen is a **P-glycoprotein *inhibitor***.
- **NOTE:** actively export drugs **out** of the cell. The effects of P-gp on the distribution, metabolism and excretion of drugs. P-gp activity, for example, **decreases the intracellular concentration** of **cancer drugs**, enabling resistance to develop to them. The same may be true for **protease inhibitors**.
- Some CYP450 inhibitors may prevent the formation of active metabolites of tamoxifen and possibly reduce the efficacy ---

(for example, amiodarone, haloperidol, paroxetine).

Raloxifene:

- Hot flashes and leg cramps.
- Vein thrombosis and pulmonary embolism {women with thromboembolic events should *not* take the drug}.

Clomiphene:

- Headache, nausea, vasomotor flushes (flashes), visual disturbances, and ovarian enlargement.
- Use of clomiphene increases the risk of multiple gestation, usually twins.

Ospemifene:

- May stimulate endometrial growth, and addition of a progestogen in women with an **intact** uterus should be considered.

PROGESTOGENS:

- Progesterone, the natural progestogen, is produced in response to luteinizing hormone (LH) by both females (secreted by the corpus luteum, during the second half of the menstrual cycle, and by the placenta) and by males (secreted by the testes).
- It is also synthesized by the adrenal cortex in both sexes.

Mechanism of action:

- 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 preventing further ovulation.
- Maintaining the endometrium during conception.

Therapeutic uses:

- Contraception.
- Hormonal therapy.

Often combined with estrogen

- Dysfunctional uterine bleeding,
- Treatment of dysmenorrhea,
- Management of endometriosis and infertility.

Medroxyproges-terone

- Progesterone (natural) is not used for contraception, because of its extensive metabolism.
- In stead, synthetic progestins are more stable to first-pass metabolism.
- These progestins include: desogestrel, drospirenone, levonorgestrel, norethindrone, norethindrone acetate, and norgestrel.

Pharmacokinetics:

- A micronized preparation of progesterone is rapidly absorbed after oral administration.
- It has a short half-life in the plasma.
- It is metabolized by the liver and excreted primarily in the urine.
- Synthetic progestins are less rapidly metabolized.
- Oral medroxyprogesterone acetate has a half-life of 30 hours.
- When injected intramuscularly or subcutaneously, the drug has a half-life of about 40 to 50 days and provides contraception for approximately 3 months.

Adverse effects:

- Headache, depression, weight gain, and changes in libido.
- Progestins that are derived from 19-nortestosterone (e.g. norethindrone, norethindrone acetate, norgestrel, levonorgestrel) possess some androgenic activity because of their structural similarity to testosterone and can cause acne and hirsutism.
- **NOTE:** 19-nor: methyl group at C-19 is removed.
- Thus, less androgenic progestins, such as norgestimate and drospirenone, may be preferred in women with **acne**.
- Drospirenone may cause hyperkalemia (due to mineralocorticoid effect) whose incidence increases with concurrent administration of drugs that increase serum K+ such as angiotensin-converting enzyme inhibitors {captopril,enalpril, lisinopril, fisinopril, quinapril, etc.}.

ANTIPROGESTIN:

- **Mifepristone (RU-486):**
- It is a progesterone antagonist.
- Administration of this drug results in (1) termination of pregnancy due to interference with the progesterone needed to maintain pregnancy {an antagonist on the progesterone receptor}.
- Mifepristone is often combined with the prostaglandin analog misoprostol to (2) induce uterine contractions.
- A single dose of 600 mg is an effective (3) emergency postcoital contraceptive, though it may result in delayed ovulation in the following cycle.
- (4) An antagonist at the glucocorticoid receptor.

- May be useful in the treatment of (5) endometriosis, Cushing's syndrome, breast cancer, and possibly other neoplasms such as meningiomas that contain glucocorticoid or progesterone receptors {Meningiomas: 90% are benign and slow-growing}.

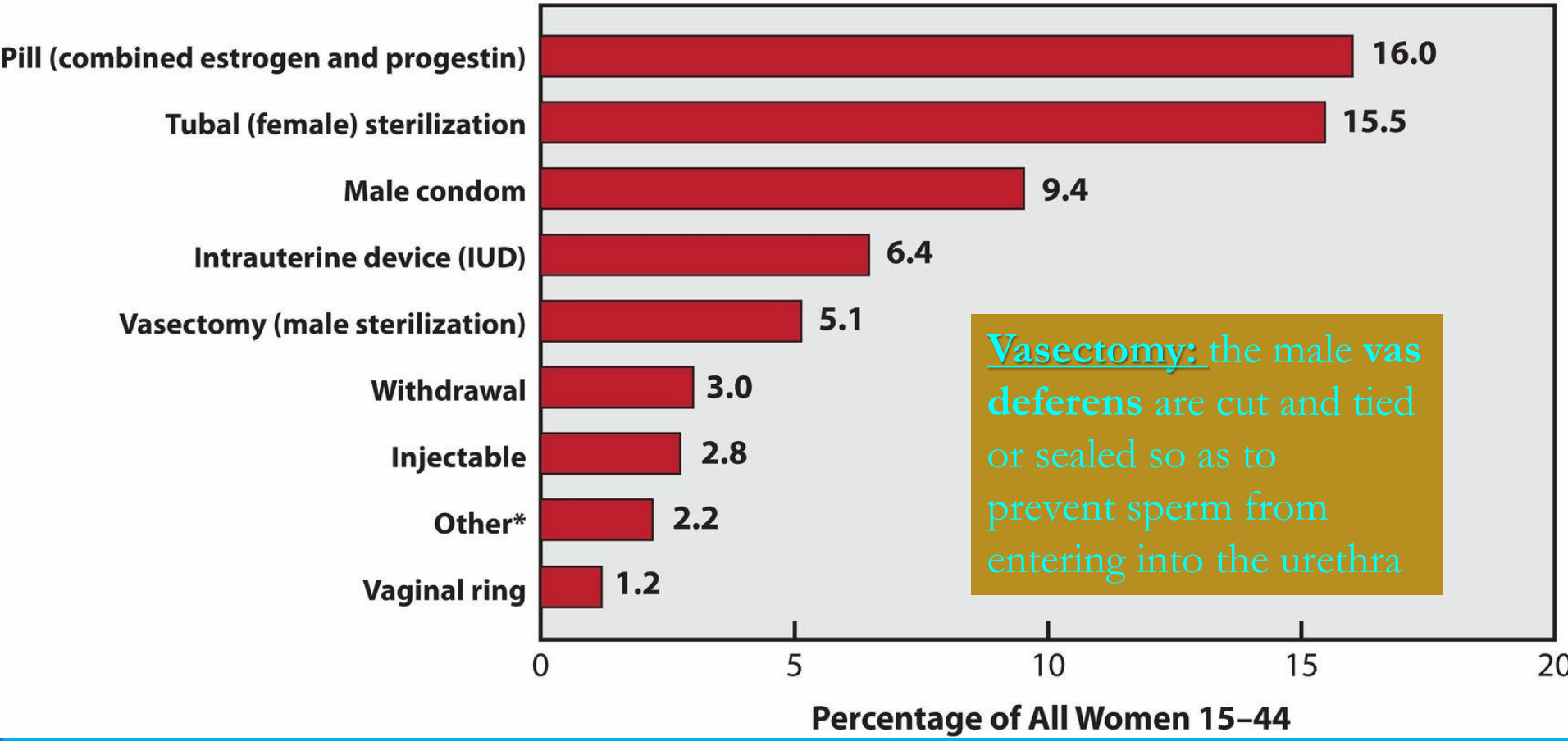
The major adverse effects are:

- Abdominal and pelvic pain.
- Uterine and vaginal bleeding (5%, needs intervention).
- Incomplete abortion.

- Because of these adverse effects, this drug is administered by physicians.
- **Lilopristone** is a potent progesterone inhibitor and abortifacient in doses of 25 mg twice daily.
- Like mifepristone, it also appears to have antiglucocorticoid activity.

CONTRACEPTIVES:

- Contraceptives may be hormonal or non-hormonal (for example, condom, diaphragm, contraceptive sponge, and copper intrauterine device).



Vasectomy: the male **vas deferens** are cut and tied or sealed so as to prevent sperm from entering into the urethra

Types of hormonal contraceptives:

1. Combination oral contraceptives:

- A combination of **estrogen** and **progestin** is the most common type of oral contraceptive.
- The most common estrogen in combination pills is ethinyl estradiol.
- The most common progestins are norethindrone, norethindrone acetate, levonorgestrel, desogestrel, norgestimate, and drospirenone.
- Very effective in preventing conception.
- **Monophasic** combination pills contain a constant dose of estrogen and progestin given over 21 to 24 days.

- **Triphasic** oral contraceptive products attempt to mimic the natural female cycle and usually contain a constant dose of estrogen with increasing doses of progestin given over 21 days.
- With most oral contraceptives, active pills are taken for 21 to 24 days, followed by 4 to 7 days of placebo, for a total regimen of 28 days.
- Withdrawal bleeding occurs during the hormone-free (placebo) interval.
- Use of extended-cycle contraception (84 active pills followed by 7 days of placebo) results in less frequent withdrawal bleeding.
- A continuous oral contraceptive product (active pills taken every day) is also available.

2. Transdermal patch:

- The contraceptive transdermal patch contains ethinyl estradiol and the progestin norelgestromin.
- During the 28-day cycle, one patch is applied each week for 3 weeks to the abdomen, upper torso, or buttock. **No** patch is worn during the 4th week, and withdrawal bleeding occurs.
- The transdermal patch has efficacy comparable to that of the oral contraceptives, but it is less effective in women weighing greater than **90** kg.

- Total estrogen exposure with the transdermal patch may be significantly greater than that seen with oral contraceptives.

3. Vaginal ring:

- The contraceptive vaginal ring contains ethinyl estradiol and etonogestrel.
- Effective (90-99%).

- The ring is inserted into the vagina and left in place for 3 weeks. After **3 weeks**, the ring is removed, and withdrawal bleeding occurs during the 4th week.
- If the ring falls out and stays out for more than 3 hours, replace it but use another method of contraception, like a **condom**, until the ring has been in place for 7 days in a row.

4. Progestin-only pills:

- Progestin-only pills (the "**MINI-PILL**") contain a progestin, usually **norethindrone**, and are administered daily to deliver a low, continuous dosage of drug.
- These preparations are less effective than combination oral contraceptives, and irregular menstrual cycles may be more frequent.
- Progestin-only pills may be used in patients who:
  - Are breastfeeding (unlike estrogen, progestins do not have an effect on milk production).
  - Have intolerance or contraindications to estrogen-containing products.

5. Injectable progestin:

- Medroxyprogesterone acetate is a contraceptive that is administered via intramuscular or subcutaneous injection every 3 months.
- This product provides high sustained levels of progestin, and many women experience amenorrhea {absence of menstruation} with medroxyprogesterone acetate. In addition, return to fertility may be delayed for several months after discontinuation.

ADVERSE EFFECTS:

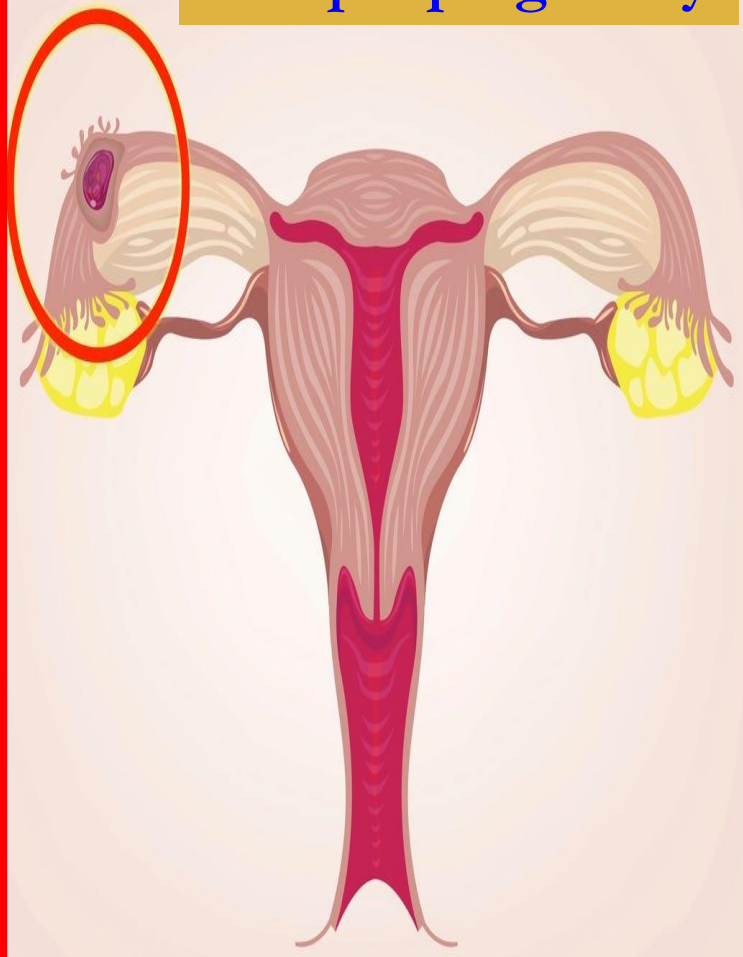
- Weight gain is a common adverse effect.
- Medroxyprogesterone acetate may contribute to bone loss and predispose patients to osteoporosis and/or fractures. Therefore, the drug should not be continued for more than 2 years unless the patient is unable to tolerate other contraceptive options.

6. Progestin implants:

- After subdermal placement in the upper arm, the **etonogestrel** implant offers contraception for up to **3** years.
- The implant is as **reliable as sterilization**, and the contraceptive effect is reversible when removed.
- Progestin implants and intrauterine devices are known as long-acting reversible contraceptives (LARC).
- **Adverse effects:** include **irregular menstrual bleeding** and **headaches**.
- The etonogestrel implant has not been studied in women who weigh more than 130% of ideal body weight and may be less effective in this population

7. Progestin intrauterine device:

- Various levonorgestrel-releasing intrauterine devices offer a highly effective method of contraception for 3 to 5 years.
- This is a suitable method of contraception for women who desire long-term contraception.
- It should be avoided in patients with {1} pelvic inflammatory disease {an infection of the upper part of the female reproductive system, namely the uterus, fallopian tubes, and ovaries, and inside of the pelvis. Often, there may be no symptoms} or a history of {2} ectopic pregnancy.



8. Postcoital contraception:

- Postcoital or emergency contraception reduces the probability of pregnancy after intercourse without effective contraception to between 0.2% and 3%.
- The most common method of emergency contraception uses a single high dose of levonorgestrel.
- For maximum effectiveness, emergency contraception should be taken as soon as possible after unprotected intercourse and preferably within 72 hours.
- The levonorgestrel emergency contraceptive regimens are generally better tolerated than the estrogen–progestin combination regimens.

- An alternative emergency contraceptive is the progesterone agonist/antagonist **ulipristal** {modulator}.
- It is indicated (as first-line therapy) for emergency contraception within 5 days of unprotected intercourse due to improved efficacy and similar side effect profile as compared to the traditional use of levonorgestrel.

- The exact mechanism of action for ulipristal is still currently debated, though there is evidence that it functions by:

1. Inhibiting ovulation.
2. It may, in fact, elicit activity on the endometrium that prevents embryo implantation.

MECHANISM OF ACTION: [of estrogens and progestins]

1. Exogenously administered estrogen in contraceptives provides **negative feedback** which blunts release of FSH by the pituitary gland and progestin inhibits LH secretion, thus preventing ovulation.
2. Progestin also **thickens** the cervical mucus, thus hampering (impeding) the transport of sperm.

❖ Withdrawal of the progestin stimulates menstrual bleeding during the placebo week.

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Adverse effects {of the combinations therapy}:

Estrogen content:

- COMMON: breast fullness, fluid retention, headache, and nausea.

- Increased blood pressure *may occur*.
- RARE: thromboembolism, thrombophlebitis, myocardial infarction, and stroke (CV complications).

Progestin content:

- Depression, changes in libido, hirsutism, and acne.

❖ Increased incidence of **cervical cancer**; because women are less likely to use barrier methods of contraception that reduce exposure to human papillomavirus, the primary risk factor for cervical cancer, [transmission via skin-skin contact].

✓ Oral contraceptives are associated with a decreased risk of endometrial and ovarian cancer.

❑ Contraindications: presence of cerebrovascular and thromboembolic disease, estrogen-dependent neoplasms, liver disease, and pregnancy.

- These severe adverse effects are most common among women who are over age 35 **and** smoke, and **estrogen**-containing contraceptives should be avoided in this population.
- **Progestin-only** products are preferred in older women who are smokers, due to a lower risk of severe adverse effects.

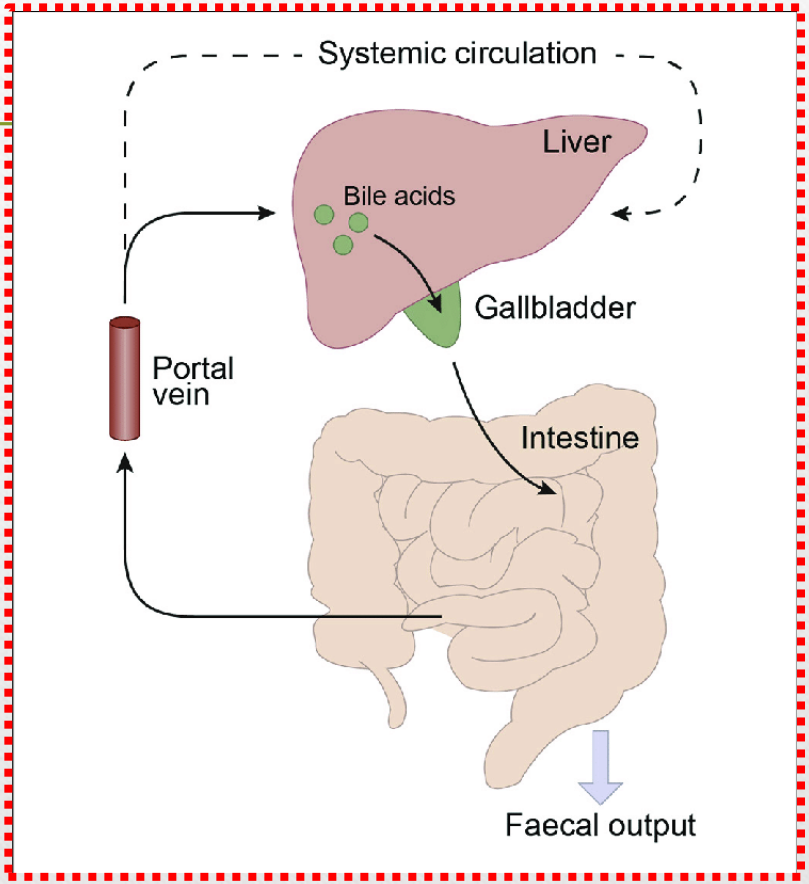
INTERACTIONS:

- **Drugs that induce the CYP3A4 isoenzyme** (for example, rifampin and bosentan {a dual endothelin (vasoconstrictor polypeptide) receptor **antagonist** used in the treatment of pulmonary artery hypertension}) significantly reduce the efficacy of oral contraceptives (**patient warning**}.
- **Antibiotics** that interrupt normal gastrointestinal flora may reduce enterohepatic recycling of estrogen (***necessary for estrogen hydrolysis***, thus increased loss in feces, thereby diminishing effectiveness of oral contraceptives {Inform your patient to use another method of contraception, e.g. condom}..

Gonadal hormones & inhibitors

Enterohepatic cycling

- **Enterohepatic recycling:** Foreign chemicals entering the alimentary tract are absorbed into portal venous blood by enterocytes, removed from blood by uptake into hepatocytes, secreted into the bile, and then deposited back into the intestinal lumen where they may be reabsorbed by intestinal cells



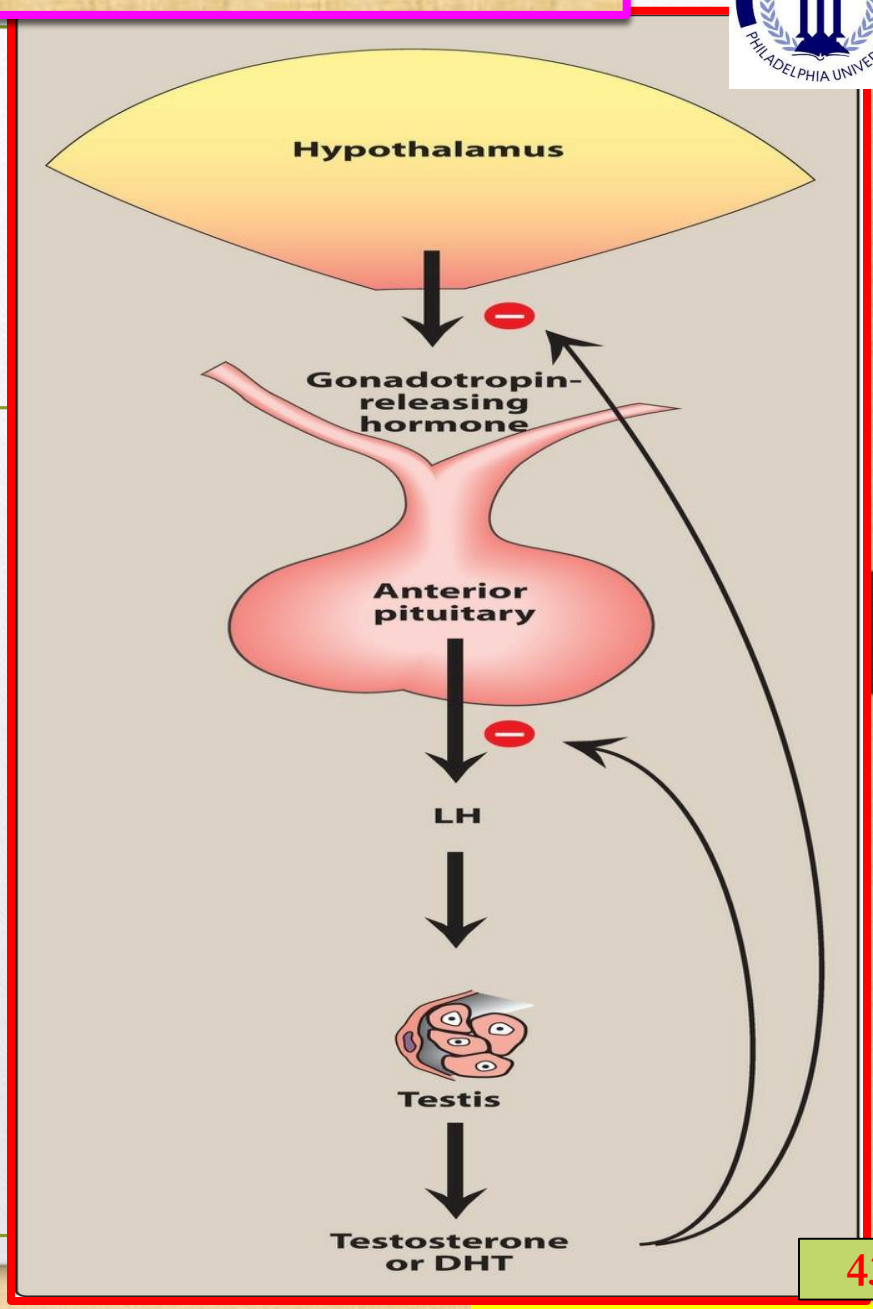
ANDROGENS:

- The androgens are a group of steroids that have anabolic and/or masculinizing effects in both males and females.
- **Testosterone**, the most important androgen in humans, is synthesized by Leydig cells in the testes and, in smaller amounts, by thecal cells in the ovaries and by the adrenal gland in both sexes.
- Other androgens secreted by the testes are 5α-dihydrotestosterone (DHT), androstenedione, and DHEA {dehydroepiandrosterone} in small amounts.
- In adult males, testosterone secretion by Leydig cells is controlled by gonadotropin-releasing hormone from the hypothalamus, which stimulates the anterior pituitary gland to secrete FSH and LH.

Gonadal hormones & inhibitors

- Testosterone or its active metabolite, DHT, inhibits production of these specific trophic hormones through a negative feedback loop and, thus, regulates testosterone production.
- They are required for:

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



- Synthetic modifications of the androgen structure:

✓ Modify solubility and susceptibility to metabolism (thus prolonging the half-life of the hormone) – pharmacokinetics.

✓ Separate anabolic and androgenic effects - pharmacodynamics.

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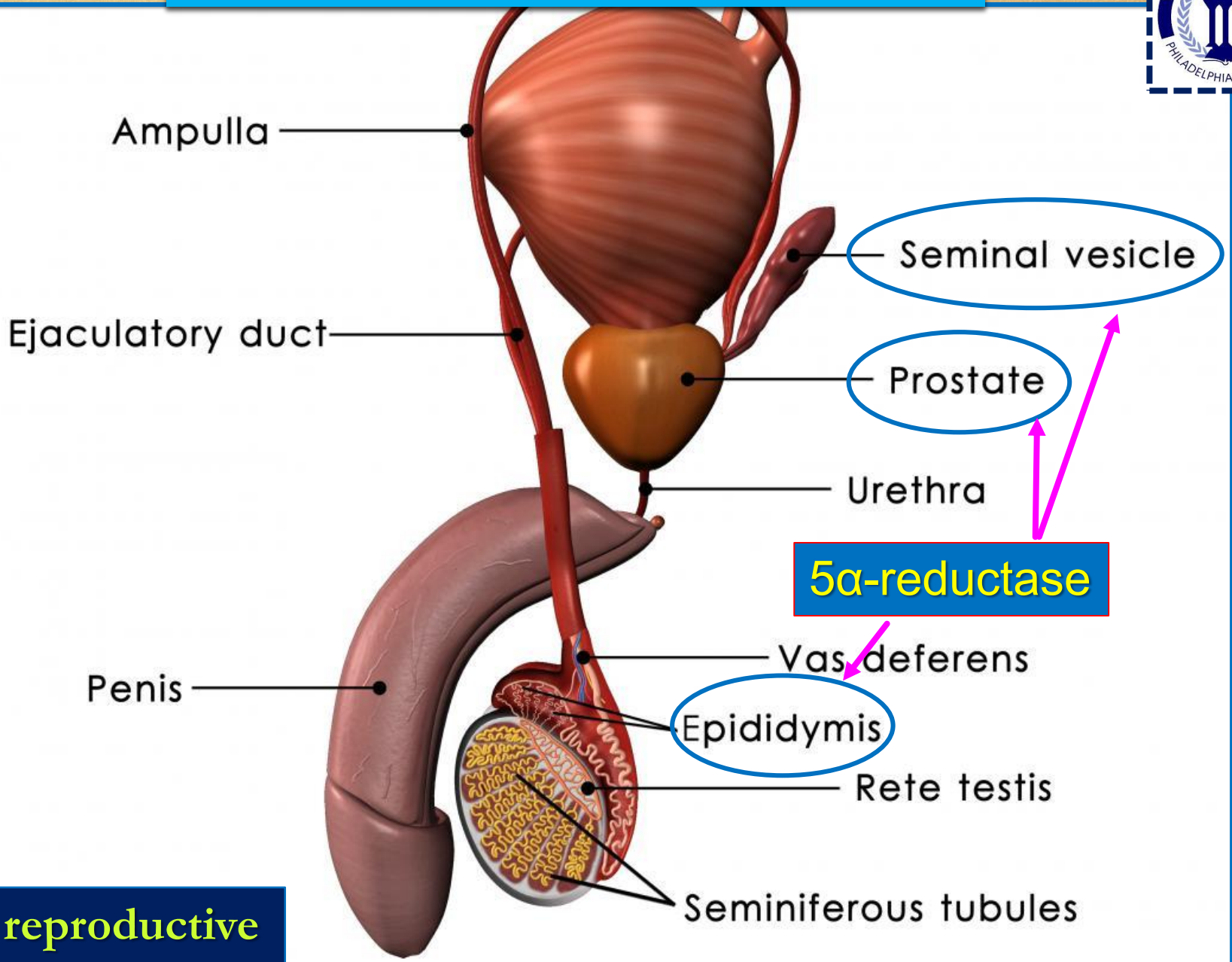
Mechanism of action:

- Like the estrogens and progestins, androgens bind to a specific nuclear receptor in a target cell.
- Testosterone is the active ligand in muscle and liver.
- In other tissues, it must be metabolized to derivatives, such as **Dihydrotestosterone (DHT).**
- 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.

Gonadal hormones & inhibitors



Male reproductive system

Therapeutic uses:

- **Androgenic** steroids are used for males with primary hypogonadism (caused by testicular dysfunction) or secondary hypogonadism (due to failure of the hypothalamus or pituitary).
- Testosterone replacement should only be used for males with hypogonadism related to medical conditions and not low testosterone associated with **aging**.
- **Anabolic** steroids can be used to treat chronic wasting associated with human immunodeficiency virus or cancer.
- An unapproved use of anabolic steroids is to increase lean body mass, muscle strength, and endurance in athletes and body builders.
- Because of the potential misuse of testosterone and its derivatives, these agents are classified as controlled substances.

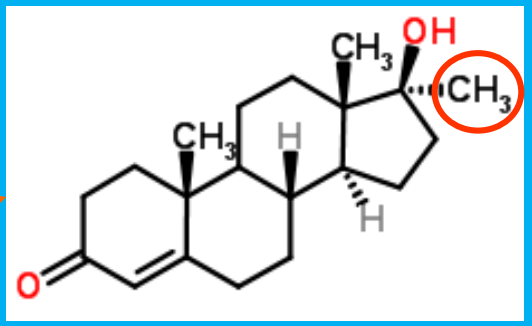
- DHEA (a precursor of testosterone and estrogen) has been touted as an antiaging hormone as well as a "performance enhancer."
- There is no definitive evidence that it slows aging.
- Formulations of testosterone or its derivatives (for example, methyltestosterone) may be used in combination with estrogen for women with menopausal symptoms unresponsive to estrogen alone.
- **Danazol**, a weak androgen, is used in the treatment of endometriosis and fibrocystic breast disease {non-cancerous, non-dangerous, but bothersome as it feels lumpy}.
- **Danazol** also possesses antiestrogenic activity.
- **Adverse effects:** weight gain, acne, decreased breast size, deepening voice, increased libido, and increased hair growth.

PHARMACOKINETICS:

1. Testosterone:

- Ineffective orally because of inactivation by first-pass metabolism.
- Therefore, testosterone is administered via a transdermal patch, topical gel or solution, buccal tablet, or implantable pellet.
- Esters of testosterone (for example, testosterone cypionate or enanthate) are administered intramuscularly.
- The **esterified** formulations are more lipid soluble and have an increased duration of action up to several weeks.
- Active metabolites of testosterone include **DHT** and **estradiol**.

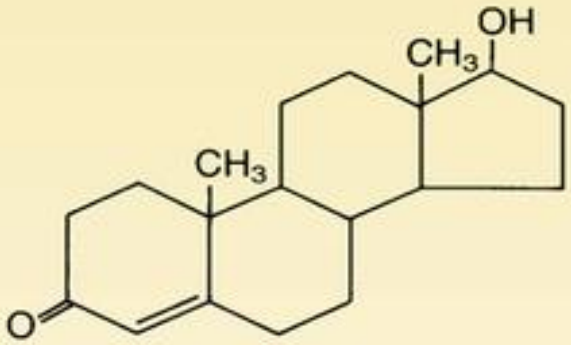
- Inactive metabolites are excreted primarily in the urine.
- Testosterone and its esters demonstrate a 1:1 relative ratio of androgenic to anabolic activity.



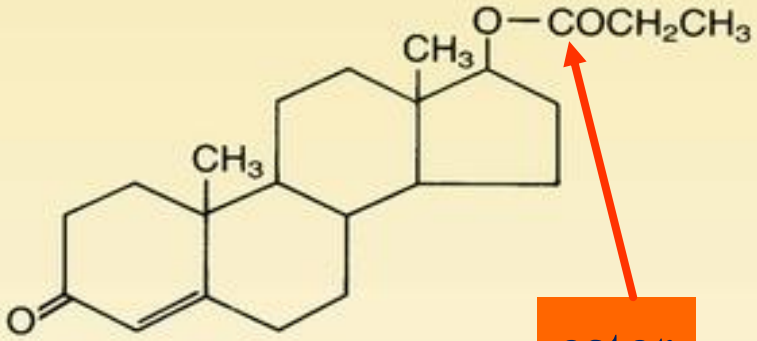
2. Testosterone derivatives:

- Alkylation of the 17α position of testosterone is associated with less hepatic metabolism and allows **oral** administration of the hormone.
- **Methyltestosterone** and **fluoxymesterone** are examples of **orally** administered testosterone derivatives.
- **Oxandrolone** and **oxymetholone** are orally active 17α-alkylated derivatives of DHT.
- **Oxandrolone** has **anabolic** activity 3 to 13 times that of testosterone.

TESTOSTERONE AND A TESTOSTERONE ESTER



Testosterone

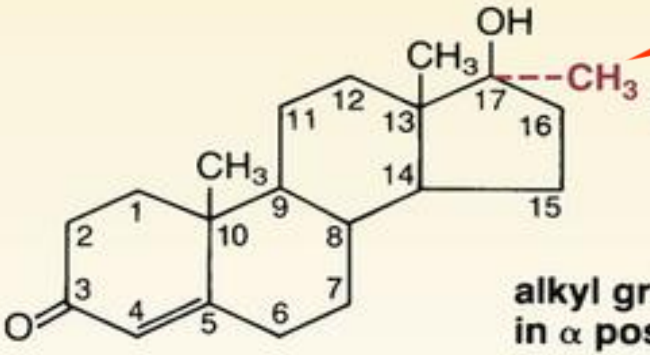


Testosterone Propionate

ester

alkyl

17-ALPHA-ALKYLATED ANDROGENS



alkyl group in α position on carbon 17

Methyltestosterone

Fluoxymesterone

Adverse effects:

1. In females:

- Androgens can cause masculinization, acne, growth of facial hair, deepening of the voice, male pattern baldness, and excessive muscle development.
- Menstrual irregularities may also occur.
- Testosterone should **not** be used by pregnant women because of possible virilization (getting male characters) of the female fetus.

2. In males:

- Excess androgen can cause priapism, impotence, decreased spermatogenesis, gynecomastia.
- Androgens can also stimulate growth of the prostate.

3. In children:

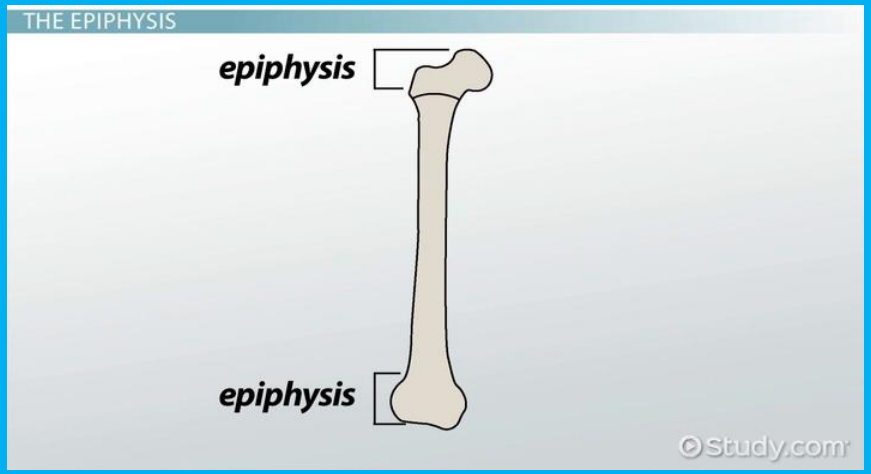
- Androgens can cause abnormal sexual maturation and growth disturbances resulting from premature closing of the epiphyseal plates (leading to short stature as growth does not occur after the premature closure).

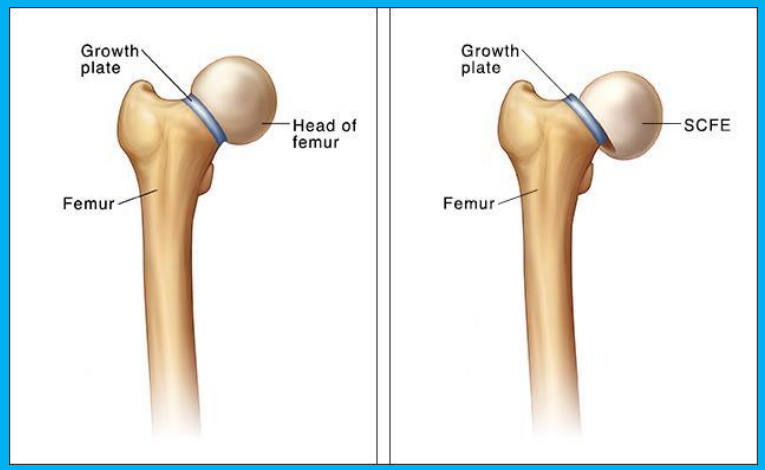
4. General effects:

- Androgens can increase serum LDL and lower serum HDL.
- They may also cause fluid retention and peripheral edema.
- Testosterone replacement therapy has been associated with a possible increased risk of myocardial infarction and stroke.
- Hepatic adverse effects have been associated with the 17α-alkylated androgens.
- Local skin irritation is a common adverse effect with topical formulations.

In athletes:

- Use of anabolic steroids (for example, DHEA) by athletes can cause premature closing of the epiphysis of the long bones, which stunts growth and interrupts development.
- High doses taken by young athletes may result in reduction of testicular size, hepatic abnormalities, increased aggression ("roid rage"), major mood disorders, in addition to the previously mentioned adverse effects.





ANTIANDROGENS:

STEROID SYNTHESIS INHIBITORS:

KETOCONAZOLE:

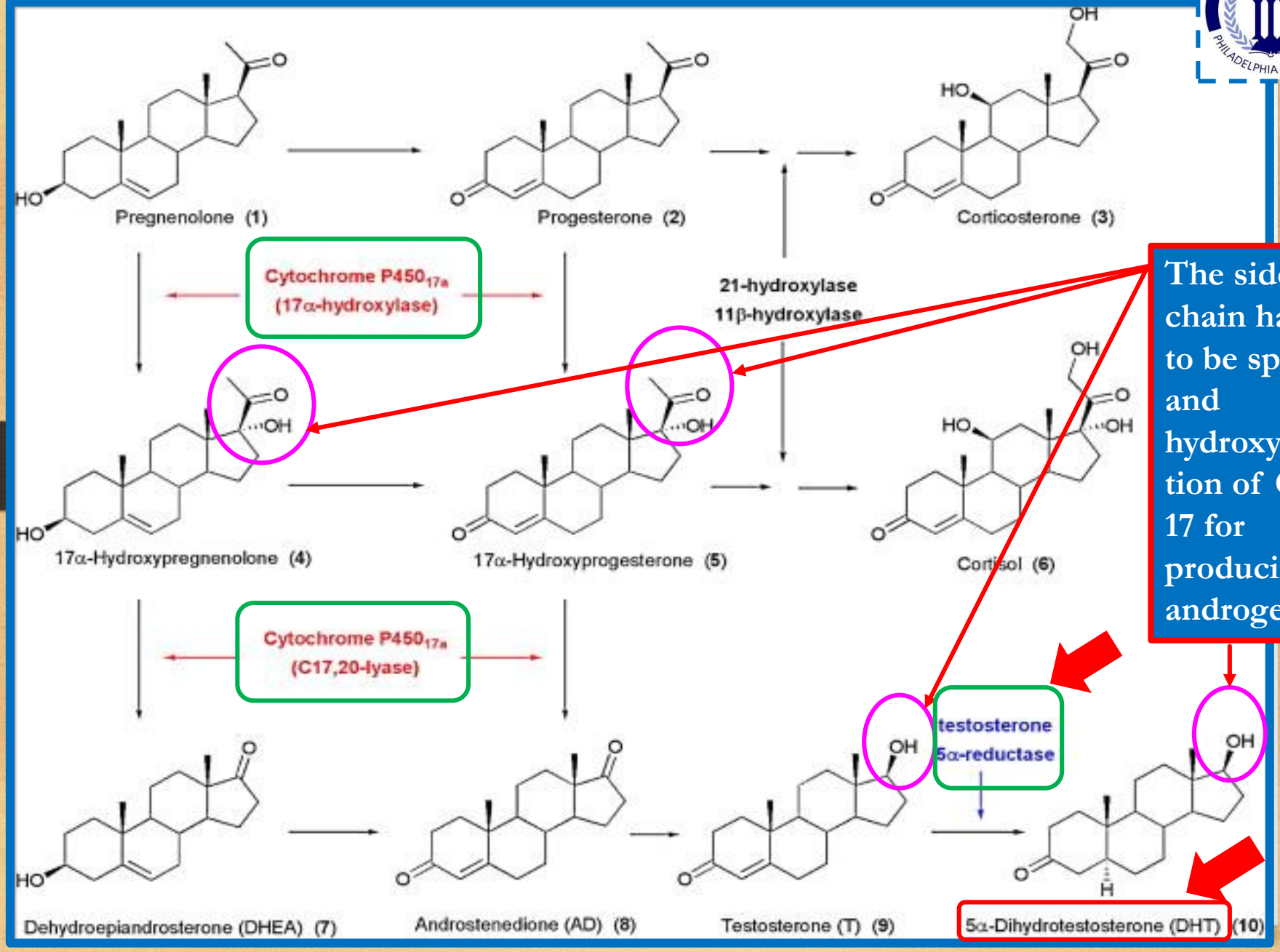
- Used primarily in the treatment of fungal disease, is an inhibitor of adrenal and gonadal steroid synthesis.
- It is cytochrome p-450 inhibitor enzyme.
- Mechanism of action as anti-steroidogenesis : blocks **cholesterol conversion to pregnenolone by inhibiting the side-chain cleavage enzyme.{ a primary pathway step).**
- It does *not* appear to be clinically useful in women with increased androgen levels because of the toxicity {hepatitis} associated with prolonged use of the 400–800 mg/d-dose required.

- It displaces estradiol and dihydrotestosterone from sex hormone-binding protein in vitro.
- It increases the estradiol:testosterone ratio in plasma in vivo by a different mechanism, thus,
- Men treated with ketoconazole often develops reversible gynecomastia during therapy {an enlargement or swelling of breast tissue}.

INHIBITION OF CONVERSION OF STEROID PRECURSORS TO ANDROGENS:

- Steroids like progesterone or pregnenolone conversion to active androgen can be attained by inhibition of **17-hydroxylation** (inhibition of the side-chain splitting enzyme).
- So many tested drugs acting via this mechanism were tested clinically and were found too toxic.

Gonadal hormones & inhibitors



The side chain has to be split, and hydroxylation of C-17 for producing androgens

- **Abiraterone**, a newer 17α-hydroxylase inhibitor, has been approved for use in **metastatic prostate cancer**.
- Since dihydrotestosterone, not testosterone, appears to be the essential androgen in the **prostate**, androgen effects in this and similar dihydrotestosterone-dependent tissues can be reduced by an inhibitor of 5α-reductase.
- **Finasteride**, an inhibitor of this enzyme, is orally active and causes a reduction in dihydrotestosterone levels that begins within 8 hours after administration and lasts for about 24 hours.
- **Finasteride** is approved in USA for benign prostate hyperplasia, BPH {moderately reduces prostate size}.
- **Dutasteride** is also prescribed for BPH but with slow onset of action and a much longer half-life than finasteride.

- **Finasteride**, in addition to approval in {1} BPH, has been used successfully in the treatment of {2} hirsutism in women and is approved for treatment of early male pattern {3} baldness in men.

RECEPTOR INHIBITORS:

- **Flutamide**: a potent antiandrogen (receptor competitive antagonist) that has been used in the treatment of prostatic carcinoma.
- **Bicalutamide**, **nilutamide**, and **enzalutamide**: anti-androgens used in patients with metastatic carcinoma of the prostate.
- **Cyproterone**: {1} hirsutism in women, and {2} to decrease sexual drive in men.

THE END

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