



# Estrogens & Androgens



## Pharmacology Team

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# Introduction

- **Sex hormones produced by the gonads are necessary for:**
  - conception
  - embryonic maturation
  - development of primary and secondary sexual characteristics at puberty.
- **The gonadal hormones are used therapeutically**
  - In replacement therapy
  - For contraception
  - In management of menopausal symptoms.
  - Some antagonists are effective in cancer chemotherapy.
- All gonadal hormones are synthesized from cholesterol

# Steroidogenesis

## Steroidogenesis

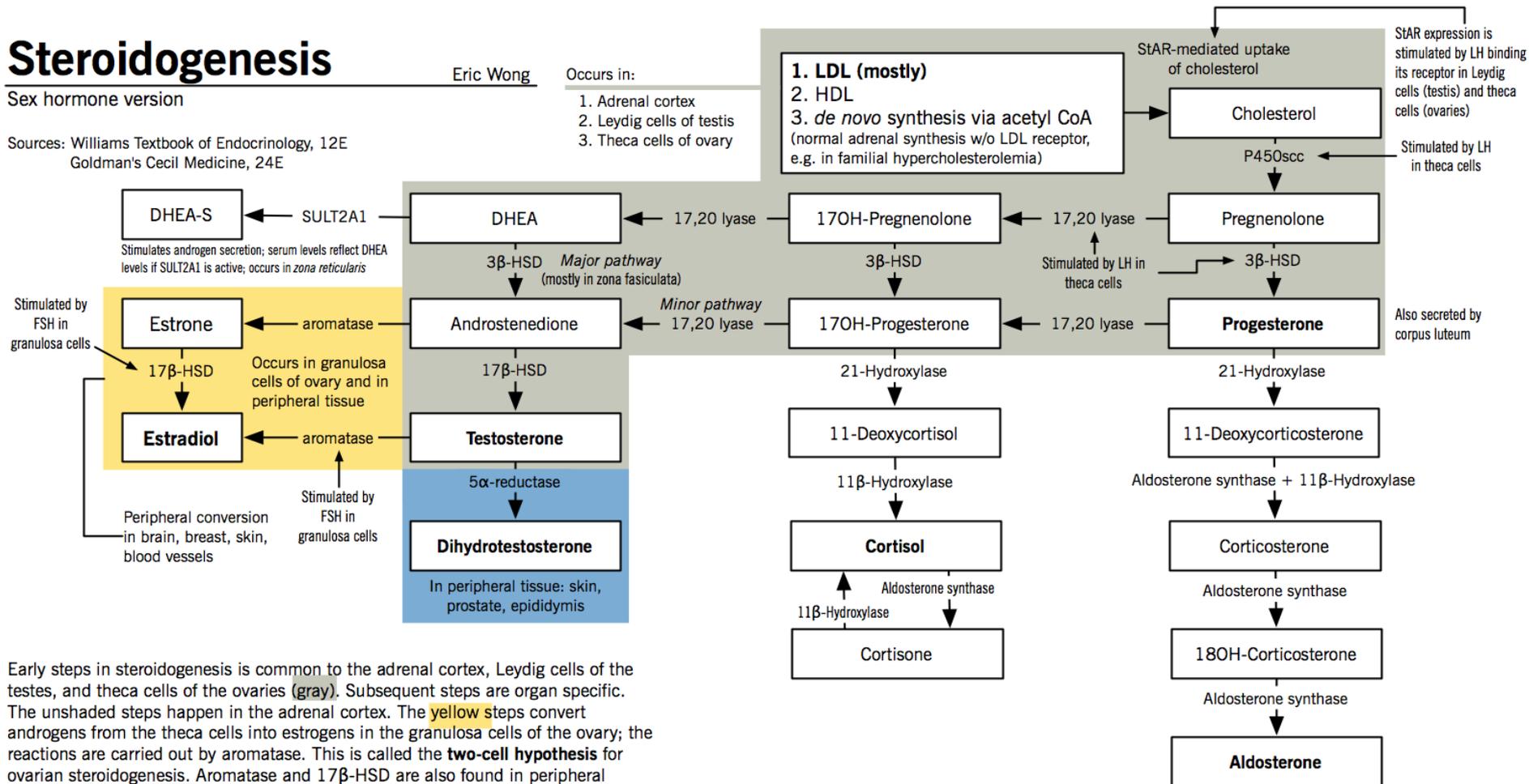
Sex hormone version

Eric Wong

Occurs in:

1. Adrenal cortex
2. Leydig cells of testis
3. Theca cells of ovary

Sources: Williams Textbook of Endocrinology, 12E  
Goldman's Cecil Medicine, 24E



Early steps in steroidogenesis is common to the adrenal cortex, Leydig cells of the testes, and theca cells of the ovaries (gray). Subsequent steps are organ specific. The unshaded steps happen in the adrenal cortex. The yellow steps convert androgens from the theca cells into estrogens in the granulosa cells of the ovary; the reactions are carried out by aromatase. This is called the **two-cell hypothesis** for ovarian steroidogenesis. Aromatase and 17β-HSD are also found in peripheral tissues. Finally, the blue step happens in peripheral tissues such as skin, prostate, and epididymis, where testosterone is converted into the more potent DHT.

# Classification of Estrogens

- **Natural estrogens include:**

- 17 $\beta$ -estradiol
- Estrone
- Estriol

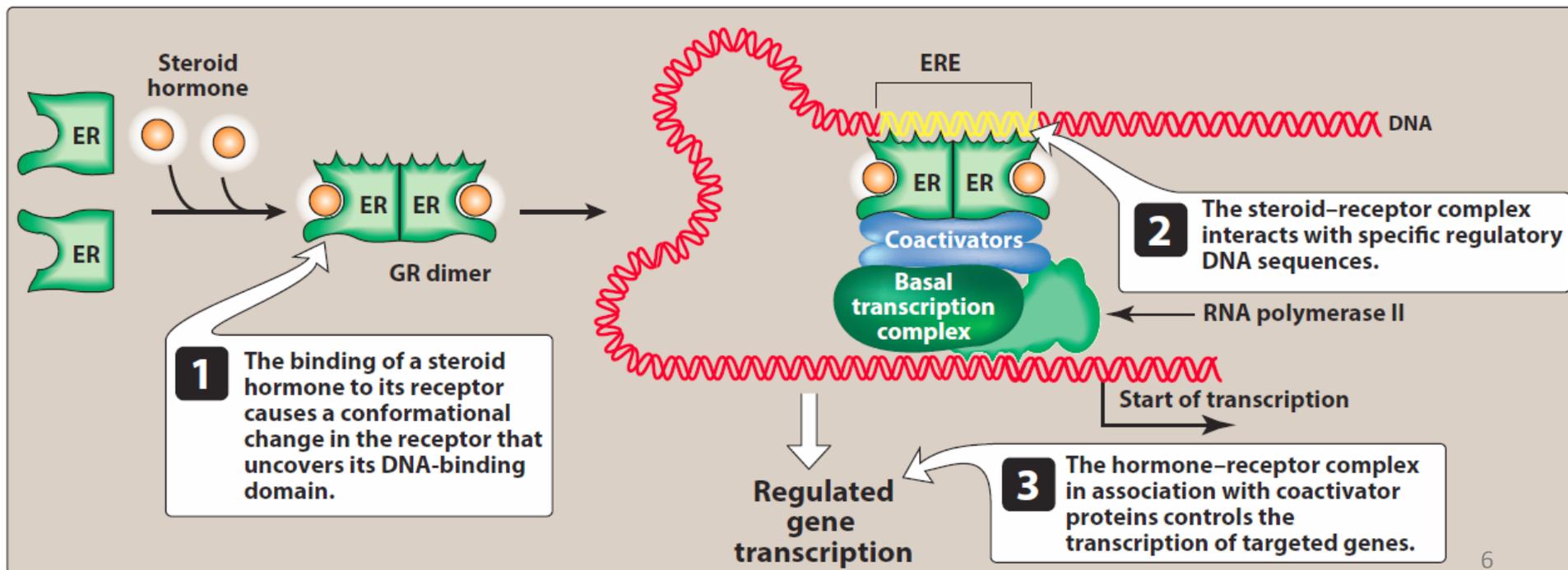
- The most potent natural estrogen is 17 $\beta$ -estradiol.
- Testosterone is the immediate precursor of estradiol
- Conversion of testosterone to 17 $\beta$ -estradiol is catalyzed by the enzyme aromatase

# Classification of Estrogens

- **Synthetic estrogens include:**
  - Steroidal agents
    - Ethinylestradiol
    - Mestranol
  - Nonsteroidal compounds:
    - Diethylstilbestrol (DES)
    - Dienestrol

# Mechanism of action of Estrogens

- 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



# Therapeutic uses of Estrogens

## Postmenopausal hormone therapy (HT):

- **Treatment of menopausal symptoms:** vasomotor instability (“hot flashes” or “hot flushes”) and vaginal atrophy.
- For women who have an intact uterus, a progestogen is always included with the estrogen therapy, because the combination **reduces the risk of endometrial carcinoma** associated with unopposed estrogen.
- The amount of estrogen used in replacement therapy is less than the doses used in oral contraception. Thus, the adverse effects are usually less pronounced

# Therapeutic uses of Estrogens

## Postmenopausal hormone therapy (HT):

- HT should be prescribed at the lowest effective dose for the shortest possible time to relieve menopausal symptoms to reduce the risk of cardiovascular events and breast cancer.
- Women who only have urogenital symptoms, such as vaginal atrophy, should be treated with vaginal rather than systemic estrogen

# Therapeutic uses of Estrogens

## Contraception:

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

## Other uses (in combination with a progestogen):

- Primary hypogonadism
- Premature menopause or premature ovarian failure

## Pharmacokinetics of Estrogens

- Synthetic estrogen analogs have a **prolonged** action and a higher **potency** compared to those of natural estrogens.
- Being fat soluble, they are **stored in adipose tissue**, from which they are slowly released

## Adverse effects of Estrogens

- Breast tenderness (common)
- Increased the risk of thromboembolic events and MI
- Peripheral edema and hypertension
- Increased the risk of breast and endometrial cancer (can be reduced by the co-treatment with progestogen)

## **Selective estrogen receptor modulator (SERM)**

- Display selective agonism or antagonism for estrogen receptors depending on the tissue type.
- This category includes Tamoxifen, Raloxifene and Clomiphene

## Mechanism of action of (SERM)

- Tamoxifen and Raloxifene compete with estrogen for binding to the estrogen receptor in breast tissue [Note: Normal breast growth is stimulated by estrogens].
- Therefore, some breast tumors regress following treatment with these agents.

## Mechanism of action of (SERM)

- Raloxifene also acts as an estrogen agonist in bone, leading to decreased bone resorption, increased bone density, and decreased vertebral fractures.
- Unlike estrogen and Tamoxifen, Raloxifene has estrogen receptor agonist activity in the endometrium; **does not predispose to endometrial cancer.**

## Mechanism of action of SERM

- Clomiphene acts as a partial estrogen agonist and interferes with the negative feedback of estrogens on the hypothalamus.
- This effect increases the secretion of GnRH and gonadotropins (LH & FSH), thereby leading to stimulation of ovulation.

## Therapeutic uses of SERM

- Tamoxifen is 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 useful for the treatment of infertility associated with anovulatory cycles.

## Adverse effects of SERM

- **Tamoxifen:**
  - Hot flashes and nausea.
  - Endometrial hyperplasia and malignancies due to its estrogenic activity in the endometrium.
- **Raloxifene:**
  - Hot flashes and leg cramps.
  - Increased risk of deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis
- **Clomiphene:**
  - Vasomotor flushes, visual disturbances, and ovarian enlargement.
  - Increased the risk of multiple births (twins or triplets)

# Anti-estrogens

- **Mechanism of action**
  - Interference with the binding of estrogen with its specific receptor
  - They may also alter the conformation of the estrogen receptor
- This class of compounds is distinguished from progestins and androgens, which also possess physiologic anti-estrogenic activity
- Ex: Fulvestrant, Danazol, Selective Estrogen Receptor Modulators, Aromatase Inhibitors

## Antiestrogens (Fulvestrant)

- Binds competitively to the estrogen receptor
- Fulvestrant appears to be an antagonist in all tissues
- Fulvestrant eventually reduces the number of functional receptors available for endogenous estrogens and diminishes estrogen action both along the hypothalamic-pituitary axis and in peripheral tissues
- Fulvestrant is used to treat women with progressive breast cancer after tamoxifen

## Antiestrogens (Danazol)

- A testosterone derivative with antiandrogen and antiestrogenic activities
- Inhibits several enzymes involved in steroidogenesis, but does not inhibit aromatase
- May bind to estrogen and androgen receptors; and inhibits gonadotropin release in both men and women.

## Antiestrogens (Danazol)

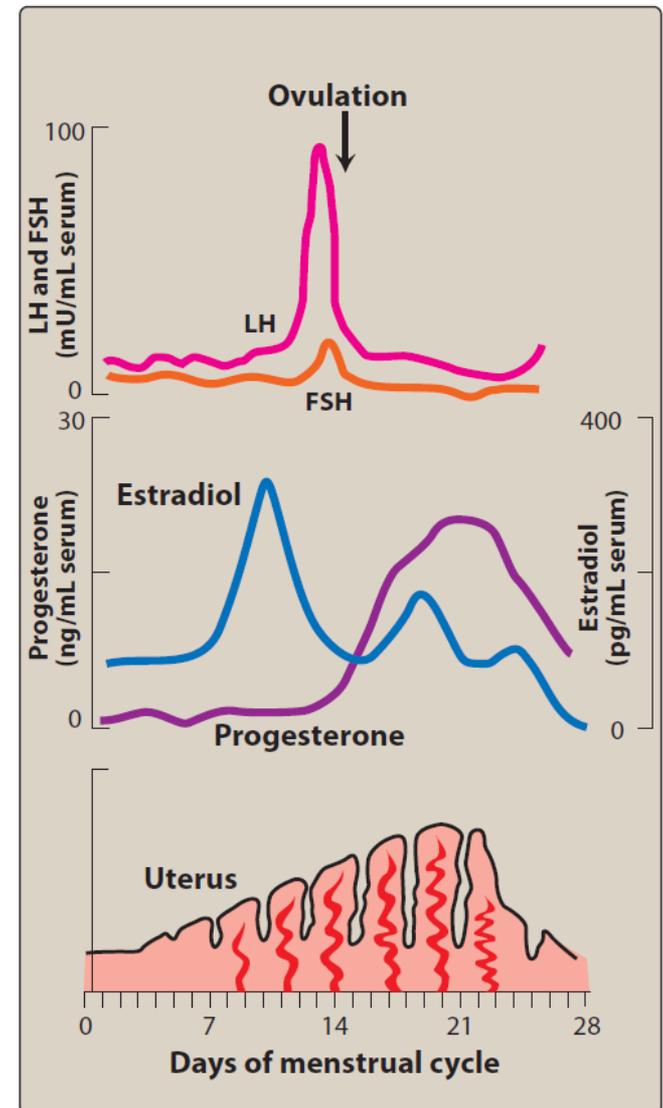
- Used to inhibit ovarian function, treat endometriosis and fibrocystic disease of the breast.
- S/E: edema, masculinization (deepening of the voice and decreased breast size) in some women, headache, and hepatocellular disease.
- Contraindicated in pregnant women or in patients with hepatic disease.

# Progestogens

- The natural progestogen, is produced in response to LH by both females and males.
- In females: secreted by the corpus luteum, primarily during the second half of the menstrual cycle, and by the placenta.
- In males: secreted by the testes (anti-estrogenic effects)
- It is also synthesized by the adrenal cortex in both sexes.
- It serves as a precursor to the estrogens, androgens, and adrenocortical steroids

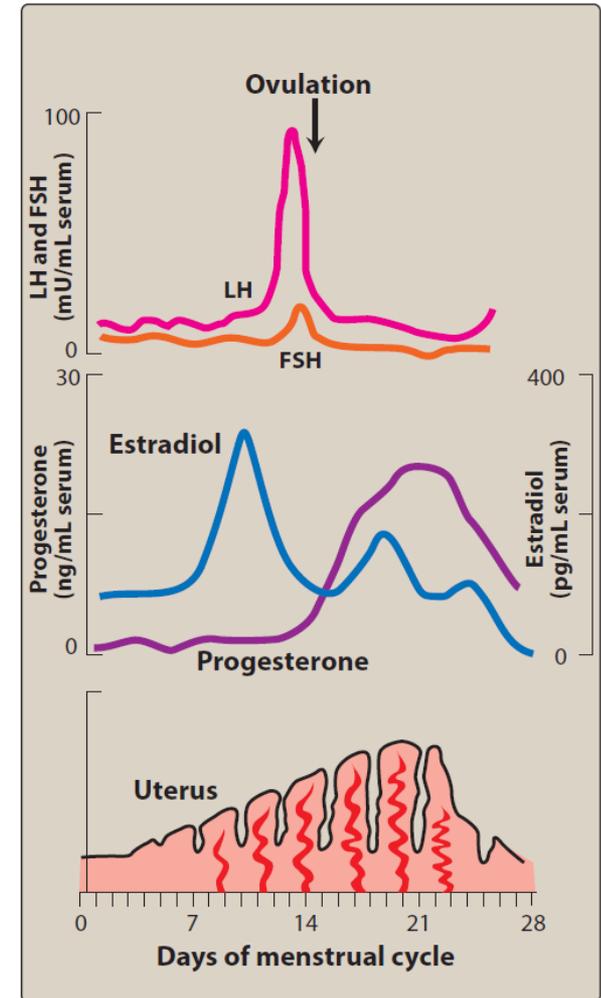
# Mechanism of action of Progestogens in Females

- It is elevated during the second half of the menstrual cycle (the luteal phase)
- It promotes the development of a secretory endometrium that can accommodate implantation of a newly forming embryo.
- The high levels of progesterone inhibits the production of gonadotropin and, therefore, prevent further ovulation



# Mechanism of action of Progestogens in Females

- If conception takes place, progesterone continues to be secreted
- Progesterone maintains 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



# Therapeutic uses of progestogens

- Contraception (+/- estrogen)
- Treatment of hormone deficiency
- Control of dysfunctional uterine bleeding
- Treatment of dysmenorrhea
- Management of endometriosis
- Management of some types of infertility

# Progestogens in Contraception

- Progestin also thickens the cervical mucus, thus hampering the transport of sperm.
- Synthetic progestogens (Progestins) are mainly used, more stable to first-pass metabolism
- **Oral Progestins include:**
  - Desogestrel
  - Drospirenone
  - Norgestrel
  - Levonorgestrel
  - Norethindrone
  - Norethindrone acetate
  - Norgestimate
  - Medroxyprogesterone

## Adverse effects Progestogens

- Headache
- Depression
- Weight gain
- Changes in libido
- Drospirenone may raise serum potassium due to antimineralocorticoid effects
- Some have prominent **androgenic activity** and can cause **acne** and **hirsutism** (Norethindrone, Norethindrone acetate, Norgestrel, Levonorgestrel)
- **Less androgenic** progestins (Norgestimate and drospirenone) may be preferred in women with acne

# Antiprogestin

- **Mifepristone** (RU-486) is a progesterone antagonist with partial agonist activity
- **Clinical use:** administered in early pregnancy to induce abortion
- Often combined with the prostaglandin analog **Misoprostol** to induce uterine contractions
- **The major adverse effects:**
  - Significant uterine bleeding
  - Possibility of an incomplete abortion

# Hormonal Contraceptives

- **Major classes of hormonal contraceptives**
  - Combination oral contraceptives
  - Transdermal patch
  - Progestin-only pills
  - Injectable progestin
  - Progestin implants
  - Progestin intrauterine device
  - Postcoital contraception

# Mechanism of action of Hormonal Contraceptives

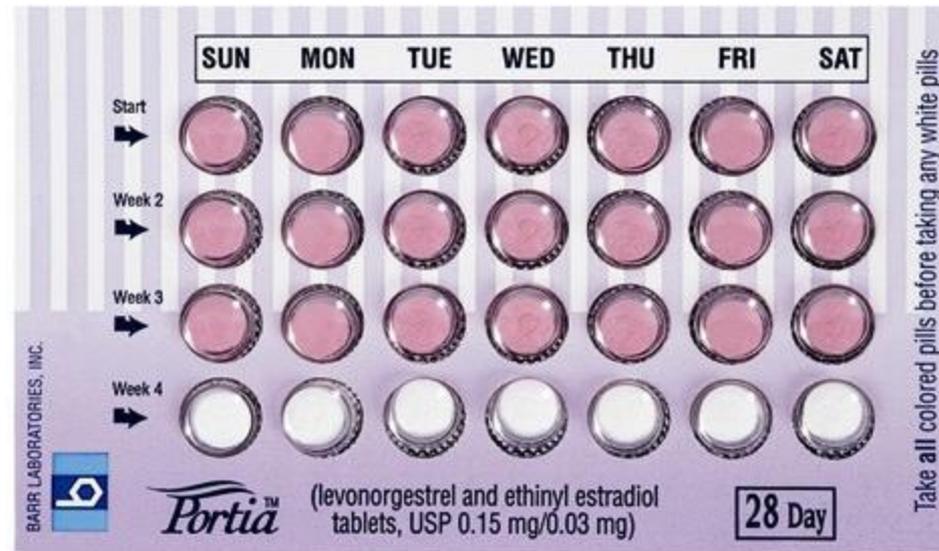
- Estrogen provides a negative feedback on the release of LH and FSH by the pituitary gland, thus preventing ovulation.
- Progestin also thickens the cervical mucus, thus hampering the transport of sperm.
- Withdrawal of the progestin stimulates menstrual bleeding during the placebo week.

## Combination oral contraceptives

- 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
- The most common estrogen in the combination pills is ethinyl estradiol.
- The most common progestins are norethindrone, norethindrone acetate, levonorgestrel, desogestrel, norgestimate, and drospirenone.

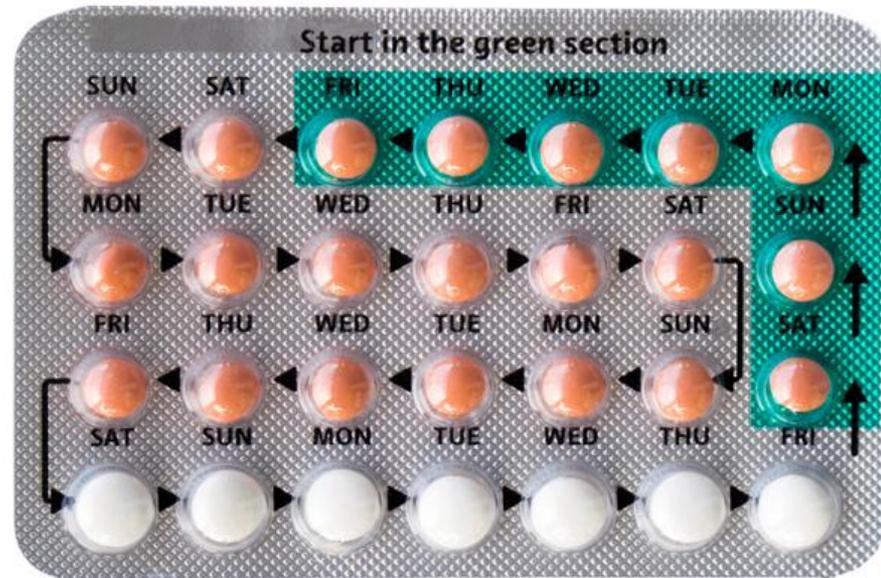
# Combination oral contraceptives

- Estrogens + Progestins
- Most common type of oral contraceptives
- **Monophasic combination pills** contain a constant dose of estrogen and progestin given over 21 to 24 days



## Combination oral contraceptives

- **Biphasic combination pills** deliver the same amount of estrogen each day, but the level of progestin is increased about halfway through the cycle



# Combination oral contraceptives

- **Triphasic combination pills**

- Attempt to mimic the natural female cycle and most contain
- Contain 3 different doses of hormones in the 3 weeks of active pills, so the hormone combination changes approximately every 7 days throughout the pill pack.
- The amount of estrogen may change as well as the amount of progestin



# Combination oral contraceptives

- Continuous dosage products” are available
- Contain ethinyl estradiol and levonorgestrel and are taken every day for 84 days followed by 7 days of inert tablets (Seasonale) or 7 days of low-dose ethinyl estradiol (Seasonique)
- Produce four menstrual periods per year

## Combination oral contraceptives

- Lybrel contains the same hormones taken continuously for 365 days to suppress menstruation completely
- These pills also affect the genital tract in ways that are unfavorable for conception: thickening cervical mucus, speeding ovum transport through the fallopian tubes, and making the endometrium less favorable for implantation

## Transdermal patch

- Alternative to combination oral contraceptives is a transdermal patch containing ethinyl estradiol and the progestin norelgestromin.
- One contraceptive 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.

## Progestin-only pills (*mini-pill*)

- Usually norethindrone
- Taken daily on a continuous Schedule.
- less effective than combination products
- May produce irregular menstrual cycles (Breakthrough bleeding is as high as 25%)
- **The mechanism of contraception** is unclear, but it is likely due to the formation of a relatively **atrophic endometrium** (which impairs implantation) and **viscous cervical mucus**

## Progestin-only pills (*mini-pill*)

- **Used for:**
  - Breast-feeding women (unlike estrogen, progestins do not affect milk production)
  - Women intolerant to estrogen
  - Smokers
  - When estrogen- containing products are contraindications

# Injectable progestin

- Medroxyprogesterone acetate is administered IM or SC
- injection every 3 months.
- **Side effects:**
  - Weight gain (common)
  - Amenorrhea (due to high sustained levels of progestin)
  - Return to fertility may be delayed for several months after discontinuation
  - Increase risk of osteoporosis and fractures (Not recommended for more than 2 years)

## Progestin implants

- Contain Etonogestrel
- Implanted subdermally
- Effective for approximately 3 years
- The implant is nearly as reliable as sterilization
- The effect is totally reversible when surgically removed
- **Principal side effects:** are irregular menstrual bleeding and headaches

# Progestin intrauterine device

- Levonorgestrel-releasing intrauterine system
- offers a highly effective method of contraception for 3 to 5 years depending on the system.
- **Suitable for:**
  - Women who desire long-term contraception
  - Those who have contraindications to estrogen therapy
- It should be avoided in patients with pelvic inflammatory disease or a history of ectopic pregnancy.

## Postcoital (emergency) contraception

- Reduces the probability of pregnancy after an episode of coitus without effective contraception
- Uses high doses of levonorgestrel (preferred) or high doses of ethinyl estradiol plus levonorgestrel.
- For maximum effectiveness, it should be taken as soon as possible after unprotected intercourse and preferably within 72 hours.
- Alternately: the progesterone agonist/antagonist ulipristal.
- Ulipristal is indicated for emergency contraception within 5 days of unprotected intercourse.

# Adverse effects oral contraceptives

- **Estrogens are associated with:**
  - Breast fullness,
  - Fluid retention
  - Headache and nausea
  - Increased blood pressure
- **Progestins are associated with**
  - Depression
  - changes in libido
  - Hirsutism
  - Acne

# Adverse effects of oral contraceptives

- **Rare side effects (most common among women over age 35 and smokes):**
  - Thromboembolism
  - thrombophlebitis
  - Myocardial infarction
  - Stroke
- Oral contraceptives are associated with a decreased risk of cervical and ovarian cancer 😊

# Contraindication of oral contraceptives

- The presence of cerebrovascular and thromboembolic disease
- Estrogen-dependent neoplasms
- Liver disease
- Pregnancy.

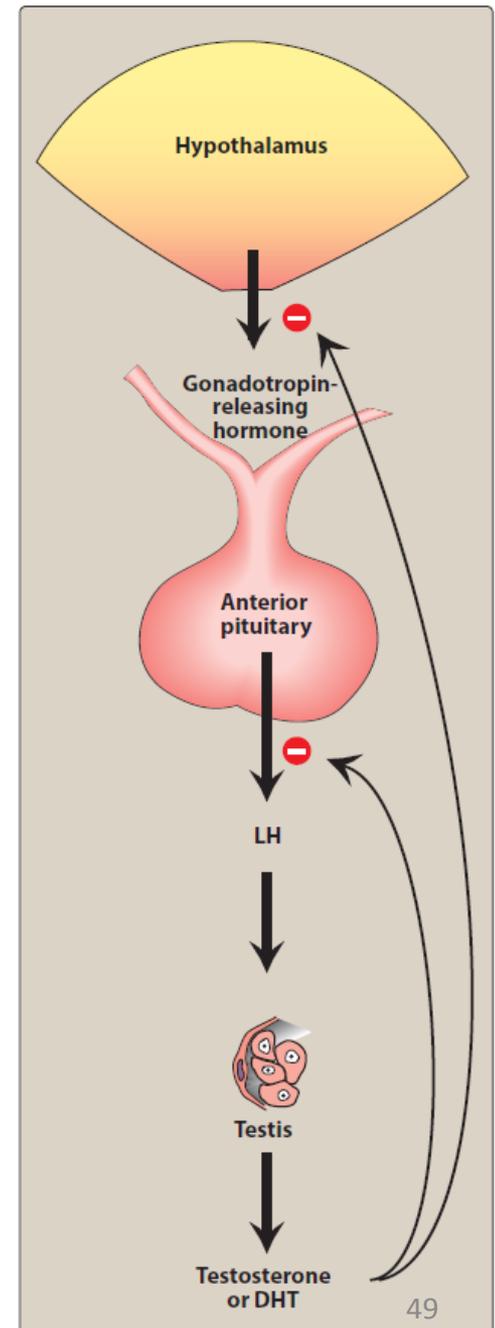
# Precautions of oral contraceptives

- Combination oral contraceptives should not be used in patients over the age of 35 who are heavy smokers
- Liver enzyme inducer drugs and those affecting enterohepatic recycling (e.g. Antibiotics) can reduce the effectiveness of contraception!

# Androgens

# Androgens

- A group of steroids that have anabolic and/or masculinizing effects in both males and females
- Testosterone is the most important androgen
- $5\alpha$ -dihydrotestosterone (DHT) is the active form of Testosterone
- In adult males, *testosterone* secretion is controlled by GnRH- FSH and LH axis.



# Androgens

## **Testosterone is synthesized by:**

- Leydig cells in the testes
- thecal cells in the ovaries (smaller amounts)
- Adrenal gland in both sexes

# Physiological functions of Androgens

- 1) Normal maturation in the male
- 2) Sperm production
- 3) Increase synthesis of muscle proteins and hemoglobin
- 4) Decrease bone resorption

## Therapeutic uses of Androgens

- Males with primary hypogonadism (caused by testicular dysfunction)
- Secondary hypogonadism (due to failure of the hypothalamus or pituitary)
- Anabolic steroids can be used to treat chronic wasting associated with human immunodeficiency virus or cancer
- Unapproved use of anabolic steroids is to increase lean body mass, muscle strength, and endurance in athletes and body builders

## Adverse effects of Androgens in Females

- Masculinization
- Acne
- Growth of facial hair
- Deepening of the voice
- Male pattern baldness
- Excessive muscle development
- Menstrual irregularities
- Should not be used by pregnant women because of possible developmental effects of the female fetus

# Adverse effects of Androgens in Males

## Excess androgens can cause:

- Impotence
- Decreased spermatogenesis
- Gynecomastia
- Stimulate growth of the prostate
- Baldness

## **Adverse effects of Androgens in children**

- Androgens can cause abnormal sexual maturation
- Growth disturbances resulting from premature closing of the epiphyseal plates, which stunts growth and interrupts development

# Adverse effects of Androgens in Athletes

- Premature closing of the epiphysis of the long bones.
- Reduction of testicular size
- Hepatic abnormalities
- Increased aggression
- Major mood disorders

## General Adverse effects of Androgens

- Can increase serum LDL and lower serum HDL.
- Fluid retention leading to edema

## Anti-androgens

- Counter male hormonal action by interfering with the synthesis of androgens or by blocking their receptors.
- **Finasteride** and dutasteride inhibit 5 $\alpha$ -reductase resulting in decreased formation of dihydrotestosterone.
- These agents are used for the treatment of benign prostatic hyperplasia.
- **Flutamide** is competitive inhibitors of androgens at the target cell. It is used for the treatment of prostate cancer.