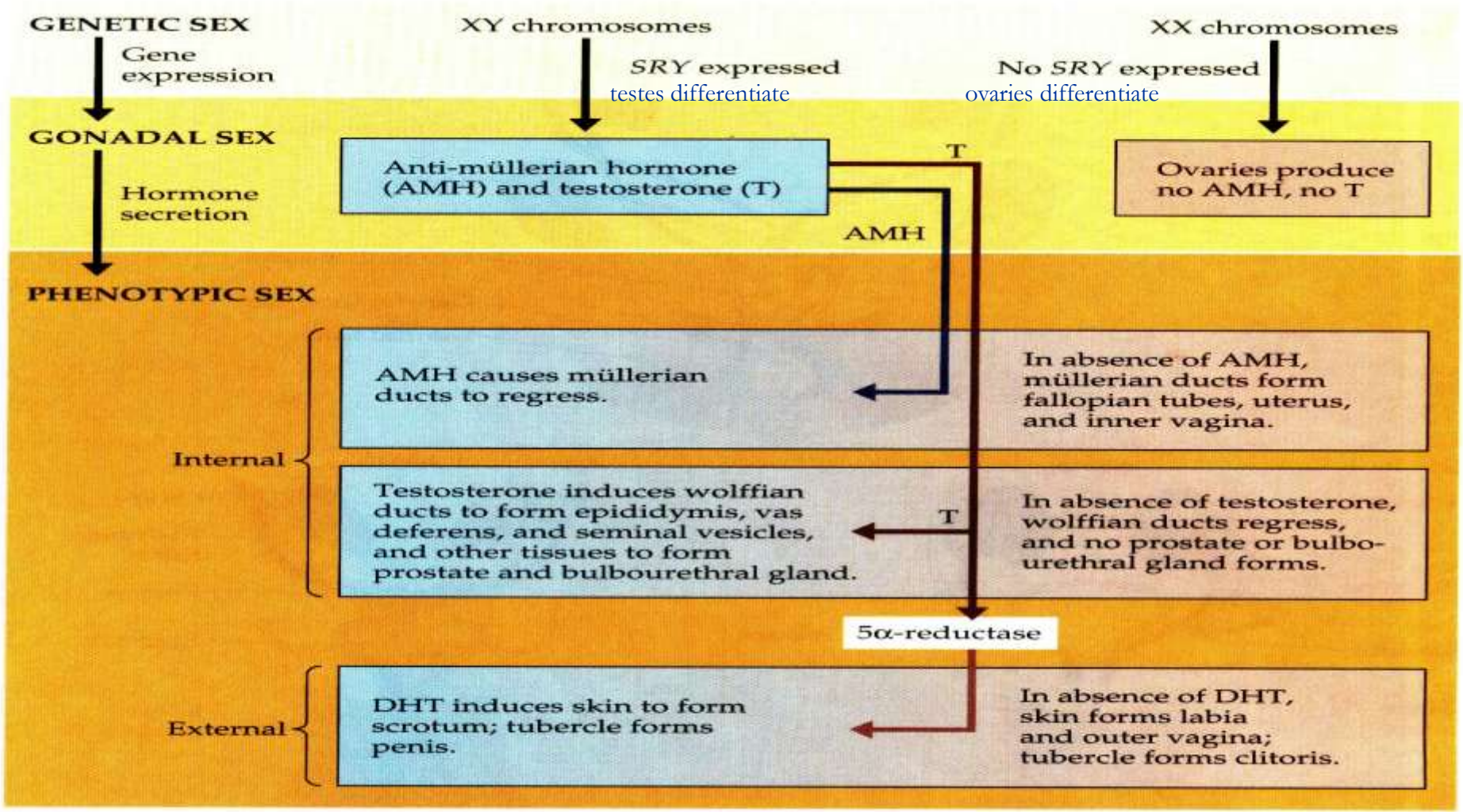
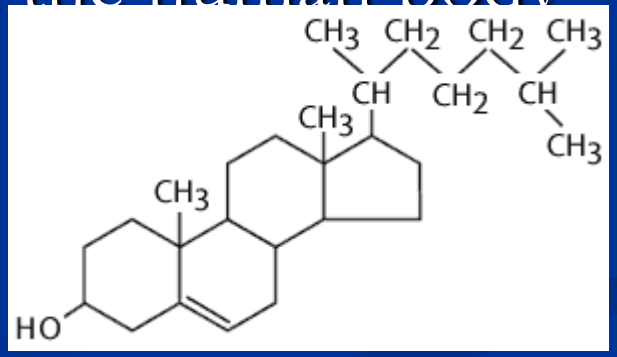

GENETIC SEX
Gene expression
XY chromosomes
SRY expressed
testes differentiate
XX chromosomes
No SRY expressed
ovaries differentiate
GONADAL SEX
Hormone secretion
Anti-müllerian hormone (AMH) and testosterone (T)
T
AMH
Ovaries produce no AMH, no T
PHENOTYPIC SEX
Internal
AMH causes müllerian ducts to regress.
In absence of AMH, müllerian ducts form fallopian tubes, uterus, and inner vagina.
Testosterone induces wolffian ducts to form epididymis, vas deferens, and seminal vesicles, and other tissues to form prostate and bulbourethral gland.
T
In absence of testosterone, wolffian ducts regress, and no prostate or bulbo-urethral gland forms.
5α-reductase
External
DHT induces skin to form scrotum; tubercle forms penis.
In absence of DHT, skin forms labia and outer vagina; tubercle forms clitoris.

Steroids basics

- Steroid hormones are all derived from cholesterol
- Cholesterol contains cyclopentanophenanthrene ring
- Estrogen and progestins are just two of the many steroids found in the human body



Cholesterol

Steroid Hormones

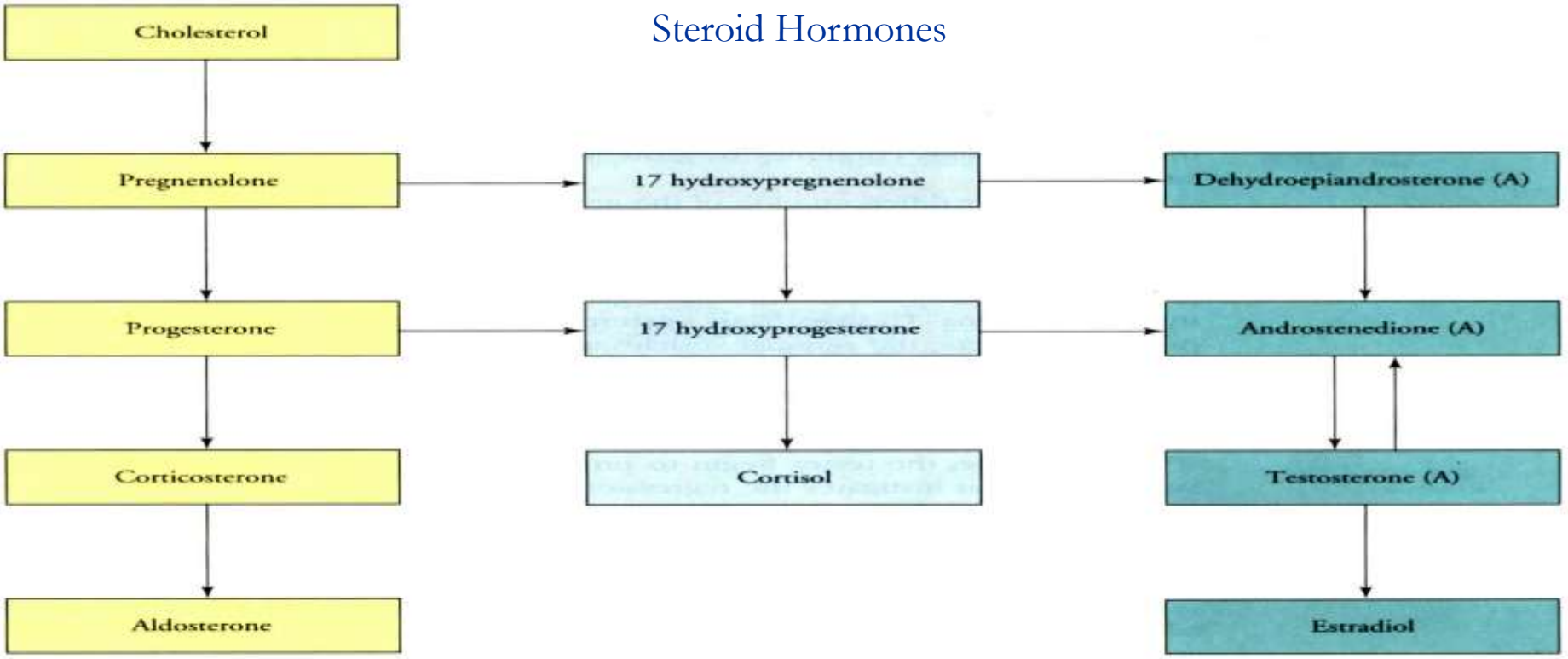


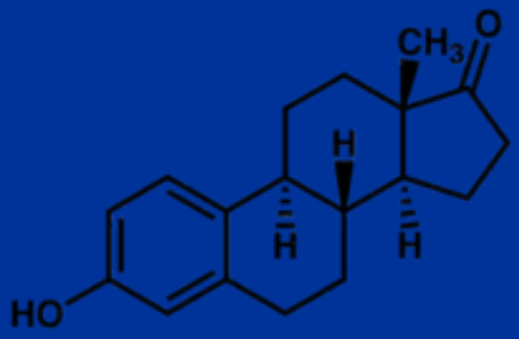
FIGURE 12.5 • The Gonadal Steroid Hormones and Related Steroid Compounds

Female Sex Hormones (Estrogens and Progestins)

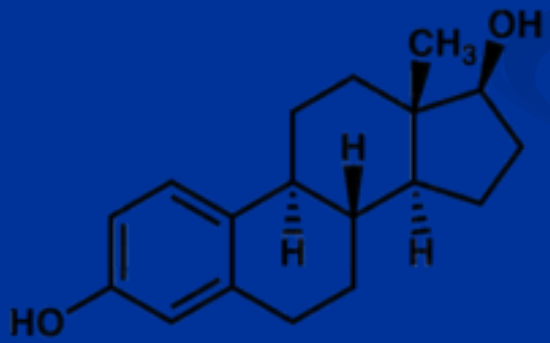
- **Control:**
  - Follicle –Stimulating Hormone (FSH) stimulate the production of Estrogens.
  - Luteinizing Hormone (LH) stimulate the production of Progestins.

Estrogens

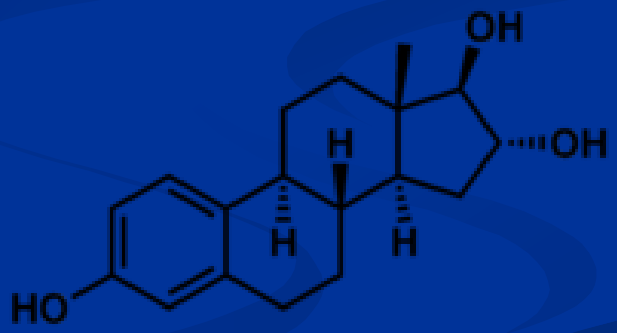
- **Fun fact:** Estrus = fertile, gen = to generate in Latin
- Three major types of natural estrogens



Estrone (E1)



Estradiol (E2)
Most common!

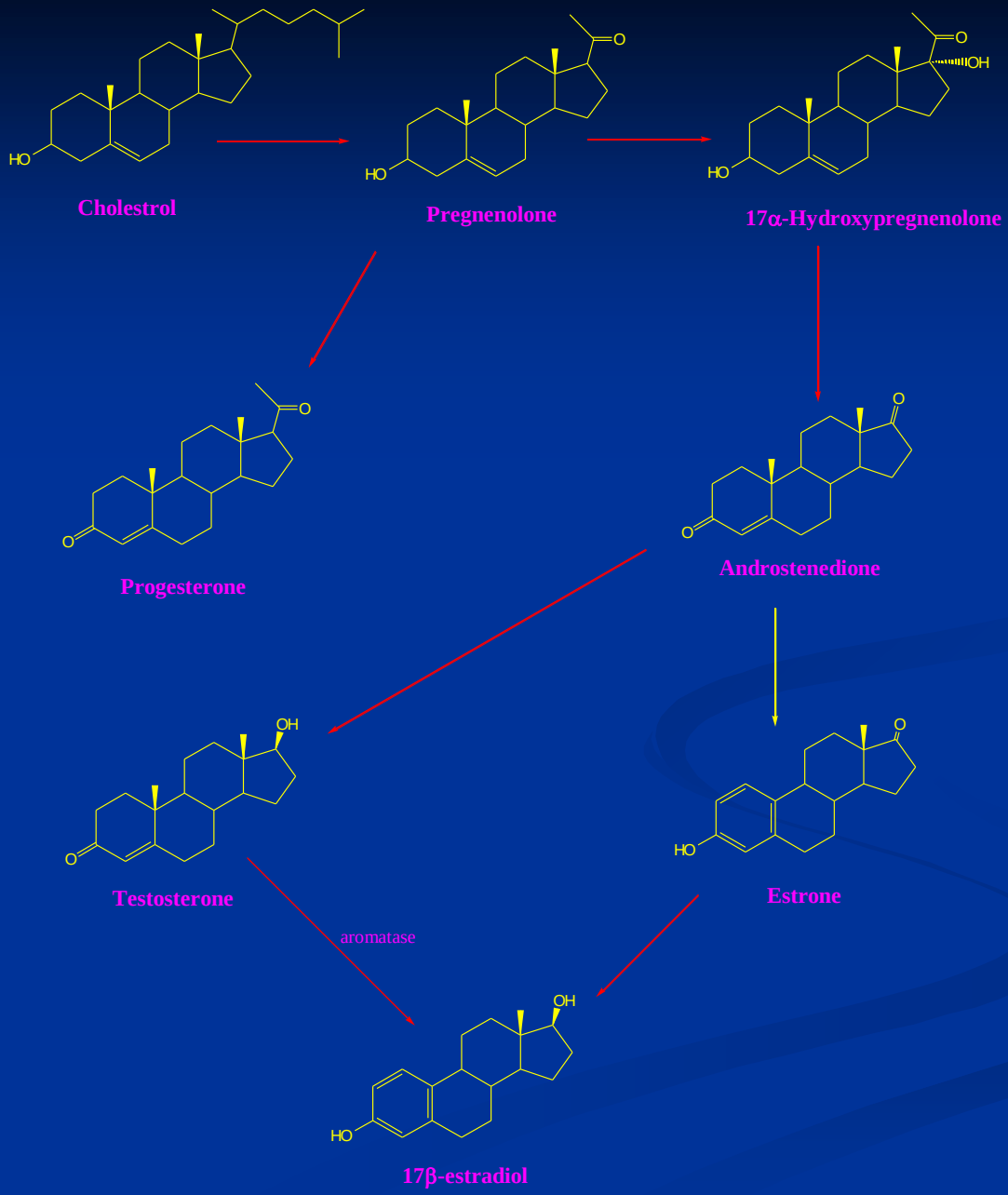


Estriol (E3)

Structure Activity Relation Ships:

- Aromatic ring with C-3-OH is essential for activity.
- Steroidal structures is not essential for activity.
- Alkylation of the aromatic ring decrease the activity.
- The 17b-hydroxyl with constant distance from 3-OH is essential for activity.
- The group between the two hydroxyl must be hydrophobic.
- Unsaturation of ring B decreases the activity.
- 17a- and 16 position when modified enhance the activity.

Biosynthesis of Female and Male sex Hormones



How estrogens and progesterone achieve their effects

Steroids like estrogens and progesterone are small, hydrophobic molecules that are transported in the blood bound to a serum globulin.

In "target" cells, i.e., cells that change their gene expression in response to the hormone, they bind to receptor proteins located in the cytoplasm and/or nucleus.

The hormone-receptor complex enters the nucleus (if it formed in the cytoplasm) and
binds to specific sequences of DNA, called the estrogen (or progesterone) response elements

How estrogens and progesterone achieve their effects

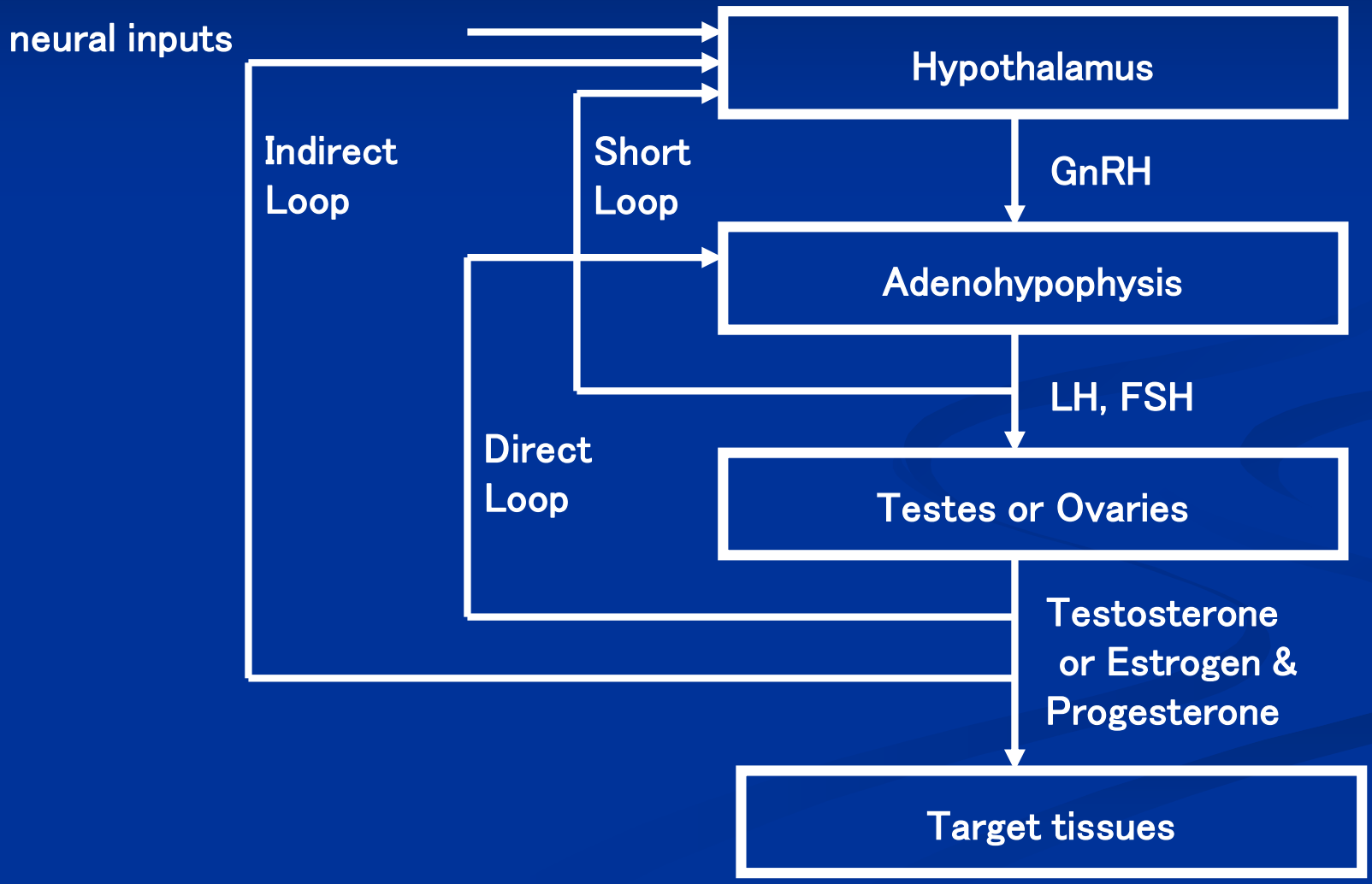
Response elements are located in the promoters of genes.
The hormone-receptor complex acts as a transcription factor (often recruiting other transcription factors to help) which
turns on (sometimes off) transcription of those genes.
Gene expression in the cell produces the response.

Regulation of Estrogen and Progesterone

The synthesis and secretion of estrogens is stimulated by follicle-stimulating hormone (FSH), which is, in turn, controlled by the hypothalamic gonadotropin releasing hormone (GnRH).

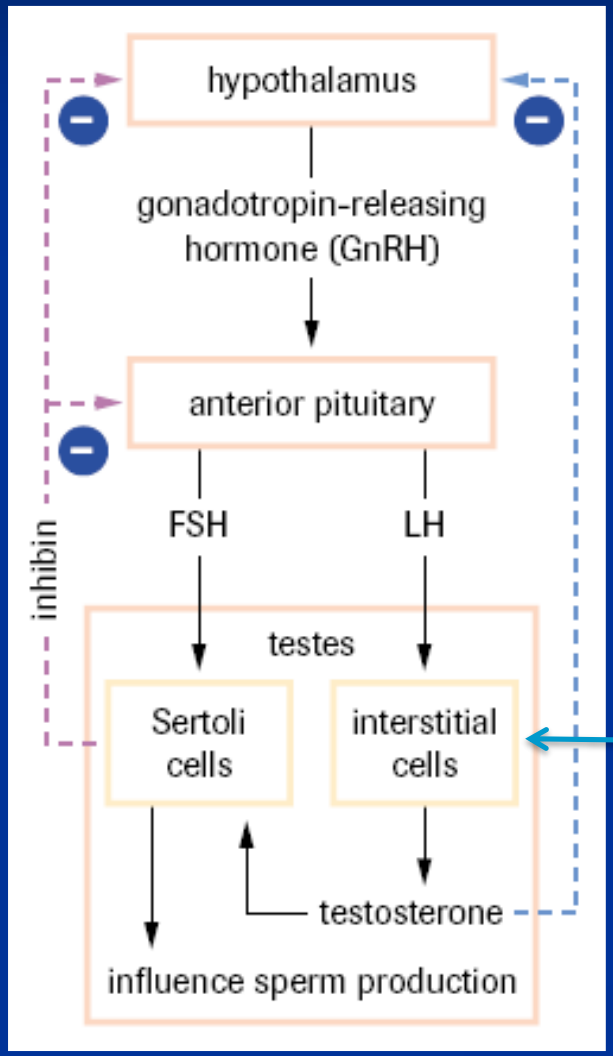
Hypothalamus→GnRH→
Pituitary→FSH→Follicle→Estrogens

Control of Sex Hormones



HPG axis & Reproductive System

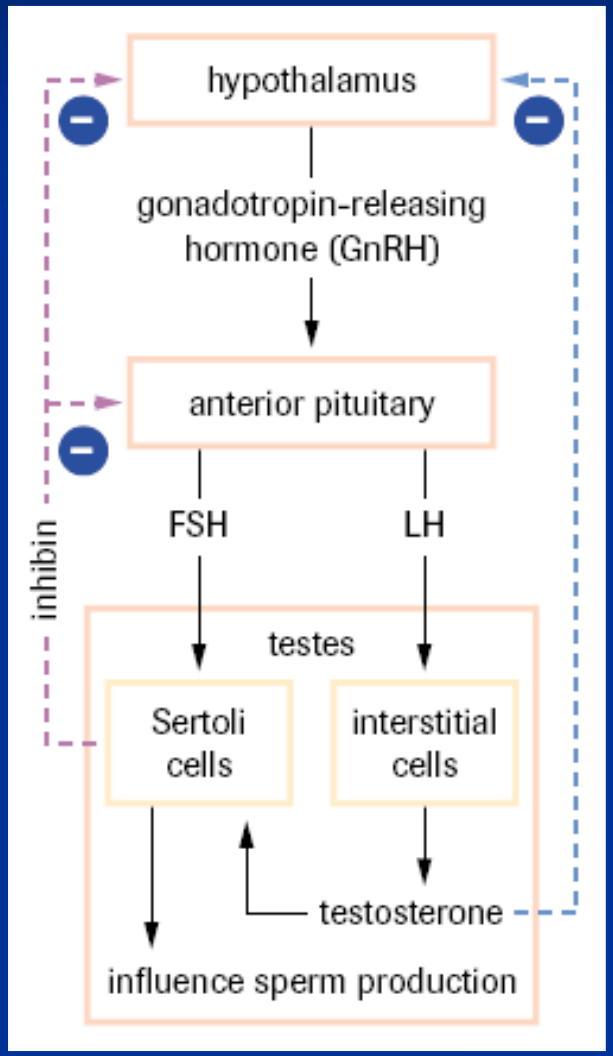
Males



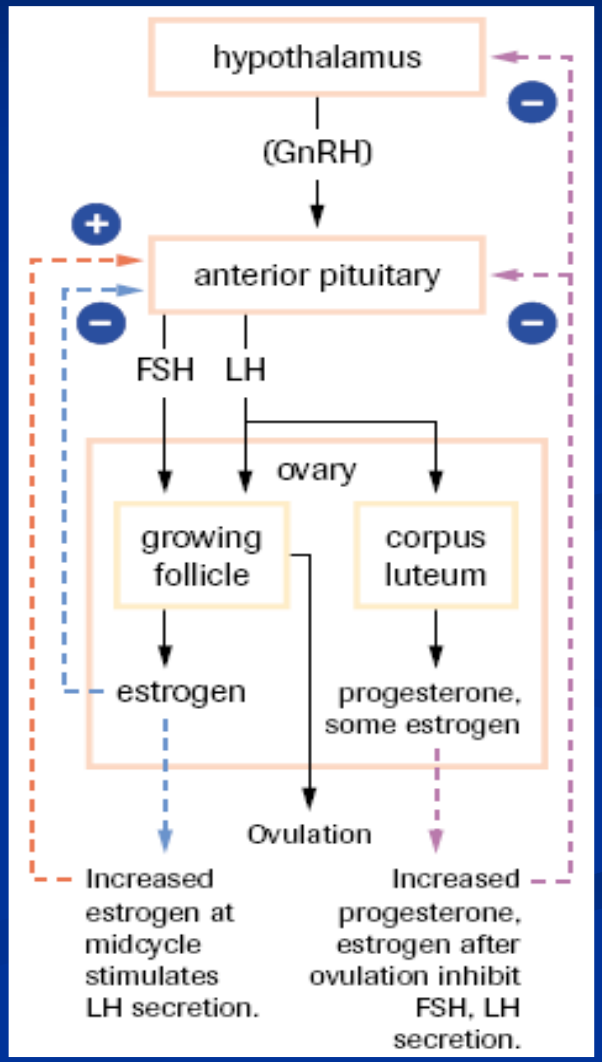
Also known as Leydig cells

HPG axis & Reproductive System

Males



Females



Physiological Effects

- Development of the female sexual organs.
- Development of the female secondary sex characters.
- Control of the menstrual cycle.

Uses

- Birth control pills.
- Failure of ovarian development.
- Menstrual disturbances.
- Suppress lactation after birth.
- Postmenopausal osteoporosis.
- Prostate cancer.

Side Effects

- Nausea, vomiting and diarrhea.
- Sodium and water retention.
- Inhibition of ovulation in large doses.
- Accelerate epiphyseal closure.

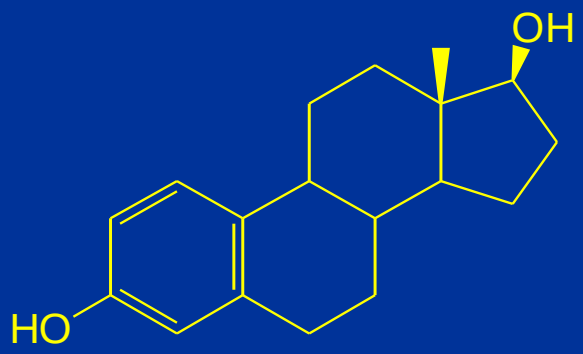
Estrogens also have non-reproductive effects.

They antagonize the effects of the parathyroid hormone, minimizing the loss of calcium from bones and thus helping to keep bones strong.

They promote blood clotting.

Steroidal Estrogenic Drugs:

- **Estradiol:**
  - Most active natural estrogen.
  - Very short duration of action due to first pass metabolism.
  - Mainly used for local effect on the uterus.
- **Ethinyl estradiol:**
  - 15- 20 more potent than estradiol orally.



17β-estradiol

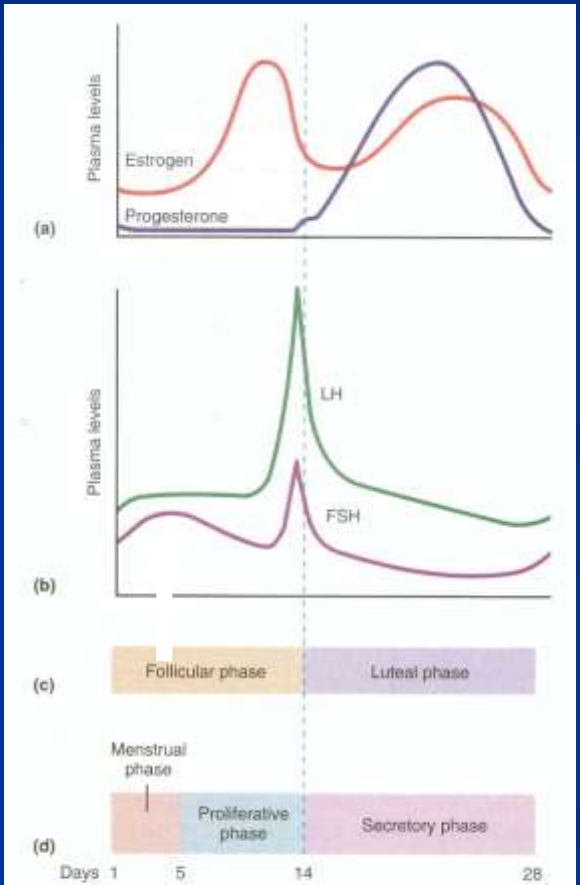
Ethinyl estradiol

(Stertoidal Semisynthetic estrogen)

1. HYPOTHALAMUS RELEASES GONADOTROPIN-RELEASING HORMONE (GnRH). This stimulates the anterior pituitary to release FSH and LH.
2. FSH STIMULATES MATURATION OF PRIMARY OOCYTE IN AN IMMATURE FOLLICLE.
3. FOLLICLE PRODUCES ESTROGEN. Estrogen: (A) builds the uterine wall (the endometrium); (B) inhibits secretion of FSH.
4. HIGH LEVELS OF ESTROGEN FURTHER STIMULATE SECRETION OF LH BY ANTERIOR PITUITARY. This plus FSH also causes ovulation of the secondary oocyte – leaving follicle without egg (the corpus luteum).
5. CORPUS LUTEUM SECRETES ESTROGEN AND PROGESTERONE. This maintains the endometrium for 15-16 days and inhibits LH.
6. (If oocyte is not fertilized and implanted in the uterine wall) CORPUS DEGENERATES (TO CORPUS ALBICANS) AND STOPS PRODUCING ESTROGEN AND PROGESTERONE.
7. WITHOUT ESTROGEN AND PROGESTERONE, ENDOMETRIUM BREAKS DOWN – MENSTRUATION OCCURS. Menstruation is the sloughing off of the enlarged endometrial wall along with blood and mucous.
8. DECREASE IN PROGESTERONE AND LH. Low LH causes secretion of FSH by pituitary again. The cycle repeats.

HORMONAL REGULATION IN NONPREGNANT FEMALE (UTERINE CYCLE)

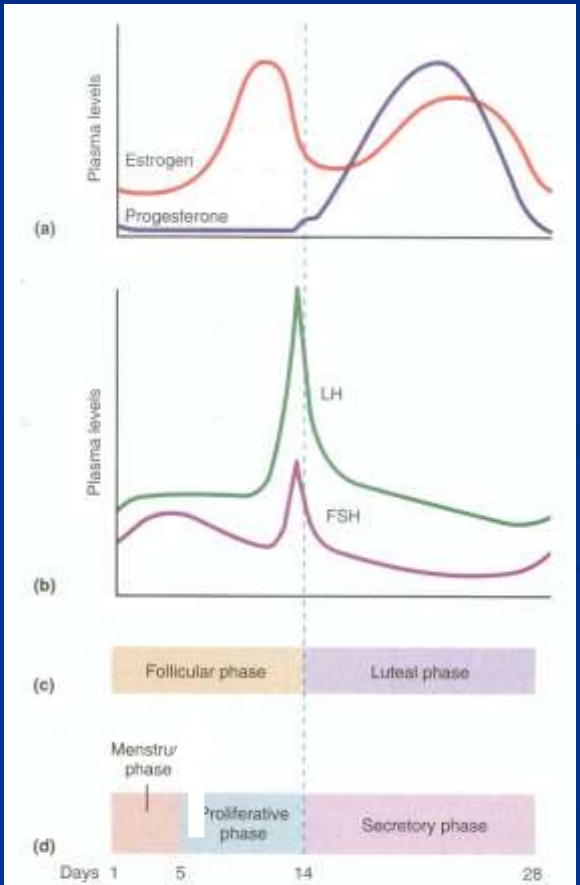
1. HYPOTHALAMUS RELEASES GONADOTROPIN-RELEASING HORMONE (GnRH). This stimulates the anterior pituitary to release FSH and LH.



Summary of events in the menstrual cycle.
(a) Plasma estrogen and progesterone levels. (b) Plasma gonadotropin levels. (c) Phases of the ovarian cycle. (d) Phases of the uterine cycle. The vertical dashed line indicates the occurrence of ovulation.

HORMONAL REGULATION IN NONPREGNANT FEMALE (UTERINE CYCLE)

2. FSH STIMULATES MATURATION OF PRIMARY OOCYTE IN AN IMMATURE FOLLICLE.



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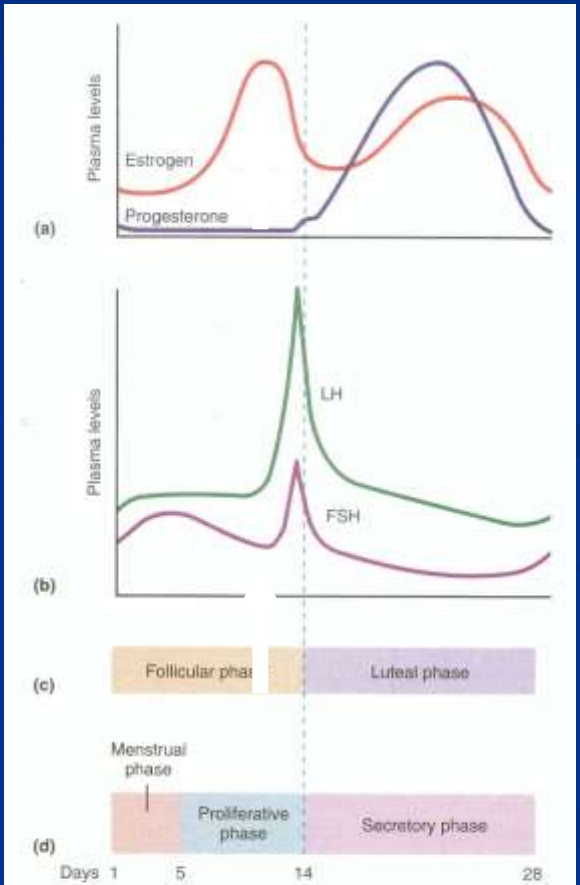
HORMONAL REGULATION IN NONPREGNANT FEMALE (UTERINE CYCLE)

3. FOLLICLE PRODUCES ESTROGEN. Estrogen: (A) builds the uterine wall (the endometrium); (B) inhibits secretion of FSH.



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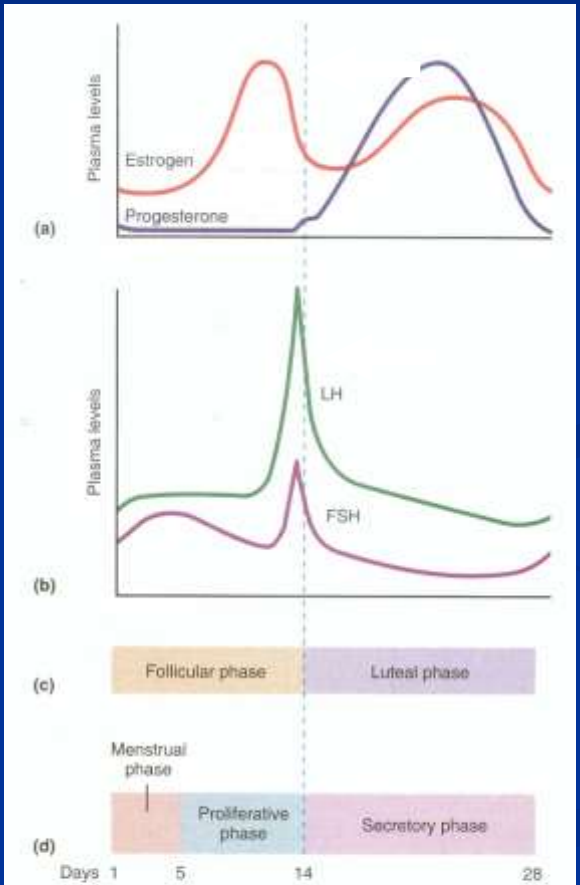
HORMONAL REGULATION IN NONPREGNANT FEMALE

4. HIGH LEVELS OF ESTROGEN FURTHER STIMULATE SECRETION OF LH BY ANTERIOR PITUITARY. This plus FSH also causes ovulation of the secondary oocyte – leaving follicle without egg (the corpus luteum). (Approximately day 15.)



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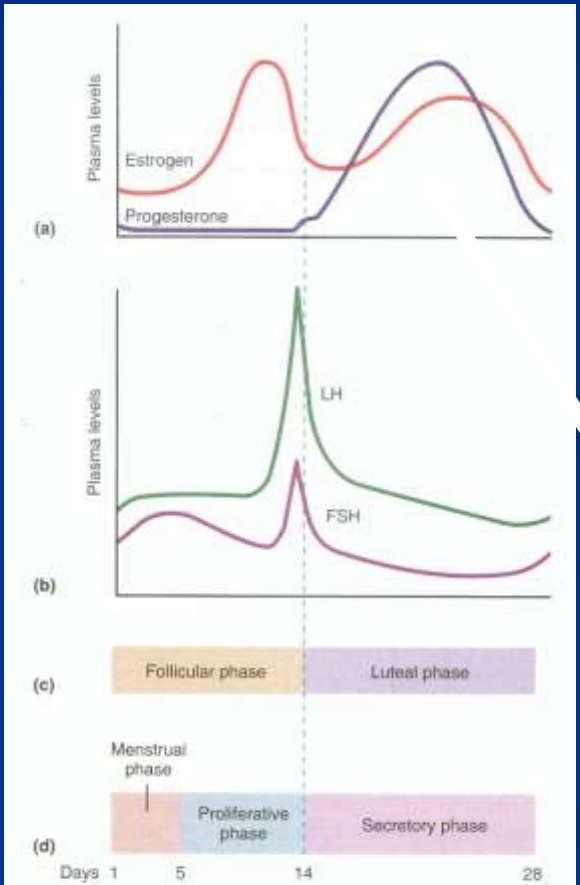
HORMONAL REGULATION IN NONPREGNANT FEMALE (UTERINE CYCLE)

5. CORPUS LUTEUM SECRETES ESTROGEN AND PROGESTERONE. This maintains the endometrium for 15-16 days and inhibits LH.



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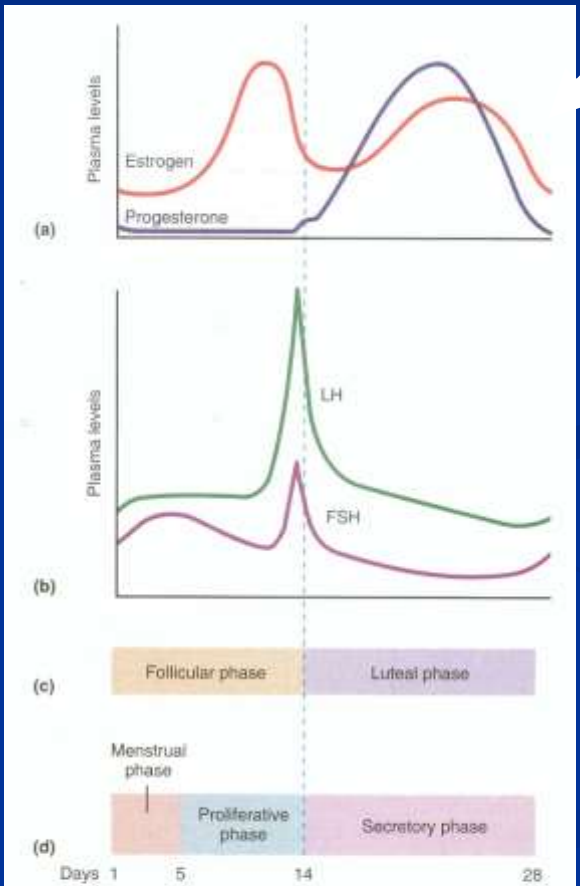
HORMONAL REGULATION IN NONPREGNANT FEMALE (UTERINE CYCLE)

6. (If oocyte is not fertilized and implanted in the uterine wall) CORPUS DEGENERATES (TO CORPUS ALBICANS) AND STOPS PRODUCING ESTROGEN AND PROGESTERONE.



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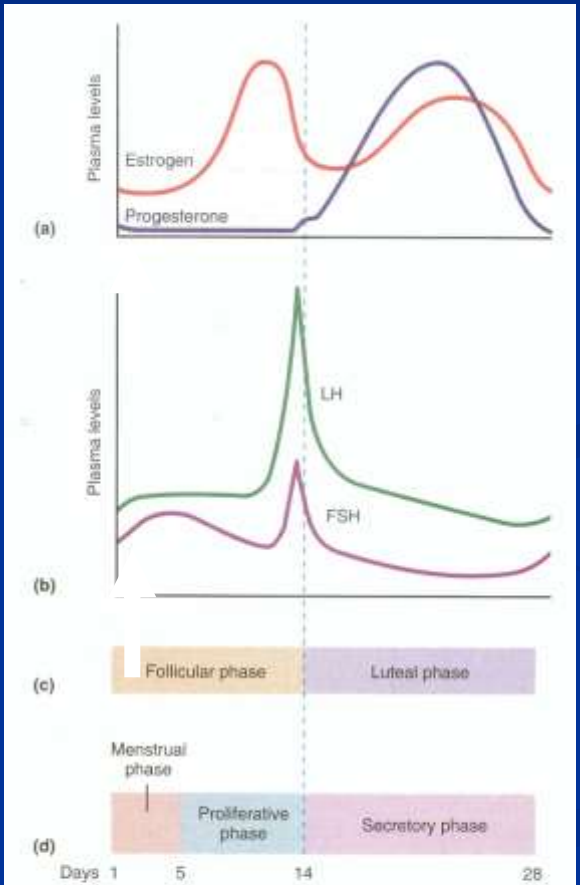
HORMONAL REGULATION IN NONPREGNANT FEMALE (UTERINE CYCLE)

7. WITHOUT ESTROGEN AND PROGESTERONE, ENDOMETRIUM BREAKS DOWN – MENSTRUATION OCCURS. Menstruation is the sloughing off of the enlarged endometrial wall along with blood and mucous.



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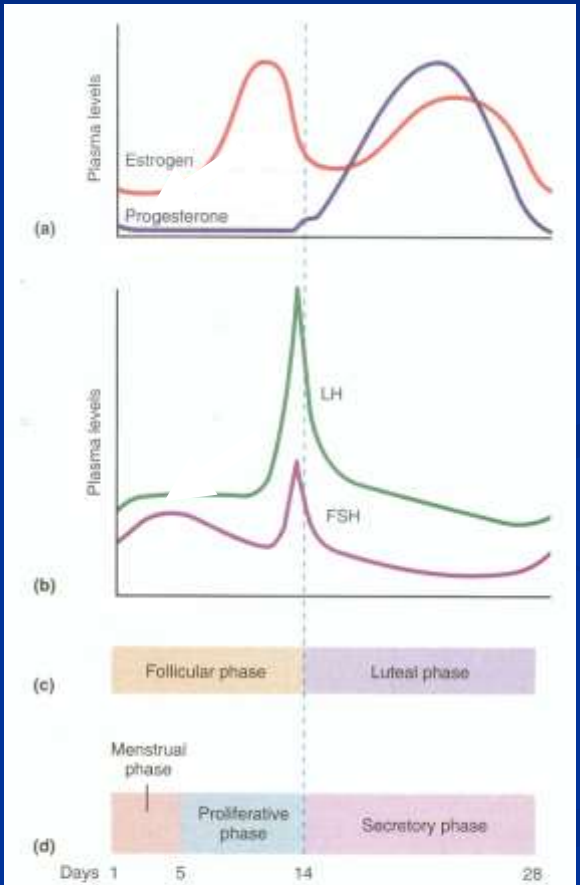
HORMONAL REGULATION IN NONPREGNANT FEMALE (UTERINE CYCLE)

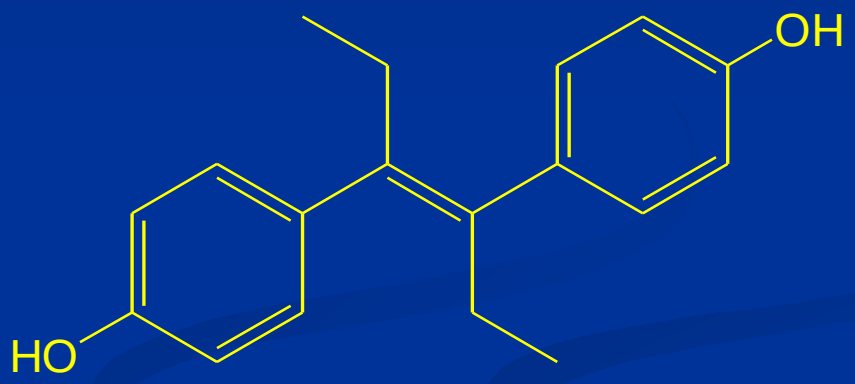
8. DECREASE IN PROGESTERONE AND LH. Low LH causes secretion of FSH by pituitary again. The cycle repeats.



Summary of events in the menstrual cycle.
(a) Plasma estrogen and progesterone levels. (b) Plasma gonadotropin levels. (c) Phases of the ovarian cycle. (d) Phases of the uterine cycle. The vertical dashed line indicates the occurrence of ovulation.

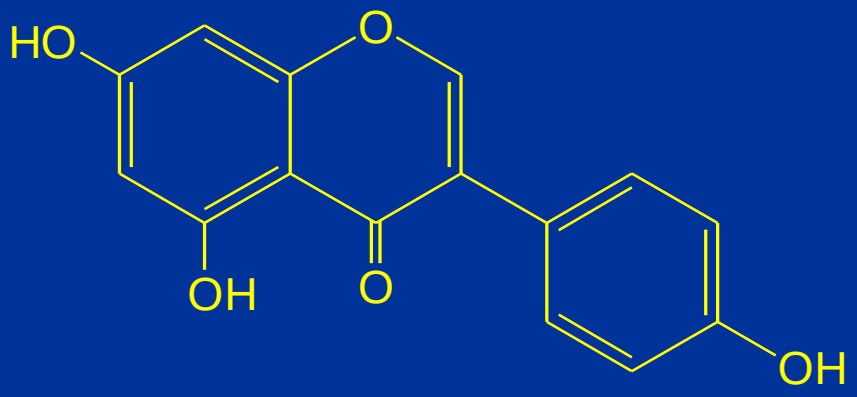
Nonsteroidal Estrogens

- **Diethylstilbesterol:**
  - The *trans* form is the active one.
  - **Advantages:**
    - As active as Estradiol.
    - Longer duration of action.
    - Orally active
    - Cheap.
  - **Disadvantages:**
    - Increase the risk of uterine cancer.
  - **Uses:**
    - Treatment of prostate cancer.

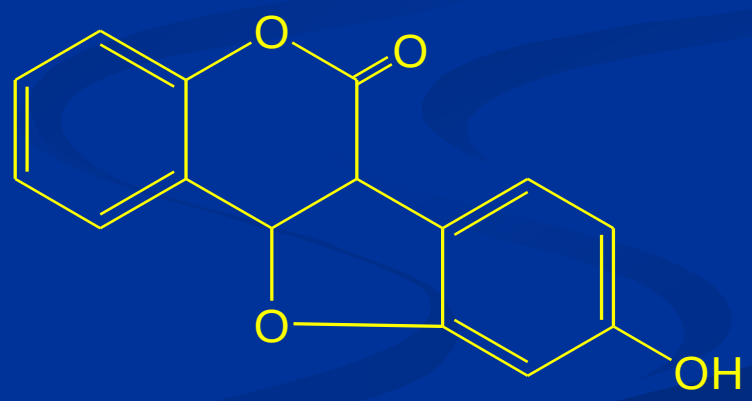


Xenoestrogens (Enviromental Estrogens)

- Estrogenic compounds with weak activity present in food and drinks.
- Isoflavones and comesterol derivatives present in family Leguminosae are examples of xenoestrogens.



Genisten



Coumesterol

Estrogen Antagonists

- Impeded Estrogens:
  - Steroids weakly bind to receptors.
  - Can compete with estrogens when reach receptors in high Concentration.
- Triphenylethylene antagonists:
  - They are related to stilbene in structure.
  - Antagonist bind strongly to the receptors.
- Aromatase inhibitors:
  - Steroidal or nonsteroidal.
  - Block conversion of androgens to estrogens.
- **<u>Uses:</u> Treatment of estrogen dependent cancers.**

Progestins

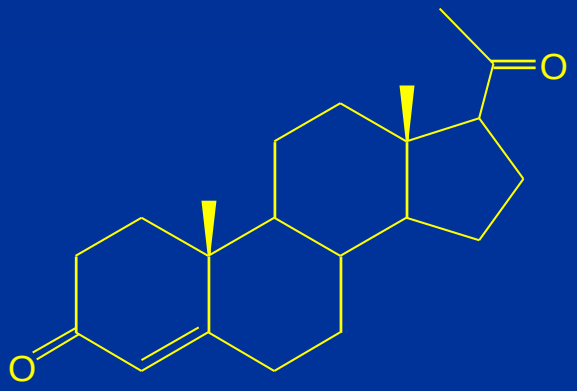
- **Progesterone in the major natural progestin.**
- **Secretion:** By the ovary mainly the corpus luteum during the second half of the menstrual cycle.
- **Physiological Effects:**
  - **Development of the endometrium.**
  - **Development of the mammary gland during pregnancy.**
  - **Milk secretion stats when its level decrease with birth.**
  - **Thermogenic action.**

Structure Activity Relation-ships:

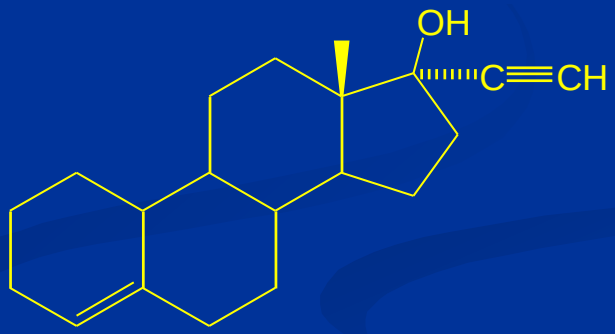
- Steroidal nucleus essential for activity.
- Have some androgenic activity.
- Removal of the 19 CH_3 increase activity.
- Unsaturation of ring B or C increase the activity.
- Removal of the keto function remove androgenic activity.

Progestrogenic Drugs

- **Lynestrenol:**
  - Semisynthetic progestin with pure progestrogenic activity.



Progesterone (Natural)



Lynesrenol (Synthetic)

Uses:

- Contraceptive pills.
- Uterine bleeding.
- Prevention of abortion.
- Amenorrhea, dysmenorrhea, endometriosis.
- Suppression of lactation.
- Endometrial, renal and breast carcinoma.
- Enhance respiration (for Hypoventilation).

Side Effects:

Nausea, vomiting, irregular bleeding, edema, weight gain, breakthrough bleeding, beast disconfort.

Progestin Antagonists:

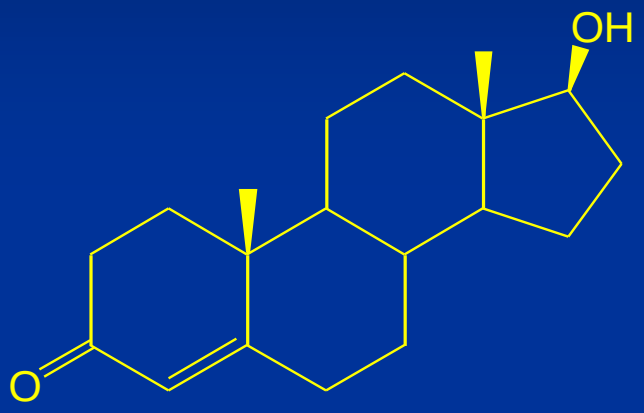
- Mifepristone:
  - Compete with the progestin receptors.
  - **Uses:**
    - Contraceptive.
    - Abortifacient.

- **Side Effects (Due to Estrogens):**
  - Increase risk of breast, vaginal and uterine cancers.
  - Increase risk of thromboembolic and vascular problems.
  - Nausea, vomiting, headache, menstrual disturbances and weight gain.

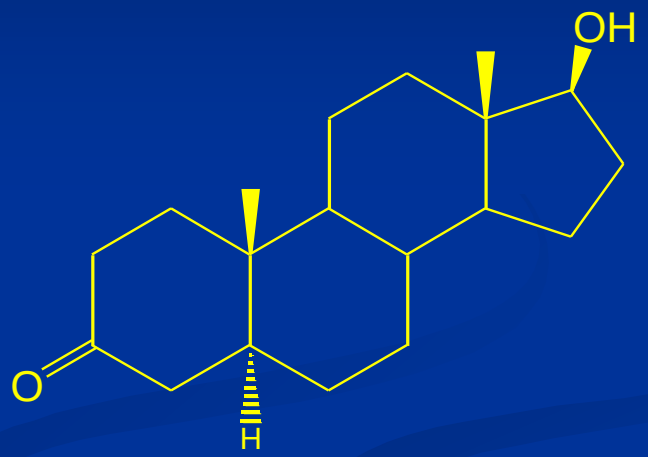
Male Sex Hormones (Androgens)

- **Control:**
  - Luteinizing Hormone (LH) or Interstatial Cell-Stimulating Hormones (ICSH) stimulate the production of Androgens.

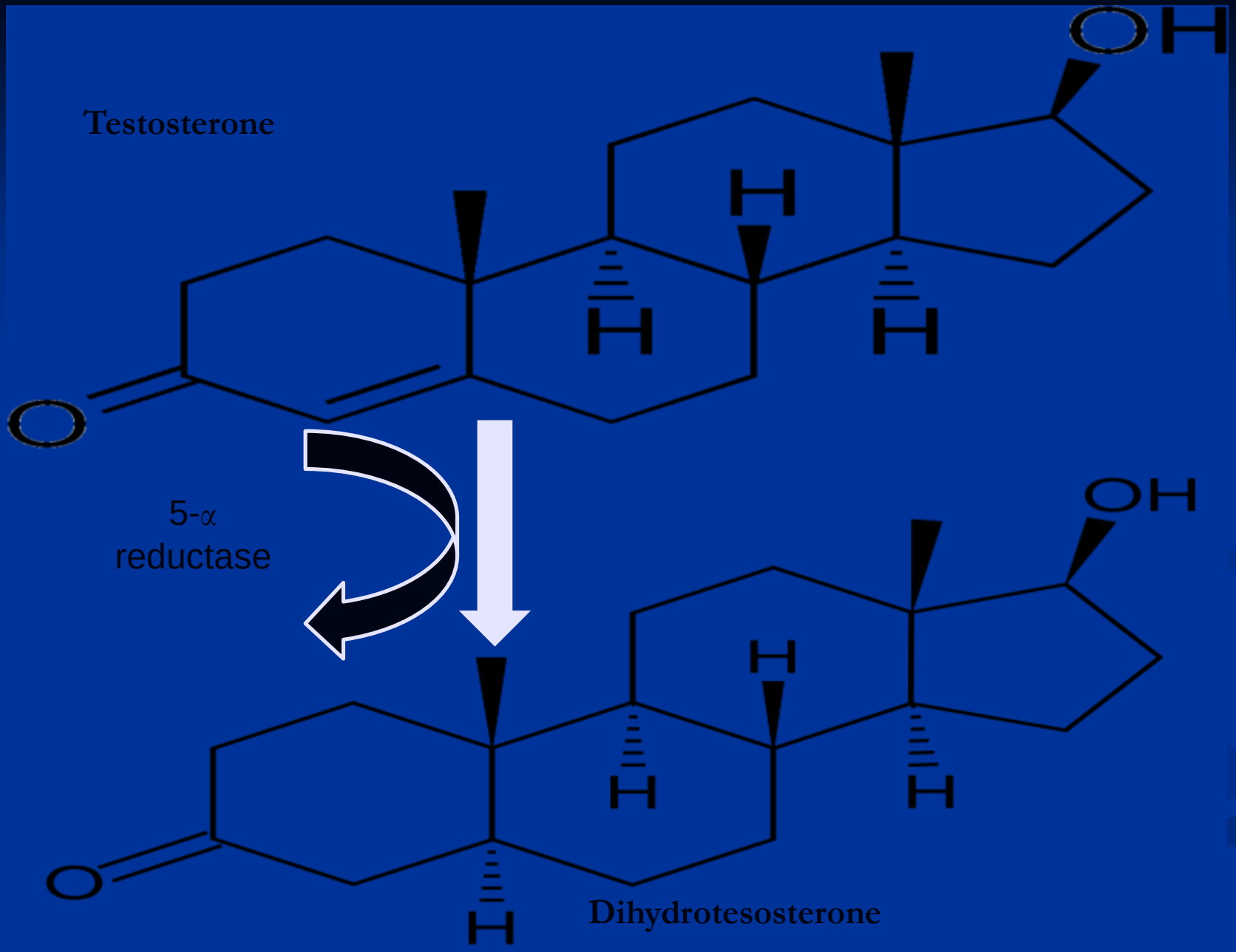
- **Natural Androgens:**



Testosterone (Natural)



Dihydrotestosterone (Natural)


Testosterone
OH
H
H
H
O
5-α
reductase
OH
H
H
H
O
Dihydrotesosterone

Males

Hypothalamus→GnRH→
Pituitary→LH→Testes→Testosterone

The level of testosterone is under negative-feedback control: a rising level of testosterone suppresses the release of GnRH from the hypothalamus. This is exactly parallel to the control of estrogen secretion in females.

Physiological Effects

- Development of the male Phenotype during embryonic life.
- Development of the male sexual organs and male secondary sex characters.
- Anabolic effect.
- Enhance growth and secretion of subaceous glands.

Uses:

- Replacement therapy in cases of hypogonadism.
- Anabolic effect.

Side Effects:

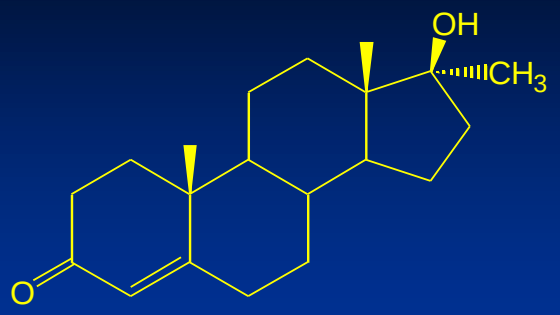
- Sodium and water retention leads to edema.
- Masculinization of women.
- Hepatic dysfunction.

Structure Activity Relation-ships:

- Steroidal nucleus essential for activity.
- The C-3 and C-17 oxygenation is not essential but they increase the activity.
- Oxidation of C-17 to carbonyl eliminates activity.
- C-17 esters prolonged the activity.
- Trans A/B ring junction is essential for activity.
- 17 α-substitutions render compounds orally active.

Androgenic Drugs

- 17 α-methyltestosterone:
  - Orally active.
  - Prolonged action.
  - Androgenic and anabolic effects.



17α-Methyltestosterone
(Semisynthetic)

- Synthetic Anabolic Steroids:
  - Norethandrolone
    - Orally active.
    - Anabolic effects.
    - C-10 CH_3 group removed to eliminate androgenic effect.

Norethandrolone
(Sythetic-Pure anabolic)

Androgen Antagonists

- **Androgen Receptor Antagonists:**
  - **Cyproterone acetate:**
    - Has antiandrogenic and progestrogenic activity.
    - Used for treatment of acne, hirsutism, prostate hypertrophy, prostate cancer and precocious puberty.
  - **Flutamide:**
    - Non steroidal antiandrogen.
    - Used for treatment of hirsutism and prostate cancer

- **5α-Reductase inhibitors:**
  - They prevent conversion of testosterone into dihydrotestosterone.
  - Used for treatment of Benign Prostatic Hyperplasia (BPH).

Male Contraceptives

- **Gossypol:**
  - Is a phenolic compound present in cotton seed oil.
  - Decrease number of sperms and impairs their motility.
  - It effect is reversible.
  - Side Effects:
    - Hypokalemia, weakness, diarrhea and edema.