

Estrogens & Antiestrogens

- **Menstrual cycle...** Changes and hormonal events

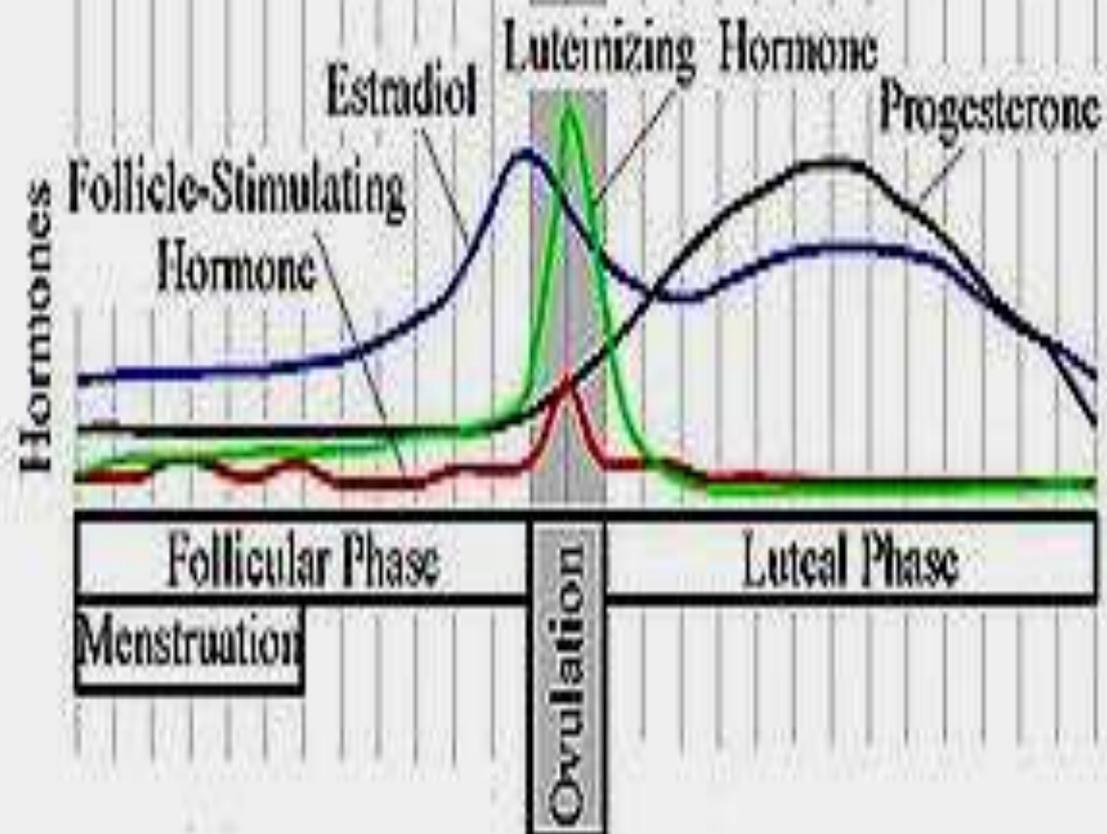
- **Natural estrogens:**

Estadiol >> Estrone > Estriol

Ineffective orally

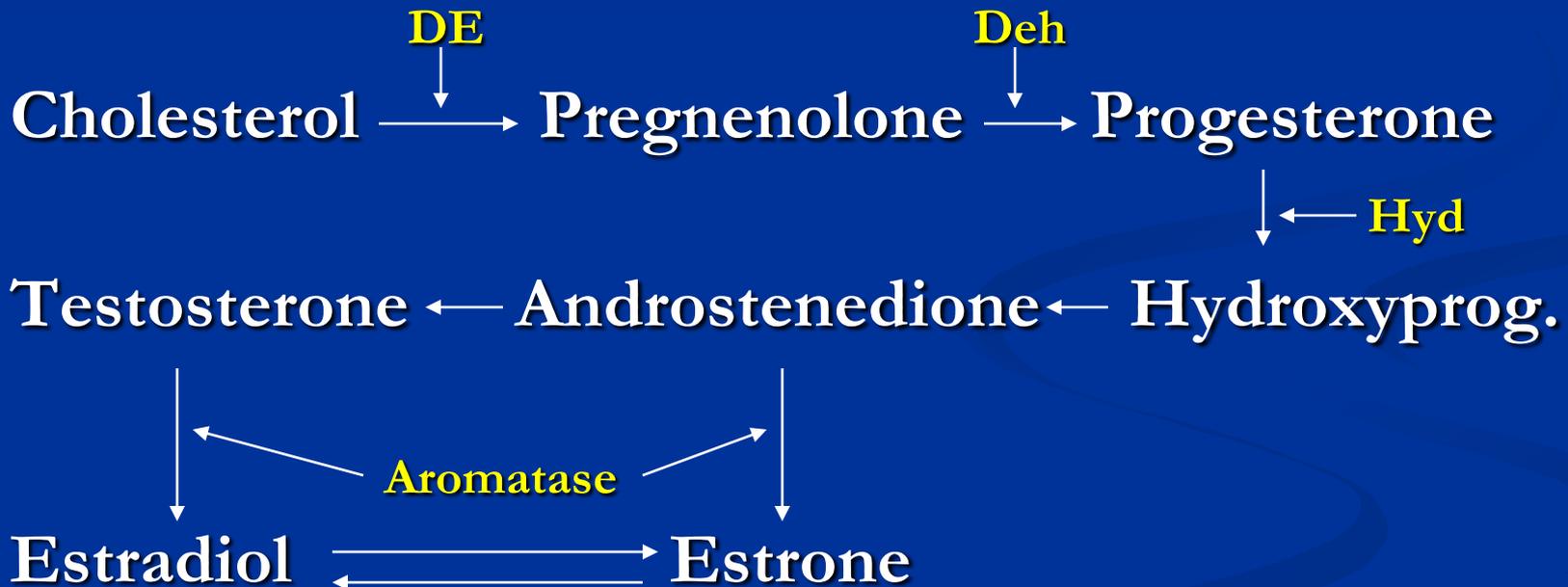
- **Synthesis:**

From cholesterol ; role of aromatase enzyme in converting androgens (testosterone & androstenedione) to estrogen



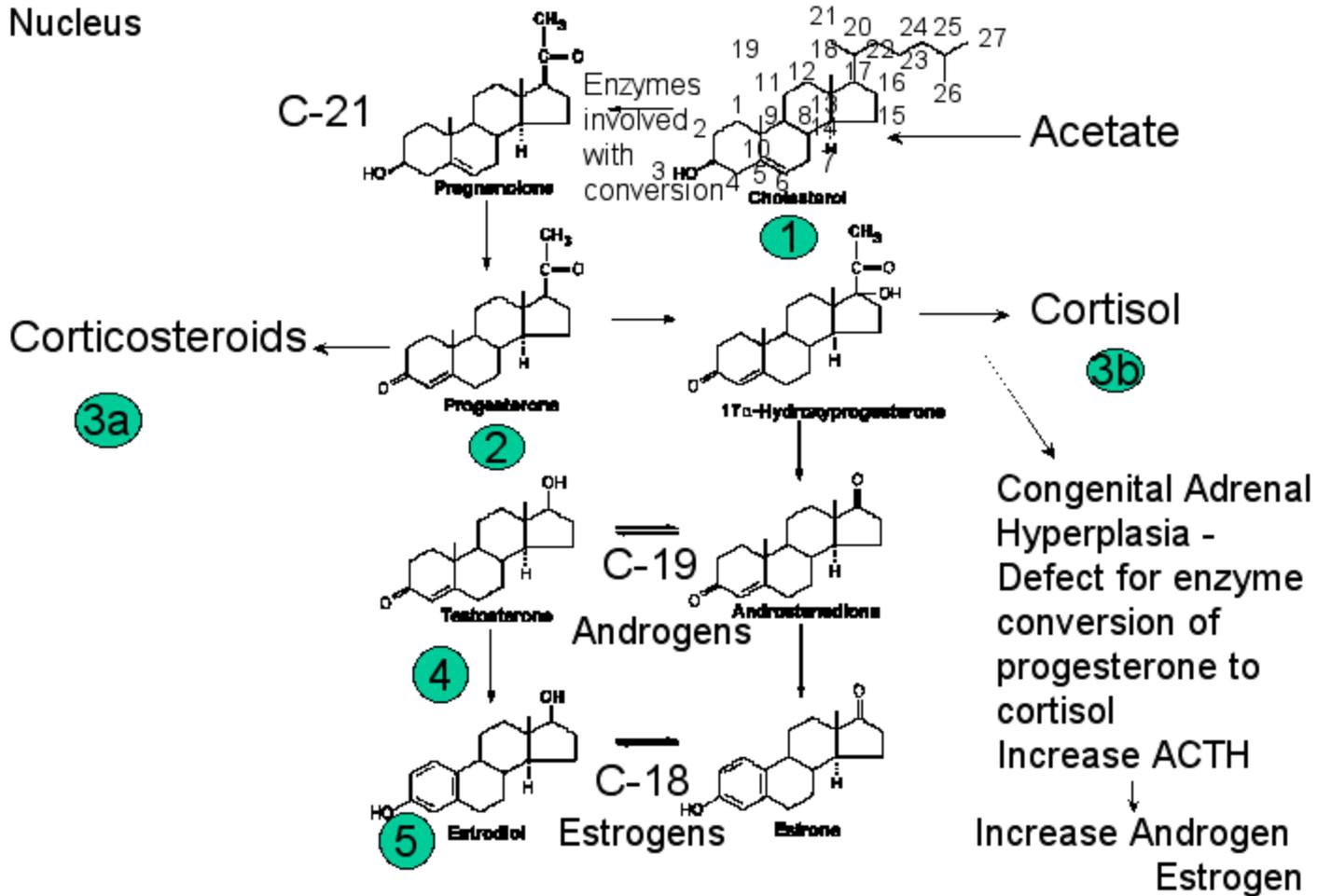
■ Estrogen synthesis:

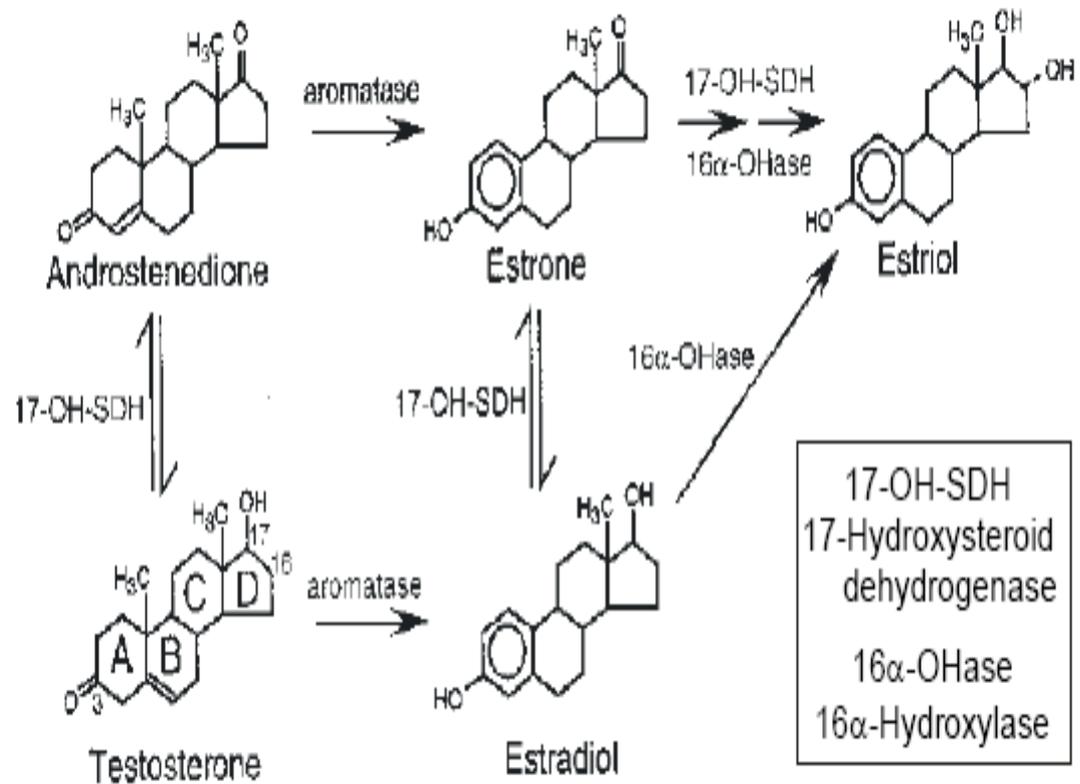
From cholesterol



Steroid Ring -
Cyclopentanoperhydrophenanthrene
Nucleus

Steroid Biosynthetic Pathway





■ **Transport:** SHBG

■ **M.O.A:**

Estrogen receptors (ER- α ; ER- β)

Modulation of gene transcription (nuclear receptors)

Stimulation of endometrial nitric oxide

synthase \rightarrow nitric oxide \rightarrow vasodilatation

\rightarrow cardioprotection

■ Estrogen actions:

- 1° & 2° sexual characteristics of females
- Proliferation of the endometrium & follicular maturation
- ↑ elasticity of skin
- ↑ synthesis of certain globulins by the liver
(SHBG, corticosteroid binding globulin & thyroid binding globulin)

Cont. estrogen actions:

- ↑ synthesis of certain clotting factors (fibrinogen, factors VII; IX & X) and ↓ activity of antithrombin III
- ↓ cholesterol, ↑ HDL & ↓ LDL blood levels
- Salt & water retention

■ Absorption & metabolism of estrogens:

Conjugation → enterohepatic circulation

■ Estrogens clinical uses:

- HRT

Postmenopausal syndrome & osteoporosis,
prevention of heart attacks

- Components of OCP's

- Prostate, breast, endometrial cancer + progesterone

- Dysmenorrhea

- Infertility

- Acne, hirsutism

■ Estrogen preparations:

- Synthetic steroidal

Estradiol benzoate; Estradiol valerate

Ethinylestradiol; Mestranol...

- Synthetic non steroidal estrogens

Diethylstilbesterol

- Conjugated estrogens

Estrone sulfonate

■ Estrogen side effects:

- Nausea & vomiting
- Headache, migrainous headache
- Dizziness, weight gain
- Salt & water retention → ↑ BP
- ↑ risk of thromboembolism and endometrial cancer
- Teratogenic effect

■ Antiestrogens:

** Competitive antagonists at estrogen receptors:

Tamoxifen & clomiphene citrate

Tamoxifen is considered an estrogen agonist on bone and endometrium; long term use of tamoxifen could lead to endometrial cancer

Tamoxifen acts also as an estrogen agonist in breast; so used in certain cases of breast cancer

Clomiphene citrate and tamoxifen act as estrogen antagonists at the level of the hypothalamus, so mainly used to manage infertility in ♂'s and ♀'s

Clomiphene citrate and tamoxifen are given orally

■ **Selective estrogen receptor modulators (SERM's):**

Nonhormonal pharmacological agents that bind estrogen receptors producing agonistic activity in certain tissues (in bone) and estrogen antagonistic effect at other tissues (breast and endometrium)

Raloxifene

Orally effective SERM widely used in the management of osteoporosis (prophylactic and R_x)

Recently some researchers consider tamoxifen and clomiphene citrate as SERM

** Aromatase inhibitors:

- Nonselective: Aminoglutithemide
- Selective: Anastrozole; Fadrozole

Mainly used in the management of breast cancer

Progesterone & Antiprogestins

■ Biosynthesis:

From cholesterol



Feedback effects

■ Physiological & Pharmacological effects:

- Endometrial differentiation, growth and development. Sudden withdrawal → bleeding (menses)
- Maintenance of pregnancy
- Breast development
- Vagina: ↓ cornification, ↑ mucus content
- Cervix: ↑ viscosity ↓ NaCl content
- Thermogenic effect
- Weak aldosterone-like effect

■ Absorption & metabolism:

Progesterone is available in oral; depo (I.M) injectable and subdermal implants dosage forms

■ Preparations:

Medroxyprogesterone; Norethindrone acetate; Norethindrone; Norgestrel; Megesterol acetate; Hydroxyprogesterone caproate; Cyproterone acetate (Ca prostate); Dydrogesterone (IVF)

■ Progesterone clinical uses:

- Components of OCP's
- Dysfunctional uterine bleeding
- Endometrial; breast; prostate cancer
- Abortion or maintaining pregnancy
- Endometriosis

■ Progesterone side effects:

Depression; weight gain; salt-water retention

■ Antiprogestins:

Mifepristone

■ Clinical uses:

- Abortifacient + PG
- Induction of labor + PG
- Progesterone-dependent cancer
- Cushing's syndrome

Contraception

I. Male contraception:

1. Behavioral

2. Mechanical (e.g. condoms) \pm spermicidal agent (nonoxynol-9)

3. Drugs

Estrogens; progestins; danazol; GnRH agonists & antagonists; spermicidal agents; gossypol

4. Surgical procedures e.g. vasectomy

II. Female contraception:

1. Behavioral

2. Mechanical

Diaphragms; condoms \pm spermicidal agents;

IUD's \pm progestins (progestasert)

3. Drugs

- Estrogen alone

Morning after pill or postcoital pill

Ethinylestradiol; DES; mestranol..... $\times 5$

- Progesterone alone

The minipill

* Norethisteron... Tab

* I.M medroxyprogesterone

Depo-provera (effect lasts in 3-6 months)

* Subdermal progesterone implants

Levonorgesrel (effect lasts in 5-6 years)

4. Sequential

Estrogen followed by progesterone

5. Combined oral contraceptive pills (COCP's)

ethinylestradiol or mestranol + Norgestrel

ethinylestradiol or mestranol + Norethisterone

* Estrogen + progesterone in different ratios
(lowest E highest P to achieve the lowest or
zero failure rate)

■ MOA of OCP's:

- Inhibition of ovulation (major mechanism)

At the level of the pituitary

- ↑ viscosity of cervical mucus
- Change in Fallopian tube motility

■ OCP's side effects:

- Nausea, vomiting, dizziness, headache, migraine, nervousness, depression
- Salt & water retention → ↑ BP
- Thromboembolic disease, embolism, MI
- Vaginal yeast growth
- Postpill amenorrhea and infertility

■ OCP's contraindications:

- History of thromboembolic disease
- Severe headache
- Severe nausea & vomiting
- Liver dysfunction
- Pregnancy
- Abnormal menstrual cycles

■ OCP's drug-drug interactions:

- Drugs inhibiting enterohepatic circulation

Ampicillin; cephalosporins; tetracyclines;
sulfonamides; co-trimoxazole

- Drugs ↑ metabolism

Phenobarbitone; phenytoin; ethosuximide;
rifampicin; griseofulvin...

- Miscellaneous interactions

+ anticoagulants → ↓ activity of anticoag. + insulin
→ ↑ insulin need