

# Estrogens & Antiestrogens

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

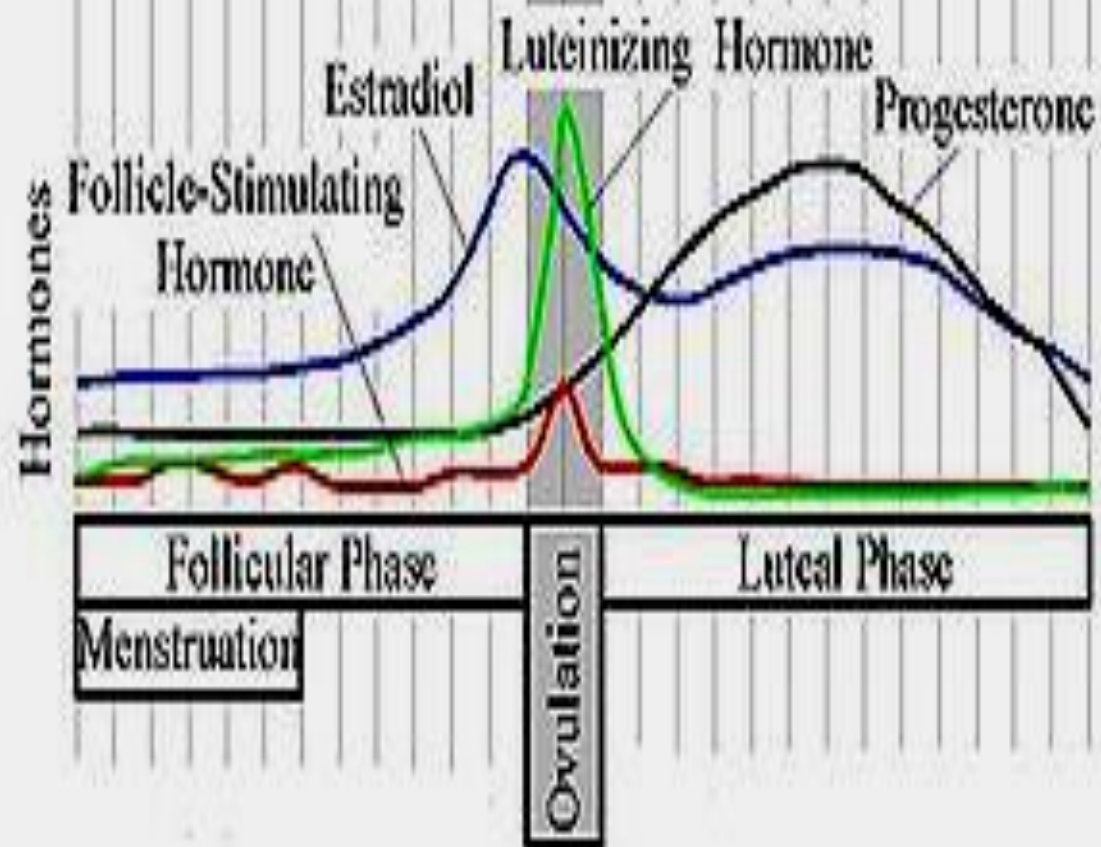
- **Natural estrogens:**

Estadiol >> Estrone > Estriol

Ineffective orally

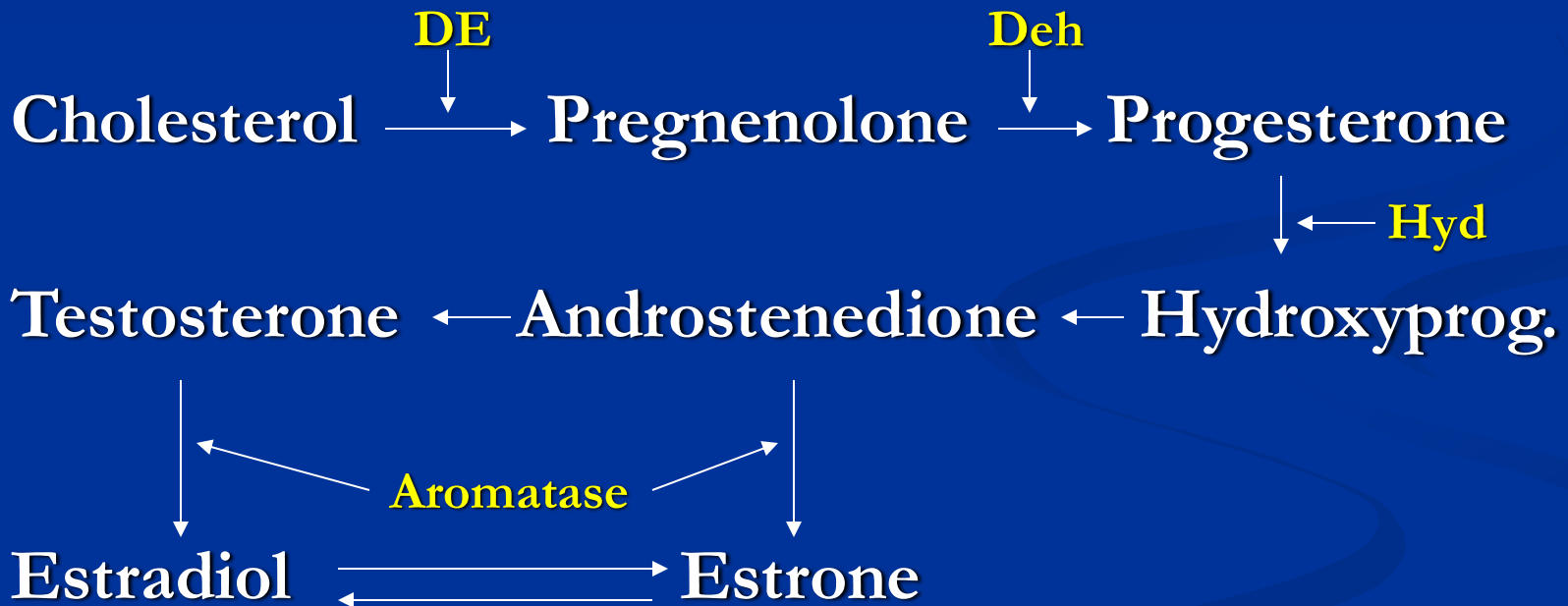
- **Synthesis:**

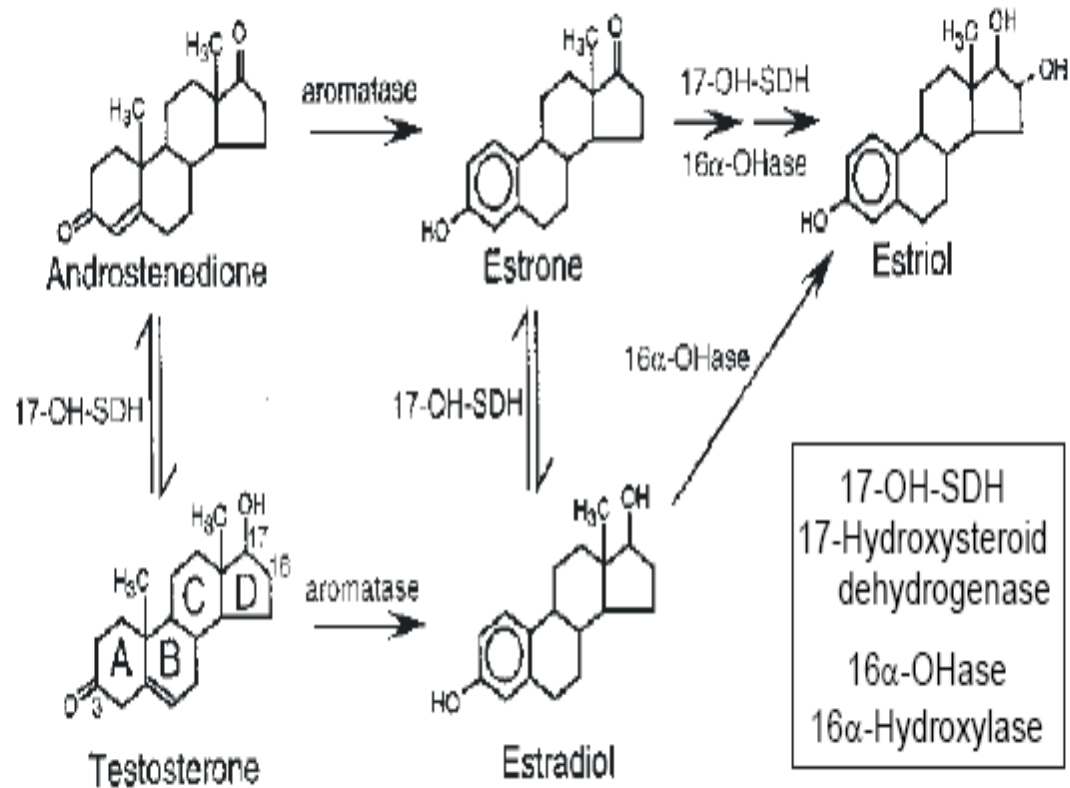
From cholesterol ; role of aromatase enzyme in converting androgens (testosterone & androsteindione) to estrogen



## ■ Estrogen synthesis:

From cholesterol





■ **Transport:** SHBG

■ **M.O.A:**

Estrogen receptors (ER- $\alpha$ ; ER- $\beta$ )

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<sub>x</sub>)

Recently some researchers consider tamoxifen and clomiphene citrate as SERM

### \*\* Aromatase inhibitors:

- Nonselective: Aminoglutithemide
- Selective: Anastrozole; Fardozole (given orally)

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