

# Estrogens, Progesterone & Contraception

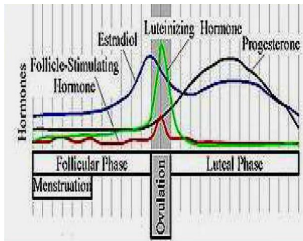
## Estrogens & Antiestrogens

### Menstrual cycle

Changes and hormonal events

### Natural estrogens

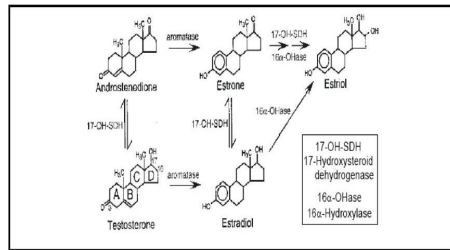
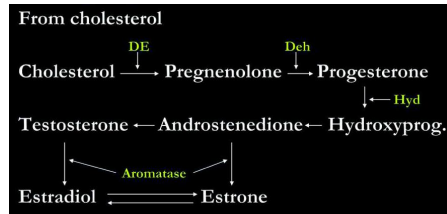
Estradiol >> Estrone > Estriol  
Ineffective orally



### Synthesis

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

### Estrogen synthesis



### Transport

SHBG

### M.O.A:

Estrogen receptors (ER-α; ER-β)  
Modulation of gene transcription (nuclear receptors)  
Stimulation of endothelial nitric oxide synthase → nitric oxide → vasodilatation → 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)
- ↑ 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 and their metabolites are metabolized by hepatic CYP450 enzymes

### 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 side effects:

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

### Estrogen preparations:

#### Synthetic steroidal

Estradiol benzoate; Estradiol valarate

Ethinylestradiol; Mestranol...

#### Synthetic non steroidal estrogens

Diethylstilbesterol

(rarely or now almost never used due to severe side effects)

Tamoxifen

is listed in literature as a non steroidal estrogen

#### Conjugated estrogens

Estrone sulfonate (Premarin®)

## 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 **antagonist** 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

Recently, some researchers consider tamoxifen and clomiphene citrate as SERM

### Selective estrogen receptor modulators (SERM's):

#### Raloxifene

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

#### \*\* Aromatase inhibitors

- Nonselective: Aminoglutethimide
- Selective: Anastrozole; Fardroze (given orally)
- Mainly used in the management of breast cancer

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

## Progesterone & Antiprogestins

### Physiological & Pharmacological effects: Biosynthesis

- 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  
Metabolized in the liver by CYP450 system

### Preparations:

Medroxyprogesterone;  
Norethindrone acetate;  
Norethindrone;  
Norgestrel;

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

### From cholesterol



### Progesterone clinical uses:

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

### Progesterone side effects:

- Depression; weight gain; salt-water

## 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) ± 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 ± spermicidal agents; IUD's ± progestins (progestasert)
- 3. Drugs**
  - Estrogen alone  
Morning after pill or postcoital pill  
Ethinylestradiol; mestranol..... \*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)**  
Ethinyl estradiol or mestranol + Norgestrel  
Ethinyl estradiol or mestranol + Norethisterone  
\* Estrogen + progesterone in different ratios (lowest E highest P to achieve the lowest or zero failure rate)  
(monophasic; biphasic or triphasic birth control pills)

- Monophasic birth control pills have the same amount of estrogen and progestin in each active pill (1 tab for 21 days)
- Biphasic birth control pills change the level of hormones one time during the menstrual cycle. During the first half of the cycle, the estrogen/progestin ratio is usually higher (1 tab for 7-10days). During the second half of the cycle, the estrogen/progestin ratio tends to be lower (1 tab for the next 11-14 days)
- Triphasic birth control pills contain three different doses of hormones so the hormone combination changes approximately every seven days throughout the cycle (1 tab E>P daily for 7 days; 1 tab E=P for the next 7 days; 1 tab E< P for the last 7 days)

## 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



<https://dorar.net/hadith/sharh/149888>

ﷺ صلى الله وسلم على خير معلمي الناس الخير