

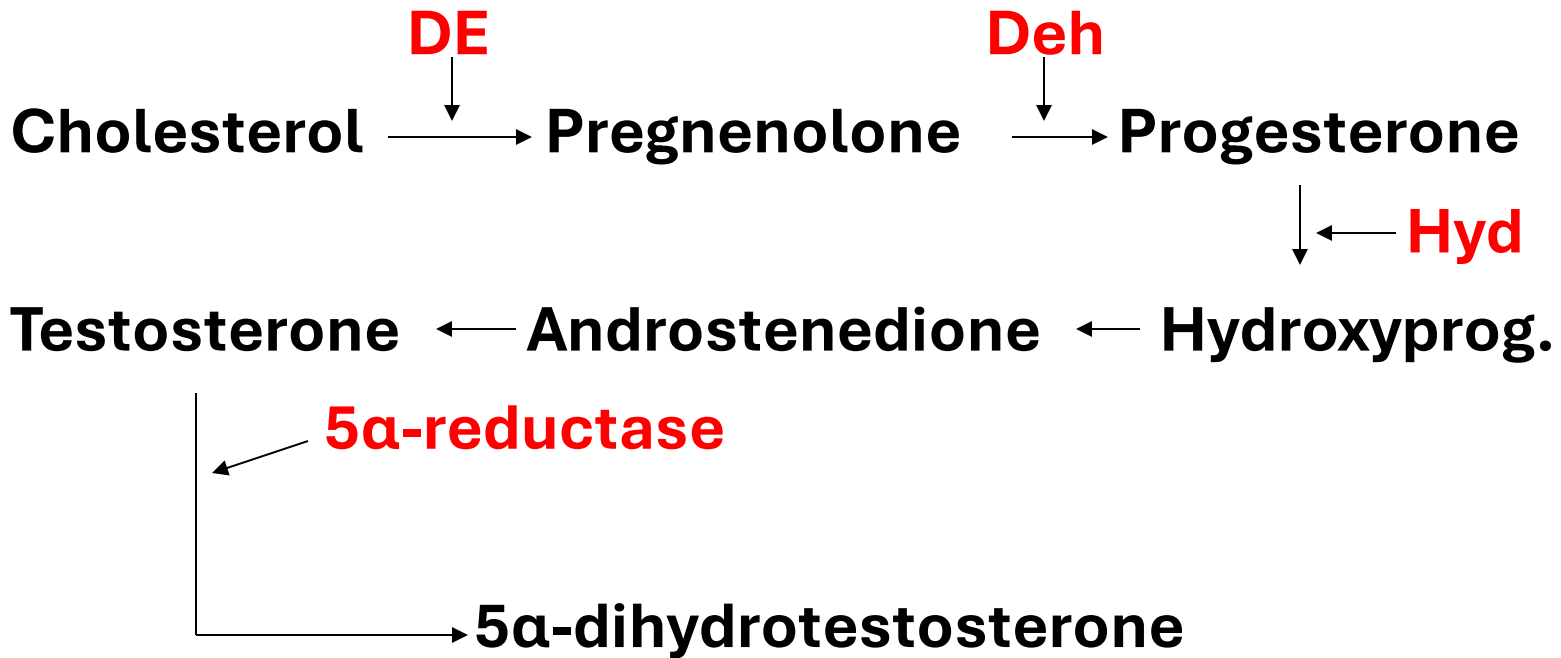
# **Androgens & Antiandrogens**

- The testis has two major functions:
  1. Spermatogenesis occurring within the seminiferous tubules
  2. Production of androgenic hormones

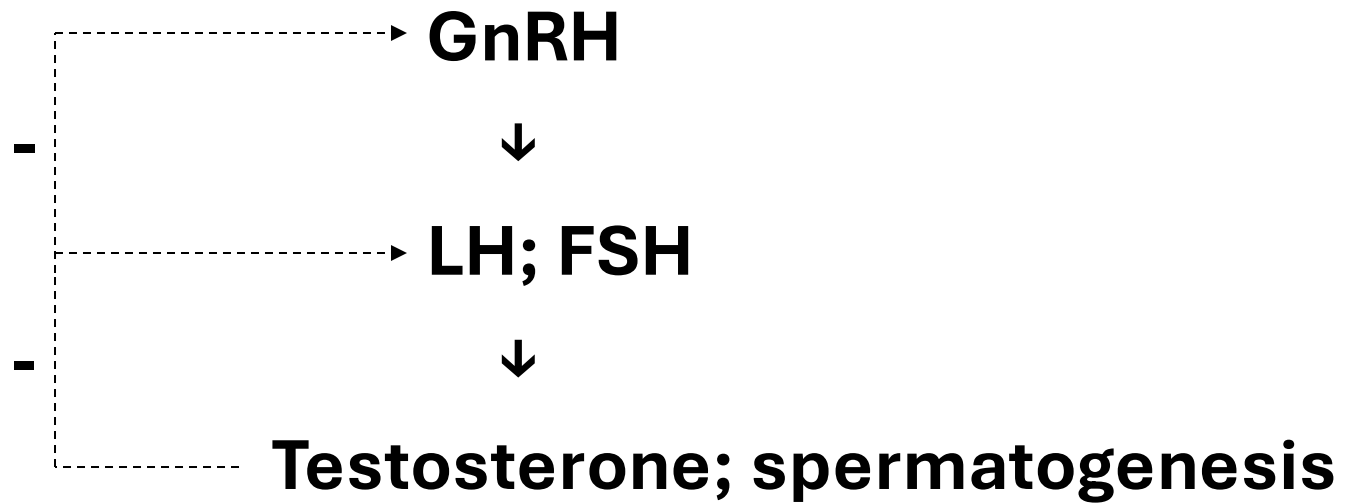
- Naturally occurring androgenic hormones are:
  1. Testosterone, the principal androgenic hormone produced by the Leydig cells of testis
  2. Dehydroepiandrosterone (DHEA) (produced in the adrenal cortex)
  3. Androstenedione (produced by both the adrenal and testes)
- The testes produce other hormones like 1) Small quantities of Estradiol 2) Inhibin and 3) Activin

- Testosterone synthesis

From cholesterol

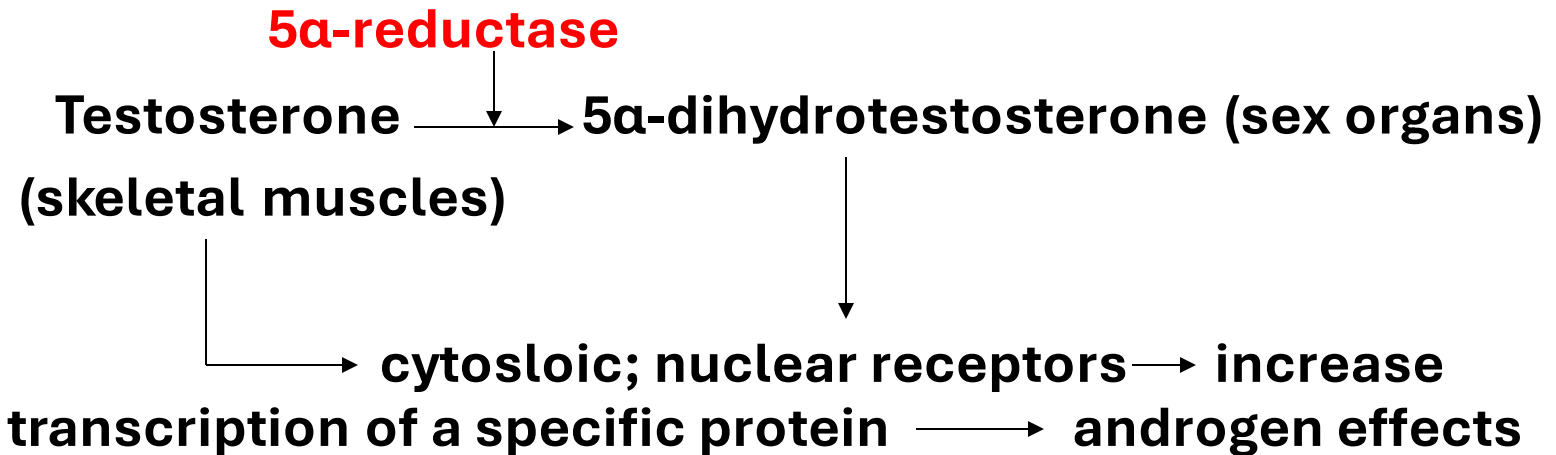


## Regulation of synthesis & release



- Transport & MOA of androgens:

## SHBG



**DHT is 10 times more potent than testosterone and mediates effects of testosterone on skin and sexual apparatus (prostate; seminal vesicle, epididymis...)**

- Testosterone physiological & pharmacological effects:
  - Virilizing=masculinizing effect
    - 1° & 2° sexual characteristics
  - ↑ Spermatogenesis
  - ↑ Erythropoiesis
  - Anabolic or growth promoting effect (bone; skeletal muscles)

- Testosterone metabolism:



- Clinical uses:

- Testosterone deficiency

Hypogonadism; impotency; ↓ libido; aging; infertility...

- Anemia; leukemia; lymphoma

- Endometriosis (Danazol is particularly used)



Cont. Testosterone clinical uses,

- Antiestrogenic effect

Breast cancer

- Anabolic effect

Osteoporosis

\*\* Use by athletes is an abuse

- Testosterone preparations:

- 1° use for androgen replacement:

- Testosterone I.M; S.C
- Testosterone propionate I.M, S.L
- Testosterone cypionate I.M; depo I.M
- Methyltestosterone O; S.L
- Fluoxymestrone O

- 1° use for breast cancer:

Testolactone (progesterone derivative and aromatase inhibitor) O

Cont. testosterone preparations,  
1° use for anabolism (osteoporosis):

Androgen:anabolic ratio=1:2 or 1:3 (promote + ve anabolism and muscular growth but little effect on sex)

- Ethylestrenol O
- Stanozolol O
- Oxandrolone O
- Nandrolone decanoate I.M
- Methandienone O

- Testosterone side effects:

- Virilization (masculinization)

Hirsutism; acne; menstrual disorders in ♀'s

- Precocious puberty & hirsutism in children

- Salt & water retention

- Jaundice; gall bladder stones  
(methyltestosterone)

- Enlargement of prostate

- ? Liver cancer

- Antiandrogens

- Estrogens: Diethylstilbesterol; mestranol...
- Progestins: Cyproterone acetate
- GnRH superagonists (Leuprolide acetate); GnRH antagonists (Ganirelix)
- Flutamide; Bicalutamide and Nilutamide
- 5 $\alpha$ - reductase inhibitors: Finasteride
- Ketoconazole
- Spironolactone
- Gossypol

- Antiandrogens clinical uses:

- Ca prostate
- Benign hyperplasia of the prostate (Finasteride)
- Severe acne and hirsutism in ♀'s (Spironolactone; Cyproterone acetate)
- Precocious puberty
- ♂ antifertility agents (♂ contraceptive) (Gossypol)
- ♂ baldness (Cyocitol solution=topical antiandrogen; Finasteride)

- Antiandrogens side effects:

↓ libido; impotency; ↓ spermatogenesis; ↓ ejaculate

# Estrogens & Antiestrogens

- Menstrual cycle... Changes and hormonal events

- Natural estrogens:

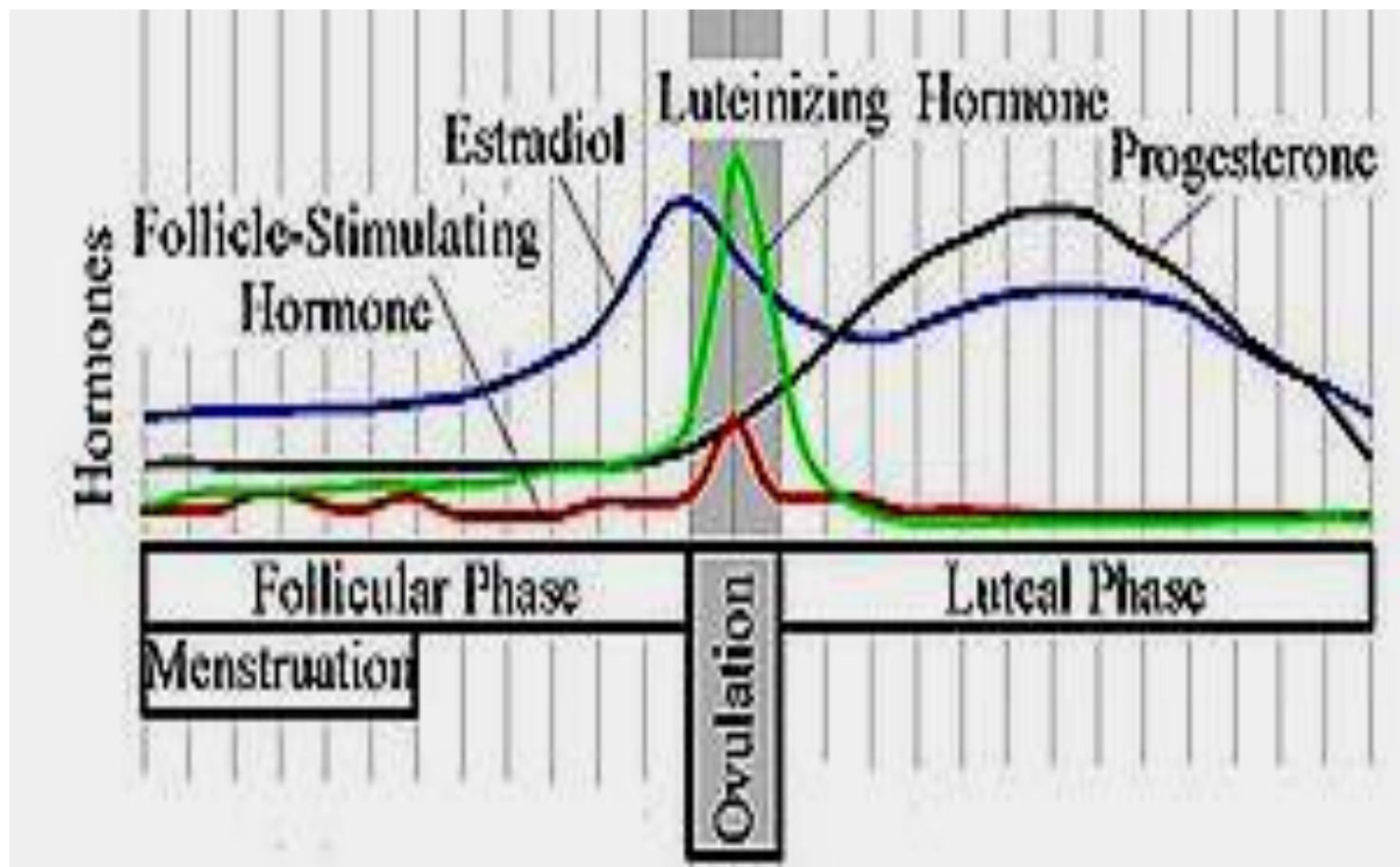
Estadiol >> Estrone > Estriol

Ineffective orally

- Synthesis:

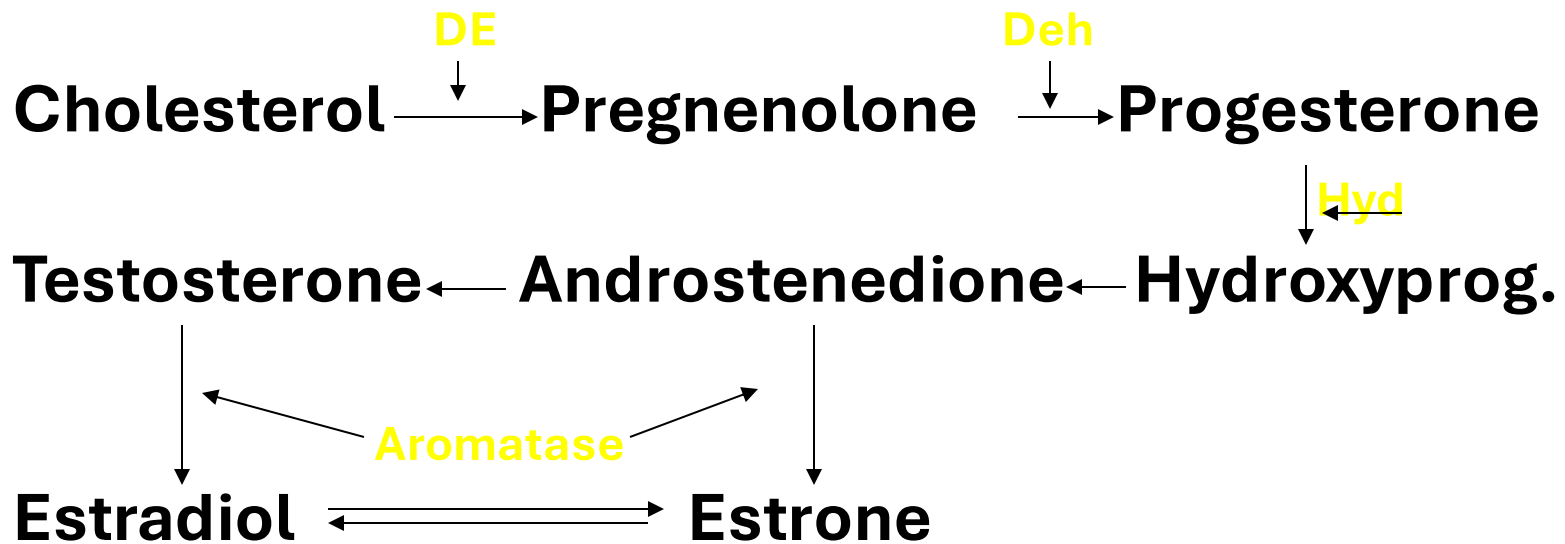
From cholesterol ; role of aromatase enzyme in converting androgens (testosterone & androsteindione) to estrogen

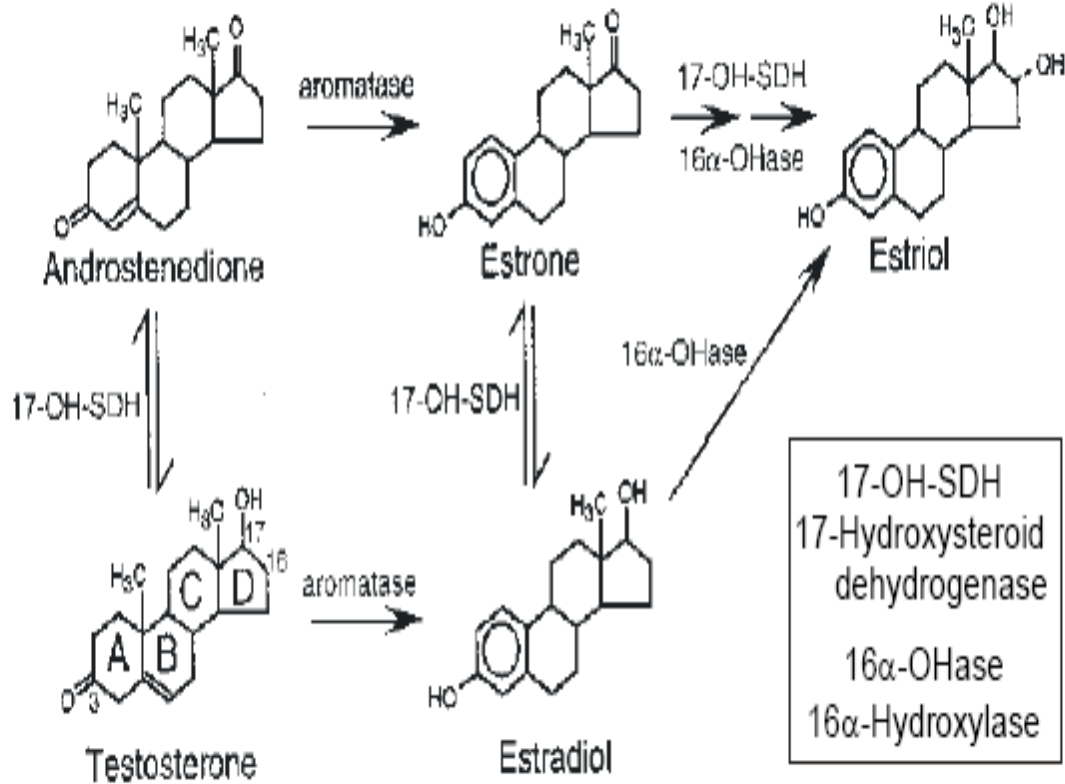




- **Estrogen synthesis:**

**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 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 preparations:

- Synthetic steroidal

Estradiol benzoate; Estradiol valerate

Ethinylestradiol; Mestranol...

- Synthetic non steroidal estrogens

Tamoxifen is listed in literature as a non steroidal estrogen

- Conjugated estrogens

Estrone sulfonate (Premarin<sup>®</sup>)



- 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 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):

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)

## Raloxifene

Orally effective SERM widely used in the management of osteoporosis (prophylactic and R<sub>x</sub>)

### \*\* Aromatase inhibitors:

- Nonselective: Aminoglutithemide
- Selective: Anastrozole; Fardrozole (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

Metabolized in the liver by CYP<sub>450</sub> system

- 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
- IVF

- Progesterone side effects:

Depression; weight gain; salt-water retention

- Antiprogestins:

Mifepristone

- Clinical uses:

- Abortifacient + PG
- Induction of labor + PG
- Progesterone-dependent cancer
- Endometriosis
- 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 P >E 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