Androgens & Antiandrogens

- The testis has two major functions:

1. Spermatogenesis occurring within the seminiferous tubules

2. Production of androgenic hormones

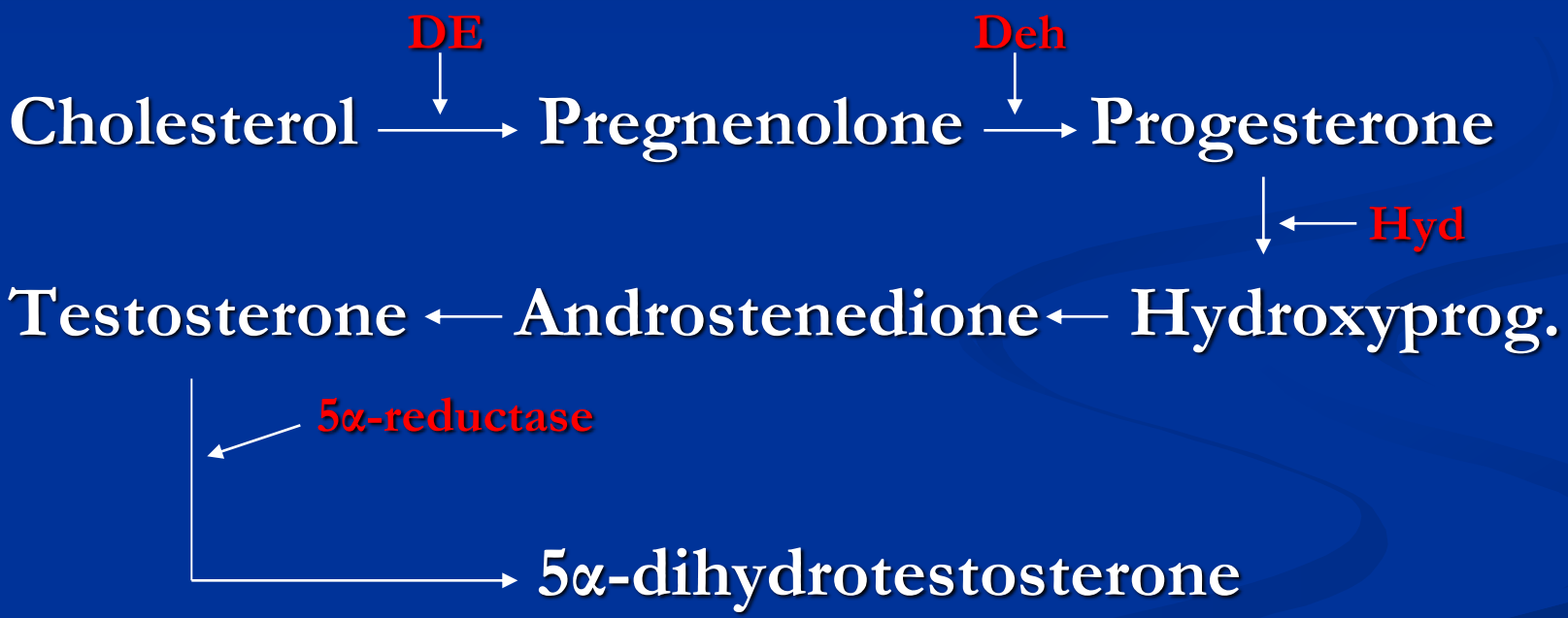
- Naturally occurring androgenic hormones are:

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)

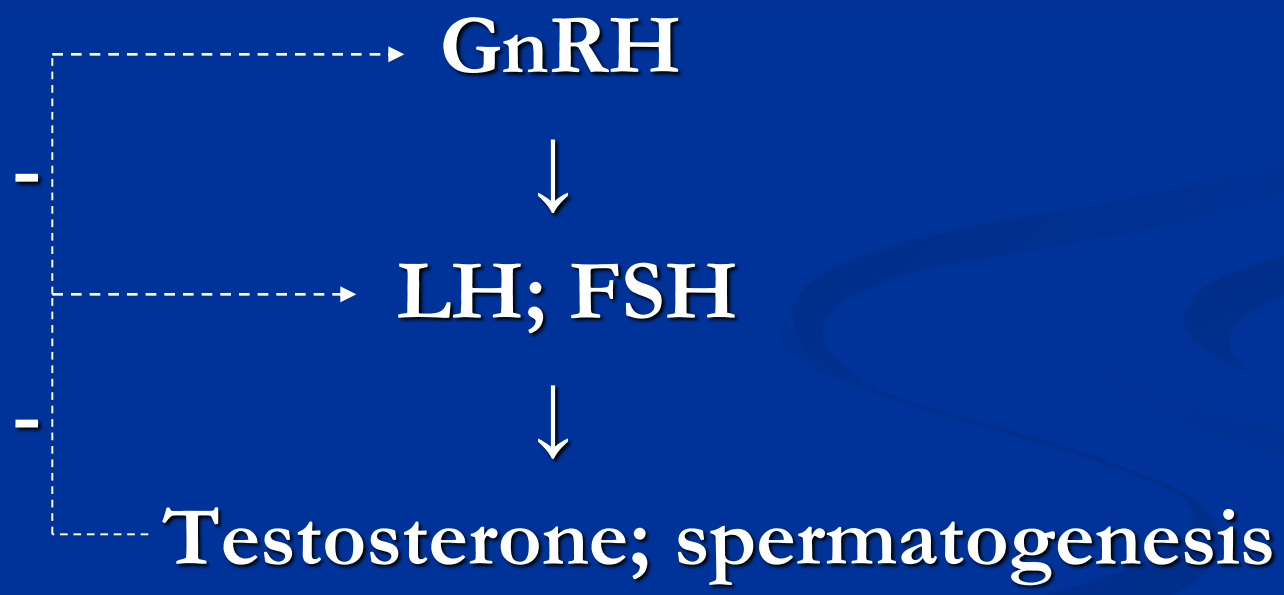
- The testes produce other hormones like 1) Small quantities of Estradiol 2) Inhibin and 3) Activin

- **Testosterone synthesis**

From cholesterol



Regulation of synthesis & release



- **Transport & MOA of androgens:**

SHBG

5α-reductase

Testosterone → 5α-dihydrotestosterone (sex organs)

(skeletal muscles)

→ cytosloic; nuclear receptors → increase transcription of a specific protein → androgen effects

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:**

Hepatic → 17-ketosteroids → Androsterone
Hepatic → 17-ketosteroids → Etiocholanolone

- **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
  - 5α- 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 (Cyoctol solution=topical antiandrogen; Finasteride)

- **Antiandrogens side effects:**

↓ libido; impotency; ↓ spermatogenesis; ↓ ejaculate

Estrogens & Antiestrogens

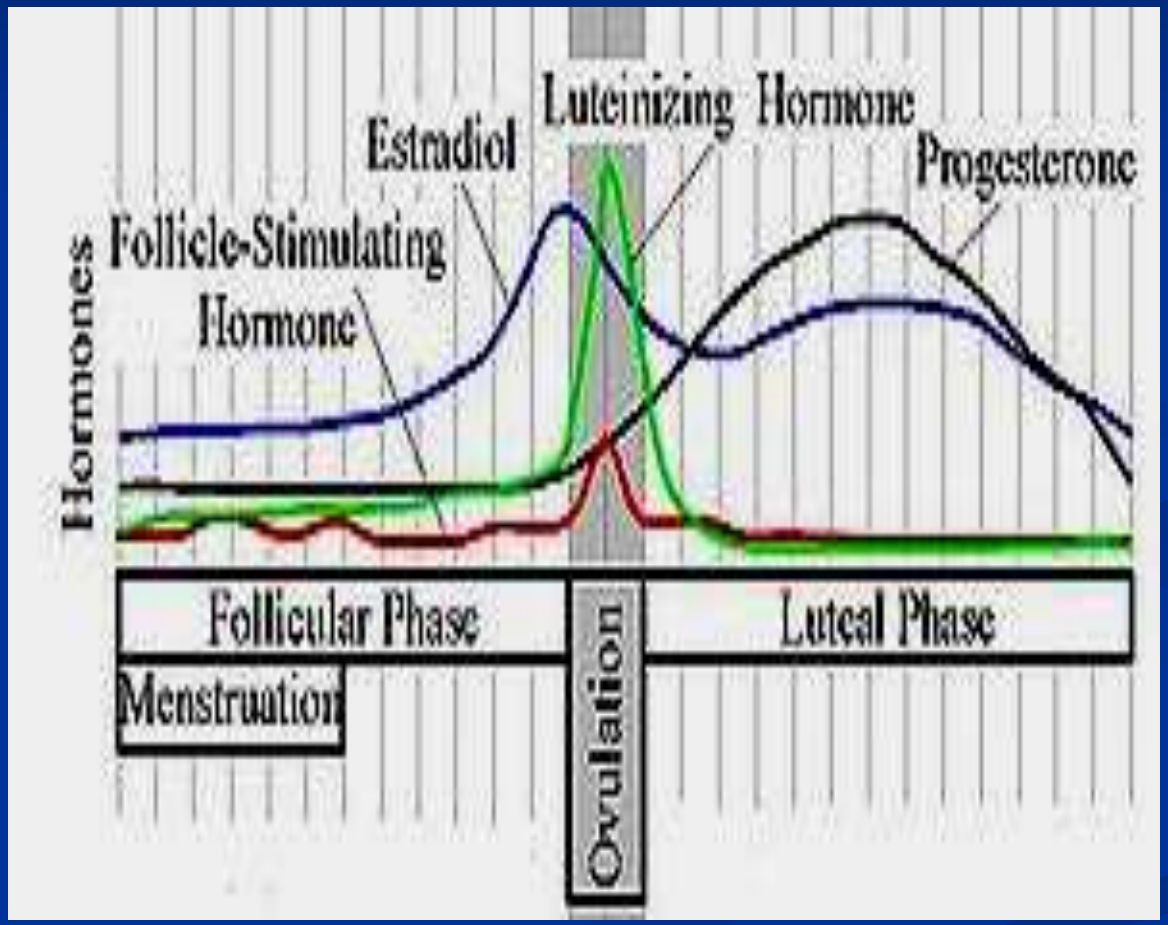
- **Menstrual cycle**... Changes and hormonal events
- **Natural estrogens:**

  Estadiol >> Estrone > Estriol

Ineffective orally

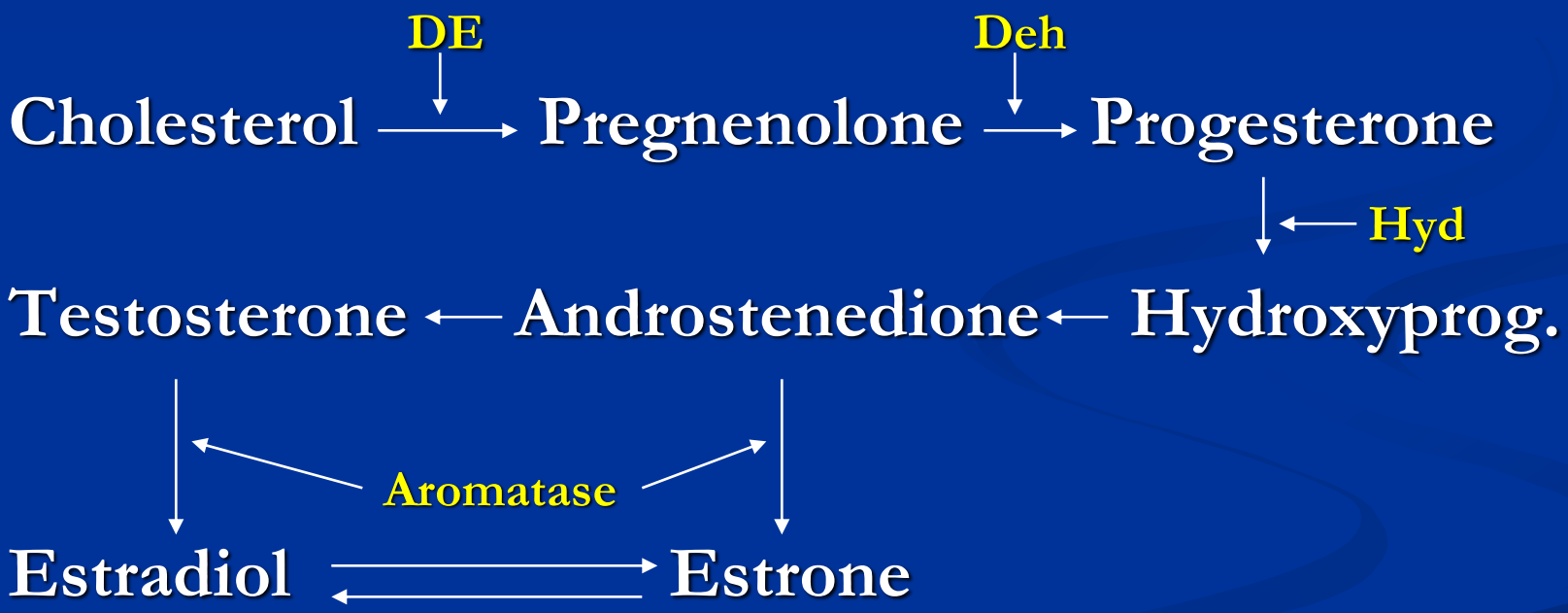
- **Synthesis:**

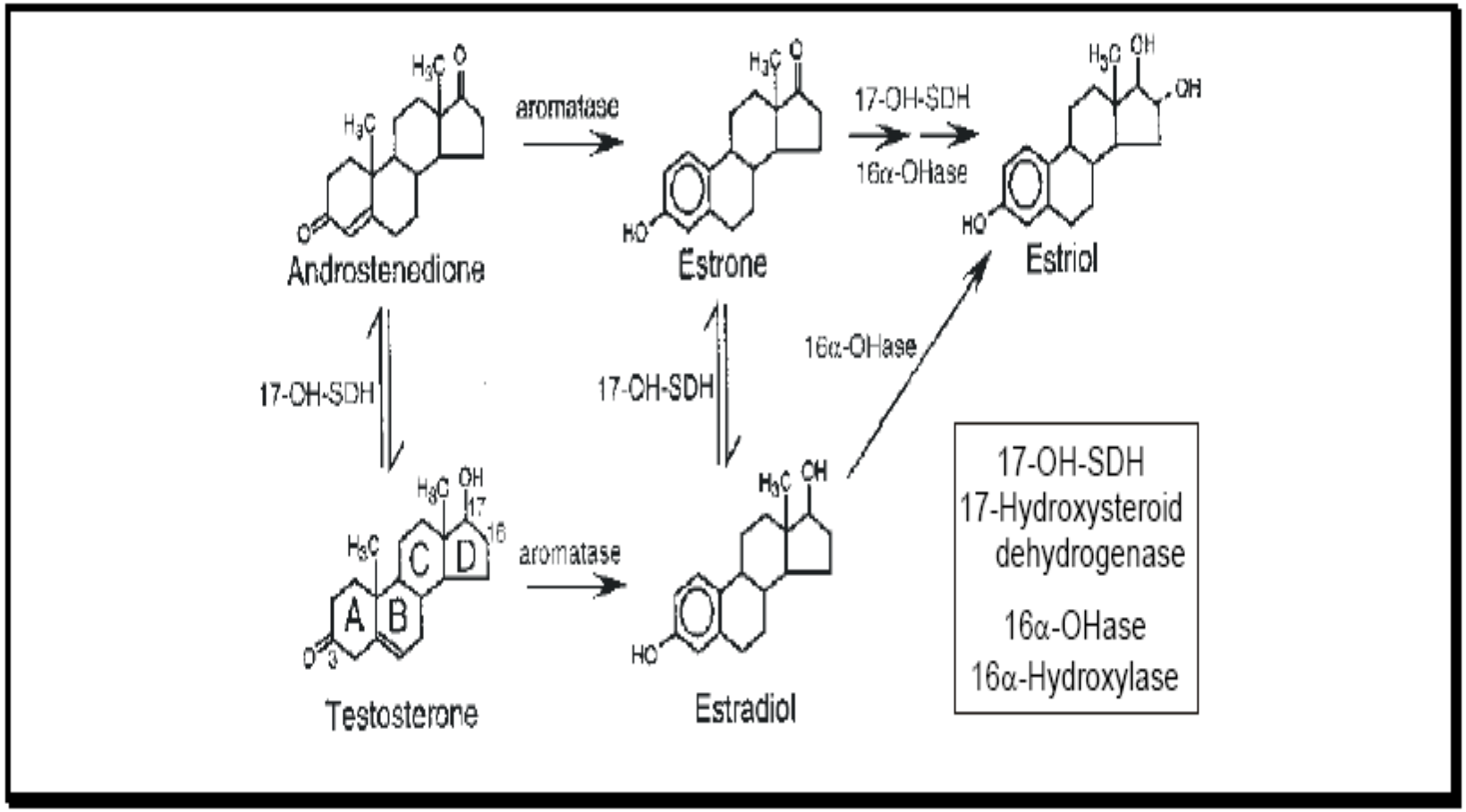
From cholesterol ; role of aromatase enzyme in converting androgens (testosterone & androsteindione) to estrogen


Luteinizing Hormone
Estradiol
Progesterone
Follicle-Stimulating Hormone
Hormones
Follicular Phase
Luteal Phase
Menstruation
Ovulation

- **Estrogen synthesis:**

From cholesterol




Androstenedione
aromatase
Estrone
17-OH-SDH
16α-OHase
Estriol
17-OH-SDH
17-OH-SDH
16α-OHase
Testosterone
aromatase
Estradiol
17-OH-SDH
17-Hydroxysteroid dehydrogenase
16α-OHase
16α-Hydroxylase

- **Transport:** SHBG
- **M.O.A:**

Estrogen receptors (ER-α; ER-β)

Modulation of gene transcription (nuclear receptors)

Stimulation of endometrial 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)

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 valarate

Ethinylestradiol; Mestranol…

- Synthetic non steroidal estrogens

Tamoxifen is listed in literature as a non steroidal estrogen

- Conjugated estrogens

Estrone sulfonate (Premarin®)

- **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_x)

**** Aromatase inhibitors:**

- Nonselective: Aminoglutithemide

- Selective: Anastrazole; Fadrozole (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_{450} 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

Diaphrams; 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; teracyclines; sulfonamides; co-trimoxazole

- Drugs ↑ metabolism

Phenobarbitone; phenytoin; ethosuximide; rifampicin; griseofulvin…

- Miscellaneous interactions

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