Estrogens & Antiestrogens

- Menstrual cycle ... Changes and hormonal events

Natural estrogens are produced by the ovaries, suprarenal glands, and placenta

- Natural estrogens:
  Estadiol >> Estrone > Estriol

1- Estadiol: major estrogen produced by he ovaries in young females, and the major estrogen produced during pregnancy.
2- Estrone: Major estrogen produced in old females after menopause and is less potent than estadiol.
3-Estriol: The least potent

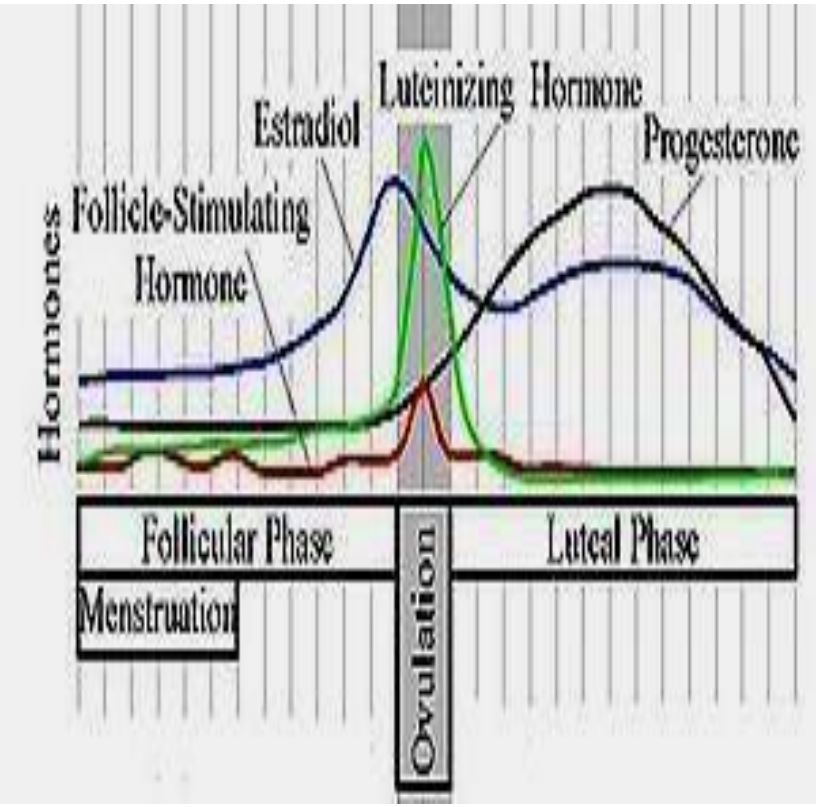
Ineffective orally

- Synthesis:

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

Abnormal uterine bleeding (due to an underlying pathology in the uterus like cancer or hormonal imbalance like hypothyroidism (dysfunctional uterine bleeding)

1- Menstrual Cycle has 3 phases: follicular phase, luteal phase, and bleeding(menstruation).
The main steroid in the first phase is estrogen
The main steroid in the second phase is progesterone, and a drop in progesterone results in bleeding and menstruation.
This is why we can stop uterine bleeding by a progesterone agonist (for example if a woman wants to go to Umrah.



LH is a hormone regulated by a positive feedback mechanism by estrogen either through:
1- upregulation of LH receptors
2- increasing the expression of alpha and beta subunits
3- increasing LH synthesis during ovulation, which results in an increase in the amount of LH released.

*Behavioral contraception can either be achieved By either the female or male by avoiding intercourse when the lady is highly fertile.
Progesterone also has a thermogenic effect causing a slight increase in the
Female body temperature, so we can benefit from this hormonal effect as a method of
Behavioral contraception which can decrease the chances of pregnancy by 80%

LH and FSH are under the regulation of GNRH, estrogen results in the increase
Of GTRH release which results in increasing GNHR receptor expression.
On the other hand, prolactin has inhibitory effects on LH and FSH

- **Estrogen synthesis:** Cholesterol is synthesized de novo from acetate and is important in both steroidogenesis + integrity of cell membranes

From cholesterol

DE Deh

Cholesterol → Pregnenolone → Progesterone

DE → desmolase

Hyd

Rate limiting step → desmolase (side chain cleaving enzyme, debranching enzyme)

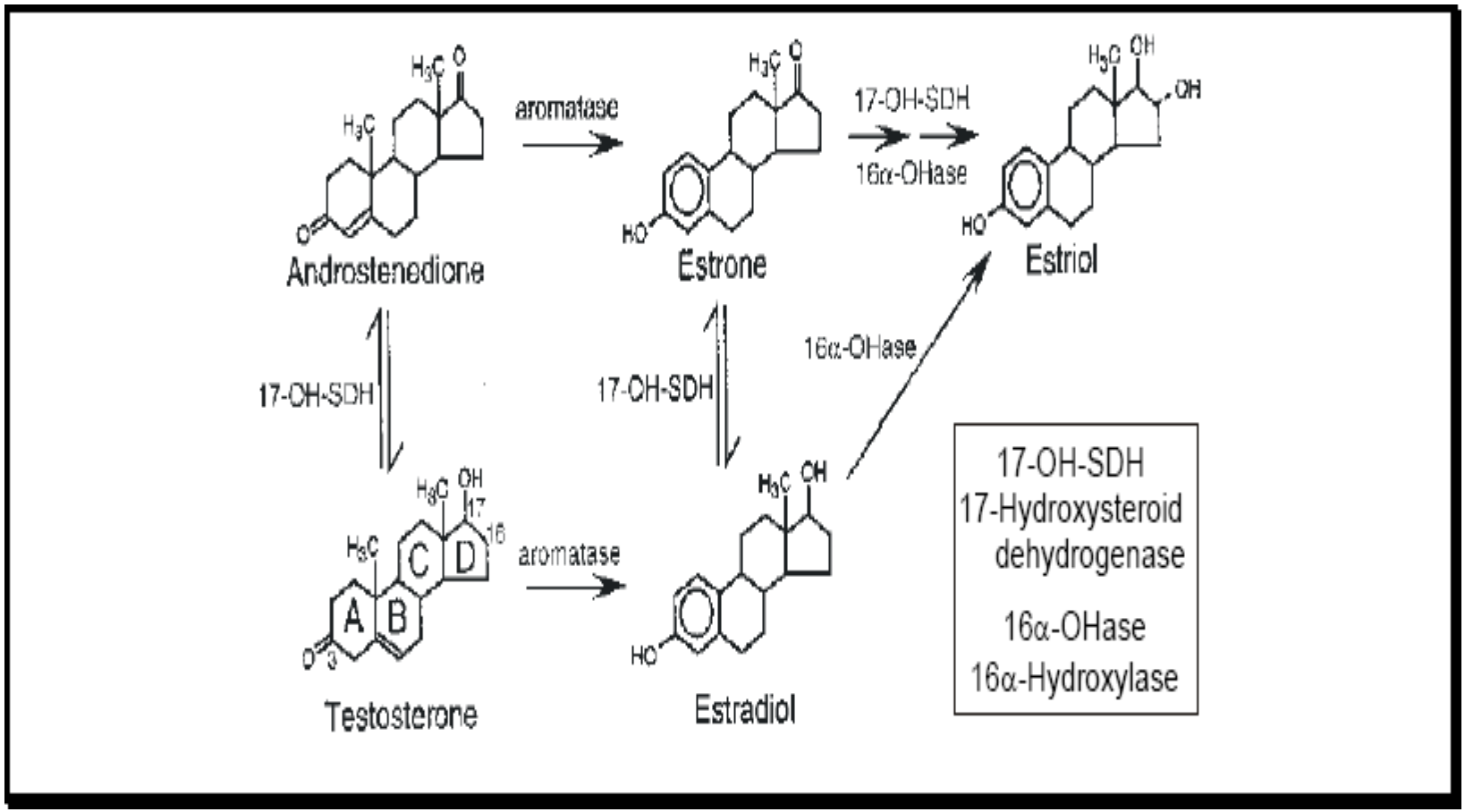
Testosterone → Androstenedione → Hydroxyprog.

Aromatase

Estradiol → Estrone

Estradiol is an androgen that is converted to estrone which is an estrogen through an aromatase rxn.

Desmolase enzyme can be inhibited by a number of drugs like aminoglutethimide, Which is used in the management & treatment of excess steroid production



Chemical modification of steroids can happen (Different steroids produced from progesterone (same precursor)

Transport: SHBG Sex hormone-binding globulin

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M.O.A:

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Estrogen receptors (ER -α; ER-β)

Modulation of gene transcription (nuclear receptors) We also have membrane and cytosolic estrogen receptors that are phosphorylated, but eventually they are translocated to the nucleus to express different proteins that mediate the effects of estrogen

Stimulation of endometrial nitric oxide synthase →→→ nitric oxide →→→ vasodilatation

That leads to induction That cause

cardioprotection Mainly after menopause(because females have a higher risk of osteoporosis, MI & IHD, not only due to Estrogen deficiency, but also due to age

Primary → female sexual organ development (ovary, uterus, breast)
Secondary → Type of voice, and softness of skin
+
Regulation of the menstrual cycle

- **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)

This explains drug & estrogen interactions

Some effects are observed with high doses of estrogen administration, those doses are
→ This increases the risk for thromboembolic phenomena

Cont. estrogen actions:

- ↑ synthesis of certain clotting factors (fibrinogen, factors VII; IX & X) and activity of antithrombin III ↓

Hypocholesterolemic agent good Bad

- ↓cholesterol, ↑ HDL & ↓ LDL blood levels
- Salt & water retention And hypertension

By CYP450

■ Absorption & metabolism of estrogens:

After oral administration it goes to the liver then to the intestines then it gets absorbed and utilized

Conjugation → enterohepatic circulation

Estrogen goes to → enterohepatic circulation because it is in the conjugated inactive form → it go
deconjugation happens → It becomes activated → reaches the intestines to get absorbed

Certain breast cancers like estrogen receptor positive ones “ER+” respond to hormonal therapy (estrogen, anti-estrogen, progesterone, anti-progesterone) according to the type of breast cancer.

Combination of estrogen & progesterone can be used in treatment of endometrial cancer

- **Estrogens clinical uses:**

- HRT Hormone replacement therapy

Postmenopausal syndrome & osteoporosis, prevention of heart attacks

- Components of OCP’s Oral contraceptive pills

- Prostate, breast, endometrial cancer + progesterone

- Dysmenorrhea Painful menses “it may occur due to slight deficiency of estroger

- Infertility

- Acne, hirsutism Male pattern hair growth in females

Used in the management of prostate cancer & spontaneous abortion (miscarriage), but due to its side effects, it is no longer used (most ladies who take it during pregnancy develop vaginal cancer).

- Estrogen preparations:

- Synthetic steroidal — Effective orally

Estradiol benzoate; Estradiol valarate

Ethinylestradiol; Mestranol...

- Synthetic non steroidal estrogens

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

- Conjugated estrogens — It undergoes deconjugation through enterohepatic circulation

Estrone sulfonate (Premarin®)

If they are severe enough, they could be considered as a complete contraindication for using estrogen

- **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

SERM --> selective estrogen receptor modulators

- **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)

so, it can be used in some breast cancers

Raloxifine is highly effective in bones through increasing their density & we can measure this huge effect by measuring the denisty of bone Using a densitometer before & after the administration of the drug and comparing Both trials

Raloxifene

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

**Aromatase inhibitors:

Because it also inhibits the enzyme demolase

- Nonselective: Aminoglutithemide
- Selective: Anastrazole; Fadrozole (given orally)

Mainly used in the management of breast cancer

Progesterone & Antiprogestins

- **Biosynthesis:**

From cholesterol

DE **Deh**

Cholesterol **Pregnenolone** **Progesterone**

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

During puberty & pregnancy

→ All steroids share this property (last point in case the arrow isn't clear).

Side effects: increases salt & water retention as we will see later on

Depo: deep intramuscular & so the effect lasts for 3-6 months

- **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)

Effective in the treatment of prostate cancer

Main progesterone used in in vitro fertilization

- 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

to prevent abortion --> give progesterone
to induce abortion --> give abortifacient

- **Antiprogestins:**

Mifepristone Mifepristone is not effective alone, so it has to be combined with Prostaglandins to induce abortion & labor

- **Clinical uses:**

- Abortifacient + PG

- Induction of labor + PG

- Progesterone-dependent cancer Any type of cancer that depends on progesterone for its growth

- Cushing's syndrome

By competing with cortisol nucleus receptor, it can be used in the treatment of Cushing's Syndrome since it acts as a competitive inhibitor.