## Sex hormones

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- Produced by the gonads.
- Necessary for conception, embryonic maturation & development of primary & secondary sexual characteristics.
- Used for hormone replacement therapy (HRT), contraception & management of menopausal symptoms.
- Several of their antagonists are effective in cancer chemotherapy.

### Estrogens:

**1. Estradiol** (also known as **17 β-estradiol** ).

- Most potent estrogen (E) produced by the ovary in the premenopausal woman.

**2. Estrone**

- An **estradiol** metabolite with approximately 1/3 of the **estradiol** potency.
- The primary E after menopause & it is generated mainly from conversion of androstenedione in peripheral tissues.

3. **Estriol**

- Another **estradiol** metabolite, it is significantly less potent than **estradiol**.
- It's the principal E produced by the placenta.

4. A conjugated E preparation contains **estrone** & **equilin** (from pregnant mares' urine) is used for HRT.

**ESTROGENS**
*Estradiol* USED IN MANY COMBINATIONS
*Estrone* MENEST
*Ethinyl estradiol* USED IN MANY COMBINATIONS
*Mestranol (w/norethindrone)* NECON 1/50, NORINYL 1+50
**SELECTIVE ESTROGEN-RECEPTOR MODULATORS (SERMs)**
*Clomiphene* CLOMID, SEROPHENE
*Ospemifene* OSPHENA
*Raloxifene* EVISTA
*Tamoxifen* TAMOXIFEN, NOLVADEX
*Toremifene* FARESTON

5. Plant-derived conjugated estrogen products are also available.

6. Synthetic E, eg. **ethinyl estradiol**, undergo less first-pass metabolism than naturally occurring steroids & thus, are effective when administered orally at lower doses.

7. Selective estrogen-receptor modulators (SERMs) eg. **tamoxifen** & **raloxifene** are nonsteroidal compounds that bind to E receptors & exert either estrogenic or antiestrogenic effects on target tissues.

**Mechanism of action**

- Estrogens diffuse across the cell membrane & bind to specific nuclear-receptor proteins. Then steroid-receptor complex interacts to initiate hormone-specific RNA synthesis resulting in synthesis of specific proteins that mediate a number of physiologic functions.

**Note**: The effects of steroid hormones are both receptor & tissue specific.

- Other actions of these hormones are more rapid, eg. activation of the E receptor in the membranes of hypothalamic cells has been shown to couple to a G protein, thereby initiating a second-messenger cascade.
- Also E increases formation & release of nitric oxide & prostacyclin from endothelial cells mediating coronary arteries dilation.

**Therapeutic uses**

1. The E & progestogen combination provides effective contraception via oral, transdermal or vaginal route.
2. Postmenopausal hormone therapy (HT).

- Due to concerns over the risks of HT, the lowest effective dose of HT for the shortest possible time is recommended to relieve menopausal symptoms such as vasomotor instability (eg. hot flushes) because E treatment reestablishes feedback on hypothalamic control of norepinephrine secretion decreasing the frequency of "hot fashes". Also E treatment reverses postmenopausal atrophy of the vulva, vagina, urethra, and trigone of the bladder. (**Note**: women who only have urogenital symptoms, such as vaginal atrophy, should be treated with vaginal rather than systemic estrogen).
- E decreases bone resorption (but has no effect on bone formation), the E-progestogen therapy is no longer the therapy of choice for osteoporosis treatment in postmenopausal women **[Note**: due to E adverse effects the current guidelines recommend use of other therapies such as **bisphosphonates (**eg. **alendronate)** over E].

**Note**: For women with intact uterus, a progestogen is always included with the E therapy, to reduce the risk of endometrial carcinoma associated with unopposed E (E only therapy). For women who have undergone a hysterectomy, unopposed E therapy is recommended because progestins may unfavorably alter the beneficial effects of E on lipid parameters.

**Estradiol** transdermal patch or gel can be used to treat postmenopausal symptoms.

3. Replacement therapy (RT) in premenopausal patients who have E deficiency, due to inadequate functioning of the ovaries (hypogonadism), premature menopause, or surgical menopause.

- Estrogen-progestogen combination is instituted to stimulate development of secondary sex characteristics in young women (11-13 years) with primary hypogonadism. Continued treatment is required after growth is completed.

**Pharmacokinetics**

**1. Naturally occurring estrogen** derivatives are readily absorbed through the GIT, skin & mucous membranes.

- Orally taken, **estradiol** is rapidly inactivated by the liver.
- Micronized **estradiol** has better bioavailability.

**2. Synthetic estrogen analogs**, such as **ethinyl estradiol**, **mestranol** & **estradiol valerate** are well absorbed after oral administration.

- **Mestranol** is metabolized to **ethinyl estradiol**, which is metabolized more slowly.
- Stored in adipose tissue, from which they are slowly released.
- Thus, the synthetic E analogs have prolonged action & higher potency.

**3. Metabolism**

- Low bioavailability of orally taken E (due to 1$^{st}$ pass metabolism), can be reduced by using transdermal (patch**,** topical gel, emulsion, spray), intravaginal (tablet, cream, ring) routes, or by injection.
- Parent drugs and their metabolites are excretion into bile & are then reabsorbed through the enterohepatic circulation. Inactive products are excreted in urine.

**Adverse effects**

- Nausea & breast tenderness.

Thromboembolism, MI, breast & endometrial CA (which can be offset by including a progestin along with the E therapy).

- Peripheral edema & hypertension.

**Selective Estrogen- Receptor Modulators (SERMs):**

The SERM are estrogen-related compounds that interact at but have different effects on different tissues, they display selective agonism or antagonism for E receptors depending on the tissue type. They includes tamoxifen, toremifene, raloxifene, clomiphene, and ospemifene.

**Mechanism of action & uses**

1. **Tamoxifen, Toremifene** & **Raloxifene**: act as E receptor antagonists in breast tissue.

- **Tamoxifen** is used in the treatment of metastatic breast CA in postmenopausal women, or as adjuvant therapy following mastectomy or radiation in breast CA.
- **Tamoxifen** & **raloxifene** are used as a prophylactic therapy in patients with high risk of breast CA.

2. **Raloxifene** also acts as an E agonist in bone, decreases bone resorption & increases bone density, & decreases vertebral fractures. Thus **raloxifene** is approved for prevention & treatment of osteoporosis in postmenopausal women.

- **Raloxifene** lowers total cholesterol & LDL.

3. **Clomiphene** acts as a partial E agonist & interferes with the negative feedback of E on the hypothalamus, increasing GnRH & gonadotropins secretion, thus it stimulates ovulation. It is useful for the treatment of infertility associated with anovulatory cycles (but it is not effective in women with ovulatory dysfunction due to pituitary or ovarian failure). **Ospemifene** exerts an estrogenic effect & reversing certain changes on vaginal tissue after menopause, thus it is indicated for the treatment of dyspareunia (painful sexual intercourse) related to menopause.

**SERMs pharmacokinetics:**

- Readily absorbed after oral administration.
- SERMs undergo enterohepatic cycling & excreted through the bile into feces.

**Adverse effects**

**1- Tamoxifen**:

- Hot flashes & nausea.
- Endometrial hyperplasia & malignancies, it is recommended to limit the time length of therapy for some indications.
- Some CYP450 inhibitors (eg. **amiodarone**, **haloperidol**, **risperidone**) may prevent the formation of **tamoxifen** active metabolites & possibly reduce its efficacy.

**2- Toremifene** adverse effects are similar to those of **tamoxifen.** But with no risk of endometrium hyperplasia & cancer.

**3- Raloxifene:**

- Hot flashes & leg cramps.

Note: **Raloxifene** has little- no effect on the endometrium.

- Increased risk of deep-vein thrombosis, pulmonary embolism & retinal-vein thrombosis. Thus **Raloxifene** should not taken by women with a past or active history of venous thromboembolic events.
- **Cholestyramine** reduces **raloxifene** absorption (should not be taken together).

**4- Clomiphene:**

- Cause dose related adverse effects, including headache, nausea, vasomotor flushes, visual disturbances & ovarian enlargement.
- **Clomiphene** use increases the risk of multiple births (twins or triplets).