

Sex hormones

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- Produced by the gonads.
- Necessary for conception, embryonic maturation & development of primary & secondary sexual characteristics at puberty.
- Used for hormone replacement therapy (HRT), contraception & management of menopausal symptoms.
- Several of their antagonists are effective in cancer chemotherapy.
- All gonadal hormones are synthesized from the precursor cholesterol, in a series of steps. Aromatization is the last step in estrogen synthesis.

Estrogens:

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

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

2. Estrone

- An **estradiol** metabolite with approximately 1/3 of the **estradiol** estrogenic potency.
- The primary circulating 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 (during pregnancy).

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

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.
- The steroid-receptor complex interacts to initiate hormone-specific RNA synthesis resulting in the 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-mediated dilation of coronary arteries occurs by the increased formation & release of nitric oxide & prostacyclin in endothelial cells.

Therapeutic uses

1. The E & progestogen combination provides effective contraception via oral or 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 flashes) because E treatment reestablishes feedback on hypothalamic control of norepinephrine secretion, leading to decreased frequency of “hot flashes”. 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). In the absence of the uterus Whereas in women who have undergone a hysterectomy, the unopposed E therapy is recommended because progestins may unfavorably alter the beneficial effects of E on lipid parameters.

- **Estradiol** transdermal patch is 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 quickly metabolized to **ethinyl estradiol**, which is metabolized more slowly.
- Stored in adipose tissue, from which they are slowly released.
- Therefore, the synthetic E analogs have prolonged action & higher potency compared to those of natural E.

3. Metabolism

- Low bioavailability of orally taken E (due to 1st 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.

Note: The endometrial cancer risk can be offset by including a progestin along with the E therapy.

- Headache, peripheral edema & hypertension.

Selective Estrogen- Receptor Modulators (SERMs):

The SERM are compounds that interact at E receptors but have different effects on different tissues, they display selective agonism or antagonism according to the tissue type, e.g., **tamoxifen** is an E antagonist in breast cancer tissue but can cause endometrial hyperplasia by acting as a partial agonist in the uterus. Other SERMs are **toremifene**, **raloxifene**, **clomiphene** & **ospemifene**.

Mechanism of action & uses

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

- **Tamoxifen** & **toremifene** are 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, thus vertebral fractures are decreased. Therefore **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 stimulating 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** is indicated for the treatment of dyspareunia (painful sexual intercourse) related to menopause.

Pharmacokinetics of SERMs:

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

Adverse effects

1- Tamoxifen:

- Hot flashes & nausea.
- Due to endometrial hyperplasia & malignancies reported with **tamoxifen** therapy, it is recommended to limiting the length of time on the drug 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 are common.

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).