Sex hormones:

- Produced by the gonads
- Necessary for conception, embryonic maturation & development of primary & secondary sexual characteristics at puberty.
- Their activity in target cells is modulated by receptors.
- Used therapeutically in replacement therapy, for contraception & in management of menopausal symptoms.
- Several antagonists are effective in cancer chemotherapy.
- All gonadal hormones are synthesized from the precursor, cholesterol, in a series of steps that includes shortening of the hydrocarbon side chain & hydroxylation of the steroid nucleus. Aromatization is the last step in estrogen synthesis.

Estrogens:

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

- Most potent estrogen produced & secreted by the ovary.
- The principal estrogen in the premenopausal woman.

2. Estrone

- A metabolite of **estradiol** that has approximately one third the estrogenic potency of **estradiol**.
- The primary circulating estrogen after menopause & it is generated mainly from conversion of androstenedione in peripheral tissues.

3. **Estriol**

- Another metabolite of **estradiol**, is significantly less potent than **estradiol**.
- Present in significant amounts during pregnancy, because it is the principal estrogen produced by the placenta.

4. A preparation of conjugated estrogens containing sulfate esters of **estrone** & **equilin** (obtained from pregnant mares' urine) is an oral preparation used for hormone replacement therapy.

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

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

6. Selective estrogen-receptor modulators (SERMs) are nonsteroidal compounds that bind to estrogen receptors & exert either estrogenic or antiestrogenic effects on target tissues. They include **tamoxifen** & **raloxifene**, among others.

Mechanism of action

- After dissociation from their binding sites on sex hormone–binding globulin or albumin in the plasma, steroid hormones diffuse across the cell membrane & bind with high affinity to specific nuclear-receptor proteins.

Note: These receptors belong to a large, nuclear hormone–receptor family that includes those for thyroid hormones & vitamin D.

- Two estrogen-receptor subtypes, α & β, mediate the effects of the hormone.

- The α -receptor may be considered as the classic estrogen receptor & the β-receptor is highly homologous to the α -receptor.
- The N-terminal portion of the α -receptor contains a region that promotes transcription activation, whereas the β-receptor contains a repressor domain.
- As a result, the transcriptional properties of the α & β estrogen receptors are different.
- Affinity for the receptor type varies with the particular estrogen. These receptor isoforms vary in structure, chromosomal location & tissue distribution.
- The activated steroid-receptor complex interacts with nuclear chromatin to initiate hormone-specific RNA synthesis. This results in the synthesis of specific proteins that mediate a number of physiologic functions.

Note: The steroid hormones may elicit the synthesis of different RNA species in diverse target tissues & therefore, are both receptor & tissue specific.

- Other pathways that require these hormones have been identified that lead to more rapid actions, eg. activation of an estrogen receptor in the membranes hypothalamic cells has been shown to couple to a G protein, thereby initiating a second-messenger cascade.
- In addition, estrogen-mediated dilation of coronary arteries occurs by the increased formation & release of nitric oxide & prostacyclin in endothelial cells.

Therapeutic uses

1. Contraception, the combination of an estrogen & progestogen provides effective contraception via the oral or transdermal 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” or “hot flushes”) & vaginal atrophy.

- Women who only have urogenital symptoms, such as vaginal atrophy, should be treated with vaginal rather than systemic estrogen.

Estrogens were previously widely used for prevention of osteoporosis, but current guidelines recommend use of other therapies such as **alendronate** over estrogen. [**Note**: Estrogen-progestogen therapy is no longer the therapy of choice for the treatment of osteoporosis in postmenopausal women because of increased risk of breast cancer, stroke, venous thromboembolism, and coronary disease].

- Estrogen may be used for prevention of osteoporosis if other therapies are inappropriate or not tolerated.
- For women who have an intact uterus, a progestogen is always included with the estrogen therapy, because the combination reduces the risk of endometrial carcinoma associated with unopposed estrogen (estrogen only therapy).
- For women who have undergone a hysterectomy, unopposed estrogen therapy is recommended because progestins may unfavorably alter the beneficial effects of estrogen on lipid parameters.

Note: The estrogen doses used in replacement therapy (RT) is substantially less than the doses used in oral contraception, thus, the adverse effects of estrogen replacement therapy tend to be less severe than those caused by estrogen used for contraception.

- **Estradiol** transdermal patch is also effective in treating postmenopausal symptoms.

3. RT in premenopausal patients who have estrogen's deficiency, which can occur due to inadequate functioning of the ovaries (hypogonadism), premature menopause, or surgical menopause.

- Estrogen usually in combination with a progestogen, is instituted to stimulate development of secondary sex characteristics in young women (11 - 13 years of age) with primary hypogonadism. Continued treatment is required after growth is completed.
- In women who have premature menopause or premature ovarian failure the estrogen & progestogen RT is usually continued until about age 50.

Pharmacokinetics

1. Naturally occurring estrogens & their esterified or conjugated derivatives are readily absorbed through the GIT, skin & mucous membranes.

- Orally taken, **estradiol** is rapidly metabolized (and partially inactivated) by the microsomal enzymes of the liver.
- Micronized **estradiol** is available & has better bioavailability.

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

- **Mestranol** is quickly demethylated to **ethinyl estradiol**, **which** is metabolized more slowly than the naturally occurring estrogens by the liver & peripheral tissues.
- Stored stored in adipose tissue, from which they are slowly released. Therefore, the synthetic estrogen analogs have a prolonged action & a higher potency compared to those of natural estrogens.

Metabolism

- Transported in the blood while bound to serum albumin or sex hormone-binding globulin.
- Low bioavailability of the orally given estrogen due to 1st pass metabolism, which can be reduced by administrating the drugs as transdermal patch**,** topical gel or emulsion, intravaginal or as injection formulations.
- Metabolized in to glucuronidated or sulfated metabolite.
- The metabolites undergo excretion into the bile & reabsorbed through the enterohepatic circulation.
- Inactive products are excreted in the urine.

Note: liver damage increase serum estrogen levels, causing feminization in males or sings of estrogen excess in females.

Adverse effects

- Nausea & breast tenderness.
- Postmenopausal uterine bleeding can occur.
- The risk of thromboembolic events, myocardial infarction & breast & endometrial cancer is increased.

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

- Headache, peripheral edema & hypertension can occur.

- Diethylstilbestrol (synthetic nonsteroidal estrogen) may cause a rare, clear-cell cervical or vaginal adenocarcinoma among the daughters of women who took this drug during pregnancy.

Selective estrogen- receptor modulators (SERMs):

A new class of estrogen-related compound. The term SERM is now reserved for compounds that interact at estrogen receptors but have different effects on different tissues; that is, they display selective agonism or antagonism according to the tissue type. For example, **tamoxifen** is an estrogen 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 is also sometimes designated as a SERM.

Mechanism of action

1. **Tamoxifen** considered to be the first SERM, it competes with estrogen for binding to the estrogen receptor in breast tissue.

Note: Normal breast growth is stimulated by estrogens. It is, therefore, not surprising that some breast tumors regress following treatment with **tamoxifen**.

2. **Raloxifene** is a second-generation SERM that is related to **tamoxifen**.

- Like **tamoxifen**, **raloxifene** also exhibits antagonism of estrogen receptors in the breast tissue. In addition, **raloxifene** decreases bone resorption & overall bone turnover. Bone density is increased & vertebral fractures are decreased.
- **Raloxifene** lowers total cholesterol & LDL in the serum, but it has no effect on HDL or triglyceride levels.

3. **Toremifene** similar to **tamoxifen.**
4. **Clomiphene** acts as a partial estrogen agonist & interferes with the negative feedback of estrogens on the hypothalamus. This effect thereby increases the secretion of gonadotropin-releasing hormone and gonadotropins leading to stimulating ovulation.

Therapeutic uses

1. **Tamoxifen** is currently used in the palliative treatment of metastatic breast cancer in postmenopausal women. It may also be used as adjuvant therapy following mastectomy or radiation in breast cancer & as a prophylactic therapy to reduce the risk of breast cancer in high risk patients.

2. **Raloxifene** is approved for the prophylaxis of breast cancer in high-risk women & also for the prevention & treatment of osteoporosis in postmenopausal women.

3. **Toremifene** its use is restricted to postmenopausal women with metastatic breast cancers.

4. **Clomiphene** has been used successfully to treat infertility associated with anovulatory cycles, but it is not effective in women with ovulatory dysfunction due to pituitary or ovarian failure.

Pharmacokinetics

- The SERMs are readily absorbed after oral administration.
- **Tamoxifen** is extensively metabolized by CYP450 enzymes.

- **Raloxifene** is rapidly converted to glucuronide conjugates through first-pass metabolism. More than 95 % of **raloxifene** is bound to plasma proteins.
- All three agents undergo enterohepatic cycling & the primary route of excretion is through the bile into feces.

Adverse effects

1- Tamoxifen:

- Hot flashes & nausea. Menstrual irregularities & vaginal bleeding can also occur.
- Due to its estrogenic activity in the endometrium, hyperplasia & malignancies. This has led to recommendations for limiting the length of time on the drug for some indications.
- Because it is metabolized by various CYP450 isozymes, **tamoxifen** is subject to many drug interactions. Some CYP450 inhibitors may prevent the formation of active metabolites of **tamoxifen** & possibly reduce the efficacy (for example, **amiodarone**, **haloperidol**, **risperidone**). Thus, concurrent drug therapy should be reviewed carefully to screen for potential drug interactions with **tamoxifen**.

2- Raloxifene

- Similar to **tamoxifen**, hot flashes & leg cramps are common adverse effects with **raloxifene**.

Note: **Raloxifene** apparently has little to no effect on the endometrium & therefore, may not predispose to uterine cancer.

- In addition, there is an increased risk of deep-vein thrombosis, pulmonary embolism & retinal-vein thrombosis. Women who have a past or active history of venous thromboembolic events should not take the drug.
- Should be avoided in women who are or may become pregnant.
- Coadministration with **cholestyramine** can reduce the absorption of **raloxifene** by 60 %. Therefore, these drugs should not be taken together.

3- Toremifene similar to those of **tamoxifen.** Data on the risk of the endometrium, hyperplasia & cancer are lacking.

4- Clomiphene

- Its adverse effects are dose related, they include headache, nausea, vasomotor flushes, visual disturbances & ovarian enlargement.
- The risk of multiple births (twins or triplets) with **clomiphene** is 3 - 5 %.