ESTROGEN

(Female Sex hormones)

Natural estrogens- Estradiol is the major estrogen secreted by the ovary.

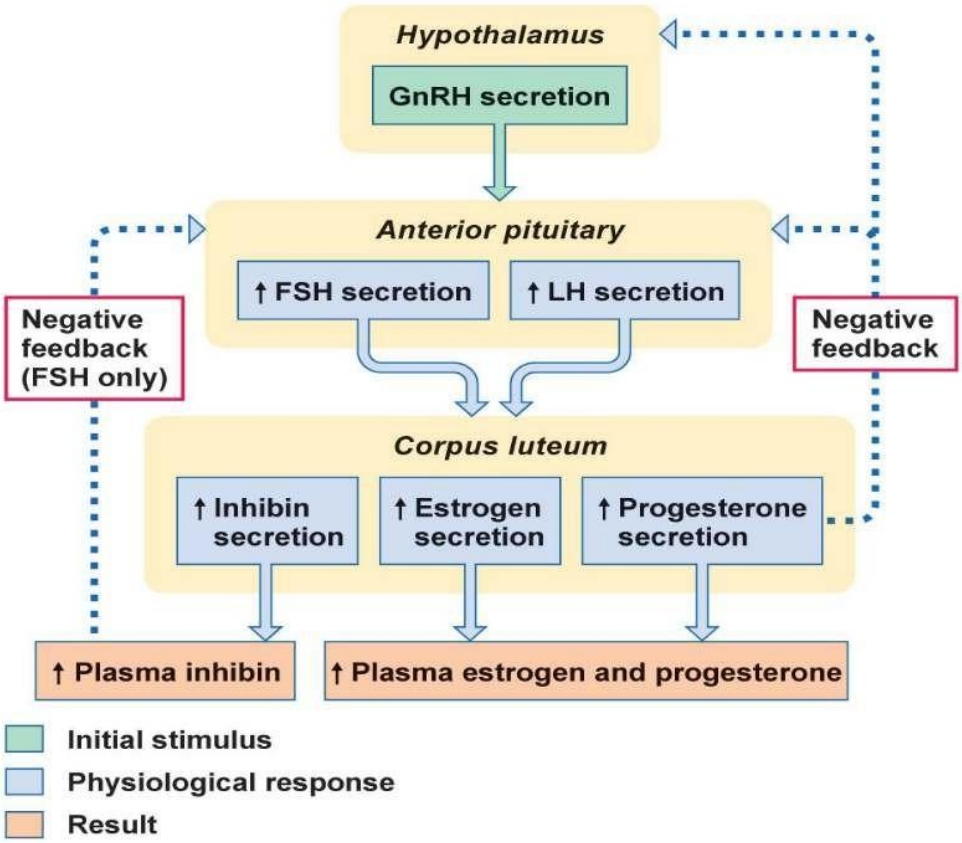
It is synthesized in the graafian follicle, corpus luteum and placenta from cholesterol

Synthetic estrogens - Natural estrogens are inactive orally and have a short duration of action due to rapid etabolism in liver. Synthetic compounds have been produced:

Steroidal- Ethinylestradiol, Mestranol, Tibolone.

Nonsteroidal- Diethylstilbestrol (stilbestrol) Hexestrol, Dienestrol

Regulation of secretion



Actions of estrogen

Sex organs: Growth of uterus, fallopian tube, and vagina

- Vaginal epithelium – thickened, stratified, cornified
- Responsible for the proliferation of endometrium in preovulatory phase
- Increase rhythmic contraction of fallopian tube and uterus
- Induce watery alkaline secretion from the cervix – favours sperm penetration
- Sensitizes uterus to oxytocin
- Deficiency of estrogen – atrophic changes

Secondary sex characters:

• Breast growth

• Pubic axillary hair

• Accumulation of fat

• Feminine body contours and behaviour are influenced

Metabolic effects – Anabolic (weaker than testosterone)

• Promotes fusion of epiphysis

• Maintains/ Prevents resorption and inhibition of osteoclast pit formation

• Expression of bone matrix proteins

• Promotes positive calcium balance

Other actions –

• Mild salt water retention

• Combination contraceptives - Impaired glucose tolerance

• Improved lipid profile

• Stimulate fibrinolytic activity

• Induce NO synthase – promote vasodilation

• Increases lithogenicity of bile and decrease bile salt secretion

Mechanism of action

• Estrogens bind to specific nuclear receptors in target cells and produce effects by regulating protein synthesis.

• Estrogen receptors (ERs) present in female sex organs, breast, pituitary, liver, bone, blood vessels, heart, CNS and in certain hormone responsive breast carcinoma cells

• The ER is analogous to other steroid receptors: agonist binding to the ligand binding domain brings about receptor dimerization and interaction with 'estrogen response elements' (EREs) of target genes

• Gene transcription is promoted

Pharmacokinetics

• Natural – Inactive orally

• Bind to Steroid Hormone Binding Protein (SHBG)

• Estradiol gets converted to estrone in liver – estriol derived from estrone

• Glucuronide and sulfate conjugation

• Excreted urine and bile

• Enterohepatic circulation

• Transdermal estradiol: 5, 10 and 20 cm2 delivers 0.025, 0.05, 0.1 mg

ADR

• Males: Suppression of libido, gynacomastia, feminisation

• Early fusion of epiphyses in children

- Pregnant women: Increase incidence of vaginal/ cervical carcinoma in female offspring
- Other genital abnormalities in male and female offspring
- Post-menopausal women: increased risk of irregular bleeding and endometrial carcinoma
- Accelerate the growth of existing breast cancer

Uses

- As contraceptive
- In Hormone Replacement Therapy
- Senile vaginitis
- Delayed puberty in girls
- Dysmenorrhoea
- Acne
- Dysfunctional uterine bleeding
- Carcinoma prostrate
- Hirsutism

ANTIESTROGEN

Clomiphene citrate

- Pure antagonist at estrogen receptor
- Inhibits estrogenic feedback – stimulates ovulation
- Used in sterility (Amenorrhoea, anovular cycles)
- ADR: Polycystic ovary, multiple pregnancy, risk of ovarian tumour
- To aid in vitro fertilization
- In men - Spermatogenesis

Selective Estrogen Receptor Modulators (SERMs)

- Tamoxifen citrate: Potent estrogen antagonist in breast carcinoma cells, blood vessels
- Partial agonist at uterus, bone, liver, pituitary
- Toremifene: Newer congener of tamoxifen
- Raloxifene: Partial agonist at bone and CVS, Antagonist in endometrium, breast
- Ormeloxifene: Supress endometrial proliferation

Aromatase inhibitors

- Letrozole, anastrozole, exemestane
- Orally active
- Reversible inhibitor
- Early breast cancer: Adjuvant therapy after mastectomy in ER +ve cases
- Advanced breast cancer
- ADR: Dyspepsia, thinning of hair, joint pain, risk of thromboembolism

PROGESTINS

These are substances which convert the estrogen primed endometrium to secretory and maintain pregnancy (Progestin = favouring pregnancy)

Natural progestin Progesterone, a 21 carbon steroid, is the natural progestin

• Derived from cholesterol.

• Secreted by the corpus luteum (10–20 mg/day) in the later half of menstrual cycle under the influence of LH

• Production declines a few days before the next menstrual flow

• If the ovum gets fertilized and implants—the blastocyst mmediately starts producing chorionic gonadotropin which is absorbed and sustains the corpus luteum in early pregnancy.

• Placenta starts secreting lots of estrogens and progesterone from 2nd trimester till term.

Synthetic progesterone

• Progesterone derivatives (21C) - Medroxy progesterone acetate, megestrol acetate, dihydrogesterone, hydroxyl progesterone caproate, nomegestrol acetate

• 19 – Nortestosterone derivative (18C)Norethindrone (Norethisterone), lynestrenol (ethinyl estrenol), allyl estrenol, levonorgestrel (Gonane)

• Newer compounds - Desogestrel, norgestimate, gestodene

Actions of estrogen

Uterus:

• Preparation of uterus for nidation and maintenance of pregnancy

• Prevention of endometrial shedding, decrease uterine motility, inhibition of immunological rejection of foetus

• Secretory changes in estrogen primed endometrium, hyperemia, tortuocity of glands

• Decreases sensitivity of myometrium to oxytocin

Cervix:

Progesterone converts the watery cervical secretion induced by estrogens to viscid, scanty and cellular secretion which is hostile to sperm penetration

Vagina:

Induces pregnancy like changes in the vaginal mucosa—leukocyte infiltration of cornified epithelium

Breast:

• Progesterone causes proliferation of acini in the mammary glands

• Along with estrogens, it prepares breast for lactation

• Withdrawal of these hormones after delivery causes release of prolactin from pituitary and milk secretion starts

CNS:

High circulating concentration of progesterone (during pregnancy) appears to have a sedative effect

Body temperature: Slight increase (Hypothalamus thermostat) Respiration: High dose stimulate respiration

Metabolism: Progestins with androgenic effect increase LDL, decrease HDL Pituitary: Weak inhibitor of Gonadotropin secretion

• Hypothalamus decreases the frequency of LH pulses

• Prevents LH surge and ovulation

Pharmacokinetics

• Orally high FPM

• Liver – Pregnanediol

• Glucuronic acid and sulfate conjugation

• Synthetis progestins

– Orally active

– Metabolised slowly

– Half-life: 8 – 24 hrs

ADR

• Breast engorgement, headache, rise in BT, edema, esophageal reflux, acne, mood swings

• Continuous: Irregular bleeding/ amenorrhoea

• 19 nor derivatives – atherogenesis

• In HRT – Increased risk of breast cancer

• Blood sugar – raise with potent agents

• Early pregnancy – Masculinization of female foetus and other congenital abnormalities

Uses

• As contraceptive

• HRT

• Dysfunctional uterine bleeding

• Endometriosis

• Premenstrual syndrome

• Threatened/ habitual abortion

• Endometrial carcinoma