Estrogens and Androgens

Part 1

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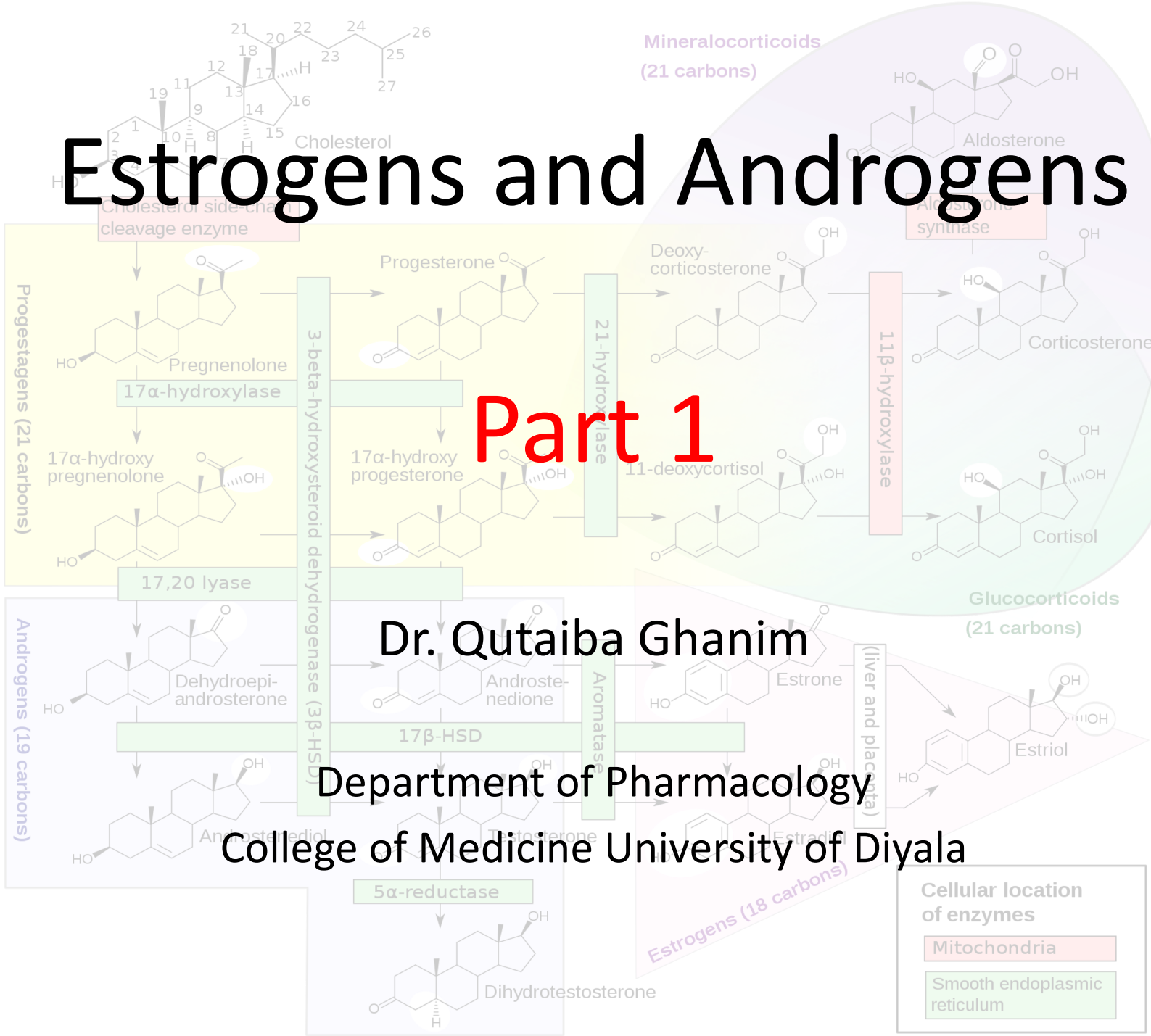


Video

Estrogens

- ***Estradiol***, also known as 17β-estradiol, is the most potent estrogen produced and secreted by the ovary. It is the principal estrogen in premenopausal women.

- ***Estrone*** is a metabolite of estradiol that has approximately one-third the estrogenic potency of estradiol. Estrone is the primary circulating estrogen after menopause.

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

Estrogens

- **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 and bind with high affinity to specific nuclear receptor proteins. 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.

- **Therapeutic uses:**

1. **Postmenopausal HT:** The primary indication for estrogen therapy in postmenopausal women is menopausal symptoms, such as vasomotor instability (for example, “hot flashes” or “hot flushes”) and vaginal atrophy.

- 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.

Estrogens

- 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.

- Delivery of estradiol by transdermal patch or gel is also effective in treating postmenopausal symptoms. Due to concerns over the risks of HT (increased risk of cardiovascular events and breast cancer), HT should be prescribed at the lowest effective dose for the shortest possible time to relieve menopausal symptoms.

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

Estrogens

2. Contraception: The combination of an estrogen and progestogen provides effective contraception via the oral, transdermal, or vaginal route.

3. Other uses: Estrogen therapy mimicking the natural cyclic pattern, and usually in combination with a progestogen, is instituted to stimulate development of secondary sex characteristics in young women with primary hypogonadism. Continued treatment is required after growth is completed.

- Similarly, estrogen and progestogen replacement therapy is used for women who have premature menopause or premature ovarian failure.

Selective Estrogen Receptor Modulators (SERMs)

- SERMs are a class of estrogen-related compounds that display selective agonism or antagonism for estrogen receptors depending on the tissue type.

- This category includes ***tamoxifen, toremifene, raloxifene, clomiphene, and ospemifene***.

- **Mechanism of action:** **Tamoxifen, toremifene, and raloxifene** compete with estrogen for binding to the estrogen receptor in breast tissue.

- In addition, **raloxifene** acts as an estrogen agonist in bone, leading to decreased bone resorption, increased bone density, and decreased vertebral fractures.

- Unlike estrogen and tamoxifen, **raloxifene** does not have appreciable estrogen receptor agonist activity in the endometrium and, therefore, does not predispose to endometrial cancer.

- **Raloxifene** also lowers serum total cholesterol and low-density lipoprotein (LDL).

Selective Estrogen Receptor Modulators (SERMs)

- ***Clomiphene*** acts as a partial estrogen agonist and interferes with the negative feedback of estrogens on the hypothalamus. This effect increases the secretion of gonadotropin-releasing hormone and gonadotropins, thereby leading to stimulation of ovulation.

- **Therapeutic uses:** Tamoxifen is currently used in the treatment of metastatic breast cancer, or as adjuvant therapy following mastectomy or radiation for breast cancer. Both tamoxifen and raloxifene can be used as prophylactic therapy to reduce the risk of breast cancer in high-risk patients.

- Raloxifene is also approved for the prevention and treatment of osteoporosis in postmenopausal women.

- Clomiphene is useful for the treatment of infertility associated with anovulatory cycles. Ospemifene is indicated for the treatment of dyspareunia (painful sexual intercourse) related to menopause.

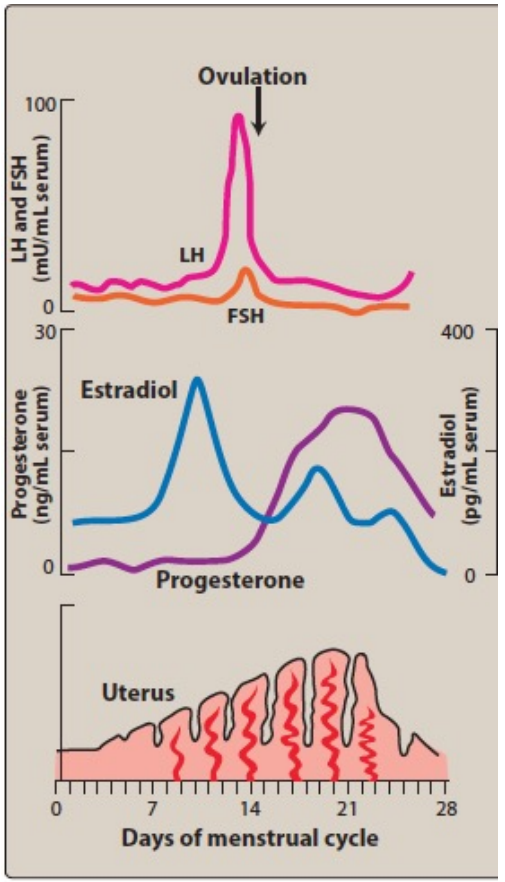
Progestogens

- Progesterone, the natural progestogen, is produced in response to luteinizing hormone (LH) by both females (secreted by the corpus luteum, primarily during the second half of the menstrual cycle, and by the placenta) and by males (secreted by the testes). It is also synthesized by the adrenal cortex in both sexes.

- **Mechanism of action:** Progestogens exert their mechanism of action in a manner analogous to that of the other steroid hormones. In females, progesterone promotes the development of a secretory endometrium that can accommodate implantation of a newly forming embryo.

- The high levels of progesterone that are released during the second half of the menstrual cycle (the luteal phase) inhibit the production of gonadotropin and, therefore, prevent further ovulation. If conception takes place, progesterone continues to be secreted, maintaining the endometrium in a favorable state for the continuation of the pregnancy and reducing uterine contractions.

- If conception does not take place, the release of progesterone from the corpus luteum ceases abruptly. This decline stimulates the onset of menstruation.



Progestogens

- Therapeutic uses: The major clinical uses of progestogens are for postmenopausal HT, contraception and the treatment of hormone deficiency.

- For contraception, they are often used in combination with estrogens. Progesterone by itself is not used widely as a contraceptive therapy because of its rapid metabolism, resulting in low bioavailability.

- These agents include ***desogestrel, levonorgestrel, norgestrel, drospirenone, norethindrone, norethindrone acetate, norgestimate, and dienogest***.

- ***Medroxyprogesterone acetate*** is an injectable contraceptive, and the oral form is a common progestin component of postmenopausal HT.

- Progestins are also used for the control of dysfunctional uterine bleeding, treatment of dysmenorrhea, and management of endometriosis and infertility.

- **Antiprogestin:** ***Mifepristone*** is a progesterone antagonist with partial agonist activity.

- Administration of this drug to females early in pregnancy usually results in abortion of the fetus due to interference with the progesterone needed to maintain pregnancy. Mifepristone is often combined with the prostaglandin analog misoprostol (administered orally or intravaginally) to induce uterine contractions.


Thank You!