The Gonadal Hormones & Inhibitors

Dr Leila Moezi

Department of Pharmacology

Email: moezil@sums.ac.ir

Learning objectives:

Following the lesson presentation students will be able to:

1. Describe the physiological effects, indications, side effects and contraindications of estrogens and progesterone
2. Describe different types of contraceptives and their benefits and side effects
3. Describe the indications, mechanism of action, side effects and contraindications of anti-estrogen and anti-progestin
4. Describe the physiological effects, indications, side effects and contraindications of androgens and anti-androgens

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THE ESTROGENS

Natural Estrogens: Estradiol, Estrone, Estriol

Synthetic Estrogens (steroidal): Ethinyl estradiol, Mestranol

Synthetic Estrogens (non-steroidal): Diethylestilbestrol

Estrogen mimetic compounds: Flavonoids (Soybeans)

Physiologic Effects:

Female Maturation: Estrogens are required for the normal sexual maturation and growth of the female. They stimulate the development of the vagina, uterus, and uterine tubes as well as the secondary sex characteristics. They stimulate stromal development and ductal growth in the breast and are responsible for the accelerated growth phase and the closing of the epiphyses of the long bones that occur at puberty. They contribute to the growth of axillary and pubic hair and alter the distribution of body fat to produce typical female body contours. Larger quantities also stimulate development of pigmentation in the skin, most prominent in the region of the nipples and areolae and in the genital region.

Endometrial Effects: Estrogen plays an important role in the development of the endometrial lining. When estrogen production is properly coordinated with the production of progesterone during the normal human menstrual cycle, regular periodic bleeding and shedding of the endometrial lining occur. Continuous exposure to estrogens for prolonged periods leads to hyperplasia of the endometrium that is usually associated with abnormal bleeding patterns.

Metabolic and Cardiovascular Effects: Estrogens have a number of important metabolic and cardiovascular effects. Estrogens also decrease the rate of resorption of bone by promoting the

apoptosis of osteoclasts and by antagonizing the osteoclastogenic and pro-osteoclastic effects of parathyroid hormone and interleukin-6. Metabolic alterations in the liver are especially important, so that there is a higher circulating level of proteins such as transcortin (corticosteroid-binding globulin [CBG]), thyroxinebinding globulin (TBG), SHBG, transferrin, renin substrate, and fibrinogen. This leads to increased circulating levels of thyroxine, estrogen, testosterone, iron, copper, and other substances. Alterations in the composition of the plasma lipids caused by estrogens are characterized by an increase in the high-density lipoproteins (HDL), a slight reduction in the low-density lipoproteins (LDL), and a reduction in total plasma cholesterol levels.

Effects on Blood Coagulation

Estrogens enhance the coagulability of blood. Many changes in factors influencing coagulation have been reported, including increased circulating levels of factors II, VII, IX, and X and decreased antithrombin III, partially as a result of the entero-hepatic circulation.

CLINICAL USES:

A. Primary Hypogonadism: Estrogens have been used extensively for replacement therapy in estrogen-deficient patients. The estrogen deficiency may be due to primary failure of development of the ovaries, premature menopause, castration, or menopause.

B. Postmenopausal Hormonal Therapy

Adverse Effects:

Uterine Bleeding, Cancer (Breast cancer, Endometrial carcinoma), Nausea, Breast tenderness, Hyperpigmentation, Increase frequency of migraine headaches, Cholestasis, Hypertension

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THE PROGESTINS

Natural Progestins: Progesterone

Progesterone is the most important progestin in humans. In addition to having important hormonal effects, it serves as a precursor to the estrogens, androgens, and adrenocortical steroids. It is synthesized in the ovary, testis, and adrenal cortex from circulating cholesterol. Large amounts are also synthesized and released by the placenta during pregnancy.

Synthetic Progestins

They are not a uniform group of compounds, and all of them differ from progesterone in one or more respects. In general, the 21-carbon compounds (hydroxyprogesterone, medroxyprogesterone, megestrol, and dimethisterone) are the most closely related, pharmacologically as well as chemically, to progesterone. A new group of third-generation synthetic progestins has been introduced, principally as components of oral contraceptives. These 19-nor, 13-ethyl" steroid compounds include desogestrel, gestodene, and norgestimate. They are claimed to have lower androgenic activity than older synthetic progestins.

Physiologic Effects:

Progesterone increases body temperature in humans. Progesterone is responsible for the alveolobular development of the secretory apparatus in the breast. It also participates in the preovulatory LH surge and causes the maturation and changes in the endometrium that are seen following ovulation.

Therapeutic Applications:

The major uses of progestational hormones are for hormone replacement therapy and hormonal contraception. In addition, they are useful in producing long-term ovarian suppression for other purposes. When used alone in large doses parenterally (eg, medroxyprogesterone acetate, 150 mg intramuscularly every 90 days), prolonged anovulation and amenorrhea result. This therapy

has been employed in the treatment of dysmenorrhea, endometriosis, and bleeding disorders when estrogens are contraindicated, and for contraception. The major problem with this regimen is the prolonged time required in some patients for ovulatory function to return after cessation of therapy. It should not be used for patients planning a pregnancy in the near future. Similar regimens will relieve hot flushes in some menopausal women and can be used if estrogen therapy is contraindicated.

Medroxyprogesterone acetate, 10–20 mg orally twice weekly—or intramuscularly in doses of 100 mg/m2 every 1–2 weeks—will prevent menstruation, but it will not arrest accelerated bone maturation in children with precocious puberty.

Progestins do not appear to have any place in the therapy of threatened or habitual abortion. Early reports of the usefulness of these agents resulted from the unwarranted assumption that after several abortions the likelihood of repeated abortions was over 90%. When progestational agents were administered to patients with previous abortions, a salvage rate of 80% was achieved. It is now recognized that similar patients abort only 20% of the time even when untreated. On the other hand, progesterone was given experimentally to delay premature labor with encouraging results. Progesterone and medroxyprogesterone have been used in the treatment of women who have difficulty in conceiving and who demonstrate a slow rise in basal body temperature. There is no convincing evidence that this treatment is effective. Preparations of progesterone and medroxyprogesterone have been used to treat premenstrual syndrome. Controlled studies have not confirmed the effectiveness of such therapy except when doses sufficient to suppress ovulation have been used.

Adverse Effects:

Progestin in these agents may increase blood pressure in some patients. The more androgenic

progestins also reduce plasma HDL levels in women. Two recent studies suggest that combined progestin plus estrogen replacement therapy in postmenopausal women may increase breast cancer risk significantly compared with the risk in women taking estrogen alone.

HORMONAL CONTRACEPTION

Two types of preparations are used for oral contraception: (1) combinations of estrogens and progestins and (2) continuous progestin therapy without concomitant administration of estrogens.

Combinations of estrogens and progestins

The combination agents are further divided into **monophasic** forms (constant dosage of both components during the cycle) and **biphasic** or **triphasic** forms (dosage of one or both components is changed once or twice during the cycle).

The most important use of combined estrogens and progestins is for oral contraception. Progestins and estrogens are also useful in the treatment of endometriosis. When severe dysmenorrhea is the major symptom, the suppression of ovulation with estrogen alone may be followed by painless periods. However, in most patients this approach to therapy is inadequate. The long-term administration of large doses of progestins or combinations of progestins and estrogens prevents the periodic breakdown of the endometrial tissue and in some cases will lead to endometrial fibros.

Adverse Effects:

Mild: Nausea, Mastalgiam, Breakthrough bleeding, Edema, Changes in serum proteins, Headache, Withdrawal bleeding

Moderate: Breakthrough bleeding, Weight gain, Skin pigmentation, Acne, Hirsutism, Vaginal infections, Amenorrhea, Hypertension

Sever: Venus thromboembolic disease, MI, Cerebrovascular disease, GI disorders, Depression, Cancer (It is now clear that these compounds *reduce* the risk of endometrial and ovarian cancer)

Contraception with Progestins Alone

Small doses of progestins administered orally or by implantation under the skin can be used for contraception. They are particularly suited for use in patients for whom estrogen administration is undesirable. They are about as effective as intrauterine devices or combination pills containing 20–30 mcg of ethinyl estradiol. There is a high incidence of abnormal bleeding. Effective contraception can also be achieved by injecting 150 mg of depot medroxyprogesterone acetate (DMPA) every 3 months. After a 150 mg dose, ovulation is inhibited for at least 14 weeks. Almost all users experience episodes of unpredictable spotting and bleeding, particularly during the first year of use. Spotting and bleeding decrease with time, and amenorrhea is common. This preparation is not desirable for women planning a pregnancy soon after cessation of therapy cause ovulation suppression can sometimes persist for as long as 18 months after the last injection. Long-term DMPA use reduces menstrual blood loss and is associated with a decreased risk of endometrial cancer. Suppression of endogenous estrogen secretion may be associated with a reversible reduction in bone density, and changes in plasma lipids are associated with an increased risk of atherosclerosis. The progestin implant method utilizes the subcutaneous implantation of capsules containing etonogestrel. These capsules release one fifth to one third as much steroid as oral agents, are extremely effective, and last for 2–4 years. The low levels of hormone have little effect on lipoprotein and carbohydrate metabolism or blood pressure. The disadvantages include the need for surgical insertion and removal of capsules and some irregular bleeding rather than predictable menses. An association of intracranial hypertension with an earlier type of implant utilizing norgestrel was observed in a small number of women. Patients

experiencing headache or visual disturbances should be checked for papilledema. Contraception with progestins is useful in patients with hepatic disease, hypertension, psychosis or mental retardation, or prior thromboembolism. The side effects include headache, dizziness, bloating and weight gain of 1–2 kg, and a reversible reduction of glucose tolerance.

Postcoital Contraceptives

Pregnancy can be prevented following coitus by the administration of estrogens alone, progestin alone, or in combination (**morning after** contraception). When treatment is begun within 72 hours, it is effective 99% of the time. The hormones are often administered with antiemetics, since 40% of patients have nausea or vomiting. Other adverse effects include headache, dizziness, breast tenderness, and abdominal and leg cramps.

Mifepristone, an antagonist at progesterone and glucocorticoid receptors, has a luteolytic effect and is effective as a postcoital contraceptive. When combined with a prostaglandin it is also an effective abortifacient.

ESTROGEN & PROGESTERONE INHIBITORS & ANTAGONISTS

Tamoxifen & related partial agonist estrogens

Tamoxifen, a competitive partial agonist inhibitor of estradiol at the estrogen receptor, was the first **selective estrogen receptor modulator** to be introduced. Tamoxifen is extensively used in the palliative treatment of breast cancer in postmenopausal women and is approved for chemoprevention of breast cancer in high-risk women. Hot flushes and nausea and vomiting occur in 25% of patients, and many other minor adverse effects are observed. Studies of patients treated with tamoxifen as adjuvant therapy for early breast cancer have shown a 35% decrease in contralateral breast cancer.

Raloxifene is another partial estrogen agonist-antagonist at some but not all target tissues. It has estrogenic effects on lipids and bone but appears not to stimulate the endometrium or breast.

Raloxifene has been approved in the USA for the prevention of postmenopausal osteoporosis and prophylaxis of breast cancer in women with risk factors.

MIFEPRISTONE (RU 486)

Mifepristone binds strongly to the progesterone receptor and inhibits the activity of progesterone. The drug has luteolytic properties in 80% of women when given in the midluteal period. However, because the compound has a long half-life, large doses may prolong the follicular phase of the subsequent cycle and so make it difficult to use continuously for this purpose. The drug also binds to and acts as an antagonist at the glucocorticoid receptor. Limited clinical studies suggest that mifepristone or other analogs with similar properties may be useful in the treatment of endometriosis, Cushing's syndrome, breast cancer, and possibly other neoplasms such as meningiomas that contain glucocorticoid or progesterone receptors.

The major adverse effect was prolonged bleeding that on most occasions did not require treatment.

Other inhibitors

Anastrozole, a selective nonsteroidal inhibitor of aromatase (the enzyme required for estrogen synthesis), is effective in some women whose breast tumors have become resistant to tamoxifen (see Chapter 54). **Letrozole** is similar. **Exemestane,** a steroid molecule, is an irreversible inhibitor of aromatase. Like anastrozole and letrozole, it is approved for use in women with advanced breast cancer. Several other aromatase inhibitors are undergoing clinical trials in patients with breast cancer. **Fadrozole** is an oral nonsteroidal (triazole) inhibitor of aromatase activity. These compounds appear to be as effective as tamoxifen. In addition to their use in

breast cancer, aromatase inhibitors have been successfully employed as adjuncts to androgen antagonists in the treatment of precocious puberty and as primary treatment in the excessive aromatase syndrome.

Fulvestrant is a pure estrogen receptor antagonist that has been somewhat more effective than those with partial agonist effects in some patients who have become resistant to tamoxifen. Fulvestrant is approved for use in breast cancer patients who have become resistant to tamoxifen.

Ovulation-inducing agents (Clomiphene)

Clomiphene is a partial agonist at estrogen receptors. Clomiphene has also been shown to effectively inhibit the action of stronger estrogens. In humans it leads to an increase in the secretion of gonadotropins and estrogens by inhibiting estradiol's negative feedback effect on the gonadotropins. The pharmacologic importance of this compound rests on its ability to stimulate ovulation in women with oligomenorrhea or amenorrhea and ovulatory dysfunction. The majority of patients suffer from polycystic ovary syndrome, a common disorder affecting about 7% of women of reproductive age. The syndrome is characterized by gonadotropin-dependent ovarian hyperandrogenism associated with anovulation and infertility. The disorder is frequently accompanied by adrenal hyperandrogenism. Clomiphene probably blocks the feedback inhibitory influence of estrogens on the hypothalamus, causing a surge of gonadotropins, which leads to ovulation.

Clomiphene is used in the treatment of disorders of ovulation in patients who wish to become pregnant. Usually, a single ovulation is induced by a single course of therapy, and the patient must be treated repeatedly until pregnancy is achieved, since normal ovulatory function does not usually resume. The compound is of no value in patients with ovarian or pituitary failure.

Adverse Effects: The most common adverse effects in patients treated with this drug are hot flushes, which resemble those experienced by menopausal patients. They tend to be mild, and disappear when the drug is discontinued. There have been occasional reports of eye symptoms due to intensification and prolongation of afterimages. These are generally of short duration. Headache, constipation, allergic skin reactions, and reversible hair loss have been reported occasionally.

The effective use of clomiphene is associated with some stimulation of the ovaries and usually with ovarian enlargement. The degree of enlargement tends to be greater and its incidence higher in patients who have enlarged ovaries at the beginning of therapy. A variety of other symptoms such as nausea and vomiting increased nervous tension, depression, fatigue, breast soreness, weight gain, urinary frequency, and heavy menses have also been reported.

ANDROGENS & ANABOLIC STEROIDS

In humans, the most important androgen secreted by the testis is testosterone. In many target tissues, testosterone is converted to dihydrotestosterone by 5α-reductase. In these tissues, dihydrotestosterone is the major active androgen. The conversion of testosterone to estradiol by P450 aromatase also occurs in some tissues, including adipose tissue, liver, and the hypothalamus, where it may be of importance in regulating gonadal function. Androstenedione, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEAS) are also produced in significant amounts in humans, although largely in the adrenal gland rather than in the testes. They contribute slightly to the normal maturation process supporting other androgen-dependent pubertal changes in the human, primarily development of pubic and axillary hair and bone maturation.

Physiologic Effects

In the normal male, testosterone or its active metabolite 5α-dihydrotestosterone is responsible for the many changes that occur in puberty. In addition to the general growth-promoting properties of androgens on body tissues, these hormones are responsible for penile and scrotal growth. Changes in the skin include the appearance of pubic, axillary, and beard hair. The sebaceous glands become more active, and the skin tends to become thicker and oilier. The larynx grows and the vocal cords become thicker, leading to a lower-pitched voice. Skeletal growth is stimulated and epiphysial closure accelerated. Other effects include growth of the prostate and seminal vesicles, darkening of the skin, and increased skin circulation. Androgens play an important role in stimulating and maintaining sexual function in men. Androgens increase lean body mass and stimulate body hair growth and sebum secretion. Metabolic effects include the reduction of hormone binding and other carrier proteins and increased liver synthesis of clotting factors, triglyceride lipase, α1-antitrypsin, haptoglobin, and sialic acid. They also stimulate renal erythropoietin secretion and decrease HDL levels.

Synthetic Steroids with Androgenic & Anabolic Action

Testosterone, when administered by mouth, is rapidly absorbed. However, it is largely converted to inactive metabolites, and only about one sixth of the dose administered is available in active form. Testosterone can be administered parenterally, but it has a more prolonged absorption time and greater activity in the propionate, enanthate, undecanoate, or cypionate ester forms. These derivatives are hydrolyzed to release free testosterone at the site of injection. Testosterone derivatives alkylated at the 17 position, eg, methyltestosterone and fluoxymesterone, are active when given by mouth.

Testosterone and its derivatives have been used for their anabolic effects as well as in the treatment of testosterone deficiency.

Mechanism of Action:

Like other steroids, testosterone acts intracellularly in target cells. In skin, prostate, seminal vesicles, and epididymis, it is converted to 5α-dihydrotestosterone by 5α-reductase. In these tissues, dihydrotestosterone is the dominant androgen. The distribution of this enzyme in the fetus is different and has important developmental implications.

Clinical Uses:

Androgen Replacement Therapy in men, Gynecological Disorders, Use as Protein Anabolic Agents, Anemia, Osteoporosis, Use as growth stimulators, Abuse in Sports, Aging

Adverse Effects:

- Masculinization (most noticeable in women & prepubertal children)
- Women (200-300 g in month): Hirsutism, Acne, Amenorrhea, Clitoral enlargement, Deepening of the voice, susceptibility to atherosclerosis
- Some androgens: progestational activity→endometrial bleeding upon discontinuation
- Na retention,
- Hepatic dysfunction
- Cholestatic jaundice
- Replacement therapy in men: acne, sleep apnea, erythrocytosis, gynecomastia, azospermia and decrease in testicular size
- Psychologic & behavioral dependence

ANTIANDROGENS

Steroid Synthesis Inhibitors

Ketoconazole, used primarily in the treatment of fungal disease, is an inhibitor of adrenal and gonadal steroid synthesis. It does not affect ovarian aromatase, but it reduces human placental aromatase activity. It displaces estradiol and dihydrotestosterone from sex hormone-binding protein in vitro and increases the estradiol:testosterone ratio in plasma in vivo by a different mechanism. However, it does not appear to be clinically useful in women with increased androgen levels because of the toxicity associated with prolonged use of the 400–800 mg/d required. The drug has also been used experimentally to treat prostatic carcinoma, but the results have not been encouraging. Men treated with ketoconazole often develop reversible gynecomastia during therapy; this may be due to the demonstrated increase in the estradiol:testosterone ratio.

Conversion of Steroid Precursors to Androgens

Since dihydrotestosterone—not testosterone—appears to be the essential androgen in the prostate, androgen effects in this and similar dihydrotestosterone-dependent tissues can be reduced by an inhibitor of 5α-reductase. Finasteride, a steroidlike inhibitor of this enzyme, is orally active and causes a reduction in dihydrotestosterone levels that begins within 8 hours after administration and lasts for about 24 hours. Finasteride has been reported to be moderately effective in reducing prostate size in men with benign prostatic hyperplasia and is approved for this use in the USA. Finasteride is not approved for use in women or children, although finasteride has been used successfully in the treatment of hirsutism in women and is approved for treatment of early male pattern baldness in men.

Receptor Inhibitors

Cyproterone and cyproterone acetate are effective antiandrogens that inhibit the action of androgens at the target organ. The acetate form has a marked progestational effect that suppresses the feedback enhancement of LH and FSH, leading to a more effective antiandrogen effect. These compounds have been used in women to treat hirsutism and in men to decrease excessive sexual drive and are being studied in other conditions in which the reduction of androgenic effects would be useful. Cyproterone acetate in a dosage of 2 mg/d administered concurrently with an estrogen is used in the treatment of hirsutism in women, doubling as a contraceptive pill.

Flutamide, a substituted anilide, is a potent antiandrogen that has been used in the treatment of prostatic carcinoma. Although not a steroid, it behaves like a competitive antagonist at the androgen receptor. It frequently causes mild gynecomastia (probably by increasing testicular estrogen production) and occasionally causes mild reversible hepatic toxicity. Administration of this compound causes some improvement in most patients with prostatic carcinoma who have not had prior endocrine therapy. Preliminary studies indicate that flutamide is also useful in the management of excess androgen effect in women.

Spironolactone, a competitive inhibitor of aldosterone also competes with dihydrotestosterone for the androgen receptors in target tissues. It also reduces 17α-hydroxylase activity, lowering plasma levels of testosterone and androstenedione. It is used in the treatment of hirsutism in women and appears to be as effective as finasteride, flutamide, or cyproterone in this condition.

Reference:

Katzung BG and Trevor AG. Basic and Clinical Pharmacology, McGraw-Hill, 13th edition, 2015.

MCQ: Which one is correct about metabolic estrogen effects?

A) Decreased plasma triglyceride

B) Increased renin substrate

C) Decreased high-density lipoproteins

D) A and B