الدكتورة
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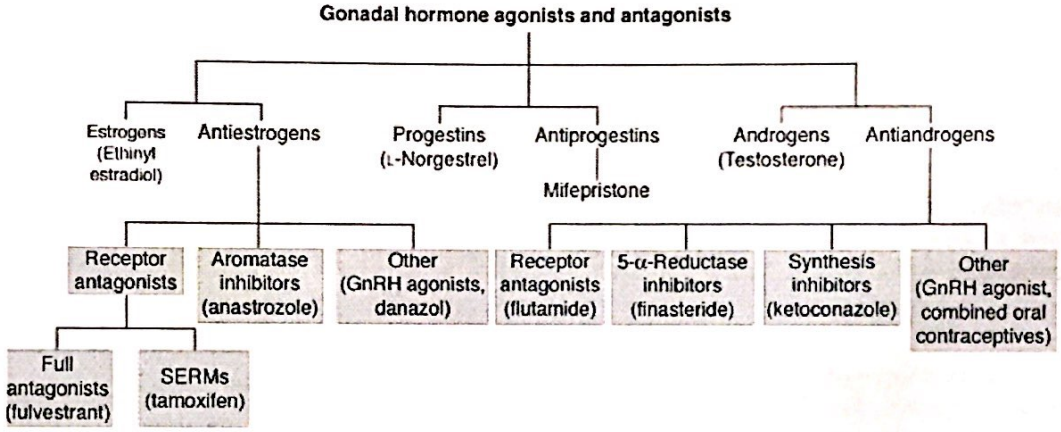
Sex (gonadal) hormones and antagontis

- The **gonadal hormones** include the steroids of the **ovary (estrogens and progestins)** and **testis (chiefly testosterone).**
- Because of their importance as contraceptives, many synthetic estrogens and progestins have been produced. These include synthesis inhibitors, receptor antagonists, and some drugs with mixed effects (ie, agonist effects in some tissues and antagonist effects in other tissues).
- Mixed agonists with estrogenic effects are called selective estrogen receptor modulators (SERMs).
- ynthetic androgens, including those with anabolic activity, are also available for clinical use.
- A diverse group of drugs with antiandrogenic effects is used in the treatment of prostate cancer and benign prostatic hyperplasia in men and hyperandrogenism in women.



Androgens

- **Testosterone** and related androgens are produced in the testis, the adrenal, and, to a small extent, the ovary.
- Many androgens have been synthesized in an effort to increase the anabolic effect without increasing androgenic action. **Oxandrolone** and **stanozolol** are examples of drugs that, in laboratory testing, have an increased ratio of anabolic–androgenic action. However, all the so-called **anabolic steroids** have full androgenic agonist effects when used in humans.

Mechanism of Action

Like other steroid hormones, androgens enter cells and bind to cytosolic receptors. The hormone–receptor complex enters the nucleus and modulates the expression of target genes.

Clinical Use

- The primary clinical use of the androgens is for **replacement therapy** in **hypogonadism.**
- Androgens have also been used to **stimulate red blood cell production in certain anemias** and to promote weight gain in patients with wasting syndromes (eg, AIDS patients).
- The anabolic effects have been exploited illicitly by **athletes to increase muscle bulk** and strength and perhaps enhance athletic performance.

Toxicity

- Use of androgens by females **results in virilization (hirsutism, enlarged clitoris, deepened voice)** and menstrual irregularity.
- In women who are pregnant with a female fetus, exogenous androgens can cause virilization of the fetus's external genitalia.
- Paradoxically, excessive **doses in men can result in feminization (gynecomastia**, testicular shrinkage, infertility) as a result of feedback inhibition of the pituitary and conversion of the exogenous androgens to estrogens. In both sexes, high doses of anabolic steroids can cause cholestatic jaundice, elevation of liver enzyme levels, and possibly hepatocellular carcinoma.

Antiandrogens

Reduction of androgen effects is an important mode **of therapy for both benign and malignant prostate disease**, precocious puberty, hair loss, and hirsutism.

Drugs are available that act at different sites in the androgen pathway.

1- **Receptor Inhibitors**

- **Flutamide** and related drugs are nonsteroidal competitive antagonists of androgen receptors. These drugs are used to decrease the action of endogenous androgens in patients with prostate carcinoma.
- **Spironolactone,** a drug used principally as a potassium-sparing diuretic, also inhibits androgen receptors and is used in the treatment of hirsutism in women.

2- **5 α-Reductase Inhibitors**

- **finasteride,** a drug used to treat benign prostatic hyperplasia and, at a lower dose, to prevent hair loss in men. Because the drug does not interfere with the action of testosterone, it is less likely than other antiandrogens to cause impotence, infertility, and loss of libido.
- **Dutasteride** is a newer 5α-reductase inhibitor with a much longer half-life than that of finasteride.

3- **Inhibitors of Steroid Synthesis**

- **Ketoconazole,** an antifungal drug, inhibits gonadal and adrenal steroid synthesis. The drug has been used to suppress adrenal steroid synthesis in patients with steroid-responsive metastatic prostate cancer.

Ovarian Hormones

The ovary is the primary source of gonadal hormones in women during the childbearing years (ie, between puberty and menopause).

The **mechanism of action of both estrogen and progesterone** involves entry into cells, binding to cytosolic receptors, and translocation of the receptor–hormone complex into the nucleus, where it modulates gene expression.

Estrogens

The major ovarian estrogen in women is **estradiol.**

Estradiol has low oral bioavailability but is available in a micronized form for oral use.

Clinical Use

- Estrogens are used in the **treatment of hypogonadism in young females.**
- Another use is as HRT in women with estrogen deficiency resulting from **premature ovarian failure, menopause, or surgical removal of the ovaries.**
- HRT ameliorates **hot flushes** and **atrophic changes in the urogenital tract.**
- It is effective also in **preventing bone loss and osteoporosis.**
- The estrogens are components **of hormonal contraceptives** (

Toxicity

- In **hypogonadal girls,** the dosage of estrogen must be adjusted carefully to **prevent premature closure of the epiphyses of the long bones and short stature.**
- When used as HRT, **estrogen increases the risk of endometrial cancer**; this effect is prevented by combining the estrogen with a progestin.
- Estrogen use by postmenopausal women is associated with a small increase **in the risk of breast cancer** and **cardiovascular events (myocardial infarction, stroke).**
- Dose-dependent toxicity includes **nausea, breast tenderness, increased risk of migraine headache, thromboembolic events** (eg, deep vein thrombosis), gallbladder disease, hypertriglyceridemia, and hypertension.
- **Diethylstilbestrol (DES),** a nonsteroidal estrogenic compound, is **associated with infertility, ectopic pregnancy, and vaginal adenocarcinoma in the daughters** of women who were treated with the drug during pregnancy in a misguided attempt to prevent recurrent spontaneous abortion.

Antiestrogens and Antiprogestins

Selective Estrogen Receptor Modulators (SERMs) are mixed estrogen agonists that have estrogen agonist effects in some tissues and act as partial agonists or antagonists of estrogen in other tissues.

Tamoxifen

- Tamoxifen is a **SERM** that is **effective in the treatment of hormone-responsive breast cancer**, where it acts as an antagonist to prevent receptor activation by endogenous estrogens.
- Prophylactic use of tamoxifen reduces the incidence of breast cancer in women who are at very high risk.
- Tamoxifen has more agonist than antagonist action on bone and **thus prevents osteoporosis** in **postmenopausal women.**

Toxicity.

- As an agonist of endometrial receptors, tamoxifen **promotes endometrial hyperplasia and increases the risk of endometrial cancer.**
- The drug also **causes hot flushes (an antagonist effect)** and **increases the risk of venous thrombosis** (an agonist effect).

Raloxifene

- Raloxifene, **approved for prevention and treatment of osteoporosis in postmenopausal women**, has a partial agonist effect on bone.
- Like tamoxifen, raloxifene has antagonist effects in breast tissue and **reduces the incidence of breast cancer in women who are at very high risk.**
- Unlike tamoxifen, the drug has no estrogenic effects on endometrial tissue.

Adverse effects include: **hot flushes (an antagonist effect)** and an **increased risk of venous thrombosis** (an agonist effect).

Clomiphene

Clomiphene is a **nonsteroidal compound with tissue-selective actions.**

- It is used to **induce ovulation in anovulatory women who wish to become pregnant.** By selectively blocking estrogen receptors in the pituitary, clomiphene reduces negative feedback and increases FSH and LH output. The increase in gonadotropins stimulates ovulation.

Pure Estrogen Receptor Antagonists

Fulvestrant is a pure estrogen receptor antagonist (in all tissues). It is **used in the treatment of women with breast cancer that has developed resistance to tamoxifen.**

Synthesis Inhibitors

Aromatase Inhibitors

Anastrozole and related compounds (eg, letrozole) are nonsteroidal **competitive inhibitors of aromatase**, the enzyme required for the last step in estrogen synthesis. Exemestane is an irreversible aromatase inhibitor. These drugs are **used in the treatment of breast cancer.**

Danazol

Danazol inhibits several cytochrome P450 enzymes involved in gonadal steroid synthesis and is a weak partial agonist of progestin, androgen, and glucocorticoid receptors.

The drug is sometimes **used in the treatment of endometriosis and fibrocystic disease of the breast.**

Progestins

Progesterone is the major progestin in humans.

Clinical Use

- Progestins are used **as contraceptives**, either **alone or in combination** with an estrogen.

- They are used in **combination with an estrogen in HRT** to prevent estrogen-induced endometrial cancer.
- Progesterone is used in **assisted reproductive technology methods** to **promote and maintain pregnancy.**

Toxicity

The toxicity of progestins is low.

- They may increase blood pressure and decrease HDL.
- Long-term use of high doses in premenopausal women is associated with a reversible decrease in bone density (a secondary effect of ovarian suppression and decreased ovarian production of estrogen) and delayed resumption of ovulation after termination of therapy.

Antiprogestins

Mifepristone is an orally active steroid antagonist of progesterone and glucocorticoids.
Its major use is as **an abortifacient in early pregnancy** (up to 49 d after the last menstrual period).
The combination of mifepristone and the prostaglandin E analog misoprostol achieves a complete abortion in over 95% of early pregnancies.

- The **most common complication** is **failure to induce a complete abortion.**
- Side effects, which are primarily due to the misoprostol, include nausea, vomiting, and diarrhea plus the vaginal cramping and bleeding associated with passing the pregnancy. Rarely, patients who used mifepristone and misoprostol for medical abortion have experienced serious infection, sepsis, and even death due to unusual infection (eg, Clostridium sordelli).

Contraceptives

- **Hormonal Contraceptives**

Hormonal contraceptives contain either a **combination of an estrogen and a progestin or a progestin alone.**
Hormonal contraceptives are available in a variety of preparations, including oral pills, long-acting injections, transdermal patches, vaginal rings, and intrauterine devices (IUDs).
Three types of **oral contraceptives** for women are available in the United States:

1- **Combination estrogen-progestin tablets** that are taken in constant dosage throughout the menstrual cycle (monophasic preparations); combination preparations (biphasic and triphasic) in which the progestin or estrogen dosage, or both, changes during the month (to more closely mimic hormonal changes in a menstrual cycle); and progestin-only preparations.
2- The progestin-only preparation an oral preparations containing a progestin (L-norgestrel) alone, causes fewer side effects than the estrogen-containing preparations.
3- The **postcoital contraceptives** (also known as "emergency contraception") prevent pregnancy if administered within 72 h after unprotected intercourse.

Mechanism of Action

The combination hormonal contraceptives have several actions, **including inhibition of ovulation** (the primary action) and **effects on the cervical mucus glands, uterine tubes, and endometrium that decrease the likelihood of fertilization and implantation.** Progestin-only agents do not always inhibit ovulation and instead act through the other mechanisms listed.

Other Clinical Uses and Beneficial Effects

- Combination hormonal contraceptives are used in young women with **primary hypogonadism to prevent estrogen deficiency.**
- To treat **acne, hirsutism, dysmenorrhea, and endometriosis.**
- Users of combination hormonal contraceptives **have reduced risks of ovarian cysts, ovarian and endometrial cancer, benign breast disease, and pelvic inflammatory disease.**
- lower incidence of **ectopic pregnancy, iron deficiency anemia, and rheumatoid arthritis.**

Toxicity

1. **Thromboembolism**

The major toxic effects of the combined hormonal contraceptives relate to the action of the estrogenic component on blood coagulation. There is a well-documented **increase in the risk of thromboembolic events (myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism)** in **older women, smokers**, women with a personal or family history of such problems, and women with genetic defects that affect the production or function of clotting factors. However, the risk of thromboembolism incurred by the use of these drugs is usually less than that imposed by pregnancy.

2. **Breast Cancer**

Evidence suggests that the lifetime risk of breast cancer in women who are current or past users of hormonal contraceptives is not changed, but there may be an earlier onset of breast cancer.

3. **Other Toxicities**

- Cause significant breakthrough bleeding, especially during the first few months of therapy.
- Other toxicities include nausea, breast tenderness, headache, skin pigmentation, and depression.
- Preparations containing older, more androgenic progestins can cause weight gain, acne, and hirsutism.
- The high dose of estrogen in estrogen-containing postcoital contraceptives is associated with significant nausea.

Drugs acting on Myomatrium

1. **Oxytocin**

- It is **used intravenously in the induction of labor** and sometimes **in uterine inertial hemorrhage** and **during abortion.**
- It produces immediately, rhythmic contraction with relaxation between i.e. it mimics normal uterine activity.

2. **Ergometrine**

It is an α adrenoceptor and dopamine agonist. It produces faster contraction superimposed on a tonic contraction.

It is **used in prevention and treatment of post-partum hemorrhage .**

3. **Prostaglandins**

- **Dinoprost** (PGF2α analogue)

It is **used to induce labor and to terminate pregnancy including missed or partial abortion**

- **Gemiprost (PGE1 analogue)**

It is used to soften cervix before operative procedure

- **Carboprost (PGF2α analogue)**

It is used in post-partum hemorrhage

Uterine relaxants

Isoxoprim, salbutamol and terbutaline

They are β2 agonists. They are given intravenously to inhibit contraction of the uterus in premature labor. They cause tachycardia , hypotension and sometimes they cause sever left ventricular failure.