Gonadal hormones & inhibitors

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Androgens

Testosterone & related androgens are produced in the testis, the adrenal cortex, & to a small extent, the ovary. In the plasma, testosterone is bound to sex hormone-binding globuline (SHBG).

Testosterone is converted in several organs including the prostate to dihydrotestosterone (DHT) by the enzyme 5-alpha reductase which is the active hormone in those tissues. Because of rapid metabolism by the liver, testosterone given orally has little effects. It may be given by injection in the form of long-acting esters or transdermal patch. Orally-active variants are also available.

Oxandrolone & stanazolol are drugs that in laboratory testing have increased ratio of anabolic-androgenic action. However all the so called anabolic steroids have full androgenic effects when used in humans.

Mechanism of action
Androgens like other steroids enter cells & bind to cytosolic receptors. The hormone-receptor complex enters the nucleus & modulates the expression of target genes.

Effects
1- Testosterone is responsible for the normal development of the male fetus & infant.
2- Testosterone is responsible for the major changes in the male at puberty (1-Growth of penis, larynx & skeleton. 2- Development of facial, pubic & axillary hair. 3- Darkening of skin. 4- Enlargement of muscle mass).
3- After puberty, testosterone acts to maintain 1- secondary sex characters 2- Fertility 3- Libido.
4- Anabolic actions that involve 1- Increased muscle size & strength. 2- Increased red blood cells production.
5- Testosterone helps maintain normal bone density.
Clinical uses of androgens
1- Replacement therapy in hypogonadism.  
2- The anabolic effects have been exploited illicitly by athletes to increase muscle bulk & strength & perhaps athletic performance.

Adverse effects
1- Use of androgens in women leads to virilization & menstrual irregularity.  
2- In women who are pregnant with a female fetus, exogenous androgens can cause virilization of the fetus’s external genitalia.  
3- Excessive dose of androgens in men can result in feminization (gynecomastia, testicular shrinkage & infertility) as a result of feedback inhibition of the pituitary & conversion of exogenous androgens to estrogens.  
4- High doses also cause behavioral effects including hostility & aggression.  
5- High doses of anabolic steroids can cause cholestatic jaundice, elevation of liver enzyme levels & possibly hepatocellular carcinoma.

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Antiandrogens

Antiandrogenic drugs

1- Inhibitors of steroid synthesis  
Ketokonazol, an antifungal drug, inhibits gonadal & adrenal steroid synthesis. The drug has been used to suppress adrenal steroid synthesis in patients with steroid-sensitive tumors

2- Gonadotropin-releasing hormone analogs  
Reduction of gonadotropins, especially LH reduces the production of testosterone. This can be done by long-acting Leuprolide or similar gonadotropin-releasing hormone agonists. These analogs are used in prostatic carcinoma.

3- Receptor blockers  
- Flutamide & bicalutamide are nonsteroidal compounds that act as competitive antagonists at androgen receptors. These drugs are used
to decrease the action of androgens in patients with prostate carcinoma.
- Spironolactone, an aldosterone receptor blocker, also blocks androgens receptor & is used in hirsutism.
- Cyproterone. It has a structural relation to progesterone & blocks, among other receptors, androgen receptors.

4- 5-alpha reductase inhibitors
Testosterone is converted to DHT by the enzyme 5-alpha reductase. Some tissues notably prostate cells & hair follicles depend on DHT rather than testosterone for androgenic stimulation. Finasteride & related drugs inhibit this enzyme & used to treat benign prostatic hyperplasia & at a lower dose to prevent hair loss in men.

5- Combined hormonal contraceptives
Combined hormonal contraceptives exert an antiandrogenic effect when used in women with hirsutism resulting from excessive production of androgenic steroids. The estrogen in the contraceptive acts in the liver to increase the production of SHBG which in turn acts to reduce the concentration of free androgens in the blood.

Clinical uses of antiandrogens (summary)
1-Benign prostate hyperplasia.
2-Malignant prostate disease.
3-Precocious puberty.
4-Hair loss.
5-Hirsutism

Estrogens

Available preparations of estrogens
1-- Estradiol. It is the major ovarian estrogen in women. Estradiol is available also as transdermal patch, oral micronized form, vaginal cream or intramuscular injection.
2-- Long acting estradiol esters as estradiol cypionate can be administered by IM injection.
3-- Conjugated estrogens from biological sources as premarin are
used for hormone replacement therapy (HRT)
4--Synthetic estrogens with high bioavailability as mestranol &
ethenyl estradiol are used in hormonal contraceptives.

Estrogens receptors major sites
Hypothalamus .....Pituitary.....Breast.....Bone.....Uterus.

Effects of estrogens
---Responsible for the growth of the gonadal organs ( Vagina...Uterus
& Fallopian tubes ) during childhood.
---Responsible for the appearance of secondary sex characteristics in
puberty  & for the growth spurt associated with puberty.
--- They reduce bone resorption.
--- They modify serum protein levels.
--- They enhance the coagulability of blood.
--- They increase plasma triglyceride levels.
--- They reduce LDL cholesterol.
---Continuous intake of estrogen, especially in combination with
progestin, inhibits the secretion of gonadotropins from the
anterior pituitary.

Clinical uses of estrogens
1---Treatment of hypogonadism in young females.
2---Hormone replacement therapy ( HRT)  in women with
A...premature ovarian failure. B...menopause. C...Surgical
removal of the ovaries.
   HRT ameliorates hot flushes & the atrophic changes in the
urogenital system.
3---HRT is effective in preventing osteoporosis .
4---The estrogens are components of hormonal contraceptives.

Adverse effects of estrogens
1---Premature closure of the epiphysis of the long bones  which may
lead to short stature in girls with hypogonadism treated treated
with estrogens .This can be prevented by carefully adjusting the dose
of estrogen.
2---Endometrial cancer risk increment when used as HRT. This can
be prevented by combining estrogen with a progestin.
3---Breast cancer risk small increment  when used by
post-menopausal women. This can not be prevented by combining
estrogen with a progestin.
4---Stroke risk small increment when used by post-menopausal women.
5---Nausea.
6---Migrain headache.
7---Thromboembolic events (eg DVT).
8---Gallbladder disease
9---Hypertriglyceridemia.
10---Hypertension.
11---Breast tendeness.

Antiestrogens

Classification of antiestrogens

1-Inhibitors of steroid synthesis
   ---Ketoconazol
   ---Aminoglutethamide
2-Gonadotropin-releasing hormone analogs
   ---Leuprolide, goserilne, nafareline, buseriline & others
3-Aromatase inhibitors
   ---Astranazole & related compounds as letrozole are nonstroidal compounds which inhibit aromatase. Aromatase catalyzes conversion of testosterone to estradiol.
   ---Exemestane, a steroidal compound which inhibits aromatase.
4-Estrogen receptor blockers (some of them are partial agonists)
   1.Clomiphene
   2.Tamoxifene
   3.Toremifene
   4.Raloxifene
   5-Fulvestrant

Progestogens (Progestins)

Progest theogens imitate the actions of the hormone progeterone. Progeterone is the major progestin in humans.
Available preparations of progestins
- Oral micronized progesterone.
- Progesterone containing vaginal cream.
- Medroxyprogesterone, a synthetic progestin.
- The 19-testosterone compounds include
  1-old ones as norethindrone & L-norgestrel are more androgenic than the newer progestins.
  2-The newer ones as norgestimate & desogestrel.

Effects of progestins
- Progesterone induces secretory changes in the endometrium.
- Progesterone is required for the maintenance of pregnancy.
- High doses suppress gonadotropin secretion & cause anovulation in women.
- Progestins changes the character of cervical mucus.

Clinical uses of progestins
- Progestins are used as contraceptives alone, Progestin- only pill (POP)
- Progestins are used as contraceptives in combination with an estrogen.
- Progestins are used in combination with an estrogen in HRT to prevent estrogen-induced endometrial cancer.
- Progesterone is used in assisted reproductive technology programs to promote & maintain pregnancy.
- Threatened abortion & habitual abortion. There is however no proof that they are always beneficial in these cases.

Adverse effects
1-They may increase blood pressure.
2-They may decrease high-density lipoproteins level (HDL).
3-Long-term use of high doses in premenopausal women is associated with
   - A delayed resumption of ovulation after termination of treatment.
   - A reversible decrease in bone density.

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Antiprogestins
1-Mifepristone. It blocks the action of progesterone at its receptors (thus it can terminate the pregnancy in the first trimester).

2-Danazol. It is a derivative of the progestogen, ethisterone. It is a rather selective inhibitor of pituitary gonadotropins secretion. This reduces ovarian functions thus leads to atrophic changes in endometrium, both uterine & elsewhere (ectopics) i.e. endometriosis.

Hormonal contraceptives

Components
Hormonal contraceptive contain either a combination of estrogen & progestin or a progestin alone.

Preparations
1-Oral pills.
2-Long-acting injections.
3-Transdermal patches.
4-Vaginal rings.
5-Intra-uterine devices (IUDs).
6-Postcoital pills, called also emergency pills. They prevent pregnancy if given within 72 hours of intercourse.

Mechanism of action of hormonal contraceptives
1-Inhibition of ovulation.
2-Effects on the cervical mucus glands.
3-Effects on uterine tubes & endometrium.

Clinical uses of hormonal contraceptives
- Contraception.
- Other uses as in acne, hirsutism, dysmenorrhea & endometriosis.

Adverse effects

1-Thromboembolism
Thromboembolism relates to the action of 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:
A-Older women. B-Smockers. C-Women with a personal history of such problems. D-Women with a family history of such problems. However the risk of thromboembloism incurred by the use of these drugs is usually less than that imposed by pregnancy.

2-Breakthrough bleeding
3-Nausea
4-Headache
5-Skin pigmentation
6-Depression
7-Breast tenderness

Contraindications & cautions of hormonal contraceptives

1-Thromboembolic diseases, present or past.
2-Carcinoma of the breast.
3-Carcinoma of the uterus.
4-Severe liver disease.
5-Pregnancy.
6-Hypertension.
7-Migrain.
8-Porphyria.
9-Others.

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