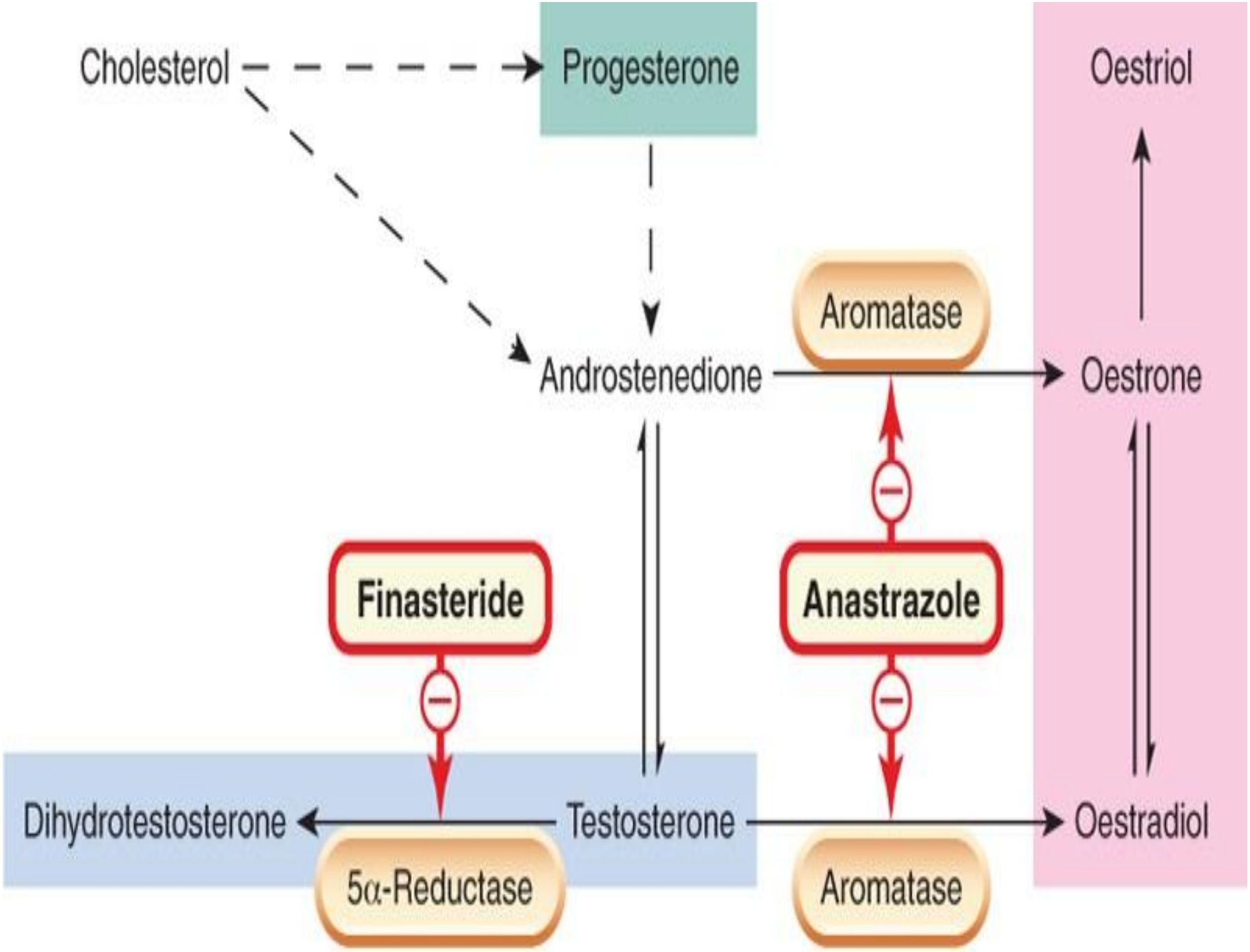
ANDROGENS AND ANTIANDROGENS


Cholesterol
Progesterone
Oestriol
Aromatase
Androstenedione
Oestrone
Finasteride
Anastrazole
Dihydrotestosterone
Testosterone
Oestradiol
5α-Reductase
Aromatase

PHARMACOKINETICS

Active metabolites

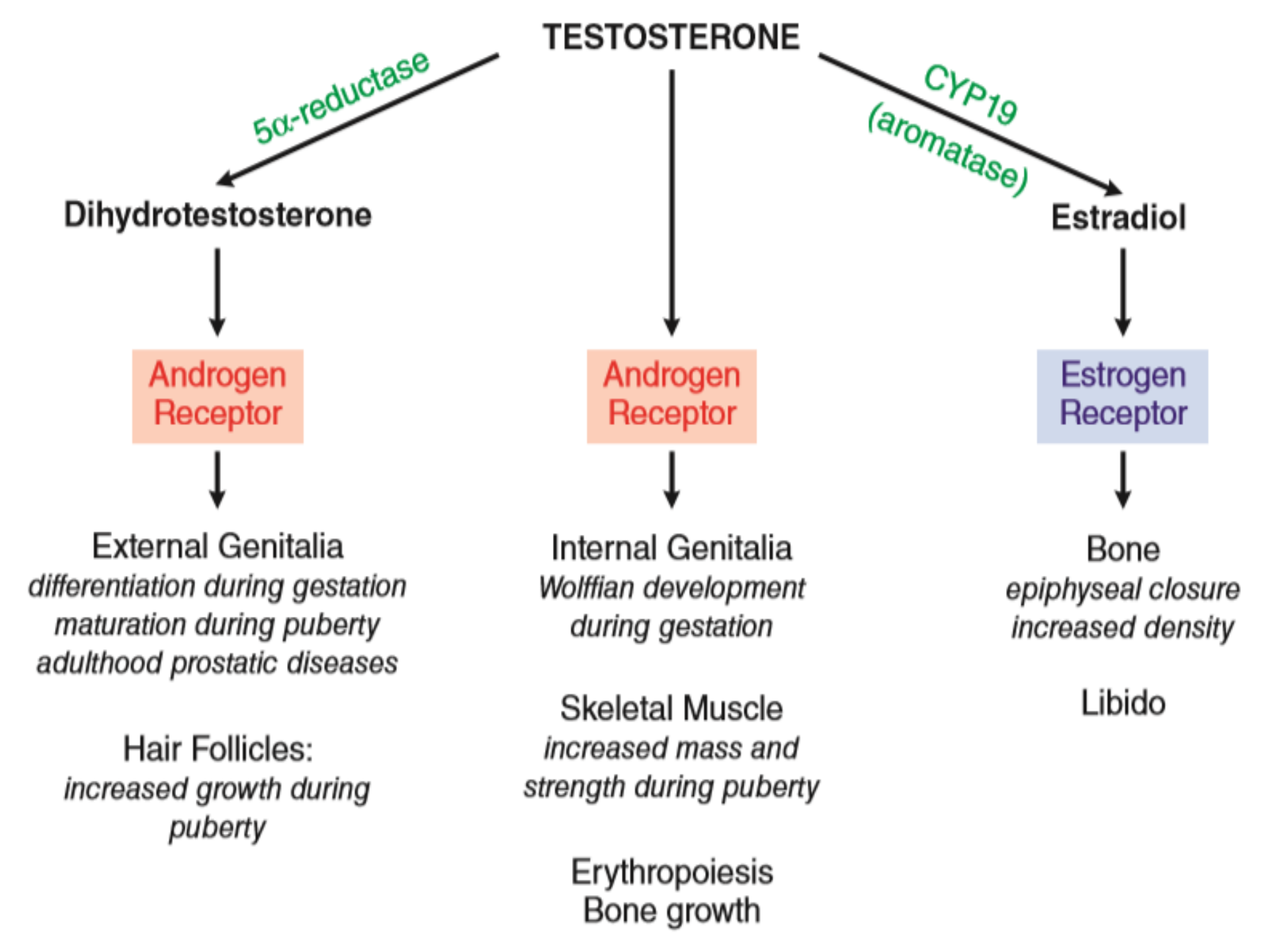
Dihydrotestosterone -- 5α reductase in prostate, seminal vesicles, epididymis, skin.

5α reductase

Type 1: in nongenital skin , liver and bone.
Type 2: in urogenital tissue in men, genital skin in both sexes.

Estradiol: liver, adipose tissue, hypothalamus.

Inactive metabolites --- Androsterone and Etiocholanolone


TESTOSTERONE
5α-reductase
CYP19
(aromatase)
Dihydrotestosterone
Estradiol
Androgen Receptor
Androgen Receptor
Estrogen Receptor
External Genitalia
differentiation during gestation
maturation during puberty
adulthood prostatic diseases
Hair Follicles:
increased growth during puberty
Internal Genitalia
Wolffian development during gestation
Skeletal Muscle
increased mass and strength during puberty
Erythropoiesis
Bone growth
Bone
epiphyseal closure
increased density
Libido

ANDROGEN DEFICIENCY

During fetal development :

Complete deficiency: entirely female external genitalia.

Less severe deficiency: incomplete virilization of external genitalia proportional to degree of deficiency ; failure of wolffian ducts to differentiate into male internal genitalia.

Before completion of puberty :

Failure of pubertal changes proportionate to degree of deficiency, eununcoid personality and gynaecomastia

After completion of puberty

Decreased libido, energy levels; slower decline in muscle mass and bone mineral density. Large decrease in hematocrit and hemoglobin levels.

In women

Decrease in energy levels, libido, muscle mass and strength, bone mineral density.

Clinical trials to determine if testosterone improves these parameters in androgen deficient women.

CLASSIFICATION

Natural: Testosterone (Dihydrotestosterone), Dehydroepiandrosterone (DHEA), Androstenedione.

Synthetic : Testosterone esters (Propionate Enanthate, Cypionate, Undecanoate)

17α Alkylated androgens : Methyltestosterone, Oxandrolone, Stanozolol, Fluoxymesterone, Danazol, Nandrolone decanoate

Transdermal Preparations

Others: Tetrahydrogestrinone

THERAPEUTIC USES

Male hypogonadism

Monitoring for efficacy

a) **Transdermal drug delivery system** : peak serum value 6-9 hours after application and 50% of peak just before next application.

b) **Testosterone esters** : administered once in two weeks, serum concentration midway between two doses should be normal.

c) Testosterone gels: mean serum concentration relatively constant between two applications

Monitoring for deleterious effects

- Testosterone administered by itself as a transdermal preparation has no “side effects”.

- Modified testosterone compounds e.g. 17α-alkylated androgens have undesirable effects even as physiological replacement.

- Acne, gynecomastia, and more aggressive sexual behavior.

- Physiological amounts do not appear to affect serum lipids or apolipoproteins.

Monitoring for deleterious effects

- Undesirable effects in concomitant illnesses if **dose excessive**: erythrocytosis, salt and water retention and peripheral edema occur.
- Men more than 40 years subject to benign prostatic hyperplasia and prostate cancer.
- 17α-alkylated androgens produce cholestasis, sometimes peliosis hepatitis, blood-filled hepatic cysts.
- Hepatocellular cancer rarely.

Monitoring at the anticipated time of puberty

Male senescence:

Approved only for men with "**classical hypogonadism**," meaning hypogonadism due to discernible pituitary or testicular disease.

Female hypogonadism

Enhancement of athletic performance

Kinds of androgens used : 17α alkylated androgens , testosterone precursors --- DHEA and androstenedione. Tetrahydrogestrinone (THG) --- novel structure, rapid metabolism to avoid detection by antidoping laboratories.

Efficacy

- Dose dependent effect on muscle strength that acts synergistically with exercise.

Side Effects

- Suppress gonadotropin secretion in high doses and endogenous testicular function.
- Results in diminished fertility, testicular size may diminish if taken long term.
- High doses: erythrocytosis, gynecomastia.
- Cause hepatotoxicity, affect serum lipid concentrations.
- Women and children experience virilization.
- Premature stunting of linear growth.

Catabolic and wasting states

Muscle wasting and cachexia associated with AIDS, COPD and severe burns.

Angioedema (hereditary impairment of C1-esterase inhibitor). Effectively prevents attacks. Stimulate hepatic synthesis of the esterase inhibitor.

Blood Dyscrasias

Availability of erythropoietin has reduced usage. Used occasionally as adjunctive treatment if refractory to first-line agents.

Danazol

Weak progestational, androgenic and gluco-corticoid activities --- suppresses ovarian function.

Uses --- endometriosis, fibrocystic breast disease, hematologic or allergic disorders --- hemophilia, idiopathic thrombocytopenic purpura and angioneurotic edema.

For endometriosis --- 600mg/day for 1 month, 400mg/day for 2 months followed by 200mg / day for 2 months.

Major adverse effects

Weight gain, edema, acne and oily skin, hirsutism, deepening of the voice, headache, hot flushes, changes in libido and muscle cramps.

Occasionally adrenal suppression.

Caution in hepatic dysfunction --- mild to moderate hepatocellular damage.

Contraindicated in pregnancy and breast-feeding --- urogenital abnormalities in the offspring.

ANTIANDROGENS

Inhibit testosterone secretion

Both agonists and antagonists of GnRH Receptors --- inhibition of LH secretion.

GnRH superactive analogs down regulate GnRH receptor --- **prostate cancer, suppress precocious puberty**, **in assisted reproductive technologies.**

Abarelix : extended release form of GnRH antagonist --- prostate cancer.

Antifungal drugs of imidazole family block synthesis of steroid hormones.

Androgen receptor antagonists : Cyproterone and cyproterone acetate

--- Has a marked progestational effect that suppresses release of LH and FSH so more effective anti-androgen effect.

Clinically tested in **precocious puberty in boys**, **inappropriate sexual behaviour in men**, **acne** and **virilization in women**

Cyproterone acetate (2 mg/d) plus an estrogen used in **hirsutism in women**, **contraceptive action**

Orphan drug status in the USA.

Androgen receptor antagonists

Flutamide, Bicalutamide, Nilutamide.

Used with GnRH analogs in **metastatic prostrate cancer**. Used alone will raise LH levels and hence testosterone levels.

Bicalutamide: once a day dose, less hepato-toxicity as compared to flutamide.

Flutamide for **hirsutism in women**.

Spironolactone : aldosterone inhibitor, weak androgen receptor antagonist, weak inhibitor of testosterone synthesis; **hirsutism in women**.

5α reductase inhibitors
Finasteride (type II),
Dutasteride (type I and II)

- Cause a decrease in serum and prostatic concentrations of dihydrotestosterone.

Use --- **BPH**. Prostatic volume decreases, urine flow rate increases.
Side effects: Impotence (mechanism not known) well documented; gynaecomastia.

Finasteride approved for **male pattern baldness**, **hirsutism in women**.