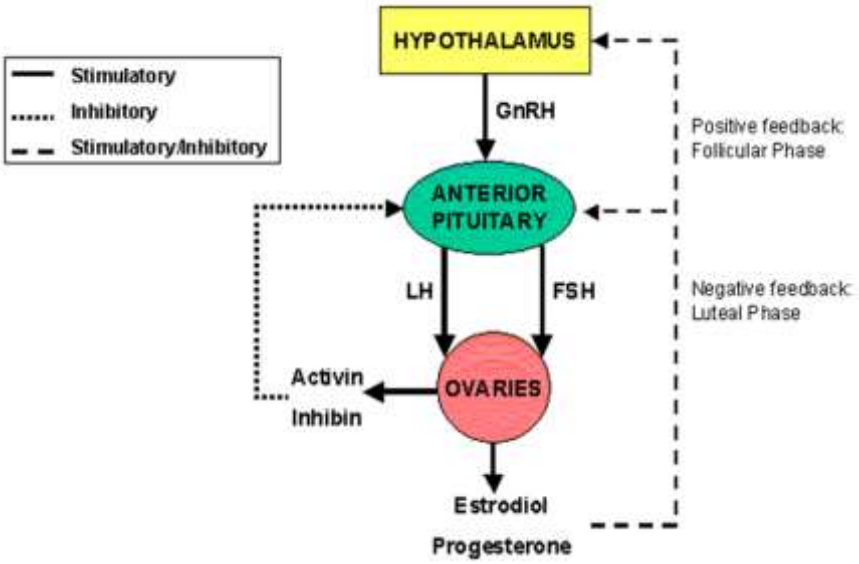
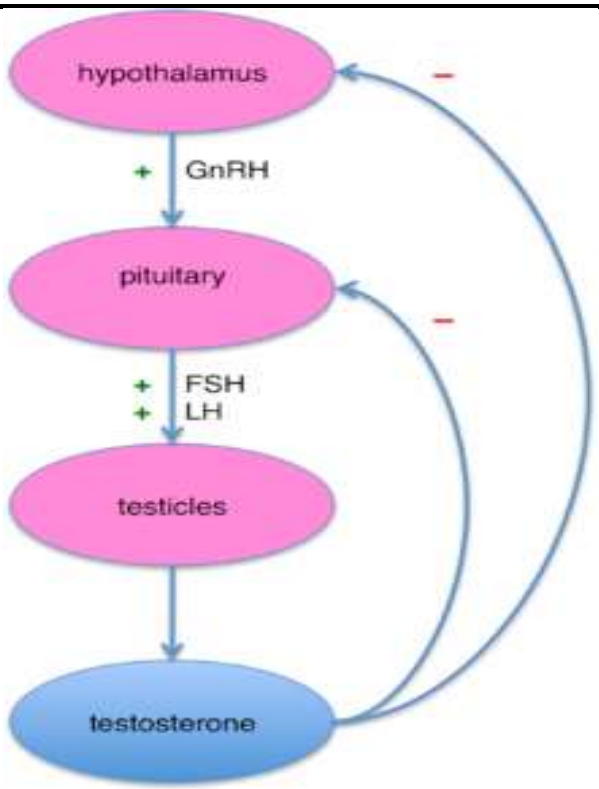
Sex Hormones

Sex hormones are secreted from gonads both in male (androgens) and female (estrogens and progestogens) under the control of gonadotrophin releasing hormone (GnRH); secreted from hypothalamus; which stimulates anterior pituitary gland to release gonadotrophins (follicle stimulating hormone; FSH and luteinizing hormone; LH).

In female



In male



Estrogens

Estrogens are required for the normal sexual maturation and growth of the female; they stimulate the development of vagina, uterus and uterine tubes as well as the secondary sex characteristics.
Two types of estrogens:
1. Naturally occurring- estradiol (the most potent and the major product of the ovary), estrone and estriol (less potent)
2. Synthetic estrogens- ethinylestradiol, mestranol undergo less first pass metabolism than the natural estrogens, so are effective orally.

Mechanism of action

After dissociation from their binding sites on sex hormone-binding globulin or albumin in plasma, they diffuse across cell membranes and bind with high affinity to specific estrogen nuclear receptors (α and β) which mediate the effects of the hormone.

Pharmacokinetics

Estrogens are readily absorbed through GIT, skin and mucus membrane.
Estradiol is rapidly metabolized compared with ethinylestradiol .
Estrogens are fat soluble, so are stored in adipose tissue from which are slowly released.
They are excreted in bile and reabsorbed through entero-hepatic circulation. Inactive products are excreted in urine.
Synthetic estrogens have longer duration of action and higher potency than natural estrogens.

Routes of administration

Oral, transdermal patch or gel, subcutaneous implants (release hormone over several months), vaginal (ring, cream, pessary) and nasal spray.

Therapeutic uses of estrogens

1. For contraception
2. Replacement therapy
a. postmennopausal -lowest effective dose for the shortest possible time, to relieve vasomotor symptoms like hot flushes, sleeplessness and vaginal dryness
b. premenopausal patients who are deficient in this hormone e.g. in premature or surgical menopause

3. Prevention and treatment of osteoporosis (but nowadays alendronate is considered as first line therapy)
4. Primary hypogonadism
5. Senile vaginitis (as pessary or cream)
6. Menstrual disorders
7. Androgen dependent carcinoma of prostate

Adverse effects
1. nausea and breast tenderness (most common)
2. headache, peripheral edema and hypertension
3. postmenopausal uterine bleeding
4. Increased risk of thromboembolism, gall stones, breast and endometrial cancer

Anti-estrogens and selective estrogen-receptor modulators

They interact with estrogen receptor but have different effects on different tissues (i.e. they are agonists or antagonists according to tissue type)

1. Clomiphene

Acts as a partial estrogen agonist, interferes with negative feedback of estrogens on hypothalamus, so increases the secretion of GnRH and gonadotrophins, leading to stimulation of ovulation
Is used in infertility associated with anovulatory cycles
Side effects: headache, nausea, vasomotor hot flushes, visual disturbances and ovarian enlargement
*Multiple ovulations and multiple pregnancies occur

2. Tamoxifen

Competes with estrogen for binding to estrogen receptor in breast tissue, **so used in** palliative treatment of metastatic breast cancer in postmenopausal women
Side effects: hot flushes and nausea, menstrual irregularity and vaginal bleeding, may cause endometrial hyperplasia and malignancies due to its estrogenic activity in endometrium

3. Raloxifene

Its **clinical use** in prevention and treatment of osteoporosis in postmenopausal women is based on its ability to decrease bone

resorption and overall bone turnover. Bone density is increased and vertebral fractures are decreased.
*It has little or no effect on endometrium
Side effects: hot flushes and leg cramps are common, increased risk of DVT and pulmonary embolism

Progesterone and proestogens (Progestins)

Progesterone ($t_{1/2}$=5 min) is the natural progestin, is produced in response to LH in both females (secreted by corpus luteum during the 2nd half of menstrual cycle and by placenta) and in males (secreted by testes)
In female it converts uterine epithelium from proliferative to secretory phase that can accommodate implantation of the newly formed embryo
The high levels of progesterone during the luteal phase inhibit production of gonadotrophins and prevent further ovulation
*If conception occurs, progesterone continues to be secreted maintaining endometrium in a favorable state for continuation of pregnancy and reducing uterine contractions
*If conception does not take place, the release of progesterone ceases abruptly, which stimulates the onset of menstruation.

Progestogens are of two types:
1. Progesterone and its derivatives (dydroprogesterone, hydroxyprogesterone, medroxyprogesterone)
2. Testosterone derivatives (norethisterone, levonorgestrel, desogestrel, gestodene)

Pharmacokinetics
Progesterone is taken orally, well absorbed, has short half life and completely metabolized by liver
Synthetic progestins are less rapidly metabolized
Duration of action of progestins lasts for 1-3 days while of medroxyprogesterone for 3 months ($t_{1/2}$=28h)

Preparations
1.Oral- norethisterone, levonorgestrel, dydrogesterone
2.Pessaries- progesterone
3.Injectable- progesterone, hydroxyprogesterone, medroxyprogesterone

Clinical uses

1. For contraception
2. Postmenopausal hormone replacement therapy
3. Dysfunctional uterine bleeding
4. Dysmenorrhea
5. Endometriosis

Adverse effects

Headache, depression, weight gain and changes in libido
The testosterone derivatives have androgenic activity causing hirsutism
Injectable medroxyprogesterone is associated with increased risk of osteoporosis (so duration of use should be limited)

Other progestogen derivatives

1. Danazol (Danol)

Is a derivative of progestogen, ethisterone. It has partial agonist androgen activity, but little progestogen activity.

Mechanism of action

It is a selective inhibitor of pituitary gonadotrophin secretion (FSH & LH) affecting the surge in the mid-menstrual cycle more than basal secretion. This reduces ovarian function, which leads to atrophic changes in endometrium both uterine and elsewhere (ectopic) i.e. endometriosis. In males it reduces spermatogenesis.

Uses

1. Endometriosis
2. Fibrocystic mastitis
3. Gynecomastia
4. Precocious puberty
5. Menorrhagia
6. Hereditary angioedema

Side effects

Virilization, acne, hirsutism

Antiprogestogens

Mifepristone

Is a competitive antagonist with partial agonistic activity
It is safe and effective in termination of pregnancy and efficacy is enhanced if its use is followed by vaginal administration of gemeprost to produce uterine contraction

Androgens

Are group of steroids that have anabolic &/or musculinizing effects in both males and females.
The most important androgen in human is testosterone; which is synthesized by leydig cells in testes.
Androgens are required for:
1. Normal maturation in male
2. Sperm production
3. Increased synthesis of muscle proteins and hemoglobin
4. Decreased bone resorption

Mechanism of action

Testosterone binds to specific nuclear receptor in target cells. It is active in liver and muscle, but in other tissues like prostate, seminal vesicle, epididymis and skin; it should be converted by 5α-reductase to dihydrotestosterone (DHT; the active metabolite) which binds to the receptor.

Pharmacokinetics

Testosterone is ineffective orally (because of the first pass metabolism), so it is administered i.m., as transdermal patch, topical gel, buccal tablets are also available.
Testosterone derivatives (fluoxymesterone, oxandrolone) are given orally.
Example of anabolic steroids-nandrolone (taken by deep i.m. injection every 3 weeks)

Therapeutic uses

1. Androgenic effect-for primary and secondary hypogonadism
2. Anabolic effect- (anabolic steroids) are used in:
   a. senile osteoporosis (because it prevents Ca^{+2} and nitrogen loss in urine)
   b. chronic wasting associated with HIV or cancer
   c. severe burns
   d. to speed recovery from surgery or chronic debilitating disease
   e. some patients with aplastic anemia
3. Endometriosis- Danazol
4. Unapproved use by athletes and body builders to increase lean body mass, muscle strength and endurance

Adverse effects

1. In female

Musculinization, acne, hirsutism, deepening of voice, menstrual irregularities

2. In male

Impotence, decreased spermatogenesis and gynecomastia, also stimulates growth of prostate

3. In children

Abnormal sexual maturation and growth disturbances resulting from premature closure of epiphysis

4. General effects

Elevation of serum LDL and reduction of HDL, so increase the risk of coronary heart disease, also causes fluid retention leading to edema

5. In athletes

cause premature closure of epiphysis, so stunts the growth and interrupts development

*High doses taken by young athletes result in reduction of testicular size, hepatic abnormalities, increased aggression and major mood disorders

Antiandrogens

Act either by:

1. interference with synthesis of androgens, or
2. blocking their receptors

1. Cyproterone (a derivative of progesterone)

It competes with testosterone for receptors in target peripheral organs, so reduces spermatogenesis even to the level of azoospermia, abnormal sperms occur during treatment. It also competes with testosterone in CNS causing impotence

Uses: a. to reduce male hypersexuality
b. prostatic cancer
c. severe female hirsutism and severe acne

2. Flutamide – is a competitive inhibitor of androgen in target cell, used in prostatic carcinoma

3. Finasteride- is used in benign prostatic hypertrophy because it inhibits 5α-reductase , so reduces production of dihydrotestosterone in prostate, therefore decreases prostate size

4. Ketoconazole- interferes with androgen and corticosteroid synthesis, so used on prostatic carcinoma and cushing's syndrome

5. Spironolactone- may help hirsutism in women