Sex hormones are needed for human development, induction of secondary sexual characteristics and reproduction. In males, androgens function to influence sperm production. In females, estrogen and progesterone function during the menstrual cycle and in the maintenance of pregnancy. Excess androgens can result in prostatic hyperplasia while the loss of testosterone gradually occurs as men age. Excess estrogen can lead to endometrial hyperplasia while a loss of estrogen leads to menopause.

Definition of Sex Hormones
Sex hormones are derived from **steroid rings** which originate as cholesterol. Males are predominant **androgen** producers while females are predominant **estrogen and progesterone** producers.

Sex hormones play a distinct role in each gender’s sexual development with androgens influencing sperm production in men. In women, estrogen and progesterone regulate the menstrual cycle and are necessary for maintaining pregnancy. **Testosterone** is produced in the male **testes** and by the **adrenal gland**. Estrogen is produced in its most potent form by the female **ovaries**.

**Physiology of Sex Hormones**

Estrogens, progesterone, and androgens act on the genomic DNA to influence gene expression. The expression changes lead to modifications in cellular function, growth, and development.

**Physiology of estrogen**

The predominant female sex hormone is estrogen. Estrogen exerts its function when it binds to estrogen receptors, which can influence metabolism and transcription factors. Estrogen is produced in several locations: the **ovary**, which makes 17β estradiol; **placenta**, which produces estriol; and in **adipose tissue**, which produces estrone from the enzyme aromatase.

In the ovary, estrogen is produced in the **two-cell method**. The **hypothalamus** produces **gonadotropin releasing hormone** (GnRH) in a pulsatile manner that induces **follicle stimulating hormone** (FSH) and **luteinizing hormone** (LH) to be released from the
anterior pituitary. LH acts on theca cells to cause the conversion of cholesterol to androstenedione by the enzyme desmolase. FSH acts on granulosa cells to convert androstenedione to estradiol.

**Estriol** is secreted by the **placenta** during pregnancy. Women who are not pregnant produce virtually no estriol. Estriol is the most predominant estrogen produced by the female during pregnancy. The production involves the **fetal adrenal gland** producing **dehydroepiandrosterone**, which is then converted by the placenta to estriol.

**Note: USMLE pearl about these three types of Estrogen Hormones.**

1. **Estradiol:** Is the young female’s hormone of femininity. It’s also called **E2**. It’s produced by aromatization of Testosterone in the Graafian follicle (granulosa cell). It’s the most potent estrogen with the highest effect on receptors.

2. **Estrone:** Is the estrogen of the menopause. It’s produced by aromatization of **androstenedione** in peripheral (fatty) tissue. It’s also called **E1**. It’s less potent than Estradiol.

3. **Estriol:** Is the placental estrogen and it’s only seen during pregnancy and its high levels reflects fetal well being. It’s also called **E3**. It’s the least potent of all estrogens. It originates from the fetal adrenal gland in the form of DHEA Sulfate and then is finally transformed to Estriol in the placenta by the sulfatase enzyme.

During pregnancy, **estrogens increase contractility of the myometrium** by upregulating factors that will aid in delivery of the baby at term.

![Estradiol Diagram](Image created by Lecturio)

**Physiology of progesterone**
Progesterone is produced during the **luteal phase of the menstrual cycle**. It is produced by the **corpus luteum** in the ovary and naturally declines as the menstrual cycle continues. The corpus luteum can be maintained from pregnancy and continue to secrete progesterone for the first few weeks. After the loss of the corpus luteum progesterone levels are maintained by the **trophoblast**. Finally, the **placenta** will produce progesterone as the pregnancy progresses.

Progesterone is needed to **maintain pregnancy**. During **conception**, progesterone induces the endometrium to prepare for **implantation**, and if implantation does not occur progesterone levels will drop off and lead to **menstruation**. Its effect on pregnancy is through **stabilization of the myometrium to inhibit contraction**; this is a counter action to estrogen’s effect on the myometrium. It also inhibits **lactation** until late in the pregnancy and progesterone affects the vaginal epithelium and cervical mucus, making it thick and impenetrable to sperm.

**Physiology of testosterone**

Testosterone is produced by the **Leydig cells of the testes**. It is also produced from the **zona reticularis of the adrenal gland**. The zona reticularis produces DHEA, DHEA sulfate, androstenedione and 11-hydroxyandrostenedione. These are then converted in the peripheral tissues to the active form **testosterone**.

There are three mechanisms by which testosterone interacts with cells:

- It can directly bind to an androgen receptor.
- In tissues that contain the enzyme 5-alpha reductase, testosterone can be converted to dihydrotestosterone.
- In tissues that contain aromatase, testosterone can be converted to estradiol.
- In addition, testosterone circulates in three manners:
  - A free form
  - bound to albumin
- bound to sex hormone binding globulin.

**USMLE pearl:** A common question involves the 5-alpha-reductase inhibitor finasteride. Dihydrotestosterone plays a big role in the growth and development of the prostate and hair pattern development. Due to this, finasteride is used to treat benign prostatic hyperplasia and male pattern baldness.

Testosterone has a broad range of effects throughout development and in sperm production. It induces **differentiation of the genitourinary tract** during the 7th week and development for the male genitalia. **Leydig cells** are the main producers of testosterone and contribute to the development of the male gonadal anatomy including the vas deferens, epididymis, and seminal vesicles.

**GnRH** causes a release of LH and FSH from the anterior pituitary in a pulsatile fashion. LH influences Leydig cells to secrete testosterone. Combined, they allow for **spermatogenesis** and **maturation** before ejaculation. The pulsatile effect also results in testosterone influencing the development of secondary sexual characteristics. Feedback on the system comes from elevated testosterone levels, which reduce the levels of GnRH secretion.

**USMLE pearl:** It is important to go over Tanner staging for both males and females. In males, testosterone’s influence leads to secondary sexual characteristics including muscle and bone growth, vocal cord thickening and spermatogenesis.

Adapted from text by Lawrence Neinstein, M.D.

**Genitals (male)**

![Illustration of the Tanner scale for males.](image)

**Tanner I**

testicular volume less than 1.5 ml; small penis of 3 cm or less (prepubertal) (typically age nine and younger)

**Tanner II**

testicular volume between 1.6 and 6 ml; skin on scrotum thins, reddens and enlarges; penis length unchanged (9-11)
Tanner III
  testicular volume between 6 and 12 ml; scrotum enlarges further; penis begins to lengthen to about 6 cm (11–12.5)

Tanner IV
  testicular volume between 12 and 20 ml; scrotum enlarges further and darkens; penis increases in length to 10 cm (12.5–14)

Tanner V
  testicular volume greater than 20 ml; adult scrotum and penis of 15 cm in length (14+)

Breasts (female)

Illustration of the Tanner scale for females.

Tanner I
  no glandular tissue: areola follows the skin contours of the chest (prepubertal) (typically age 10 and younger)

Tanner II
  breast bud forms, with small area of surrounding glandular tissue; areola begins to widen (10–11.5)

Tanner III
  breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast (11.5–13)

Tanner IV
  increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast (13–15)

Tanner V
  breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla. (15+)

Pubic hair (both male and female)

Tanner I
  no pubic hair at all (prepubertal) (typically age 10 and younger)
Tanner II
small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum (males) or on the labia majora (females) (10-11.5)

Tanner III
hair becomes more coarse and curly, and begins to extend laterally (11.5-13)

Tanner IV
adult-like hair quality, extending across pubis but sparing medial thighs (13-15)

Tanner V
hair extends to medial surface of the thighs (15+)

Pathophysiology Related to Sex Hormones

Estrogen-related pathophysiology

Loss of estrogen leads to menopause, which naturally occurs and is defined as 12 months of amenorrhea. During this time, there is a loss of estradiol production from the ovaries. The estrogen drop-off is significant with only adipose tissue still producing estrone. This overall loss of estrogen leads to symptoms of hot flashes, bloating, mood changes, depression, headache, insomnia. These symptoms often come on before or during the onset of menopause.

Osteoporosis is commonly seen in conjunction with menopause. It is the result of a loss of estrogen’s effect on the bone cells - osteoblasts, which normally inhibit apoptosis, and on osteoclasts, which normally induce apoptosis. This results in osteoclasts destroying more bone than osteoblasts can produce. A loss in bone mineral density occurs, which results in an increased risk of fractures of the wrist and hip. The level of loss of bone mineral density is diagnosed with a DEXA scan. A T-score of -2.5 or lower qualifies as osteoporosis. A T-score of -1.0 to -2.5 signifies osteopenia, meaning below-normal bone density without full osteoporosis.

Treatments are bisphosphonates such as alendronate (drug names end with -ate).

Calcium and vitamin D work in conjunction where vitamin D allows for absorption of calcium from the small intestine and helps with bone mineralization.

Cardiovascular disease also increases at the onset of menopause. Women lag behind men in average ages for cardiac events by 10 years due to estrogen’s protective effects on cardiac vasculature. The mechanism is believed to be due to lowering LDL and increasing HDL levels.

Menopausal treatment is done for symptoms relief. Estrogen therapy works to help restore the lost estrogens. The therapy has been used alone and with progesterone/progestins. Estrogen can be taken orally, transdermally or vaginally. There is an increased risk of endometrial and breast cancer due to estrogen’s trophic effect on the endometrium and breast epithelium.

Testosterone-related pathophysiology

As men age, they gradually decrease the amount of testosterone they produce at about a rate of 1% from the age of 30 onward. In obese men, adipose tissue converts testosterone to estradiol by aromatase. The increased estradiol production causes inhibition of the hypothalamus pituitary axis leading to lower levels of testosterone production.
Much like estrogen, there are three distinct methods to administer exogenous testosterone:

- **Oral testosterone agents** are the least effective because their absorption undergoes processing by the liver, which results in metabolism of much of the oral form.
- **Injections** can be done in a depot form with extended discharge, so it can release an average amount per week.
- **Topical and transdermal** can release low doses on a daily basis.

Exogenous testosterone use has been shown to cause oligospermia and azoospermia due to disruption of the hypothalamus pituitary axis.

In women, excess androgens can lead to physical changes that manifest as acne, hirsutism, virilization and reproductive dysfunction. This is seen in polycystic ovarian syndrome, where excess LH can induce androgen production.

**Benign prostatic hyperplasia (BPH)** is a very common condition that occurs as men naturally age. Testosterone acts on the prostate gland’s growth where it is converted by 5α reductase to stimulate hyperplasia. This leads to symptoms in men of increased frequency, urgency, straining, nocturia. BPH is treated with a 5α reductase inhibitor, such as finasteride.

**Anabolic steroids** are commonly used by weight lifters to increase their strength in a short period of time. Most often they will use testosterone and other androgenic compounds which work to stimulate muscle growth. They can have many adverse effects: behavioral, endocrine and dermatological.

### Antiestrogens

**Selective estrogen receptor modulators** (SERMs) are used to block estrogen’s function in breast cancer. Many breast cancers have estrogen receptor α, which can be blocked by the drug tamoxifen. The selective aspect of SERMs comes from its inhibitory effects on growth in breast cancer. In the endometrium however, it has a stimulatory effect causing endometrial hyperplasia, which puts the woman at risk of endometrial cancer. To mitigate these effects, progesterone is given to help dampen the hyperplasia.

**Aromatase inhibitors** can be used to block the production of estrone by aromatase in adipocytes. This can be used to treat gynecomastia.

### Antiprogestins

Antiprogestins can be used as forms of birth control.

When combined with a prostaglandin, such as misoprostol, they can be used to induce abortions as the morning after pill. Mifepristone is used to block progesterone’s maintenance effect thus stimulating myometrial expulsion of the embryo.

Birth control is usually combined with estrogen and antiprogestin. The antiprogestin norethindrone inhibits FSH and LH being released from the anterior pituitary.
Antiandrogens

**Spironolactone** will block androgen receptors and lower testosterone levels. This can be used to treat the symptoms of **polycystic ovarian syndrome** in females. Spironolactone also acts as a **diuretic** acting upon the collecting duct of the nephron.

5α reductase inhibitors, such as **finasteride**, function to decrease the conversion of testosterone to dihydrotestosterone. **Dihydrotestosterone** has a stronger effect than testosterone alone, leading to **prostatic hyperplasia** and **male hair pattern**. Blocking dihydrotestosterone production mitigates the symptoms of BPH and aids in the treatment of male pattern baldness.

References

medscape.com


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