

DISORDERS OF SEX HORMONES

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7.4 SEX HORMONES DISORDER

The sex hormones are a group of hormones responsible for controlling reproduction, puberty, birth, and lactation. The Sex hormone disorders, also referred to as reproductive hormone disorders which are affected the different glands and organs of the body. These are responsible for the production of the sex hormones. The sex hormones includes testosterone (male) and estrogen (female) are substances that essential in almost every body function, but more so in sexual functions and reproduction. Both testosterone and estrogen are present in males and females, but the levels differ according to sex. Males have higher levels of testosterone and females have higher levels of estrogen. Sex hormone disorders disrupt the normal production of hormones,

7. 4.1 POLYCYSTIC OVARIAN SYNDROME (PCOS) (FEMALE DISORDER)

Definition: Polycystic ovary syndrome (PCOS) is a hormonal disorder common among women of reproductive age. Women with PCOS may have infrequent or prolonged menstrual periods or excess male hormone (androgen) levels. The ovaries may develop numerous small collections of fluid (follicles) and fail to regularly release eggs.

Introduction: This disorder is characterized by oligomenorrhea (irregular menstrual cycles) or amenorrhea (no menstrual cycles) with symptoms of hyperandrogenism (extra male like hormones) such as acne and hirsutism (extra male like hair growth). This is the most common endocrine disorder in young females.

Etiology: The Signs and symptoms of PCOS may vary (I) *Irregular periods:* Infrequent, irregular or prolonged menstrual cycles are the most common sign of PCOS. (II) *Excess androgen:* Elevated levels of male the hormone may result in physical signs, such as excess facial and body hair (hirsutism), and occasionally severe acne and male-pattern baldness. (III). *Polycystic ovaries:* The ovaries might be enlarged and contain follicles that surround the eggs. As a result, the ovaries might fail to function regularly.

The exact cause of PCOS is unknown. Early diagnosis and treatment along with weight loss may reduce the risk of long-term complications such as type 2 diabetes and heart disease. (I) *Excess insulin:* Insulin is the hormone produced by the pancreas that allows cells to use sugar. If the cells become resistant to the action of insulin, then blood sugar levels can rise and the pancreases produce more insulin. The excess insulin increase androgen production, causing difficulty with ovulation. (II) *Low-grade inflammation:* This term is used to describe white blood cells' production of substances to fight infection. If the women is suffered from PCOS type of low-grade inflammation that stimulates polycystic ovaries to produce androgens, which can lead to heart and blood vessel problems. (III). *Heredity.* Certain genes might be linked to PCOS. (IV) *Excess androgen.* The ovaries produce abnormally high levels of androgen, resulting in hirsutism and acne.

Pathogenesis: Polycystic ovary syndrome (PCOS) appear to have more frequent releases of LH, the pulse frequency of gonadotropin-releasing hormone (GnRH) be accelerated in PCOS. The increasing order the GnRH pulse generator favors the synthesis and release of LH over FSH. The concentration of LH increases relative to FSH, the ovaries preferentially synthesize testosterone. The insulin acts synergistically with LH to increase androgen production within the cell. The insulin also inhibits the hepatic synthesis of SHBG, which normally binds testosterone. The higher levels of unbound or "free" testosterone increase the biologic activity of the circulating hormone. The testosterone further inhibits (whereas estrogen stimulates) the hepatic synthesis of SHBG.

An increase in free and total serum testosterone levels results in androgenization, the most obvious features of which are hirsutism, acne, and diffuse alopecia. Hyperandrogenemia interferes with the hypothalamic-pituitary axis, leading to anovulation. The absence of a dominant follicle prevents development of nondominant follicles, resulting in the formation of multiple ovarian cysts. High androgen levels also affect metabolic parameters such as lipid concentrations.

The PCOS typically have hyperinsulinemia. Thus, the concentration of free testosterone is often elevated, whereas the total testosterone level may be only slightly increased.

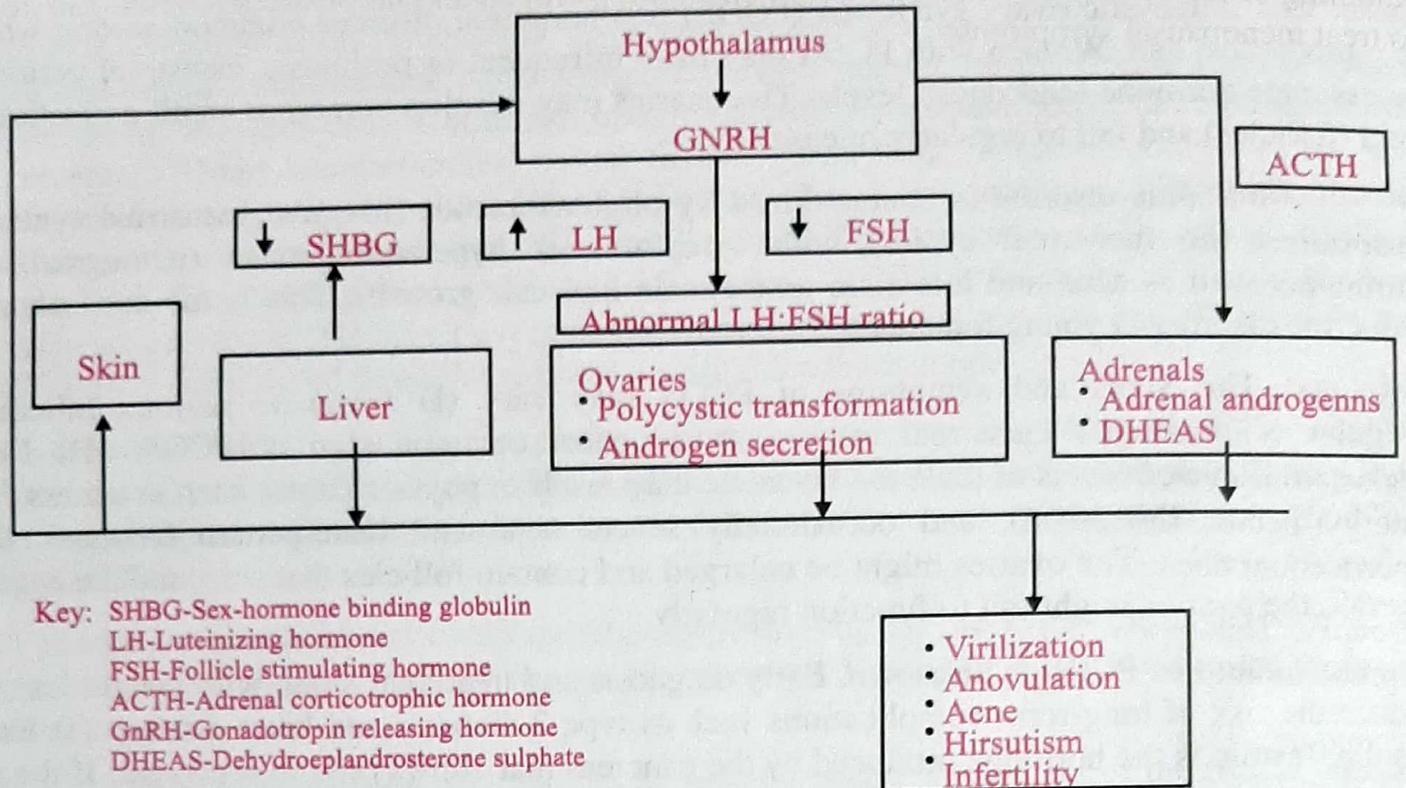


Fig. 7.9 Neuroendocrine Dysfunction Polycystic Ovary Syndrome

7.4.2 HIRSUTISM

Hirsutism is the growth of excessive hair in a male pattern. This would include face, chest, abdomen and back. This is usually due to the increased production of androgens (male hormones). Disorders in which hirsutism is seen include: polycystic ovarian syndrome, congenital adrenal hyperplasia, ovarian tumors or adrenal tumors. Blood tests are used to help determine a cause. Occasionally, there is no cause found for the hair growth (idiopathic hirsutism). Medical treatment varies by the underlying cause of the hirsutism. Topical treatments including electrolysis and laser can be used to decrease hair growth.

Androgen Excess: Androgen excess refers to the overproduction of male hormones. This can result from ovarian or adrenal tumors. Other disorders such as polycystic ovarian syndrome, Cushing's syndrome (the overproduction of cortisol), hyperprolactinemia and congenital adrenal hyperplasia can cause extra male hormones to be produced. In women androgen excess can cause hirsutism (excessive hair growth), acne, male pattern baldness, menstrual cycle irregularities and infertility. Diagnosis is generally made through blood tests. CT scans of adrenal glands and ovaries are occasionally needed. Treatments vary by the underlying cause of the androgen excess.

Menopause/perimenopause : Menopause is defined as the cessation of menstrual cycles. This usually occurs at about the age of 50 in most women. For 2 to 8 years preceding this, menstrual cycles may be irregular. This is referred to as the menopausal transition or perimenopause. As estrogen and progesterone levels decline women may experience a variety of symptoms. These

symptoms can include hot flashes, sleep disturbances, fatigue, irritability, decreased sex drive, vaginal dryness and depression. Long term estrogen deficiency can result in osteoporosis (thinning of the bones). A variety of treatments both estrogen and non-estrogen based can be used to treat menopausal symptoms.

7.4.3 HYPOGONADISM: (MALES DISORDER)

Definition: Male hypogonadism is a condition in which the body does not produce enough of the testosterone hormone; the hormone that plays a key role in masculine growth and development during puberty.

Introduction: Hypogonadism refers to the decreased production of testosterone. This can result from the pituitary gland (master gland in the brain for hormone production) not stimulating the testicles to make testosterone or the failure of the testicles to produce adequate testosterone. The testosterone levels are low in male decreased libido (sex drive), erectile dysfunction, decreased energy, decreased muscle mass and thinning of the bones. Testicle size may also decrease and sperm count decrease. There are two basic types of hypogonadism

Primary: This type of hypogonadism – also known as primary testicular failure – originates from a problem in the testicles.

Secondary: This type of hypogonadism indicates a problem in the hypothalamus or the pituitary gland –parts of the brain that signal the testicles to produce testosterone. The hypothalamus produces the gonadotropin releasing hormone, which signals the pituitary gland to make the follicle-stimulating hormone (FSH) and luteinizing hormone. The luteinizing hormone then signals the testes to produce testosterone. Either type of hypogonadism may be caused by an inherited (congenital) trait or something that happens later in life (acquired), such as an injury or an infection

Etiology: Hypogonadism symptom is characterized by serum testosterone levels < 300 ng/dL in combination with at least one clinical sign or symptom. Signs of hypogonadism include absence or regression of secondary sex characteristics, anemia, muscle wasting, reduced bone mass or bone mineral density, oligospermia, and abdominal adiposity. Symptoms of post pubescent hypogonadism include sexual dysfunction (erectile dysfunction, reduced libido, diminished penile sensation, difficulty attaining orgasm, and reduced ejaculate), reduced energy and stamina, depressed mood, increased irritability, difficulty concentrating, changes in cholesterol levels, anemia, osteoporosis, and hot flashes. In the prepubertal male, if treatment is not initiated, signs and symptoms include sparse body hair and delayed epiphyseal closure.

The causes of primary hypogonadism include: autoimmune disorders, such as Addison's disease and hypoparathyroidism, genetic disorders, severe infections, liver and kidney diseases, radiation exposure and surgery on sex organs

Central, or secondary, hypogonadism may be due to: genetic disorders, such as Kallmann syndrome (abnormal hypothalamic development), infections, including HIV and AIDS, pituitary disorders, inflammatory diseases, including sarcoidosis, tuberculosis, and histiocytosis, nutritional deficiencies and use of steroids or opiates (especially long-term usage)

Pathophysiology The cerebral cortex signals the hypothalamus to stimulate the production of testosterone. To do this, the hypothalamus releases the gonadotropin-releasing hormone in a

pulsatile fashion, which stimulates the pituitary gland – the portion of the brain responsible for hormones involved in the regulation of growth, thyroid function, blood pressure, and other essential body functions. Once stimulated by the gonadotropin-releasing hormone, the pituitary gland produces the follicle-stimulating hormone and the luteinizing hormone. Once released into the bloodstream, the luteinizing hormone triggers activity in the Leydig cells in the testes. In the Leydig cells, cholesterol is converted to testosterone. When the testosterone levels are sufficient, the pituitary gland slows the release of the luteinizing hormone via a negative feedback mechanism, thereby, slowing testosterone production. With such a complex process, many potential problems can lead to low testosterone levels. Any changes in the testicles, hypothalamus or pituitary gland can result in hypogonadism.

7.4. 4 ERECTILE DYSFUNCTION (ED)

Definition: Erectile dysfunction (ED) is the inability to get or keep an erection firm enough to have sexual intercourse. It's also sometimes referred to as impotence.

Introduction: Erectile dysfunction is the inability to acquire or maintain an erection that is satisfactory for sexual intercourse. This may also be referred to as impotence. Any medical condition which can decrease blood flow to the penis may result in ED. Common causes of ED are smoking, diabetes, high blood pressure, alcohol and depression. Additionally, some prescription medications can also cause ED.

Etiology: the symptoms of erectile dysfunction are trouble getting an erection, difficulty maintaining an erection during sexual activities and reduced interest in sex, premature ejaculation, delayed ejaculation and anorgasmia, which is the inability to achieve orgasm after ample stimulation. The following are causes of erectile dysfunction, and many men have more than one potential cause:

Aging: There are two reasons first, older men are more likely to develop diseases (such as heart attacks, angina, cardiovascular disease, strokes, diabetes mellitus, and high blood pressure) that are associated with erectile dysfunction. Second, the aging process alone can cause erectile dysfunction in some men by causing changes in the muscle and tissue within the penis.

Diabetes mellitus: The increased risk of erectile dysfunction among men with diabetes mellitus may be due to the earlier onset and greater severity of atherosclerosis (hardening of the arteries) that narrows the arteries and thereby reduces the delivery of blood to the penis.

Hypertension: Men with high blood pressure have an increased risk of developing erectile dysfunction. Hypertension can cause troubles with erections related to atherosclerosis or from low levels of nitric oxide being made from the arteries in the penis.

Cardiovascular diseases: The most common cause of cardiovascular atherosclerosis, the narrowing and hardening of arteries that reduces blood flow. Hardening of the arteries to the penis and pelvic organs, atherosclerosis, causes insufficient blood flow into the penis.

Cigarette smoking: Cigarette smoking aggravates atherosclerosis and can cause vasospasm (spasms of the arteries) and thereby increases the risk for erectile dysfunction.

Substance abuse: Marijuana, heroin, cocaine, methamphetamines, crystal meth, and narcotic and alcohol abuse contribute to erectile dysfunction. Alcoholism, in addition to causing nerve damage, can lead to atrophy (shrinking) of the testicles and lower testosterone levels.

Low testosterone levels: Testosterone (the primary sex hormone in men) is not only necessary for sex drive (libido) but also is necessary to maintain nitric oxide levels in the penis. Therefore, men with hypogonadism (low testosterone with symptoms) can have low sex drive and erectile dysfunction.

Medications: Many common medicines produce erectile dysfunction as a side effect.

Depression and anxiety: Psychological factors may be responsible for erectile dysfunction. These factors include stress, anxiety, guilt, depression, widower syndrome, low self-esteem, posttraumatic stress disorder, and fear of sexual failure (performance anxiety).

Pathogenesis: Stimulation of erection originates in the higher centers of the brain that result in upregulation of (NANC) Noradrenergic and norcholinergic activity and withdrawal of sympathetic activity in the nerves innervating the corpora cavernosa and small arteries of the penis. This increase in NANC and cholinergic activity results in upregulated Nitric Oxide (NO) release from the endothelium and NANC nerve terminals. The NO diffuses into the smooth muscle of the corpora cavernosa and small arteries/arterioles of the penis and binds to the reduced heme iron of soluble guanylate cyclase, activating the enzyme and increasing the formation of cGMP from GTP. cGMP-dependent protein kinase activity opens potassium channels in smooth muscle cells and increases the uptake of calcium into stores. This leads to a decrease in intracellular calcium concentration and smooth muscle cell relaxation. This increases blood flow into the corporal sinuses and the cavernosal sinuses expand trapping blood in the corpora producing a penile erection. Detumescence is initiated by release of vasoconstrictors from sympathetic terminals and endothelium. A cGMP specific phosphodiesterase (type 5) breaks down the cGMP to GTP and terminates the actions of cGMP. kinase/RhoA activation has been shown to mediate detumescence and maintain flaccidity. Rho kinase inhibits the regulatory subunit of myosin phosphatase within smooth muscle cells and maintains contractile tone under low-cytosolic calcium concentrations. Upregulated Rho-kinase activity has been reported in ED.

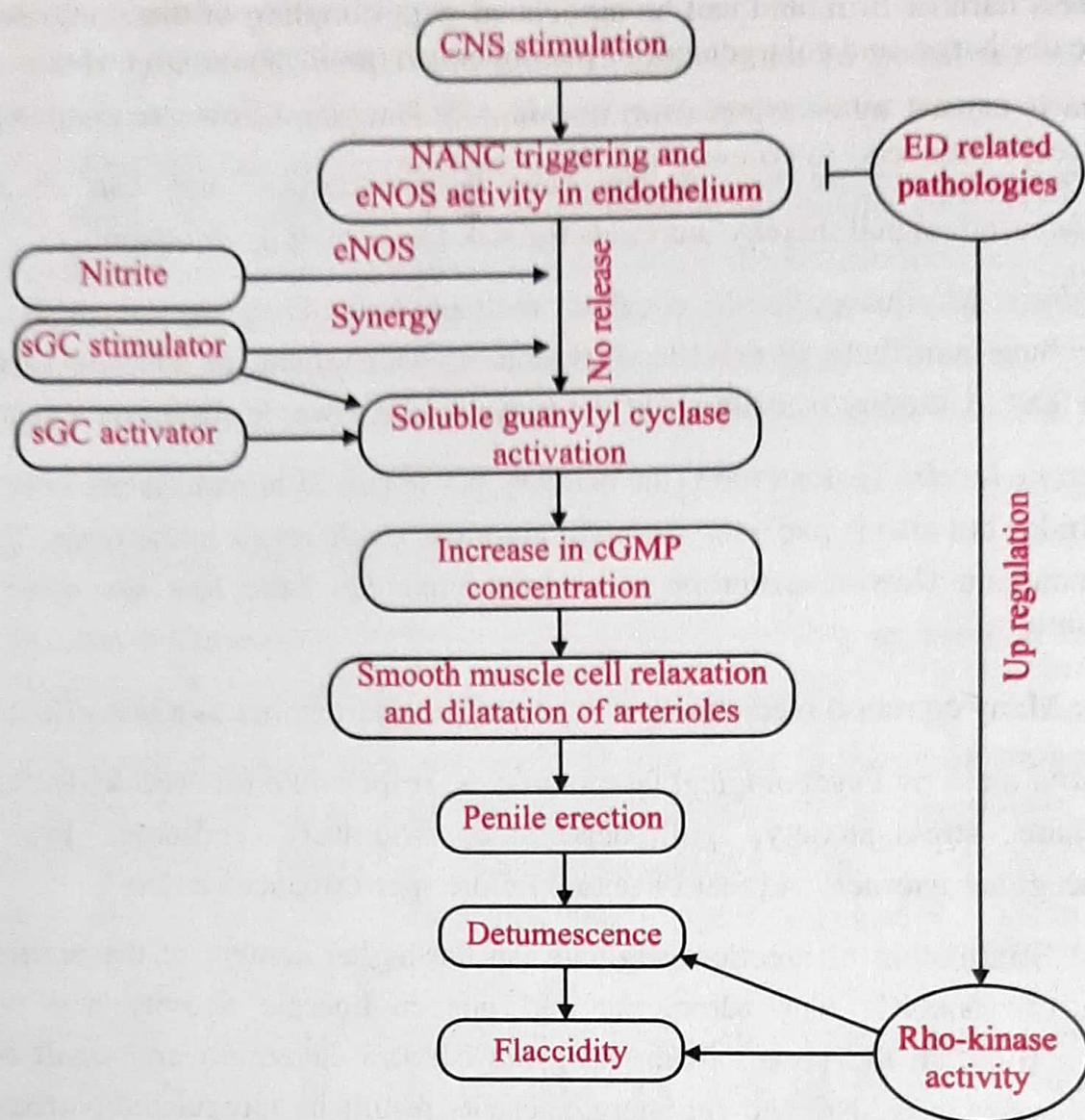


Fig. 7.10 Systematic pathway for the control of penile erection and detumescence.

7.4.5 GYNECOMASTIA

The increase in breast tissue in a man is referred to as gynecomastia. This can occur during puberty and resolve on its own. Gynecomastia can also be due to medications, hypogonadism, thyroid disease, malnutrition, testicular cancers, adrenal cancers, liver disease or kidney disease. The cause of the gynecomastia is usually determined by physical exam, history and blood tests. Additional testing may include testicular ultrasounds or CT scan.

Etiology: The primary symptom of gynecomastia is enlargement of the male breasts. As mentioned before, gynecomastia is the enlargement of glandular tissue rather than fatty tissue. It is typically symmetrical in location with regard to the nipple and may have a rubbery or firm feel. Gynecomastia usually occurs on both sides but can be unilateral in some cases. The enlargement may be greater on one side even if both sides are involved. Tenderness and sensitivity may be present, although there is typically no severe pain. The most important distinction with gynecomastia is differentiation from male breast cancer, which accounts for about 1% of overall cases of breast cancer. Cancer is usually confined to one side, is not necessarily centered around

the nipple, feels hard or firm, and can be associated with dimpling of the skin, retraction of the nipple, nipple discharge, and enlargement of the underarm (axillary) lymph nodes.

Gynecomastia is caused by estrogen from the mother to newborn. Breast buds are common in baby boys. Breast buds tend to go away gradually by 6 months of age, but they can last longer in some babies. In preteen boys, gynecomastia can also be caused by an estrogen-producing tumor. Breast buds are common during puberty. The buds may last up to 2 years, but they tend to go away within the first year.

Gynecomastia is caused by the hormonal changes of puberty in teen boys. Gynecomastia occurs in many boys during early puberty to middle puberty. It usually goes away within 6 months to 2 years

Pathophysiology: The imbalance between estrogen action relative to androgen action at the breast tissue level appears to be the main etiology of gynecomastia. Elevated serum estrogen levels may be a result of estrogen-secreting neoplasms or their precursors (eg, Leydig or Sertoli cell tumors, human chorionic gonadotropin [hCG] producing tumors, and adrenocortical tumors) but more commonly are caused by increased extragonadal conversion of androgens to estrogens by tissue aromatase (as occurs in obesity). Levels of free serum testosterone are decreased in patients with gonadal failure, which can be primary (Klinefelter syndrome, mumps orchitis, castration) or secondary (hypothalamic and pituitary disease). Androgen resistance syndromes due to impaired activity of enzymes involved in the biosynthesis of testosterone can also be associated with gynecomastia.

The balance between free testosterone and estrogen is also affected by serum levels of sex hormone—binding globulin, which is the proposed mechanism of gynecomastia in certain conditions, such as hyperthyroidism, chronic liver disease, and the use of some medications such as spironolactone.

Receptors of androgens can also have genetic defects or become blocked by certain medications (eg, bicalutamide, used in the treatment of prostate cancer), and the receptors of estrogens can be activated by certain medications or environmental exposures. Of note, patients with pubertal gynecomastia have normal levels of serum estradiol, testosterone, and dehydroepiandrosterone-sulfate and a normal estrogen-testosterone ratio. However, free testosterone levels in these patients are lower than those of controls without gynecomastia.