

Hypogonadism

What is hypogonadism?

Hypogonadism is the clinical manifestation of the impaired function of the gonads, which in men are the testes and in women are the ovaries. Certain patients have hypogonadism from birth, while others may develop the condition later in their life. The disease has different features in males and in females, before and after the onset of puberty.



Hypogonadism is a disorder where the testes in men and ovaries in women do not work properly. It can be very distressing. Thanks to the discovery and development of gender specific hormone treatments, men and women with hypogonadism can lead a normal life.

If onset is in pre-pubertal boys, signs and symptoms of lack of testicular function include a change of male hair distribution, including facial, chest, and axillary hair, poor development of skeletal muscles, and disturbance of bone growth resulting in abnormally long arms and legs. Blood levels of the male hormone testosterone are low. Also observed are missing laryngeal enlargement, failure of vocal chord thickening, and alterations in body fat distribution. When hypogonadism occurs in males after puberty, low concentration of testosterone in the blood causes lack of energy, weakness, lethargy and diminished sexual function, reduced bone mass and often anaemia.

In girls with hypogonadism before puberty, impaired ovarian function leads to failure of progression through puberty. The absence of periods (primary amenorrhoea) is the most common feature. Blood levels of estradiol are low. When hypogonadism occurs after puberty, irregular periods or absence of periods (secondary amenorrhoea) is the usual concern. The patients develop ovarian suppression which manifests as infertility, decreased libido, breast atrophy, and osteoporosis.

Testis and ovary function are part of a hormonal loop which consists of two components in the brain (the hypothalamic region and the pituitary gland) and the gonads themselves. This hypothalamic-pituitary-gonadal axis acts like a waterfall. A hypothalamic generator releases luteinising hormone-releasing hormone (LHRH). In response to these LHRH pulses, the pituitary secretes follicle-stimulating hormone

(FSH) and luteinising hormone (LH), which in turn stimulate testis and ovary. The increased blood levels of the gonadal hormones (androgens in men and estrogens in women) leads to lowered FSH and LH secretion at the pituitary level, completing the negative feedback loop.

Hypogonadism may occur if this hypothalamic-pituitary-gonadal axis is interrupted at any level. Primary or hypergonadotrophic hypogonadism results if the gonad does not produce the amount of sex hormone sufficient to suppress secretion of LH and FSH at normal levels. Hypogonadotrophic hypogonadism may result from hypothalamic

LHRH deficiency or from inability of the pituitary to secrete LH and FSH. Most commonly, hypogonadotrophic hypogonadism is observed after hypothalamic-pituitary injury from tumours, trauma, or radiation.

Who does hypogonadism affect?

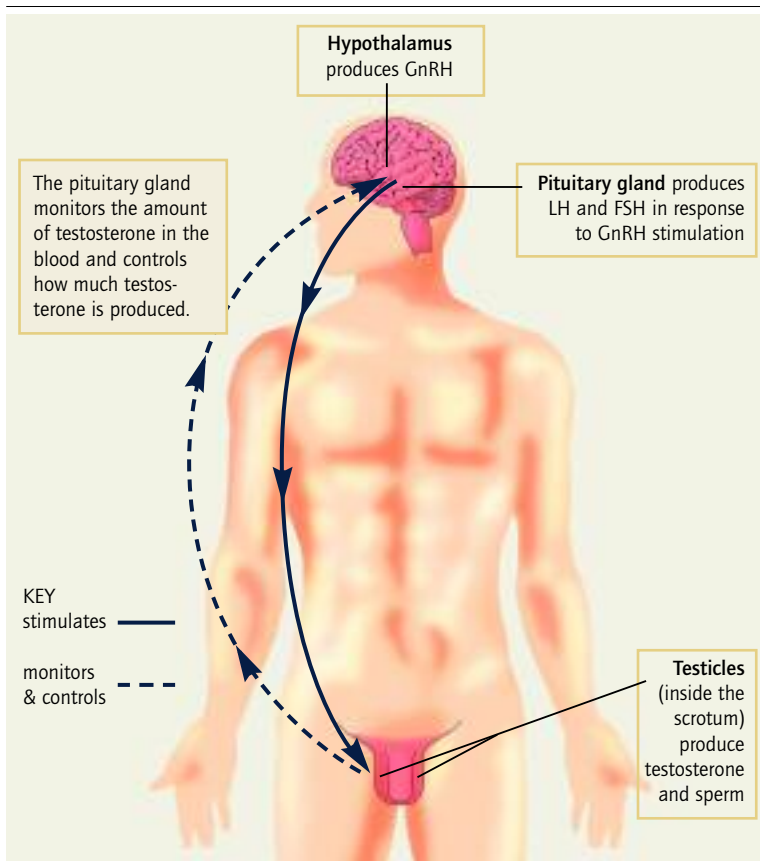
For male patients with primary hypogonadism, the most common cause is a genetic disorder known as Klinefelter syndrome, a chromosome abnormality which occurs in one case per approximately 1,000 live births. Primary hypogonadism is more common in boys than in girls because the incidence of Klinefelter syndrome is higher than the incidence of the equivalent condition for girls, Turner syndrome. Hypogonadotrophic hypogonadism in men occurs more rarely. It is estimated, though, that less than five per cent of men with hypogonadotrophic hypogonadism are diagnosed and are receiving hormone replacement therapy (HRT); around a fifth of men aged more than 50 years are believed to have androgen deficiency.

For women with primary hypogonadism, the most common cause is a genetic disorder known as Turner syndrome, a chromosome abnormality which occurs with an incidence of one case per approximately 5,000 live births. The incidence of hypogonadotrophic hypogonadism in females is equal to that in males.

No increase in mortality exists in patients with hypogonadism. Morbidity for men and women includes infertility, anaemia and an increased risk of osteoporosis. There does not appear to be a racial pattern.

Present treatments:

In men, low blood levels of testosterone should be increased. HRT may be given as a bi-weekly intramuscular injection, as a patch form, or a gel preparation. In Europe, there exist a number of transdermal testosterone therapies, including gels containing one per cent testosterone or in the form of dermal patches containing the active compound. Several formulations are available, including a scrotal patch and several patches that may be applied at other sites. Patches are changed daily. Another treatment option is the prescription of tablets which dissolve in the mouth. Additionally, there are hormone implants. These cylindrical pellets are inserted under the skin in the abdomen, buttock or thigh. They are given once every three to six months. Oral preparations of testosterone are still available but rarely used.



The action of gonadotrophin-releasing hormone (GnRH) from the hypothalamus on the pituitary, and the subsequent action of LH and FSH from the pituitary on the testes to stimulate testosterone and sperm production

In women, estrogen should be increased. To initiate pubertal development in girls, HRT can be given orally as conjugated estrogen or as a patch applied twice weekly. Transdermal application allows a very low starting dose of estrogen which is desired in young girls with bone ages below 12 years. Starting at higher doses may cause rapid closure of epiphyses and growth will be halted. Women taking estrogen also need to take progesterone replacement unless they have undergone a surgical removal of the uterus. Progesterone agents are added during the last 12 to 14 days of the menstrual cycle to transform the proliferative inner lining of the uterus (endometrium) into the secretory state.

Men and women with hypogonadism can lead a normal life with HRT.

To restore fertility, preparations called human chorionic gonadotrophin (hCG) or human menopausal gonadotrophin (hMG) are given as intramuscular injections to treat men and women, respectively. In men, they act on the testicles and encourage the production of sperm and testosterone. While on gonadotrophin injections, there is no need to take testosterone or estrogen replacement therapy.

What's in the development pipeline?

At the end of 2003, a new androgen replacement depot received its first approval in a European country for the treatment of hypogonadism in men. The slow releasing depot formulation means it can be administered by just four injections a year, which is a vast improvement over existing treatments for testosterone deficiency, which require an average of 22 injections per year.

At the end of February 2004, it was found that the benefits of HRT in males suffering from hypogonadism are maintained for more than a year. Using a one per cent once-daily testosterone gel, researchers reported significant improvements in sexual function, mood, lean body mass and bone mineral density.

Research has shown a higher incidence of hypogonadotropic hypogonadism with concomitant conditions such as diabetes and AIDS. According to latest results, some 30 per cent of men suffering from type 2 diabetes are affected, because of the improper functioning of the hypothalamic-pituitary axis. Research into new treatments for patients suffering from diseases such as diabetes and AIDS will therefore reduce the overall prevalence of hypogonadism.

The longer-term future:

Hypogonadism can be seen as an area in which the development of new medicines over the past twenty years has been very successful. With the improvements in outcome now achievable, the somewhat slower pace of new development can be taken as a sign of a job well done.

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