Male Hypogonadism in Children

Male hypogonadism in children refers to a condition where the testes produce little or no sex hormones, including testosterone. This can result in delayed or incomplete puberty. There are two main types of male hypogonadism in children:

1. **Primary hypogonadism:** This occurs when there is a problem with the testes themselves, leading to reduced testosterone production. Causes of primary hypogonadism in children may include genetic disorders (such as Klinefelter syndrome), undescended testicles (cryptorchidism), testicular injury or trauma, certain infections (mumps orchitis), or radiation/chemotherapy treatments.

2. **Secondary (or central) hypogonadism:** This type of hypogonadism occurs when there is a problem with the hypothalamus or pituitary gland in the brain, which regulate testosterone production. Causes of secondary hypogonadism in children may include genetic disorders (such as Kallmann syndrome), pituitary tumors or damage, brain trauma, or certain medications.

Symptoms and Signs of Male Hypogonadism in Children

Clinical presentation depends on whether, when, and how testosterone and sperm production are affected.

If androgen deficiency or defects in androgen activity occur during the first trimester (< 12 weeks gestation), differentiation of internal wolffian ducts and external genitals is inadequate. Presentation may range from ambiguous external genitals to normal-appearing female external genitals. Androgen deficiency during the second and third trimesters may cause a microphallus and partially or completely undescended testes.

Androgen deficiency that develops early in childhood has few consequences, but if it occurs when puberty is expected, secondary sexual development is impaired. Such patients have poor muscle development, a high-pitched voice, inadequate phallic and testicular growth, a small scrotum, sparse pubic and axillary hair, and absent body hair. They may develop gynecomastia and grow to eunuchoidal body proportions (arm span exceeds height by 5 cm; pubic to floor length exceeds crown to pubic length by > 5 cm) because fusion of the epiphyses is delayed and long bone growth continues.

Diagnosis of Male Hypogonadism in Children

- Measurement of testosterone, LH, and FSH
- Karyotyping (for primary hypogonadism)

Diagnosis of male hypogonadism in children is often suspected based on developmental abnormalities or delayed puberty but requires confirmation by testing, including measurement of testosterone, LH, and FSH. LH, and especially FSH, levels are more sensitive than testosterone levels, especially for detecting primary hypogonadism. Testing should be done in the morning and requires pediatric-specific assays (often labeled as ultrasensitive or immunochemiluminometric [ICMA]).

LH and FSH levels also help determine whether hypogonadism is primary or secondary:

- High levels, even with low-normal testosterone levels, indicate primary hypogonadism.
- Levels that are low or lower than expected for the testosterone level indicate secondary hypogonadism.

In boys with short stature, delayed pubertal development, low testosterone, and low FSH and LH levels may indicate constitutional delay. Unlike constitutional delay, in which there is a transient decrease in these hormones that normalizes with time, the gonadotropins and testosterone do not normalize with time.

Elevated serum FSH levels with normal serum testosterone and LH levels typically indicate impaired spermatogenesis but not impaired testosterone production. In primary hypogonadism, it is important to determine the karyotype to investigate for Klinefelter syndrome.

Interpretation of testosterone, FSH, and LH levels for diagnosis of hypogonadism requires an understanding of how the levels vary. Before puberty, serum testosterone levels are < 20 ng/dL (< 0.7 nmol/L); in adulthood, levels are > 300 to 1200 ng/dL (12 to 42 nmol/L). Serum testosterone secretion is primarily circadian. In the 2nd half of puberty, levels are higher at night than during the latter part of the day. A single sample obtained in the morning can establish that circulating testosterone levels are normal. Because 98% of testosterone is bound to carrier proteins in serum (usually sex hormone–binding globulin), alterations in these protein levels alter total testosterone levels. Measurement of total serum testosterone (protein bound and free) is usually the most accurate indicator of testosterone secretion.

Although serum LH and FSH levels are pulsatile, testing can be valuable. Puberty begins when GnRH secretion increases and serum LH rises disproportionately to FSH. Early in

puberty, early morning levels are preferred. Serum LH levels are usually below 0.2 mIU/mL (0.2 units/L) before puberty and range from 2 to 12 mIU/mL (2 to 12 units/L) during later stages of puberty and into adulthood. Serum FSH levels are usually < 3 mIU/mL (< 3 units/L) before puberty and fluctuate between 5 and 10 mIU/mL (5 and 10 units/L) during the 2nd half of puberty and into adulthood.

Measurement of inhibin B and anti-müllerian hormone levels can help assess gonadal function in boys with suspected hypogonadism. Both are functional markers of Sertoli cells, which play an important role in spermatogenesis and account for the majority of testicular growth before puberty. Unlike LH and FSH, these markers are easily measured before puberty. For older boys with delayed puberty and suspected secondary hypogonadism, low levels of inhibin B, which normally rise at puberty, are more suggestive of secondary hypogonadism than constitutional delay.

The human chorionic gonadotropin (hCG) stimulation test is done to assess the presence and secretory ability of testicular tissue. Multiple protocols exist. In one protocol, a one-time dose of hCG 100 units/kg IM is given. hCG stimulates Leydig cells, as does LH, with which it shares a structural subunit, and stimulates testicular production of testosterone. Testosteronelevels should double after 3 to 4 days.

Treatment of Male Hypogonadism in Children

Symptoms of male hypogonadism in children may include delayed puberty, lack of development of secondary sexual characteristics (such as facial hair, deepening of voice), small testicles, decreased muscle mass, growth retardation, and in some cases, infertility.

Treatment for male hypogonadism in children depends on the underlying cause and may include:

1. **Hormone replacement therapy (HRT):** Testosterone replacement therapy may be prescribed to stimulate puberty and promote the development of secondary sexual characteristics. This can be administered via injections, patches, gels, or implants.

2. **Treatment of underlying conditions:** If hypogonadism is caused by a specific medical condition, such as a pituitary tumor or genetic disorder, treatment of the underlying condition may help restore normal hormone production.

3. **Monitoring and support:** Regular monitoring by healthcare professionals is essential to assess hormone levels, track growth and development, and adjust treatment as needed. Psychological support and counseling may also be beneficial for children and their families to cope with the emotional aspects of the condition.

Early diagnosis and appropriate management of male hypogonadism in children are crucial for promoting normal growth and development, as well as optimizing long-term health outcomes.