Ockham Technical Synopsis *is a recurring series prepared for internal staff and consultants of Ockham Development Group Inc. (Ockham). Highlighting current and emerging issues and challenges in clinical research, these publications are intended to disseminate intelligence captured during the execution of key clinical trials and are therefore updated on a continuous basis.*

MALE HYPOGONADISM

NATURAL HISTORY AND OUTCOME

Disease Definition

Male hypogonadism is a condition in which the body doesn't produce enough of the sex hormone testosterone. As many as 5 million men in the United States may not produce enough testosterone — the hormone that plays a key role in masculine growth and development during puberty.

Testosterone – the effects of which begin after conception, stimulating the formation of male sex organs – continues to play an important role through puberty and adulthood by triggering male characteristics and maintaining sex drive.

Hypogonadism may be present at birth, or it can develop later in life due to injury or infection. The effects and what can be done about them depend on the cause and at what point in life hypogonadism occurs.

During fetal development, low testosterone can cause incomplete formation of sex organs. Low testosterone levels before puberty can permanently affect growth and development. After puberty, the development of hypogonadism is more likely to cause temporary problems that may improve with treatment. Some types of hypogonadism can be treated with testosterone replacement therapy.

SYMPTOMS

Hypogonadism can occur during fetal development, puberty or adulthood. Depending on when it develops, the signs and symptoms differ.

Fetal Development

If the body doesn't produce enough testosterone during fetal development, growth of external sex organs may be impaired. Depending at when it develops, and how much testosterone is present, a child that is genetically male may be born with:

- Female genitals
- Ambiguous genitals (genitals that are neither clearly male or female)
- Underdeveloped male genitals.

Puberty

During puberty, male hypogonadism may slow growth and affect development. It can cause:

- Decreased development of muscle mass
- Lack of deepening of the voice
- Impaired growth of body hair
- Impaired growth of the penis and testicles
- Excessive growth of the arms and legs in relation to the trunk of the body
- Development of breast tissue (gynecomastia).

Adulthood

In adult males, hypogonadism may alter certain masculine physical characteristics and impair normal reproductive function. Signs and symptoms may include:

- Erectile dysfunction
- Infertility
- Decrease in beard and body hair growth
- Increase in body fat
- Decrease in size or firmness of testicles
- Decrease in muscle mass
- Development of breast tissue (gynecomastia)
- Loss of bone mass (osteoporosis).

Hypogonadism can also cause mental and emotional changes. As testosterone decreases, some men may experience symptoms similar to those of menopause in women. These may include:

- Fatigue
- Decreased sex drive
- Difficulty concentrating
- Hot flashes
- Irritability
- Depression.

CAUSES

Male hypogonadism means the testicles don't produce enough of the male sex hormone testosterone. 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 gonadotropin-releasing hormone, which signals the pituitary gland to make follicle-stimulating hormone (FSH) and luteinizing hormone. 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, such as an injury or an infection (acquired).

Primary Hypogonadism

Common causes of primary hypogonadism include:

- Klinefelter 's syndrome. This condition results from a congenital abnormality of the sex chromosomes, X and Y. A male normally has only one X and one Y chromosome. In Klinefelter's syndrome, two or more X chromosomes are present in addition to one Y chromosome. The Y chromosome contains the genetic material that determines the sex of a child and related development. The extra X chromosome that occurs in Klinefelter's syndrome causes abnormal development

of the testicles, which in turn results in underproduction of testosterone.

- Undescended testicles. Before birth, the testicles develop inside the abdomen and normally move down into their permanent place in the scrotum two months before birth. One or both of the testicles may not be descended at birth. This condition often corrects itself within the first few years of life without treatment. If not corrected in early childhood, it may lead to malfunction of the testicles and reduced production of testosterone.
- Mumps orchitis. If a mumps infection involving the testicles in addition to the salivary glands (mumps orchitis) occurs during adolescence or adulthood, long-term testicular damage may occur. This may affect normal testicular function and testosterone production.
- Hemochromatosis. Too much iron in the blood can cause testicular failure or pituitary gland dysfunction affecting testosterone production.
- Injury to the testicles. Because of their location outside the abdomen, the testicles are prone to injury. Damage to normally developed testicles can cause hypogonadism. Damage to one testicle may not impair testosterone production.
- Cancer treatment. Chemotherapy or radiation therapy for the treatment of cancer can interfere with testosterone and sperm production. The effects of both treatments often are temporary, but permanent infertility may occur. Although many men regain their fertility within a few months after treatment ends, preserving sperm before starting cancer therapy is an option that many men consider.
- Normal aging. Older men generally have lower testosterone levels than younger men do. As men age, there's a slow and continuous decrease in testosterone production. The rate that testosterone declines varies greatly among men. As many as 30 percent of men older than 75 have a testosterone level that's below normal.

Secondary Hypogonadism

In secondary hypogonadism, the testicles are normal but function improperly due to a problem with the pituitary or hypothalamus. A number of conditions can cause secondary hypogonadism, including:

- Kallmann syndrome. Abnormal development of the hypothalamus — the area of the brain that controls the secretion of pituitary hormones — can cause hypogonadism. This abnormality is also associated with impaired development of the ability to smell anosmia.
- Pituitary disorders. An abnormality in the pituitary gland can impair the release of hormones from the pituitary gland to the testicles, affecting normal testosterone production. A pituitary tumor or other type of brain tumor located near the pituitary gland may cause testosterone or other hormone deficiencies. Also, the treatment for a brain tumor such as surgery or radiation therapy may impair pituitary function and cause hypogonadism.
- Inflammatory disease. Certain inflammatory diseases such as sarcoidosis, histiocytosis, tuberculosis and some fungal infections involve the hypothalmus and pituitary gland and can affect testosterone production, causing hypogonadism.
- HIV/AIDS. This virus can cause low levels of testosterone by affecting the hypothalamus, the pituitary and the testes.
- Medications. The use of certain drugs, such as opiate pain medications and some hormones, can affect testosterone production.
- Obesity. Being significantly overweight at any age may be linked to hypogonadism.

RISK FACTORS

Hypogonadism can be inherited. Other risk factors for hypogonadism include:

- Kallmann syndrome
- Undescended testicles as an infant
- Mumps infection affecting your testicles
- Injury to your testicles
- Testicular or pituitary tumors
- HIV/AIDS
- Klinefelter's syndrome
- Hemochromatosis
- Previous chemotherapy or radiation therapy.

TESTS AND DIAGNOSIS

Doctors may test blood levels of testosterone if a patient has any of the signs or symptoms of hypogonadism. Early detection in boys can help prevent problems from delayed puberty. Early diagnosis and treatment in men offers better protection against osteoporosis and other related conditions.

Doctors base a diagnosis of hypogonadism on symptoms and results of blood tests that measure testosterone levels. Because testosterone levels vary and are generally highest in the morning, blood testing is usually done early in the day.

If tests confirm low testosterone, further testing can determine if a testicular disorder or a pituitary abnormality is the cause. Based on specific signs and symptoms, additional studies can pinpoint the cause. These studies may include:

- Hormone testing
- Semen analysis
- Pituitary imaging
- Genetic studies
- Testicular biopsy

Testosterone testing also plays an important role in managing hypogonadism by helping determine the right dosage of medication, both initially and over time.

TREATMENTS AND DRUGS

Adults

Treatment for male hypogonadism depends on the cause and whether you're concerned about fertility.

- Testosterone Replacement Therapy. For hypogonadism caused by testicular failure, doctors use male hormone replacement (TRT). TRT can restore sexual function and muscle strength and prevent bone loss. In addition, men receiving TRT often experience an increase in energy, sex drive and sense of well-being.
- If a pituitary problem is the cause, pituitary hormones may stimulate sperm production and restore fertility. TRT can be used if fertility isn't an issue. A pituitary tumor may require surgical removal, medication, radiation or the replacement of other hormones.
- Assisted reproduction. Although there's often no effective treatment to restore fertility in a man with primary hypogonadism, assisted reproductive technology may be helpful. This technology covers a variety of techniques designed to help couples who have been unsuccessful in achieving conception.

Boys

- Testosterone replacement therapy (TRT). In boys, TRT can stimulate puberty and the development of secondary sex characteristics, such as increased muscle mass, beard and pubic hair growth, and growth of the penis. Pituitary hormones may be used to stimulate testicle growth. An initial low dose of testosterone with gradual increases may help to avoid adverse effects.

Types of Testosterone Replacement Therapy

Several testosterone delivery methods exist. Choosing a specific therapy depends on your preference of a particular delivery system, the side effects and the cost. Methods include:

- Injection. Testosterone injections are safe and effective. Injections are given in a muscle about every two weeks. Your symptoms may come and go between doses. You or a family member can learn to give TRT injections at home. If you're uncomfortable giving yourself injections, a nurse or doctor can give the injection.
- Patch. A patch containing testosterone (Androderm) is applied each night to your back, abdomen, upper arm or thigh. The site of the application is rotated to maintain seven-day intervals between applications to the same site to lessen skin reactions.
- Gel. You rub testosterone gel (AndroGel, Testim) into your skin on your lower abdomen, upper arm or shoulder. As the gel dries, your body absorbs testosterone through your skin. Gel application of testosterone replacement therapy appears to cause fewer skin reactions than patches do. Don't shower or bathe for several hours after a gel application to be sure it gets absorbed. A potential side effect of the gel is the possibility of transferring the medication to your partner. You can avoid this by avoiding skin-to-skin contact until the gel is completely dry or by covering the area after an application.
- Gum and cheek (buccal cavity). Striant, a small putty-like substance, delivers testosterone through the natural depression above your top teeth where your gum meets your upper lip (buccal cavity). This product quickly sticks to your gumline and, as exposed to saliva, softens into a gel-like form, allowing testosterone to be absorbed into your bloodstream. Side effects may include gum irritation or pain, bitter taste or headache.
- Oral. Taking testosterone orally is not recommended for long-term hormone replacement. Testosterone taken by mouth may cause liver problems, raise your cholesterol and increase your risk of heart disease.