KLINEFELTER SYNDROME

Klinefelter's Syndrome, Ks, Xxy Male, Xx Male, Xxxy Male, XXXy Male, XXXxy Male

The set of symptoms that result from two or more X chromosome in males.

About Klinefelter syndrome

The term Klinefelter syndrome (KS) describes a group of chromosomal disorders in which there is at least one extra X chromosome to a normal male karyotype, 46,XY.

XXY aneuploidy is the most common disorder of sex chromosomes in humans, with prevalence of one in 500 males. Klinefelter syndrome is not inherited; it usually occurs as a random event during the formation of reproductive cells, it is called nondisjunction, and it results in a reproductive cell with an abnormal number of chromosomes. In this case containing an extra X chromosome.

Some males with Klinefelter syndrome have the extra X chromosome only in some of their cells (mosaic Klinefelter syndrome). In addition, 46,XX males also exist and it is caused by translocation of Y material including sex determining region (SRY) to the X chromosome during paternal meiosis. Formal cytogenetic analysis is necessary to make a definite diagnosis, and more obvious differences in physical features tend to be associated with increasing numbers of sex chromosomes. However, Klinefelter syndrome is usually underdiagnosed, with an estimated 25% of the expected number of patients being ever diagnosed, and only a minority being diagnosed in childhood. If the diagnosis is not made prenatally, 47,XXY males may present with a variety of subtle clinical signs that are age-related.

As babies and children, XXY males may have weaker muscles and reduced strength. Also they have hypospadias, small phallus or cryptorchidism and developmental delay. As they grow older, they tend to become taller than average. They may have less muscle control and coordination than other boys of their age. The older child or adolescent may be discovered during an endocrine evaluation for delayed or incomplete pubertal development with eunuchoid body habitus, gynecomastia, and small testes. These boys do not produce as much testosterone as other boys, they have a less muscular body, less facial and body hair, and broader hips. As teens, XXY males also have weaker bones, and a lower energy level than other males.

By adulthood, XXY males look similar to males without the condition, although they are often taller. In adults, possible characteristics vary widely and include little to no sign of affectedness, a lanky, youthful build and facial appearance, or a rounded body type with some degree of gynecomastia (increased breast tissue) or breast malignancy. Gynecomastia is present to some extent in about a third of affected individuals, a slightly higher percentage than in the XY population. About 10% of XXY males have gynecomastia noticeable enough that they may choose to have cosmetic surgery.
Affected males are often infertile, or may have reduced fertility. Advanced reproductive assistance is sometimes possible.

The term hypogonadism in XXY symptoms is often misinterpreted to mean "small testicles" or "small penis". In fact, it means decreased testicular hormone/endocrine function. Because of this (primary) hypogonadism, individuals will often have a low serum testosterone level but high serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. Despite this misunderstanding of the term, however, it is true that XXY men may also have microorchidism (i.e., small testicles).

XXY males are also more likely than other men to have certain health problems that typically affect females, such as autoimmune disorders, breast cancer, venous thromboembolic disease, and osteoporosis. In contrast to these potentially increased risks, it is currently thought that rare X-linked recessive conditions occur less frequently in XXY males than in normal XY males, since these conditions are transmitted by genes on the X chromosome, and people with two X chromosomes are typically only carriers rather than affected by these X-linked recessive conditions.

Some degree of language learning or reading impairment may be present, and neuropsychological testing often reveals deficits in executive functions, although these deficits can often be overcome through early intervention. There may also be delays in motor development which can be addressed through occupational therapy and physical therapy. XXY males may sit up, crawl, and walk later than other infants; they may also struggle in school, both academically and with sport.

**Associated diseases**

Risk of acquiring breast carcinoma in 47,XXY is relatively increased, with relative risk exceeding 200 times. The cause may result from the estradiol to testosterone ratio being severalfold higher than that of karyotypically normal men or possibly due to an increased peripheral conversion of testosterone to estradiol in men with Klinefelter syndrome.

Associated endocrine complications include diabetes mellitus, hypothyroidism, and hypoparathyroidism. Autoimmune diseases, such as systemic lupus erythematosus, Sjogren syndrome, and rheumatoid arthritis, are more common in Klinefelter syndrome, with frequencies similar to those found in 46,XX females. Development of varicose veins and leg ulcers may result from venous stasis. Decreased bone density occurs in 25% of patients with Klinefelter syndrome, possibly reflecting the impact of decreased bone formation, increased bone resorption and/or hypogonadism.

**Complication**

- delayed puberty
- learning disabilities
- infertility, osteoporosis
- problems with blood vessels
- increased risk of breast cancer
- lung disease
- autoimmune disorders

**Risk factors**

Klinefelter syndrome usually occurs randomly. An older mother might increase the risk slightly.
Although most patients with Klinefelter syndrome are infertile, there have been a few patients with reports of pregnancy without assisted medical technology, typically in mosaic cases. With the introduction of intracytoplasmic sperm injection, which involves the use of sperm extraction from deep within the testicles of patients with non-mosaic Klinefelter syndrome, some XXY men will have an increased chance of fathering a child. A study of 42 men with Klinefelter syndrome revealed that the sperm retrieval rate was 72% per testicular sperm extraction attempt, and 69% (29 of 42 men) had adequate sperm found using intracytoplasmic sperm injection. Thus, testicular sperm extraction and intracytoplasmic sperm injection may be considered in males with azoospermia and Klinefelter syndrome.

**Prevention**

Klinefelter syndrome cannot be prevented. This genetic disorder occurs randomly, but can be diagnosed very soon i.e. during preimplantation genetic screening of early embryo.

**Symptoms**

- microorchidism, or under-developed testes
- gynecomastia, or female-type development of breast tissue
- risk of developing breast cancer: at least twenty times higher than normal
- long arms and legs
- large hands and feet
- short trunk
- less than normal facial, body, and pubic hair
- pubic hair is distributed in same manner as women
- infertility
- erectile dysfunction
- wider hips
- shoulders equal length with hips
- decreased libido
- high pitched voice
- taurodontism, or enlarged molars
- slightly increased risk of autoimmune disorder
- mild developmental, learning, and behavioral difficulties
- delayed speech and language acquisition
- academic and reading difficulties
- attention deficit disorder
- poor self-esteem
- insecurity
- shyness
- poor judgment
- inappropriate assertive activity
- decreased ability to deal with stress
- fatigue
- weakness
- normal intelligence in most cases
- subnormal intelligence or mental retardation associated with a higher number of X chromosomes
- diminished short term memory
- prone to epilepsy and essential tremor
- psychiatric disorders involving anxiety, depression, neurosis, and psychosis: more common than general population

**Therapies**

**Self therapy**
There is no self-therapy of infertile men with Klinefelter syndrome, but there are many ways to treat the symptoms of the XXY condition.

**Educational treatments**
As children, many XXY males qualify for special services to help them in school. Teachers can also help by using certain methods in the classroom, such as breaking bigger tasks into small steps.

**Other therapeutic options**
A variety of therapists, such as physical, speech, occupational, behavioural, mental health, and family therapists, can often help reduce or eliminate some of the symptoms of the XXY condition, such as poor muscle tone, speech or language problems, or low self-confidence.

**Conventional medicine**

**Pharmacotherapy**
The age for testosterone replacement in these patients is controversial, yet clear clinical and biochemical signs of hypoandrogenism are an undisputed indication for the initiation of androgen therapy. Androgen replacement therapy should begin at puberty, around age 12 years, in increasing dosage sufficient to maintain age appropriate serum concentrations of testosterone, estradiol, follicle stimulating hormone (FSH), and luteinizing hormone (LH).

**Surgical therapy**
There is no surgical therapy for this condition.

**Assisted reproduction**
Their ejaculate is usually azoospermic, and levels of testosterone are typically low to low-normal. A major advancement in recent years has been the introduction of IVF with ICSI which allows successful fertilization even with immature sperm or sperm obtained directly from testicular tissue. IVF-ICSI allows for pregnancy in couples where the man has irreversible testicular azoospermia as long as it is possible to recover sperm material from the testes. Thus men with non-mosaic Klinefelter’s syndrome have fathered children using IVF-ICSI. Pregnancies have been achieved in situations where azoospermia was associated with cryptorchism and sperm where obtained by testicular sperm extraction (TESE).

**Find more about related issues**

**Diagnoses**

**Azoospermia**
Complete absence of sperm in the ejaculate of a man.
Learn more at: [www.fertilitypedia.org/therapy/diag/azoospermia](http://www.fertilitypedia.org/therapy/diag/azoospermia)

**Erectile dysfunction**
The inability (that lasts more than 6 months) to develop or maintain an erection of the penis during sexual activity.
Learn more at: [www.fertilitypedia.org/therapy/diag/erectile-dysfunction](http://www.fertilitypedia.org/therapy/diag/erectile-dysfunction)

**Undescended testes**
In the case of cryptorchidism one or both testes are absent from the scrotum. It is is the most common etiologic factor of azoospermy in the adult.
Learn more at: [www.fertilitypedia.org/therapy/diag/undescended-testes](http://www.fertilitypedia.org/therapy/diag/undescended-testes)
Thyroid disorders
A medical condition impairing the function of the thyroid.
Learn more at: www.fertilitypedia.org/therapy/diag/thyroid-disorders

Non-obstructive azoospermia
Complete absence of sperm in the ejaculate due to testicular failure.
Learn more at: www.fertilitypedia.org/therapy/diag/non-obstructive-azoospermia

Oligozoospermia
Semen with a low concentration of sperm and is a common finding in male infertility.
Learn more at: www.fertilitypedia.org/therapy/diag/oligozoospermia

Hypogonadism
A medical term which describes a diminished functional activity of the gonads – the testes and ovaries.
Learn more at: www.fertilitypedia.org/therapy/diag/hypogonadism

Lupus erythematosus
Collection of autoimmune diseases in which the human immune system becomes hyperactive and attacks normal, healthy tissues.
Learn more at: www.fertilitypedia.org/therapy/diag/lupus-erythematosus

Sertoli cell-only syndrome
The absence of any developmental stage of sperm cell in the testes.
Learn more at: www.fertilitypedia.org/therapy/diag/sertoli-cell-only-syndrome

Hypoandrogenism
A medical condition characterized by not enough androgenic activity in the body.
Learn more at: www.fertilitypedia.org/therapy/diag/hypoandrogenism

Breast cancer
A cancer that develops from breast tissue.
Learn more at: www.fertilitypedia.org/therapy/diag/breast-cancer

Rheumatoid arthritis
A long-term autoimmune disorder that primarily affects joints.
Learn more at: www.fertilitypedia.org/therapy/diag/rheumatoid-arthritis

Organs

Hypothalamus
A region of the forebrain that regulates body temperature, some metabolic processes and governs the autonomic nervous system.
Learn more at: www.fertilitypedia.org/edu/organs/hypothalamus

Penis
External male sex organ that additionally serves as the urinal duct.
Learn more at: www.fertilitypedia.org/edu/organs/penis

Pituitary gland
An endocrine gland, about the size of a pea, whose secretions control the other endocrine glands and influence growth, metabolism, and maturation.
Learn more at: www.fertilitypedia.org/edu/organs/pituitary-gland
Seminiferous tubules
Tube structures within the testes where spermatogenesis occurs.
Learn more at: www.fertilitypedia.org/edu/organs/seminiferous-tubules

Testes
Male gonads which produce both sperm and androgens, such as testosterone, and are active throughout the reproductive lifespan of the male.
Learn more at: www.fertilitypedia.org/edu/organs/testes

Reproductive cells

Spermatogonium
An undifferentiated male germ cell with self-renewing capacity representing the first stage of spermatogenesis.
Learn more at: www.fertilitypedia.org/edu/reproductive-cells/spermatogonium

Biological control

Gonadotropin-releasing hormone
A releasing hormone responsible for the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary.
Learn more at: www.fertilitypedia.org/edu/biological-control/gonadotropin-releasing-hormone

Luteinizing hormone
A hormone, that stimulates ovulation and the development of the corpus luteum in females, and the production of androgens in males.
Learn more at: www.fertilitypedia.org/edu/biological-control/luteinizing-hormone

Progesterone
Steroid hormone, secreted by the ovaries, whose function is to prepare the uterus for the implantation of a fertilized ovum and to maintain pregnancy.
Learn more at: www.fertilitypedia.org/edu/biological-control/progesterone

Risk factors

High level of FSH
It is a condition with high serum FSH concentration.
Learn more at: www.fertilitypedia.org/therapy/rf/high-level-of-fsh

Low level of testosterone
An abnormally low testosterone production which may occur because of testicular or hypothalamic-pituitary dysfunction.
Learn more at: www.fertilitypedia.org/therapy/rf/low-level-of-testosterone

Symptoms

Abnormal sperm morphology
A normal sperm morphology of less than 4% of sperms in an ejaculate.
Learn more at: www.fertilitypedia.org/edu/symptoms/abnormal-sperm-morphology

Absence of sperm in ejaculate
The medical condition of a man whose semen contains no sperm.
Learn more at: www.fertilitypedia.org/edu/symptoms/absence-of-sperm-in-ejaculate
**Decreased level of testosterone**
Testosterone levels lower than the reference ranges.
Learn more at: [www.fertilitypedia.org/edu/symptoms/decreased-testosterone-level](http://www.fertilitypedia.org/edu/symptoms/decreased-testosterone-level)

**Delayed puberty**
An organism has passed the usual age of onset of puberty with no physical or hormonal signs.
Learn more at: [www.fertilitypedia.org/edu/symptoms/delayed-puberty](http://www.fertilitypedia.org/edu/symptoms/delayed-puberty)

**Developmental delay**
When a child takes longer than other children of the same age to reach expected milestones in movement, behaviour and learning.
Learn more at: [www.fertilitypedia.org/edu/symptoms/developmental-delay](http://www.fertilitypedia.org/edu/symptoms/developmental-delay)

**Gynecomastia**
A disorder of the endocrine system in which there is a non-cancerous swelling of the breast tissue in boys or men.
Learn more at: [www.fertilitypedia.org/edu/symptoms/gynecomastia](http://www.fertilitypedia.org/edu/symptoms/gynecomastia)

**Hypospadias**
A birth defect of the urethra in the male where the urinary opening is not at the usual location on the head of the penis.
Learn more at: [www.fertilitypedia.org/edu/symptoms/hypospadias](http://www.fertilitypedia.org/edu/symptoms/hypospadias)

**Immobile or dead spermatozoa in semen**
A condition in which spermatozoa in semen are either immobile or dead.
Learn more at: [www.fertilitypedia.org/edu/symptoms/immobile-or-dead-spermatozoa-in-semen](http://www.fertilitypedia.org/edu/symptoms/immobile-or-dead-spermatozoa-in-semen)

**Impaired muscle and beard development**
Reduced body hair and loss of muscle mass in males.
Learn more at: [www.fertilitypedia.org/edu/symptoms/impaired-muscle-and-beard-development](http://www.fertilitypedia.org/edu/symptoms/impaired-muscle-and-beard-development)

**Increased level of FSH**
A condition with high serum follicle-stimulating hormone (FSH) concentration.
Learn more at: [www.fertilitypedia.org/edu/symptoms/increased-level-of-fsh](http://www.fertilitypedia.org/edu/symptoms/increased-level-of-fsh)

**Infertility**
The failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.
Learn more at: [www.fertilitypedia.org/edu/symptoms/infertility](http://www.fertilitypedia.org/edu/symptoms/infertility)

**Lack of semen with ejaculation**
Aspermia is the complete lack of semen with ejaculation.
Learn more at: [www.fertilitypedia.org/edu/symptoms/lack-of semen-with-ejaculation](http://www.fertilitypedia.org/edu/symptoms/lack-of semen-with-ejaculation)

**Low concentration of sperm**
A condition refers to semen with a low concentration of sperm.
Learn more at: [www.fertilitypedia.org/edu/symptoms/low-concentration-of-sperm](http://www.fertilitypedia.org/edu/symptoms/low-concentration-of-sperm)

**Low facial and body hair growth**
Decrease of facial and body hair in males.
Learn more at: [www.fertilitypedia.org/edu/symptoms/low-facial-and-body-hair-growth](http://www.fertilitypedia.org/edu/symptoms/low-facial-and-body-hair-growth)

**Low semen volume**
A condition in which a man has an unusually low ejaculate (or semen) volume, less than 1.5 ml.
Learn more at: [www.fertilitypedia.org/edu/symptoms/low-semen-volume](http://www.fertilitypedia.org/edu/symptoms/low-semen-volume)
Reduced sperm motility
The decreased ability of sperm cell to move progressively.
Learn more at: www.fertilitypedia.org/edu/symptoms/reduced-sperm-motility

Small penis
An adult penis with an erect length of less than 7 cm or 2.76 inches.
Learn more at: www.fertilitypedia.org/edu/symptoms/small-penis

Small testes
Abnormally small testicular volume.
Learn more at: www.fertilitypedia.org/edu/symptoms/small-testes

Therapies

Egg donation
Process by which a woman donates eggs for purposes of assisted reproduction or biomedical research.
Learn more at: www.fertilitypedia.org/edu/therapies/egg-donation

ICSI
A micromanipulative fertilization technique in which a single sperm is injected directly into an egg.
Learn more at: www.fertilitypedia.org/edu/therapies/icsi

Micro TESE
Microsurgical method used to identify areas of sperm production within the testes with the aid of optical magnification.
Learn more at: www.fertilitypedia.org/edu/therapies/micro-tese

Pharmacotherapy of Klinefelter
Hormonal therapy, which is used as an adjuvant treatment of Klinefelter syndrome.
Learn more at: www.fertilitypedia.org/edu/therapies/pharmacotherapy-of-klinefelter

Preimplantation genetic screening
The term PGS is used to denote procedures that do not look for a specific disease but to identify embryos at risk of de-novo occurring aneuploidies
Learn more at: www.fertilitypedia.org/edu/therapies/preimplantation-genetic-screening-1

Sperm donation
The procedure in which a man (sperm donor) provides his sperm for fertility treatment.
Learn more at: www.fertilitypedia.org/edu/therapies/sperm-donation

Standard IVF
A process in which an egg is fertilised by sperm outside the body: in vitro. Own or donated gametes may be used.
Learn more at: www.fertilitypedia.org/edu/therapies/standard-ivf

TESE
Removal of a small portion of testicular tissue in order to extract a few viable sperm.
Learn more at: www.fertilitypedia.org/edu/therapies/tese
There is one Y chromosome and two X chromosomes - one is extra.

A person with typical untreated (surgery/hormones) Klinefelter 46,XY/47,XXY mosaic, diagnosed at age 19.

Sources

“Klinefelter syndrome” —sourced from Wikipedia licensed under CC BY-SA 3.0
“Klinefelter syndrome and other sex chromosomal aneuploidies” —by Visootsak and Graham licensed under CC BY 2.0

“Clinical Presentation of Klinefelter’s Syndrome: Differences According to Age” —by Pacenza et al. licensed under CC BY 3.0

“Klinefelter’s syndrome” —by Ariana and Jongin licensed under CC BY-SA 3.0

“Azoospermia” —sourced from Wikipedia licensed under CC BY-SA 3.0

“Human karyotype” —by Nami-ja licensed under CC0

“Man with Klinefelter syndrome” —by Gin licensed under CC BY-SA 3.0