

Understanding Klinefelter's or XXY Syndrome (KS)



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What is Klinefelter's or XXY Syndrome (KS)?

Klinefelter's Syndrome is a sex chromosome variation occurring in 1 in every 650 males. It is a random genetic disorder that is not hereditary.

Klinefelter's Syndrome is also known as XXY syndrome.

Normally, males have one X and one Y chromosome in their cells. Males affected with KS have at least one additional X chromosome.

In KS males the extra chromosome impacts their:

- Bone strength
- Breast size
- Energy level
- Hair growth
- Height
- Fertility
- Hip girth
- Language development
- Learning
- Muscle mass
- Social development
- Thought processes

Only 25-30% of males with KS are actually ever diagnosed. Often diagnosis is made when investigating infertility issues in couples. Early diagnosis and management at around the time of puberty can have a profoundly positive impact of the long-term physical, mental and reproductive health of boys with KS.

Not all men with KLINEFELTER SYNDROME are 100% infertile. Intracytoplasmic sperm injection can produce a child – see page 11.

Klinefelter's syndrome is also known as XXY syndrome.

Recognising KS

Klinefelter's Syndrome is a disorder that has high variability in the physical signs and symptoms associated with the condition.

Because some of the physical symptoms are subtle or not present only 30-40% of KS males fit the stereotypical KS "image". In part, this accounts for the high percentage of KS men that are never diagnosed during their lifetime. Often KS children are managed for learning, behavioural, motor skills, developmental and speech difficulties when the underlying reason for these problems remains unidentified.

Young children and pre-pubescent KS boys are especially difficult to recognise and it is only at puberty and during their teens that the signs of KS become more easily recognisable. The key physical characteristic common to almost all teenage and adult KS males is very small under-developed testicles

Babies and Toddlers

A geneticist can diagnose KS before your son is born through a foetal cytogenetic analysis.

Your paediatrician may suspect Klinefelter's syndrome if your infant son has:

- Undescended testicles (cryptorchidism)
- Hypospadias (urine dribbles out of an opening on the underside of his penis)

In 25% of boys, there is a telltale condition called clinodactyly, where the little finger curves toward the ring finger because the middle bone is wedge-shaped instead of rectangular.

However, 75% of boys with KS will develop normal height and weight until they reach age four or five.

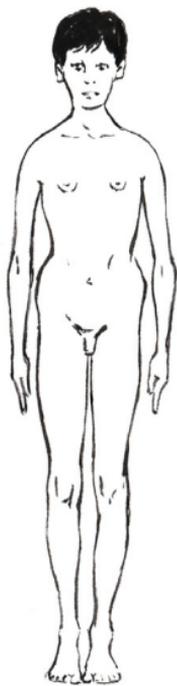
School-Age Boys

Your doctor may investigate your school-age son for KS if he has this characteristic appearance:

- Tall stature
- Knock-knees (genu valgum)
- High arches (pes cavus)

You may ask your doctor to investigate your son for Klinefelter's syndrome if he has some of these characteristics.

- Above average height
- Attention Deficit Hyperactivity Disorder (ADHD)
- A learning disability (especially dyslexia, reading difficulties, and/or data retrieval problems)
- A mild intellectual disability
- Poor expressive and receptive language skills
- Taurodontism (enlarged molar teeth)
- Rudimentary breast development



Typical KS Boy

Puberty

Your doctor may suspect Klinefelter's syndrome when a boy reaches puberty if he has:

- Small testicles (volume less than 4ml)
- A high-pitched voice

- A sparse beard and sparse body hair
- Gynecomastia (enlarged breasts)
- Feminine fat distribution
- Disproportionately long arms and legs compared to body length
- Taller than average height
- Taurodontism (enlarged molar teeth)

If your doctor suspects your son has the Klinefelter's syndrome, he will likely order the following blood tests to determine levels of:

- FSH (follicle stimulating hormone)
- LH (luteinizing hormone)
- Oestradiol
- Testosterone
- Karyotype (a genetic test)

If diagnosed, experts recommend explaining to your affected child he has Klinefelter's syndrome when he reaches his mid-to-late teens. By then, he should be mature enough to better understand its implications.

Adult Men

Most men with Klinefelter's Syndrome do not exhibit overt symptoms beyond what is displayed from puberty onwards. You may first notice a problem if you experience:

- Lack of libido
- Low sexual motivation
- Erectile difficulties



Adult KS Male

- Infertility
- Varicose veins that tend to ulcerate or clot (thrombosis)
- Mitral valve prolapse (heart)
- Poor self-esteem
- Psychological distress

KS Facts

- Females do not develop Klinefelter's Syndrome
- KS does not occur more in one race than any other
- KS does not affect a male's lifespan greatly (possible one to two year reduction)
- 75% of males with KS are undiagnosed until adulthood, when they have reproductive problems
- Older mothers are more likely to have a KS child
- KS is the most common numerical chromosomal disorder in males
- 63-85% of KS males have decreased testosterone levels from adolescence onwards
- 70% of men with KS experience erectile dysfunction by 25 years of age
- 10-39% of KS adults develop diabetes
- 64% of KS boys are taller than genetically expected
- 40% of KS men have osteopenia and 10% have osteoporosis. They are more at risk of bone fracture.
- >95% of adolescents and adults KS men have small testes (less than 4ml, grape size or smaller)
- 99% of adolescent and adult KS men are infertile
- 33% of KS boys experience psychosocial issues especially shyness
- 27% of KS boys have an attention deficit disorder

- 76% of KS boys experience some learning difficulties
- 64% of KS boys are taller than genetically expected

What Are The Variants of KS?

- 80% – 90% of affected males have 47,XXY (one additional X chromosome). Most boys with the 47, XXY karyotype have normal intelligence.
- 10% have mosaicism (46,XY/47,XXY). Men with Klinefelter's syndrome mosaicism are often fertile and can father a child through modern technology.
- Very rare and more serious variants are 48,XXYY; 48,XXXYY; 49,XXXYY; 49,XXXXY; 47,X,i(Xq)Y and 47,X,del(X)Y). Boys with these rare variants have intellectual disabilities that increases with more X chromosomes.

What Causes KS?

Klinefelter's syndrome occurs after the mother's egg is fertilized. Chromosome pairs are supposed to separate, ensuring two daughter cells receive one chromosome each. In KS, the pair does not disjoin (separate). Both of the chromosomes in the pair go to one daughter cell. The other daughter cell receives none.

This happens more frequently in older mothers, and is called meiotic nondisjunction.

As a result of this genetic problem, the KS baby develops an abnormal pituitary gland, testicles, and hypothalamus portion of the brain. The boy's testicles degenerate, so they cannot produce enough sperm in later life. Nor can they produce sufficient amounts of the hormone testosterone at puberty to stimulate normal male physical appearance and development. Healthy tissue is replaced by clear, glassy collagen fibers, called hyaline. The

boy has scar tissue (fibrosis) in his seminiferous tubules, where his sperm form. Feminine breasts develop in late puberty for 50% of KS adolescents. Tests show elevated gonadotropin levels, which mean the male is sterile. Psychosocial problems and low self-esteem result from the feminising effects of the hormone oestradiol.

In 1942 Dr. Harry Klinefelter discovered the syndrome while working with nine male patients at Massachusetts General Hospital in Boston. The actual genetics were worked out later, from 1956 to 1959 by doctors Joe Hin Tjio, Albert Lavan, and Patricia Jacobs.

What Are The Treatment Options?

Boys with KS do not need a special diet or to restrict their activities. Hospital care is not required. Treatment is on an out-patient basis.

The hormone testosterone is the treatment choice for Klinefelter's syndrome. Gradually testosterone will virilise the boy giving him male secondary sex characteristics like a beard, body hair, and a male-pattern fat distribution.

If KS is identified early, at around the age of 12 years old the doctor will commence your son on testosterone supplementation. In Australia testosterone treatment options include injections, patches, gels, solutions and creams.



Testosterone Molecule and Esters

Testosterone injections come in two forms, short and long acting versions. In general the testosterone found in injections is in the form of an 'ester'. By adding an ester to the testosterone molecule it becomes less soluble in water and more soluble in oil, this in turn slows its release into the bloodstream once injected. Esters that are less soluble in oil are referred to as 'short' acting injections and those more soluble in oil are 'long' acting injections.

Injection treatment for boys often begins with a 50mg short acting dose on a monthly basis. The doctor will closely monitor the growth and development of male secondary sex characteristics and check the gonadotropin hormone levels.

In years past, adult males with KS visited the doctor every two or three weeks to receive an intramuscular injection of 200-250 mg of testosterone enanthate or cypionate. Alternatively patients could receive testosterone implants on a six monthly basis. More recently, long acting injections, gels, solutions and creams have replaced short acting injections due to their patient-friendly mode of application and flexibility with regards to dose.

A 1% gel, 2% solution and a 5% testosterone cream are applied to the skin, usually the upper body – back, chest, torso, inner and upper arms. Patients are required to wear covered clothing on the site of application to avoid passive transfer of residual testosterone to the skin of other people.

A 2% testosterone cream is available for scrotal application. Because scrotal skin is thinner, has a lesser fat content and a higher blood flow compared to upper body skin absorption of testosterone is much higher. Additionally, this significantly lowers the risk of transfer to partners and children.

Testosterone skin patches provide physiological testosterone

replacement. Night-time application leads to a pattern of circulating concentration similar to what is normally seen in healthy males. Patches must be applied daily and there is a relatively high incidence of skin reactions which may be sufficiently severe to lead to discontinuation of use. Dosage adjustments can be difficult as patches are a fixed dose and must not be cut.

Oral testosterone capsules are a less favoured replacement option. They can have wide fluctuations in circulating concentrations due to erratic absorption, and sometimes gastrointestinal intolerance. The use of oral testosterone is generally confined to patients who are intolerant of other preparations.

Seeking Medical Assistance

Your family doctor is generally the first point of contact if Klinefelter's syndrome is suspected in boys. Men who have not previously been identified as having KS often are diagnosed as part of a couples fertility treatment. A key distinguishing feature of KS is very small testicles in teenage boys and men. Diagnosis of testicular size can be undertaken with the aid of an orchidometer. This is a tool that doctors use to measure the volume of the testes. In KS adolescents and adults testicular volume is generally always less than 4ml.



Once your doctor suspects KS you may also benefit from consulting with these specialists as early detection and intervention is beneficial.

Geneticist: A geneticist can diagnose KS before a child is born through a foetal cytogenetic analysis. A genetic counsellor may help explain Klinefelter's syndrome thoroughly to a KS boy.

Endocrinologist: A hormone specialist can regularly monitor the effectiveness of the testosterone replacement therapy. The endocrinologist will order blood tests for testosterone, FSH, LH, and oestradiol. The endocrinologist may order an echocardiogram for mitral valve prolapse, x-rays, and a bone density test for osteoporosis.

Physiotherapist (PT): KS boys may have weaker muscles (hypotonia) and slower reflexes. As a result he may seem less coordinated and more clumsy than his peers and also have poor posture. A physiotherapist can help strengthen muscles and improve coordination.

Speech Therapist: A KS boy may require help to understand complex language before he starts school. Ask your family physician for a referral to a speech therapist.

Occupational Therapist (OT): Some KS boys have motor dyspraxia, a nervous system disorder where he has difficulty planning and executing complex movements and tasks. Obsolete terms for dyspraxia are clumsy child syndrome, congenital maladroitness, and sensory integration disorder. Dyspraxia often co-occurs with learning disabilities, dyslexia, and attention deficit disorder. An occupational therapist (OT) can help train affected boys to move with more coordination. The OT can fit the child with small, inconspicuous, and inexpensive assistive devices like pen grips.

Psychologist: Enlarged breasts and finding out about being infertile often places psychological stress on affected men and teenagers, so seek help from a psychologist familiar with Klinefelter's syndrome. Visit the Australian Psychological Society

at www.psychology.org.au/FindaPsychologist/ to find a local psychologist suitable for your needs.

Special Education: Get a thorough psychoeducational examination through your son's school or developmental paediatrician. The written evaluation you will receive lists your son's strengths and weaknesses, and recommends an appropriate classroom placement. A psychoeducational exam will list additional resources available in your area, so you can tailor your son's education.

Surgeon: You may want to consult a surgeon about mastectomy (breast removal) or reduction if breast enlargement is significant. Around 10% of XXY males have breast enlargement great enough to require surgery. Gynecomastia (enlargement of breast tissue in males) increases the chance of breast cancer.

Fertility Experts: Not all men with Klinefelter's syndrome are infertile. Some have oligospermia (low sperm production). If you wish to father a child and have a low sperm count, a fertility expert may be able to help. They can extract sperm directly from your testicles during a biopsy, choose a viable sperm, and inject it into a woman's egg. This process is called ICSI (intracytoplasmic sperm injection). The resulting child will not have a risk of developing Klinefelter's syndrome above that of the general population. If the specialist finds more than one viable sperm, you may choose to have them frozen for future pregnancies. While it is possible for men who have Klinefelter's syndrome to father a child via ICSI, the success rate is not high.

It is vitally important, especially in children and teenagers diagnosed with KS, that families seek or access support services such as psychology, physiotherapy, speech pathology, nutrition care, social services as well as medical support to assist with managing life with KS. In Australia there are no specialty KS clinics. In the USA, John Hopkins Medicine Klinefelter Clinic in Baltimore and Nemours/DuPont Hospital for Children eXtraordinary Kids

Clinic in Delaware are speciality whole health care centres dedicated to KS patient support.

Testosterone In Humans

Natural testosterone is a steroid hormone, normally produced by the Leydig cells in the testes of men, and the ovaries and adrenal glands in women.

Testosterone is classified as an androgen (masculinizing substance). Androgens control masculine secondary sex characteristics, like male hair growth patterns (beard, armpits, chest and groin), deep voice, and male fat distribution. It is crucial for the development and maintenance of the male sex organs (testes and penis), other benefits include;

- Testosterone is the primary hormone responsible for sexual function, sexual motivation, sexual arousal and fantasy in men of all ages
- Testosterone is responsible for maintaining muscle mass and muscle strength
- Testosterone plays a pivotal role in bone metabolism. It slows bone loss and builds replacement bone
- Testosterone exerts a strong influence on mood, energy levels and concentration

Testosterone Levels

Testosterone production increases when a boy enters puberty. A good testosterone target range for an adult male with KS to maintain is 10-35nmol/L (300-1250ng/dL) of blood serum. Ideally the supplemented testosterone level should be mid-normal range.

The table below provides a guide to the “normal” ranges in men for the most common hormone components measured in blood.

These are guidelines only. Your laboratory adjusts its normal values for the local population it serves. It may use different units of measure.

		UNIT OF MEASURE	NORMAL ADULT MALE
Sex Hormones	GH	ng/mL	0 to 8
	FSH	mIU/mL	1.4 to 18.1
	LH	mIU/mL	1.5 to 9.3
	HCG	mIU/mL	0
	Progesterone	ng/mL	<1
	Oestradiol	pg/mL	<54
	Prolactin	ng/mL	< 20
	Testosterone	ng/dL	375 to 1,200 USA
		nmol/L	10 to 35 AUS
	Free testosterone	pg/mL	50-175 USA
	pmol/L	175-600 AUS	
SHBG	nmol/L	6 to 50	

Further Information

Further information about Klinefelter's syndrome can be found at the following websites.

www.andrologyaustralia.org

www.nichd.nih.gov - search 'KS Condition Information'

www.checkyourballs.com.au

www.AXYS.org.au

www.xxy47.co.za

klinefelter.jhu.edu

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