Klinefelter syndrome

A guide for the patient
with Klinefelter Syndrome

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The syndrome in brief


Birth and Infancy


My follow up


Childhood


My contacts


Puberty


Recommended tests


Young adult


My results


Adult


My treatment

The syndrome in brief

The syndrome in brief

Klinefelter syndrome (KS) is the set of signs or symptoms of men born with at least one extra X chromosome.

Chromosomes

Human cells usually contain 46 chromosomes (23 pairs), including 2 «sex chromosomes» (X and Y). We call them "sex chromosomes" because normally women have two X-chromosomes (46, XX) and men have one X and one Y chromosome (46, XY). Sometimes there is a problem with the number of chromosomes. There can be less than 46 or more than 46.

47, XXY

One possible problem is when a male has more than one X chromosome. In men with KS, 47, XXY is the most common chromosome number variation.

Consequences

Chromosomes contain genes. An extra X chromosome can cause genes to act (be expressed) differently. An extra X chromosome mainly affects the testes, which as a result do not develop and function normally. An extra X chromosome can also impact other body functions such as metabolism (how your body changes food to energy).

Frequency

Having an extra chromosome is not very uncommon. About 1 in 500-600 males have KS (47, XXY). KS is not passed on to children.

Signs and symptoms

The signs and symptoms of KS vary:

- tall stature with long arms/legs
- puberty that usually starts normally, but may be incomplete
- small testes
- low hormone (testosterone) levels
- difficulty to have children without medical therapy

Some boys and men have only subtle signs:

- learning difficulties (especially language) or attention problems
- feeling tired (fatigue)
- moody (irritability)
- anxiety
- lack of self-confidence

In most cases, KS is diagnosed during puberty or adulthood. We think that most men with KS (2 out of 3) are never diagnosed.

Diagnosis

KS diagnosis is made by testing the chromosomes (karyotype) and measuring hormone levels in the blood. A chromosome test can be done before birth or at any time during life.

Insurance

The costs for care and treatment are usually covered by health insurance. Depending on where you live, some special requests and forms must be completed.

Birth and Infancy

At birth,

At birth, a male with Klinefelter syndrome (KS) typically has normal weight, height, sleep, eating and behavior. Sometimes, one or both testes (testicles) are not descended in the scrotum (cryptorchidism) and the penis is unusually small (micropenis).

Karyotype

When the testes or penis are not normal, a test of chromosomes (karyotype) can be done to make a KS diagnosis.

Hormones

At 2-3 months of age, other tests can be done:

- hormones from the testes: testosterone , AMH (antimüllerian hormone) and Inhibin B
- hormones from the brain (pituitary gland) that control the testes: LH (luteinizing hormone) and FSH (follicle stimulating hormone)

Treatment

Testes that are not located in the scrotum can be fixed by surgery. It is best if surgery is done by the age of 2 years. If the penis is unusually small, testosterone can be given to increase the size.

Childhood

Many children with Klinefelter syndrome (KS) have normal intelligence and grow and develop normally.

Some children may have:

- delayed speech and language
- learning difficulty or problems understanding (comprehension)
- reading learning difficulties
- attention deficit disorder
- social problems (feel shy, reserved or insecure)
- problems with coordination

If these problems occur, speech therapy and extra school support can be very helpful.

Other signs can be:

- unusually long arms and legs.
- bones that are slow to mature (delayed bone maturation)
- curved spine (scoliosis)
- dental problems (the molars)

Treatment in Children and Teenagers

Puberty

Puberty starts when the pituitary gland (in the brain) starts making hormones (LH and FSH) that stimulate the testes. The testes will grow and start to make hormones (testosterone) and sperm (spermatozoa). However, in males with Klinefelter syndrome (KS) the testes do not develop normally.

Males with KS may have:

- firm testes (about the size of a hazelnut in its shell) that stay small (4-6 ml)
- low male hormones (testosterone)
- low sperm and fertility problems (infertility) in adulthood

Sometimes other signs occur. These may include:

- late (delayed) or incomplete puberty
- low muscle mass
- increased fat mass
- little facial and body hair
- low bone mass (osteoporosis)
- unusual body proportions (tall height, large arm span)
- gynecomastia (breast development)
- reading learning difficulties
- problems with body image or low self-esteem

Treatment in Children and Teenagers

Young adult

Young adulthood (16 to 25 years-old) is a time when many changes occur:

- increased independence
- increased role of peers
- sense of one's body (body image)
- sense of one's identity
- developing sexuality

This period from 16-25 years is often called "transition". It describes the change from childhood to adulthood.

Young adults with Klinefelter syndrome (KS) benefit from care by different types of providers (a multidisciplinary team) including:

- family physician (primary care)
- pediatric / adult endocrinologists
- fertility specialist (urologist)
- speech therapist
- geneticist
- behavioral health specialist / psychologist / psychiatrist
- support groups

Treatment in Children and Teenagers

Adult

Adult

With proper treatment, men with Klinefelter syndrome (KS) can lead a pretty normal life. Regular medical appointments are important because men with KS have increased risk for certain health problems including:

- feeling frustrated or distressed (e.g., anxiety, depression)
- excess fat around the belly. Being overweight or obese increases the risk of other health problems of the blood vessels (e.g., atherosclerosis) and how your body changes food to energy (e.g., type 2 diabetes)
- weak, fragile bones (osteoporosis)
- dental problems (taurodontism)
- curved spine (scoliosis)
- blood clots in the legs (thrombosis)
- autoimmune diseases (e.g., lupus, rheumatoid arthritis, thyroid disorders)
- Rarely: increased cancer risk (e.g., breast, blood, bone marrow or lymph nodes).

Fertility problems are covered in a different section.

Treatment in Adults

Treatment in Children and teenagers

A balanced diet and regular physical activity are recommended for all males with Klinefelter syndrome (KS). Regular medical and dental visits are also important. Most children and teens do not need a specific therapy. Instead, care should be tailored to individual needs and may include:

- additional support at school (e.g., special education, tutors)
- discussing concerns about body-image or self-esteem with caregivers or a behavioral health specialist.

Most teens with KS will start puberty normally.

Some boys will need testosterone replacement therapy (TRT). TRT is used to help develop muscles, signs of puberty (e.g., facial hair, deepening of voice) and sexual function (erections), but will not make the testes grow in size. TRT is also very important for bone health and may increase energy and indurance. Regular doctor visits are important to monitor TRT.

Treatment in adults

Hormonal treatment in adults

Most adult men with KS have low testosterone levels. Testosterone replacement therapy (TRT) is recommended to increase testosterone to normal levels. TRT is also very important for bone health. There are several types of TRT. Common types of TRT include injections (given by a healthcare provider or the patient) or applying a gel to the skin (daily). You can talk to your doctor about options for TRT.

TRT helps improve sexual desire (libido) and erections. TRT does not increase the size of the testes. TRT does not help improve fertility (sperm).

Breast tissue (gynecomastia)

In some cases, breast tissue (gynecomastia) is very bothersome. Specialized surgeons can perform surgery to reduce the size of the breast - but it is rarely necessary.

Metabolism

Metabolism refers to how your body changes food to energy. Men with KS have increased risk for metabolic problems including being overweight or obese. A healthy balanced diet and regular physical exercise is recommended for all men with KS. This is important to control weight gain and have a healthy metabolism. Low testosterone can cause metabolic problems so it is important to take TRT as prescribed by your doctor. Stopping TRT can increase your risk for metabolic problems like obesity and type 2 diabetes.

Other treatments

Some adults with Klinefelter syndrome and certain associated health problems will need to adress these with specific treatments.

Fertility disorders are covered in a different section.

Fertility

Fertility

During normal puberty, special cells in the testes develop to make spermatozoa (sperm). In teens with KS, the special cells do not develop and start to die off during the teen years. The loss of cells causes infertility. Sperm is rarely seen in the semen of men with KS (low or no sperm).

Testosterone replacement therapy (TRT) will not improve fertility. Men with KS need special techniques and surgery to get sperm (e.g., testicular sperm extraction, TESE). TESE can get sperm in about half (i.e., 30-50%) of men with KS.

Sperm found during surgery can be frozen and stored (cryopreservation). The sperm can be used by fertility specialists for assisted fertility (in vitro fertilization, IVF). IVF is a procedure done in a laboratory. Sperm is injected into an egg to fertilize it. The cells are grown in the laboratory for a short time and then implanted into the woman's uterus.

Some patients are able to have children using assisted fertility, but these techniques are not always successful.

Recommended tests

Adapted from Gravholt et al. Endocrine Reviews, 2018

Test	Childhood	Puberty	Adult
Growth	1x/yr	1-2x/yr	
Weight and body composition	1x/yr	1x/yr	1x/yr
Testosterone		2x/yr	1x/yr
LH, FSH		2x/yr	1x/yr
Estradiol, AMH, Inhibin B		1x/yr	1x/yr
Calcium, Phosphate, alkaline phosphatase, Vitamine D		1x/yr	1x/yr
Blood count (hemoglobin, hematocrit)		1x/yr	1x/yr
Liver enzymes		1x/yr	1x/yr
Lipid profile		1x/yr	1x/yr
Fasting glucose, Insulin, HbA1c		1x/yr	1x/yr
PSA			1x/yr
Bone density (DXA)		1x/2-3 yr	1x/2-3 yr
Auto-immune screening (e.g. thyroiditis, celiac disease)	X	X	X
Cardiovascular assessment			X
Atheroscelorisis risk evaluation			X
Tumor screening			X
Testosterone treatment (if high LH)		X	X
Fertility consultation		X	X
Sperm count		X	X
Testicular biopsy / TESE			X
Neuropsychologist (if needed)	X	X	X
Academic support (if needed)	X	X	X
Physical activity & balanced diet	X	X	X

My follow-up

Karyotype	
Test date	
Laboratory	

Birth			
Weight		Length	
Cryptorchidism		Penile size	

Minipuberty (0-6months)		Date	
LH		FSH	
Testosterone		Inhibin B	
AMH		Other	

Infancy / Childhood	
Increased height	
Delayed growth/milestones	
Dental problems	
Motor difficulties	
Delayed speech	
Learning difficulties	
Attentional problems	
Psychologist	
Other	

Puberty	
First signs of puberty	
First signs of growth spurt	
Other	

Other health problems		Date of diagnosis	
Gynecomastia		Date	
Obesity		Date	
Diabetes		Date	
Osteoporosis		Date	
Orthopedic problems		Date	
Phlebitis		Date	
Autoimmune diagnosis		Date	
Other		Date	

Fertility consultation		Date of diagnosis	
Sperm count/analysis		Date	
Cryopreservation		Date	
Microdissection		Date	

My treatments

Treatment	Dose	Frequency	Start-Date	End-Date

My contacts

Contacts	Name	City	Telephone
Pediatrician			
Pediatric endocrinologist			
Speech & Language			
Psychologist			
Fertility specialist			
Primary care provider			
Adult endocrinologist			

Links	
Association for X and Y Chromosome Variations	National Institute of Health
Klinefelter's Syndrome Association - UK	Klinefelter Syndrome Association - Canada
Deutsche Klinefelter-Syndrom Vereinigung e.V.	AXYS Australia
Verein Klinefelter-Syndrom Schweiz	Association de Porteurs d'Anomalies Chromosomiques

My Results

Growth	Value	Units	Date
Height			
Weight			
BMI			
Armspan			

Testicular function	Value	Units	Date
Testosterone			
Estradiol E2			
LH			
FSH			
AMH/MIS			
Inhibin B			
Testicular ultrasound			
Sperm count			
Biopsy/TESE			
Other			

Bone health	Value	Units	Date
Vitamine D(25 OH))			
Calcium			
Phosphate			
Alk. Phos.			
Bone density (DXA)			
Other			

Metabolism	Value	Units	Date
HbA1c			
Glucose			
Insulin			
Total Cholesterol			
HDL cholesterol			
Other			
Other			

Other	Value	Units	Date
TSH			
IGF1			
Hematocrit			
Liver enzymes)			
Thyroid			
Celiac			
Other			
Other			