BMJ Best Practice

Klinefelter syndrome

Straight to the point of care

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Summary

Klinefelter syndrome (KS) is a chromosome variation affecting around 1 in 660 males in which an extra X chromosome is present, resulting in a genetic karyotype of 47,XXY. Karyotype analysis is required for definitive diagnosis.

The extra X chromosome leads to testicular hypofunction and testosterone deficiency, which can result in small testes, infertility, and other symptoms/signs of hypogonadism (e.g., reduced facial/pubic hair, gynecomastia). Developmental delay in childhood is common, particularly affecting speech.

Symptoms and signs of KS may be subtle and the majority of affected individuals function fairly normally and are never diagnosed. Among those who are diagnosed, this most commonly happens following evaluation for male infertility, although prenatal diagnosis is becoming increasingly common.

Treatment focuses on testosterone therapy, typically starting in adolescence and continuing lifelong, together with neuropsychological and educational support tailored to the individual's age and symptoms. Assisted reproductive technologies such as testicular sperm extraction have improved the prospects for men with KS to father biological children, although use of donor sperm or adoption remains a common alternative for many affected individuals.

Men with KS have a significantly increased risk of many long-term health conditions, including diabetes, cardiovascular disease, osteoporosis, and breast cancer.

Definition

Klinefelter syndrome (KS) is a sex chromosome aneuploidy (abnormal chromosome number) that is defined by the presence of an extra X chromosome.[1][2][3] Around 90% of individuals with KS have the 47,XXY karyotype (47 chromosomes, with an extra X), with the remainder having mosaic karyotypes such as 46,XY/47,XXY (i.e., the extra X chromosome is present in some cells but other cells have the typical male karyotype of 46,XY).[4]

Epidemiology

Klinefelter syndrome (KS) is the most common male sex chromosome disorder, affecting around 1 in 660 males. This prevalence estimate is based on pooled data from several large studies involving chromosome analysis of newborns. However, the majority of affected individuals are never diagnosed, hence the diagnosed prevalence rate is significantly lower.[1] [2]

- Data on the proportion of expected cases that are diagnosed varies between countries. In Denmark and the UK, it has been estimated that only around one quarter of affected individuals are diagnosed, whereas a study in Australia estimated a pick-up rate of 50%.[1] [6]

The 2021 European Academy of Andrology guideline reports that among individuals who do receive a diagnosis of KS, 21% are diagnosed prenatally, 10% to 12% in prepubertal childhood, 16% at puberty, and 51% as adults.[3]

- The peak age range for diagnosis is the late-20s to mid-30s, with most cases picked up during evaluation for male infertility.[1] [7]
- Prenatal diagnosis is becoming increasingly common, via fetal anomaly screening.[3] [4] [8] [9] [10]

There are few data on ethnic differences in prevalence, although one small US study suggested higher prevalence among males of Asian compared with white ethnicity.[4]

Late diagnosis and nondiagnosis are both frequent, and individuals with more subtle clinical features often never receive a diagnosis. Ascertainment bias may therefore obscure the epidemiologic picture and true morbidity and mortality may differ significantly from reported estimates.[4]

Etiology

The additional X chromosome in the sperm or egg occurs randomly and hence Klinefelter syndrome (KS) is not an inherited or heritable disorder. The extra X chromosome arises from nondisjunction errors during either meiosis I or meiosis II divisions in spermatogenesis or oogenesis, with a roughly 50/50 split between disjunction of maternal versus paternal origin.[3] There is a weak association with increasing maternal age and this is attributable to increased maternal meiosis I errors.[3] [5]

In mosaic KS, the error in the division of sex chromosomes occurs in the zygote post-fertilization.

Pathophysiology

The pathophysiology of KS is poorly understood, with the link between genotype and phenotype only partially explained.[4] Both hypogonadism and genetic effects are believed to contribute to the spectrum of clinical features associated with KS.[4] The androgen receptor (AR) gene is of interest regarding correlation between genotype and phenotypic variation as it contains a highly polymorphic trinucleotide repeat that is correlated with physiologic androgen effects and may be associated with androgen-dependent features of KS.[3]

Emerging evidence shows that the extra X chromosome leads to profound changes in methylation of DNA and transcriptomic changes, not only on the sex chromosomes but also on all the autosomes, with the phenotypic traits seen in KS explained by organ-specific genomic changes involving multiple genes.[5] [11]

Testicular degeneration and abnormal testicular function begins in childhood (perhaps even in utero) and accelerates during puberty. From early- to mid-puberty onward, impairment of Leydig cells (the primary source of testosterone) results in hypergonadotropic hypogonadism, with extensive fibrosis and hyalinization of seminiferous tubules.[1] [2][3] [4] Most adolescents and adults with KS have azoospermia in the ejaculate. However, pockets of normal spermatic tubular structure and focal spermatogenesis may be found within the highly disordered testicular architecture, perhaps due to a mechanism to eject the supernumerary X chromosome.[1] [2][4]

The additional copy of the SHOX gene in the pseudoautosomal region of the X chromosome may contribute to faster childhood growth but the growth acceleration mechanism is not through increased growth hormone secretion and is therefore presumed to be through a direct genetic effect of the gene on the growth plate.[2]

The effect of an additional X chromosome on brain function and cognitive development has been well studied but the mechanisms of the chromosomal interference and any explanations for the nonspecific effects seen in KS are poorly understood.[12] [13]

Case history

Case history #1

A 27-year-old man attends the infertility clinic with his partner for evaluation. They have been trying unsuccessfully to conceive for 24 months. Sperm analysis shows azoospermia. On examination, subtle clinical features of hypogonadism are seen, including small testes, excessive abdominal fat accumulation, and sparse facial hair. On questioning about symptoms, the man says he has a low libido and suffers from fatigue. Two early-morning fasting blood samples show testosterone levels of 260 nanograms/dL (9 nanomol/L), with LH/FSH levels of 25 IU/L and 56 IU/L, respectively. Karyotype analysis is arranged and the result shows 47,XXY.

Case history #2

A 5-year-old boy presents with a history of slow expressive speech development compared with his peers. His parents say his nonidentical twin brother is much more vocal and more physically and verbally dominant in family settings. The boy took longer than his brother to learn to walk and to feed himself with a spoon and he still has poor pencil control. He is now embarrassed that his penis is smaller than his brother's and gets teased about this by him.

Other presentations

In adolescence, puberty begins on time with testicular growth starting normally but may stall after a year or two, with the testes reducing in size.[2][5] Gynecomastia is common.[2] The usual pattern of becoming slimmer and more muscular as puberty progresses is absent, with boys who have KS often gaining weight around the abdomen and hips. Adolescent boys may also struggle to keep up with their peers at school and suffer from difficulties with planning their time and tasks. They may experience social and psychological challenges and spend a lot of time alone.[2]

Approach

Key points

- The presenting features of Klinefelter syndrome (KS) vary with age and developmental stage. Prepubertal clinical features are typically subtle and nonspecific. Many individuals never receive a diagnosis and most who do are not diagnosed until they are adults, although this may change over time with increasing rates of prenatal diagnosis.[1] [2] [3] [4]
- Symptoms and signs of **testosterone deficiency** are the most common feature, usually emerging when puberty begins normally but fails to complete.[2] [3][5] [14] [15] The only clinical examination feature reliably seen in individuals with KS is small testes from mid-puberty onward. **Infertility** is the most frequent presenting symptom in adults, affecting >99% of men with KS.[4] In childhood, there may be developmental and learning delays, particularly with expressive language.[2]
- Testosterone in postpubertal boys and adults with KS is typically in the low or low-normal range, with elevated gonadotropins (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) present in the vast majority.[1] [2] [3] [4]
- A definitive diagnosis of KS requires **karyotype analysis** confirming the presence of an extra X chromosome (47,XXY).[3]

General principles

KS is a sex chromosome aneuploidy (abnormal chromosome number) in which an extra X chromosome is present, resulting in a genetic karyotype of **47,XXY**.[1] [2] [3]

- The extra X chromosome leads to testicular hypofunction and KS is the most frequent cause of primary hypogonadism.[2] [3] [4] [16]

KS is the **most common male sex chromosome disorder**, affecting around 1 in 660 males.[1] [2]

- Around 90% of cases have the 47,XXY karyotype (47 chromosomes, with an extra X), with the remainder having mosaic karyotypes such as 46,XY/47,XXY (i.e., the extra X chromosome is present in some cells but other cells have the typical male karyotype of 46,XY).[4]
- The mosaic form of KS has been reported to be associated with a milder symptom presentation, although further research is needed to confirm this.[4]

Definitive diagnosis requires confirmation of the extra X chromosome on **karyotype analysis**.[3]

History

The key clinical features of KS are symptoms and signs of **testosterone deficiency**, in some cases accompanied by **language and developmental delay**.[1] [2] [3] [4]

- However, the symptoms of KS are highly variable and sometimes subtle, with many boys and men functioning fairly normally.[2] [3]
- The combination of tall stature with small testes in an otherwise physically healthy male child may raise the possibility of KS.[7] Suspicion is heightened if this is accompanied by developmental delay, especially with expressive language most affected.[2] [17] [18] Puberty that starts on time but stalls after a year or two is another suggestive sign.[2] [3] [5] [14] [15]
- In practice, the majority of diagnoses occur during evaluation for **male infertility**.[4]

The presenting features depend on the individual's age at evaluation. Prepubertal clinical features are very nonspecific and very few individuals with KS are diagnosed during childhood.[3] [4]

- Most **newborn boys** with KS have no unusual features of note and major congenital abnormalities are unusual.[2] In rare cases, cryptorchidism (undescended testes) may be present.[3]
- In **infants and children**, key symptoms that should prompt consideration of KS are:[2] [3] [12] [17] [19]
    - *Speech or developmental delay*. Learning and developmental delays are common in KS and most often noted between 1-5 years of age, but are often nonspecific and do not necessarily point to the diagnosis.[13] [17] [20] Some degree of learning disability has been reported in >75% of boys with KS, with delayed speech development in 40%.[1] [4] Expressive verbal ability is most often affected; toddlers may be slow to start speaking but their receptive comprehension is usually normal.[2] [21] Some boys with KS have problems with attention and executive cognitive function, which can lead to expressions of frustration.[2] [3] In rare cases, a boy with KS may be very slow to start walking and KS will be identified on chromosomal testing.[22] Boys with KS will often be receiving special educational support, although a specific diagnosis is unlikely to have been made.[1] [2] [3]
    - *Behavioral differences*. Infants are sometimes reported as being easy to manage and not as demanding as their siblings.[2] Boys with KS may be quiet and passive but impulsivity may be present and difficulties with self-expression and executive tasks may lead to temper tantrums and anger outbursts.[2] [23] One population-based study found an increased risk of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders among individuals with KS.[24]
    - *Social and psychological issues*, which can continue into adolescence and adulthood.[3] Social skills may take longer to develop and boys with KS sometimes feel isolated and/or prefer their own company.[2] KS has been reported to be associated with difficulties identifying and verbalizing emotions.[3]
    - *Tall stature with disproportionately long legs*, following a growth spurt in childhood.[3] [4] Tall stature affects around 30% of individuals with KS and is believed to be due to the presence of three copies of the SHOX gene, but extreme tall stature is unusual.[1] [2] [4] [23] Infant length is typically within age-related norms and the rate of height increase tends to accelerate throughout childhood, so that by school age, boys with KS may be on a higher centile than their siblings and that predicted by mid-parental height.[2]
    - *A small penis and/or testes*.[3] Decreased penile size is seen in 10% to 25% of boys with KS.[1] In rare cases, cryptorchidism may be present, but it is rare for boys with KS to fulfill the criteria for micropenis (stretched length ≥2.5 standard deviations [SD] below the mean for age).[3]
- In **adolescence**, puberty begins on time but may not fully complete.[2] [3] [5] [14] [15]
    - *Biochemical and clinical hypogonadism* develops from late puberty, typically beginning at around 14 years of age at Tanner stage 5 of puberty.[2]
    - Testicular growth begins normally but is then followed by involution and a *reduction in testes size*.[2] [4]
    - *Gynecomastia* is common, affecting around one third of adolescents and adults with KS.[2]
    - *A high abdominal fat mass* often becomes apparent during adolescence, together with decreased muscle mass and strength; this is in contrast to the typical male pattern of

slimming down and becoming more muscular as puberty progresses. These features are present in around half of adolescents with KS and they persist into adulthood.[4] However, they are very nonspecific for KS.[2]
- *Deficits in expressive language skills* are more common than in peers without KS.[3]
- Note that there is *no* overall increase in gender dysphoria reported in individuals with KS.[25]

- In **adult men**, *infertility* is the most common presenting symptom, affecting >99% of men with KS, and can be due to oligospermia or more commonly azoospermia.[4]
  - The prevalence of KS is 3% to 4% among all infertile men, 6% among those with a total sperm count <10 million/ejaculate, and 10% to 15% in those with nonobstructive azoospermia.[3]
  - More than 90% of individuals with KS are azoospermic.[2]
- Other common symptoms of hypogonadism that may be present at the point of diagnosis in men with KS include:[1] [3]
  - *Small testes* (bi-testicular volume <6 mL): present in >95%.[1] [26]
  - *Lack of facial and pubic hair*: present in 60% to 80% and 30% to 60%, respectively.[1] It can be helpful to compare with the norm for the family.
  - *Gynecomastia*: affecting 38% to 75%.[1]
  - *Psychosexual problems*: in particular, low libido.[3]
  - *Obesity*, with a high fat:lean mass ratio, particularly around the abdomen and hips.[2] [3]
  - *Lethargy and fatigue*, although this is a very nonspecific feature of hypogonadism.[2]

Diagnostic delay and nondiagnosis

Many individuals with KS **never receive a diagnosis**, likely because of lack of awareness among healthcare professionals together with the phenotypic variability and mild clinical features in many affected boys and men.[3] [4] [23]

- Most diagnoses are made in adult men, with a reported average age at diagnosis in the mid-30s.[4]
- The 2021 European Academy of Andrology guideline reports that among individuals who do receive a diagnosis of KS, 21% are diagnosed prenatally, 10% to 12% in prepubertal childhood, 16% at puberty, and 51% as adults.[3]

Prenatal diagnosis is becoming increasingly common.[3] [4] [8]

- In the US, the American College of Obstetricians and Gynecologists (ACOG) recommends offering all pregnant women prenatal screening for fetal chromosome abnormalities including sex chromosome aneuploidies (SCAs) such as KS.[8] The American College of Medical Genetics (ACMG) strongly recommends noninvasive prenatal screening (NIPS) via analysis of cell-free fetal DNA in maternal blood as the most sensitive and specific screening test for SCAs in singleton pregnancies.[9] [27] This can be done starting from around 10 weeks of gestation. Because of the risk of false positives, amniocentesis or chorionic villus sampling followed by karytopye analysis is needed to confirm a prenatal diagnosis of KS.[3] [8] [28]

Risk factors

The additional X chromosome in males with KS occurs randomly and KS is not a heritable disorder. The extra chromosome arises from nondisjunction errors during spermatogenesis or oogenesis and can be inherited from either parent, with a roughly 50/50 split between maternal and paternal disjunction.[1] [3]

- **Advanced maternal age** is a weak risk factor for having a son with KS and this is believed to be attributable to a higher rate of maternal meiosis I errors in older women.[3] [5]
- The effect of advanced paternal age is controversial, with studies finding conflicting results but no clear association confirmed.[29] [30] [31]

Physical exam

The only clinical examination feature reliably seen in individuals with KS is **small testes from mid-puberty** onward. The testes may be firm or soft.[2] [4][14] [18] Testicular volume can be measured using the Prader orchidometer.

- The testes are typically normal in size or only slightly small in prepubertal childhood. They begin to enlarge normally at the onset of puberty, typically around 11-12 years of age. However, they rarely progress beyond a bi-testicular volume of 10 mL and then usually shrink to around 3-5 mL (the size of an almond kernel) in older adolescents due to a stalling of puberty.[2] [4]
- Almost all adult men with KS have a bi-testicular volume <6 mL.[1] [26]

Prader orchidometer

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Gynecomastia may be seen on exam in around one third of adolescents with KS and up to three-quarters of adult men. However, this is very nonspecific for KS.[1] [2]

Sparse facial, pubic, and axillary hair may be noted in postpubertal adolescents and adult men.[1]

A **high abdominal fat mass** may be seen, beginning in childhood and persisting into adulthood.

- Central obesity ("pot belly" and wider hips) is common after the adiposity rebound at 6-7 years of age.[2]

Consider KS in the differential diagnosis if examination of a newborn identifies a micropenis (stretched length ≥2.5 SD below the mean for age, usually with a diminished circumference) or undescended testes, but bear in mind that infants with KS are usually phenotypically normal.[2] [3]

Look for an **upward shift in height centiles** in childhood.

- Boys with KS grow more quickly than the norm throughout childhood, often resulting in a height centile higher than predicted (based on mid-parental height). Tall boys with KS have disproportionately longer legs.[3] [4]
- However, extreme tall stature is unusual in individuals with KS.[2]

Initial investigations

Hypergonadotropic hypogonadism (i.e., primary hypogonadism) is a key feature of KS and is confirmed by **elevated levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH)**, together with **low testosterone levels**.[1] It is seen in >75% of adult men with KS.[4]

- In KS, testosterone, LH, and FSH levels are typically normal until the start of puberty, after which FSH and LH begin to increase.[1]
- Testosterone may be within the age- and pubertal stage-related range in early puberty but typically fails to rise in late puberty, leading to low levels compared with boys without KS.[1] This biochemical hypogonadism is generally detectable from around age 14 years (at Tanner stage 5 of puberty), when the usual accelerated nocturnal rise in testosterone becomes blunted.[2]
- Low testosterone levels are present in the majority of adult men with KS, and nearly all affected men have elevated LH levels, reflecting primary testicular (Leydig cell) damage.[3]
- Compensated hypergonadotropic hypogonadism (i.e., elevated LH levels but testosterone levels in the low end of the normal range) is seen in a substantial proportion of pubertal adolescents with KS. This compensatory mechanism allows pubertal development to proceed normally.[3]

A definitive diagnosis of KS requires **karyotype analysis** of sex chromosomes.[3]

The order in which hormone levels and genetic investigations are undertaken will depend on the age at which KS is suspected as a possible diagnosis and the presenting symptoms/signs that underlie that suspicion.

Testosterone levels

Investigation of testosterone levels may be indicated:

- As part of the workup for an adult man who presents with infertility.[32] This is the most common scenario in which KS is diagnosed.[4]
- When evaluating a postpubertal adolescent or adult man who presents with symptoms/signs of testosterone deficiency (e.g., small testes, gynecomastia, lack of facial/pubic hair, sexual dysfunction).[23]
- For ongoing monitoring of an individual who has been diagnosed with KS in childhood. If KS has been diagnosed prenatally, the 2021 European Academy of Andrology guideline recommends checking testosterone levels in the first 2-3 months of life to aid in diagnosis of micropenis.[3] If KS

is diagnosed in childhood, it is usual practice to start evaluating testosterone on a regular basis (e.g., annually) once puberty has started or when clinical signs of hypogonadism are seen.

Measure total serum testosterone with an **early-morning fasting sample** (8-9 a.m.). Check the level on two different days before confirming a diagnosis of hypogonadism.[32]

- An early-morning sample is important for accurate measurement as testosterone levels follow a diurnal pattern and this is when levels are at their highest. They also vary day to day, making it important to check the level on two separate mornings.[2] [32]
- Testosterone levels can be suppressed by intake of food, hence the recommendation for a fasting level.[32]

Testosterone in postpubertal boys and adults with KS is typically in the **low or low-normal range**.[2][14][18]

- Be aware that a normal testosterone level therefore does not exclude KS. Some adolescents and adult men with KS have testosterone levels in the lower end of the normal range but this group often have symptoms/signs of testosterone deficiency.
- A level less than 300 nanograms/dL (<10.4 nanomol/L) is generally accepted as being consistent with hypogonadism in a postpubertal adolescent or adult man, but reference ranges vary between laboratories so check your local protocol.

Gonadotropin levels

In KS, serum LH and FSH levels are typically normal until puberty, after which they become elevated.[2][14][18][23] Elevated gonadotropins have been reported in >95% of postpubertal individuals with KS.[1]

If hypogonadism is confirmed as part of evaluation for infertility or for symptoms/signs of testosterone deficiency, it is essential to **measure serum LH and FSH** to confirm the hypogonadism is primary (i.e., due to testicular failure).[23]

- KS is the most common cause of primary hypogonadism, in which low testosterone levels are accompanied by elevated gonadotropins.[1]

If KS is diagnosed in childhood, it may be helpful to monitor serum LH and FSH levels once clinical signs of puberty are seen and annually thereafter.

- However, bear in mind that raised gonadotropins per se are not an indication to start testosterone therapy.[3]

If KS has been diagnosed prenatally, the 2021 European Academy of Andrology guideline recommends checking LH levels in the first 2-3 months of life to aid in diagnosis of micropenis.[3]

Chromosomal karyotype analysis

If suspicion for KS is high, **request karyotype analysis of sex chromosomes** (usually from a blood lymphocyte sample - check your local laboratory protocol). There is no clear consensus on the clinical symptoms/signs that warrant karyotype analysis for suspected KS.

- The US Endocrine Society guideline on hypogonadism recommends karyotype analysis to diagnose KS in any individual who has primary hypogonadism confirmed based on low total serum testosterone (in two early-morning fasting samples) and high serum LH and FSH, especially if bi-testicular volume <6 mL.[32]

- The 2021 European Academy of Andrology KS guideline states that karyotype analysis is indicated in the following scenarios:[3]
    - Men with nonobstructive azoospermia or severe oligozoospermia (total sperm count <10 x 10^6/ejaculate or sperm concentration <5 x 10^6/mL)
    - Men with primary hypogonadism (low serum testosterone level) and elevated serum gonadotropins (LH and FSH) combined with small testicular volume (<5 mL per testis)
    - Boys born with cryptorchidism, especially if bilateral, who do not experience spontaneous descent of the testes by 1 year of age.

Occasionally, KS may be identified unexpectedly when a karyotype analysis is performed to investigate developmental delay (e.g., in speech and/or walking) in a toddler over 2 years of age.[2]

In KS, karyotype analysis will confirm the presence of **an extra X chromosome**.[1] [2] [3]

- Around 90% of individuals with KS have the 47,XXY karyotype (47 chromosomes, with an extra X).
- The remainder have mosaic karyotypes such as 46,XY/47,XXY (i.e., the extra X chromosome is present in some cells but other cells have the typical male karyotype of 46,XY).[4]

Ensure counseling takes place prior to karyotype analysis.

- Parental consent will be needed for a child and the boy himself must also consent if he has legal capacity (e.g., Gillick competence). Check your local legal guidelines around capacity.

Other investigations

Inhibin B levels are typically normal until puberty in males with KS, after which they decrease to a low-normal or subnormal level.[1] [2] [23]

- Inhibin B is most often requested during investigation of fertility prospects in individuals with KS.

DIAGNOSIS

History and exam

Key diagnostic factors

infertility (common)

- The most common presenting symptom, affecting >99% of men with KS.[4]
    - More than 90% of men with KS are azoospermic.[2]
    - The great majority of diagnoses of KS are made in men who are undergoing evaluation for infertility.[3] [4]
- The European Academy of Andrology recommends karyotype analysis for KS in any man with nonobstructive azoospermia or severe oligozoospermia (total sperm count <10 million/ejaculate or sperm concentration <5 x 10^6/mL).[3]
    - The prevalence of KS is 3% to 4% among all infertile men, 6% among those with a total sperm count <10 million/ejaculate, and 10% to 15% in those with nonobstructive azoospermia.[3]

failure to complete pubertal maturation (common)

- The vast majority of boys with KS begin pubertal maturation on time, but fail to complete it in the usual timeframe.[2][14]
- - Puberty typically stalls after a year or two and remains incomplete.[2] [3] [5] [14] [15]
  - Biochemical and clinical hypogonadism develops from late puberty, typically occurring at around 14 years of age at Tanner stage 5 of puberty.[2]

small testes (common)

- The only clinical examination feature reliably seen in individuals with KS is small testes from mid-puberty onward. The testes may be firm or soft.[2] [4][14] [18] Testicular volume can be measured using the Prader orchidometer.
- - The testes are typically normal in size or only slightly small in prepubertal childhood.
  - They begin to enlarge normally at the onset of puberty, typically around 11-12 years of age. However, they rarely progress beyond a bi-testicular volume of 10 mL and this is then followed by involution, with the testes shrinking to around 3-5 mL (the size of an almond kernel) in older adolescents due to the onset of hypogonadism.[2] [4]
  - Bi-testicular volume is <6 mL in >95% of adult men with KS.[1] [26]
- Rarely, in severe phenotypes, a boy may be born with reduced testicular volume due to intrauterine hypogonadism.[3]

Prader orchidometer

Created by BMJ Knowledge Centre

expressive speech delay in early childhood (common)

- Delayed speech development has been reported in 40% of children with KS.[1] [4] Expressive verbal ability is most often affected; toddlers may be slow to start speaking but their receptive comprehension is usually normal.[2] [21]
- Among adolescents with KS, deficits in expressive language skills are more common than in peers without KS.[3]

micropenis (uncommon)

- Rarely, in severe phenotypes, a boy may be born with micropenis (stretched length ≥2.5 standard deviations [SD] below the mean for age) due to intrauterine hypogonadism.[3] KS is part of the differential diagnosis if examination of a newborn boy identifies this sign.[2] [3]
- Decreased penile size is seen in 10% to 25% of boys with KS but it is very rare for them to fulfill the criteria for micropenis.[3]

cryptorchidism (uncommon)

- In rare cases, newborn boys with KS may have cryptorchidism although this is very rare.[3] KS is part of the differential diagnosis if examination of a newborn boy identifies this sign.[2] [3]
- For more information, see Cryptorchidism .

Other diagnostic factors

developmental delay (common)

- Learning and developmental delays are most commonly noted between 1-5 years of age but are nonspecific and do not necessarily point to the diagnosis.[13] [17] [20]
  - Some degree of learning disability has been reported in >75% of boys with KS.[1] [4]
  - Some boys with KS have problems with attention and executive cognitive function, which can lead to expressions of frustration.[2] [3]
  - Boys with KS will often be receiving special educational support.[1] [2] [3]
- In rare cases, a boy with KS may be very slow to start walking and KS will be identified on chromosomal testing.[22]

behavioral problems in childhood (common)

- Common in boys with KS.
  - Infants are sometimes reported as being easy to manage and not as demanding as their siblings.[2]
  - Boys with KS may be quiet and passive, but impulsivity may be present and difficulties with self-expression and executive tasks may lead to temper tantrums and anger outbursts.[2] [23]
  - One population-based study found an increased risk of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders among individuals with KS.[24]

tall stature (common)

- Affects around 30% of KS individuals and is believed to be due to the presence of three copies of the SHOX gene.[1] [2] [4] [23]
  - Infant length is typically within age-related norms.

- The rate of height increase tends to accelerate throughout childhood so that by school age, boys with KS may be on a higher centile than predicted (based on mid-parental height and/or compared with siblings).[2]
- Look for an upward shift in height centiles during childhood.

- Tall individuals with KS have disproportionately longer legs.[3] [4]
-
  - However, extreme tall stature is unusual.[2]

lack of facial and pubic hair (common)

- May be noted in adolescents and adult men.[1]
-
  - Lack of facial and pubic hair (e.g., compared with close male relatives) have a reported prevalence of 60% to 80% and 30% to 60%, respectively.[1]
  - A sign of hypogonadism.

gynecomastia (common)

- Seen on exam in around one third of adolescents and up to three-quarters of adult men with KS.[1] [2] However, this is a nonspecific sign.

sexual dysfunction/reduced libido (common)

- Sexual dysfunction or low libido in adult men may be related to low testosterone levels but this is not typical in adolescents.[2] [14]

high fat-to-muscle ratio/abdominal obesity (common)

- Weight gain can begin in childhood or adolescence and often persists into adulthood.
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  - Central obesity (“pot belly” and wider hips) is common after the adiposity rebound at 6-7 years.[2]
  - A high abdominal fat mass, together with decreased muscle mass and strength, are present in around half of adolescents with KS but are very nonspecific signs.[2] [4]
  - Obesity is often seen in adulthood, particularly around the abdomen and hips.[2] [3]

social/ psychological issues (common)

- Social skills may take longer to develop and boys with KS sometimes feel isolated and/or prefer their own company.[2]
- KS has been reported to be associated with difficulties identifying and verbalizing emotions.[3]
- Social and psychological issues may continue into adolescence and adulthood.[3]

fatigue (common)

- Fatigue/lethargy is a nonspecific finding that is common in individuals with hypogonadism.

Risk factors

Weak

increased maternal age

- An association of KS with increased maternal age can be attributed to a higher rate of maternal meiosis I errors.[3] [5]

Investigations

1st test to order

Test	Result
chromosomal karyotype • Definitive test if KS suspected. Usually from a blood lymphocyte sample - check your local laboratory protocol. • There is no clear consensus on the clinical symptoms/signs that warrant karyotype analysis for suspected KS. • The US Endocrine Society guideline on hypogonadism recommends karyotype analysis to diagnose KS in any individual who has primary hypogonadism confirmed based on low total serum testosterone (in two early-morning fasting samples) and high serum LH and FSH, especially if bi-testicular volume <6 mL.[32] • The 2021 European Academy of Andrology KS guideline states that karyotype analysis is indicated in the following scenarios: men with nonobstructive azoospermia or severe oligozoospermia (total sperm count <10 x 10^6/ejaculate or sperm concentration <5 x 10^6/mL); *or* men with primary hypogonadism (low serum testosterone level) and elevated serum gonadotropins (LH and FSH) combined with small testicular volume (<5 mL per testis); *or* boys born with cryptorchidism, especially if bilateral, who do not experience spontaneous descent of the testes by 1 year of age.[3] • Occasionally, KS may be identified unexpectedly when a karyotype analysis is performed to investigate developmental delay (e.g., in speech and/or walking) in a toddler over 2 years of age.[2] • In KS, karyotype analysis will confirm the presence of an extra X chromosome.[1] [2] [3] • Ensure counseling takes place prior to karyotype analysis.	**common result is non-mosaic 47,XXY; mosaic 46,XY/47,XXY may be found in milder cases**
serum total testosterone • Measure with an early-morning (8-9 a.m.) fasting sample.[32] Check the level on two different days before confirming a diagnosis of hypogonadism.[32] • Most useful in diagnosing hypogonadism in late adolescence and adulthood.[3] Hypogonadism is a key feature of KS.[1] [4] • Testosterone levels are typically normal in childhood and the early stages of puberty but typically fail to rise in late puberty.[1] • This biochemical hypogonadism is generally detectable from around age 14 years (at Tanner stage 5 of puberty), when the usual accelerated nocturnal rise in testosterone becomes blunted.[2] • Testosterone in postpubertal boys and adult men with KS is typically in the low or low-normal range.[2][14] [18] Be aware that a normal testosterone level therefore does not exclude KS. • If KS has been diagnosed prenatally, check testosterone levels in the first 2-3 months after birth.[3] • If KS is diagnosed in childhood, it is usual practice to start evaluating testosterone on a regular basis (e.g., annually) once puberty has started or when clinical signs of hypogonadism are seen	**subnormal or within the lower part of the age-related range from late puberty onward: in an adult man, an early-morning fasting serum total testosterone level <300 nanograms/dL (<10.4 nanomol/L) is generally accepted as being consistent with hypogonadism**

Test	Result
serum LH/FSH • In KS, serum LH and FSH levels are typically normal until puberty, after which they become elevated.[2][14][18] • If hypogonadism is confirmed as part of evaluation for infertility or for symptoms/signs of testosterone deficiency, it is essential to measure serum LH and FSH to confirm the hypogonadism is primary (i.e., due to testicular failure).[23] • KS is the most common cause of primary hypogonadism, in which low testosterone levels are accompanied by elevated gonadotropins.[1] • If KS is diagnosed in childhood, it may be helpful to monitor serum LH and FSH levels once clinical signs of puberty are seen and annually thereafter. • However, bear in mind that raised gonadotropins per se are not an indication to start testosterone therapy.[3] • If KS has been diagnosed prenatally, check LH levels in the first 2-3 months after birth.[3]	**usually raised from the start of puberty onward**

Other tests to consider

Test	Result
inhibin B • Inhibin B levels are typically normal until puberty in males with KS, after which they decrease to a low-normal or subnormal level.[1] [2] [23] • Most often requested during investigation of fertility prospects in individuals with KS.	**may be low-normal or subnormal**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Other male sex chromosome aneuploidies	• Distinct conditions with their own phenotypes include 47,XYY; 48,XXXY; 48,XXYY; and 49,XXXXY.[14][20] [33] • Many of these conditions (48,XXXY; 48,XXYY; and 49,XXXXY) have a more severe phenotype, with more significant symptoms and signs (including more marked developmental delay) than those typically seen in KS.[4] A dysmorphic bone structure, especially of the wrists and elbows (e.g., radio-ulnar synostosis), is more typical of complex aneuploidies.[20] • 47,XYY individuals have normal size testes.	• Chromosomal karyotype analysis.
Other causes of developmental delay	• Variable depending on the condition. May be more global developmental delay, with receptive comprehension affected, whereas in KS expressive speech is most often affected and receptive comprehension is usually normal.[21]	• Chromosomal karyotype analysis (in the case of other genetic conditions). • Educational/clinical psychological assessment for specific learning difficulties (e.g., dyslexia, attention deficit hyperactivity disorder).
Central (secondary) hypogonadism	• Absence of developmental, social, and behavioral issues which can be seen in KS. • Central (secondary) causes of hypogonadism include parasellar tumor or apoplexy of pituitary macroadenoma.	• Normal or low gonadotropin levels (LH/FSH).
Marfan syndrome	• Relevant family history; musculoskeletal signs (e.g., high arched palate, scoliosis, pectus excavatum, flat feet, arachnodactyly with positive thumb sign); ocular lens subluxation; aortic dilation or dissection.[34] [35] [36]	• Echocardiography may detect aortic regurgitation, dilation, or dissection. • Slit-lamp eye exam may show lens abnormalities.

Criteria

Karyotype analysis

A full chromosomal karyotype is the sole confirming criterion. Klinefelter syndrome (KS) is confirmed by a genetic karyotype of 47,XXY.[1][2][3]

- Around 90% of individuals with KS have the 47,XXY karyotype (47 chromosomes, with an extra X), with the remainder having mosaic karyotypes such as 46,XY/47,XXY (i.e., the extra X chromosome is present in some cells but other cells have the typical male karyotype of 46,XY).[4]

Karyotype 47,XXY is specific to KS; other sex chromosomal karyotypes (e.g., 47,XYY; 48,XXXY and 48,XXYY; 49,XXXXY) are different conditions with their own phenotypes.[14][20][33]

Approach

Key points

- Treatment interventions for Klinefelter syndrome (KS) depend on the age at diagnosis and the severity of the symptoms/signs. Multidisciplinary care is the ideal, especially for any individual with a severe phenotype.[1] [2] [4]
- If KS is diagnosed prenatally or in childhood, early intervention is recommended and must be tailored to the boy's individual developmental, learning, or behavioral challenges.[2] [3]
- **Testosterone therapy** is the mainstay of treatment for postpubertal adolescents and adult men, with the goal of reversing clinical and biochemical hypogonadism.[3]
- **Fertility counseling** is important, as >90% of men with KS are azoospermic.[2] [4] Assisted reproductive technologies such as testicular sperm extraction (TESE) or microscopic TESE (mTESE) have improved the prospects for men with KS to have biological children, although use of donor sperm or adoption remains a common alternative option. Performing TESE/mTESE in young adulthood appears to offer the best chance of extracting viable sperm for cryopreservation.[2] [3]
- Adults with KS have a significantly increased risk of developing **diabetes, cardiovascular disease, osteoporosis, and breast cancer**. This can be minimized with testosterone therapy, lifestyle advice, and regular surveillance of risk factors.[3] [4][23]

Treatment of Klinefelter syndrome (KS) focuses on testosterone replacement therapy (from adolescence onward), together with neuropsychological and adaptive therapies tailored to the individual's age and symptoms. Specific interventions vary based on the age and developmental stage at diagnosis and the severity of the phenotype.

- Multidisciplinary specialist care from a team with specific expertise in KS is the ideal, particularly for patients with a severe phenotype who will benefit from input from pediatricians, endocrinologists, infertility specialists, speech-language therapists, psychologists, and primary care physicians.[1] [2] [4] [23]

Individuals diagnosed prenatally or in childhood

When KS is diagnosed prenatally or in childhood, there is an opportunity to ensure early intervention, although evidence is lacking that this improves long-term adult outcomes.[3] Parents can be reassured that the majority of boys and men with KS function fairly normally.[2]

- The goals of treatment differ based on the age of the boy and the specific developmental delays. It is important to have a **full developmental and cognitive pediatric assessment** to direct individual therapies for any learning or behavioral challenges.[2] [17] [18] Many boys with KS will require speech-language therapy, special educational support, and psychological counseling, but this must be targeted to their individual needs.[2] [18] [23]
- For any boy diagnosed prenatally, ensure **ongoing monitoring of speech development, learning and educational progress, and psychosocial problems**. This should start from the point of diagnosis and continue into adolescence so that appropriate support can be provided as needed.[3]

Testosterone therapy

Testosterone therapy is a key element in the management of KS and is a mainstay of treatment for postpubertal adolescents and adult men.[2] The aim is to normalize testosterone and luteinizing hormone (LH) levels to the mid-normal range, although treatment can also be guided by symptom response with the goal of reversing clinical hypogonadism.[1]

Benefits of testosterone therapy include:[2] [3]

- Promotion of pubertal maturation and reduction of gynecomastia.
- Improved bone mineral density and hence a reduced risk of developing osteoporosis in adulthood.
- Reduced fat mass and improved muscle strength. This attenuates the increased prevalence of diabetes and cardiovascular disease among men with KS.[4]
- Improved libido and mood.

Starting testosterone therapy in adolescents

Testosterone therapy should be supervised by a pediatric endocrinologist and can be considered in adolescents when it becomes clear that spontaneously secreted testosterone has become insufficient to support continued normal pubertal maturation.

A decision to **start testosterone therapy can be based on the diagnosis of either biochemical or clinical hypogonadism**.[2] [23]

- Low testosterone levels on early-morning testing confirm the onset of biochemical hypogonadism, which usually begins in late puberty (Tanner stage 5).[2]
- Symptoms/signs of clinical hypogonadism may occur earlier than the onset of biochemical hypogonadism. They include:[2]
    - Slow virilization (i.e., stalled pubertal progress).
    - Gynecomastia. Note that testosterone therapy can alleviate or resolve gynecomastia but is most effective if started at the first appearance of breast tissue enlargement.
    - Micropenis (stretched length ≥2.5 standard deviations [SD] below the mean for age).
    - High body mass index/obesity. The typical male pattern is to slim down and become more muscular as puberty progresses. Failure of this change to occur may be an indication for treatment to start.
    - Lethargy (a weak indication on its own).

Do not base a decision to initiate testosterone therapy solely on rising gonadotropin (LH/follicle-stimulating hormone [FSH]) levels.[3] [14] [15]

- Gonadotropin levels will begin to rise from the start of puberty but, in isolation, this is not a sign to begin treatment if the individual has not yet developed testosterone deficiency or clinical signs of hypogonadism.
- However, in the authors' experience, all patients with rising levels of LH/FSH will have some clinical features of hypogonadism that are a sufficient indication to start testosterone therapy, albeit these may be subtle signs: for example, high fat mass/low muscle mass detected on dual-energy x-ray absorptiometry (DXA) scanning.

An informed **discussion about fertility** is recommended prior to initiation of testosterone therapy in adolescence.[3]

Testosterone therapy in adults

In adult men with KS, the principles of testosterone therapy are the same as for any other man with primary hypogonadism. For more detail, see Hypogonadism in men .

- If testosterone therapy has been started during adolescence, it should be continued into adulthood.
- If KS is diagnosed in an adult man, **postpone initiation of testosterone therapy if there is a plan in the near term to attempt sperm retrieval** for fertility treatment.[1] [3][23] [32]

Lifelong treatment is normally recommended to help prevent complications of hypogonadism such as osteoporosis and obesity.[1]

Rare indications for testosterone therapy in children

Evidence is insufficient to support the routine use of testosterone in KS in infancy and prepubertal childhood, but consider referral to a pediatric endocrinologist if **micropenis** is present (stretched length ≥2.5 SD below the mean for age).[2] In this rare scenario:

- The European KS guideline recommends that short-term, low-dose testosterone therapy may be justified if serum levels of testosterone are found to be abnormally low and LH levels are elevated.[3]
- The British Society for Paediatric Endocrinology and Diabetes guideline recommends short-term, low-dose testosterone therapy (either via monthly injections for 3 months or topical application).[38]

- Formulation and dose regimen of testosterone is individualized by the pediatric endocrinologist.

If **cryptorchidism** is noted, refer to pediatric urology.[2] For more detail, see Cryptorchidism .

Choice of testosterone regimen

There are many formulations of testosterone available for administration. Options include oral, transdermal, intramuscular, intranasal, and buccal formulations, although the availability of these formulations varies between countries.[3] [39] [40] Buccal formulations are not available in the US.

- Transdermal testosterone gel is the preferred mode for managing pubertal replacement and allows for easy dose escalation.[1] [2]

- For longer-term replacement for adults, either the transdermal gel or the long-acting intramuscular injection (testosterone undecanoate) tends to be best for adherence purposes.[2]
- Intramuscular or subcutaneous injection with testosterone enanthate or testosterone cypionate is also commonly used in the US. In other parts of the world, intramuscular formulations with mixed testosterone esters may be used.

For more detail on the options for adults, see Hypogonadism in men .

Regular monitoring is needed to ensure adherence, assess effectiveness, adjust dosing, and monitor any adverse effects.

- Monitoring should include **regular checks of serum testosterone, gonadotropins, and hematocrit**, initially at 3-6 months (depending on the testosterone formulation), then at 12 months and annually thereafter.[3] [32]

Fertility treatment

More than 90% of individuals with KS are **azoospermic**.[2] [4]

- In the other 10%, mobile spermatozoa may be found in the semen and can be cryopreserved for use in assisted reproduction.[3]

Among those who are azoospermic, techniques such as **testicular sperm extraction (TESE) or microscopic testicular sperm extraction (mTESE)** have improved the prospects of having biological children.[2] [3]

- Focal spermatogenesis may be identified, with the possibility of attempting TESE/mTESE to harvest viable sperm for use in intracytoplasmic sperm injection (ICSI).[3]
- A meta-analysis suggested a success rate for sperm retrieval of 44% in men with KS. Age, testosterone and FSH levels, and testicular volume were found to have no significant impact on outcome.[41]

The optimal timing for attempting sperm extraction with TESE/mTESE is unclear.[2]

- Because testicular fibrosis and hyalinization is progressive in KS, starting when gonadotropin levels begin to rise in early puberty, there is debate about whether to harvest and cryopreserve sperm as early as possible after diagnosis in adolescents and young men with KS.[3] However, there is increasing evidence that this option should not be offered to individuals ages <16 years because mTESE has lower retrieval rates for germ cells in this age group compared with those ages 16-30 years.[42]
- On balance, performing TESE/mTESE in **young adulthood** rather than delaying until an individual is keen to have a biological child maximizes the potential for obtaining viable sperm.[2] [3]
- When KS is diagnosed in an adult man who has a current or potential wish for biological children, initiation of **testosterone therapy should be delayed until after TESE/mTESE**.[3]

In spite of these advances in reproductive technology, use of donor sperm or adoption remains the best chance of having a child for many men with KS, although cultural factors may influence the decision for some men.[23] [32]

Counseling for possible infertility

Many young adult males with KS are emotionally less mature than their peers and the concept of fertility prediction/estimation needs careful counseling.[2]

- In particular, the emotional consequences of knowing they are going to be infertile needs careful consideration prior to discussion of the results of any semen analysis procedures.
- The benefit of carrying out a surgical sperm retrieval at the optimal time must be balanced against the potential psychological distress if no sperm is found.
- Some men with KS may have a reduced capacity to understand complex explanations so key points are best presented in a simple structured way, backed up by written text.

Other aspects of care

Adults with KS have a significantly increased risk of **insulin resistance, obesity, metabolic syndrome, and cardiovascular disease**.[3] [23]

- Almost half of men with KS fulfill the criteria for metabolic syndrome compared with 10% of controls, and the reported prevalence of type 2 diabetes is 10% to 39%.[1]

- Increased insulin resistance associated with hypogonadism does not fully explain this increased risk. Poorly understood epigenetic mechanisms are also thought to be a contributory factor, hence the increased risk is only partially attenuated by testosterone therapy.[3]
- Along with testosterone therapy, lifestyle advice, regular surveillance of cardiovascular risk, and standard pharmacologic interventions to manage risk factors are all important.[2] Annual checks of weight, waist circumference, blood pressure, fasting glucose, HbA1c, and lipid profile are recommended in all adult men with KS.[3]
- See Type 2 diabetes mellitus in adults and Metabolic syndrome .

The increased risk of **osteopenia/osteoporosis** requires careful monitoring, although it is attenuated by testosterone therapy.[4]

- The risk of lower bone mass begins around mid-puberty, preventing the achievement of peak bone mass.[3] Osteopenia and osteoporosis have a reported prevalence of 5% to 40% and 10%, respectively, among men with KS.[1]
- Low bone density is not a typical feature of KS in childhood or adolescence.[2] Nonetheless, assessment of vitamin D and calcium status is recommended throughout childhood and adolescence, with DXA to evaluate bone mineral density every 2 years if vitamin D deficiency is identified.[3]
- For men diagnosed as adults, a baseline DXA and fracture risk assessment is recommended, with subsequent monitoring dependent on the individual's risk level.[3] If osteoporosis develops, it can be treated as per standard guidelines for the condition. See Osteoporosis .

Men with KS are also at increased risk of breast cancer (approximately fourfold risk compared with non-KS males, although the lifetime risk is still low).[4]

- Breast examination to check for cancer risk is recommended in any adult with KS, initially at the point of diagnosis and thereafter on an individual basis according to risk.[3]

Neurocognitive challenges can persist into adulthood, often necessitating referral to a neuropsychologist.[4]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing		(summary)
children		
	1st	multidisciplinary care
	plus	individualized educational and/or psychological support
with micropenis	adjunct	testosterone therapy
adolescents		
	1st	multidisciplinary care
	plus	individualized educational and/or psychological support
	plus	testosterone therapy
	plus	fertility counseling
adults		
	1st	multidisciplinary care ± psychological support
	plus	testosterone therapy
	plus	fertility counseling ± assisted reproductive technology
	plus	lifestyle measures and cardiovascular disease/osteoporosis risk reduction

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing

children

1st **multidisciplinary care**

» Specific treatment interventions for KS vary depending on the age and developmental stage at diagnosis and the severity of the phenotype.

» Multidisciplinary specialist care from a team with specific expertise in KS is the ideal, particularly for patients with a severe phenotype who will benefit from input from pediatricians, endocrinologists, speech-language therapists, psychologists, and primary care physicians.[1] [2] [4] [23]

plus **individualized educational and/or psychological support**

Treatment recommended for ALL patients in selected patient group

» If KS is diagnosed prenatally or in childhood, early intervention is recommended and must be tailored to the boy's individual developmental, learning, or behavioral challenges.[2] [3]

- It is important to have a full developmental and cognitive pediatric assessment to direct individual therapies for any learning or behavioral challenges.[2] [17][18] Many boys with KS will require speech-language therapy, special educational support, and psychological counseling, but this must be targeted to their individual needs.[2] [18] [23]
- For any boy diagnosed prenatally, ensure ongoing monitoring of speech development, learning and educational progress, and psychosocial problems so that appropriate support can be provided as needed.[3]
- Parents can be reassured that the majority of boys and men with KS function fairly normally.[2]

with micropenis **adjunct** **testosterone therapy**

Treatment recommended for SOME patients in selected patient group

» Evidence is insufficient to support the routine use of testosterone in KS in infancy and prepubertal childhood.

Ongoing

» Consider referral to a pediatric endocrinologist if micropenis is present (stretched length ≥2.5 standard deviations [SD] below the mean for age).[2] In this rare scenario:

- The European KS guideline recommends that short-term, low-dose testosterone therapy may be justified if serum levels of testosterone are found to be abnormally low and luteinizing hormone (LH) levels are elevated.[3]
- The British Society for Paediatric Endocrinology and Diabetes guideline recommends short-term, low-dose testosterone therapy (either via monthly injections for 3 months or topical application).[38]
- Formulation and dose regimen of testosterone is individualized by the pediatric endocrinologist.

» If cryptorchidism is noted, refer to pediatric urology.[2] For more detail, see Cryptorchidism .

» Complications of testosterone deficiency are rare in children with KS. Low bone density is not a typical feature of KS in childhood; a risk of reduced bone mass generally begins in mid-puberty.[2] [3] Nonetheless, assessment of vitamin D and calcium status is recommended throughout childhood and adolescence, with dual-energy x-ray absorptiometry (DXA) to evaluate bone mineral density every 2 years if vitamin D deficiency is identified.[3]

adolescents

1st **multidisciplinary care**

» Specific treatment interventions for KS vary depending on the age and developmental stage at diagnosis and the severity of the phenotype. From adolescence onward, testosterone replacement therapy becomes a mainstay of management.

» Multidisciplinary specialist care from a team with specific expertise in KS is the ideal, particularly for patients with a severe phenotype.[1] [2] [4] [23]

plus **individualized educational and/or psychological support**

Treatment recommended for ALL patients in selected patient group

» Depending on the severity of the phenotype, adolescents with KS may have educational,

Ongoing

social, and psychological problems. In particular, deficits in expressive language skills are more common in adolescents with KS than among their non-KS peers.[3] Ongoing monitoring of speech, educational, and psychosocial development is recommended, with support provided as needed.[3] In some cases, referral to a neuropsychologist may be indicated.[4]

plus **testosterone therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» testosterone transdermal: consult specialist for guidance on dose

» Testosterone therapy is a key element in the management of KS and is a mainstay of treatment for postpubertal adolescents.[2]

» Benefits of testosterone therapy include:[2] [3]

- Promotion of pubertal maturation and reduction of gynecomastia
- Increased bone mineral density and hence a reduced risk of developing osteoporosis in adulthood
- Reduced fat mass and increased muscle strength[4]
- Improved mood.

Starting testosterone therapy

» Testosterone therapy should be supervised by a pediatric endocrinologist and can be considered in adolescents when it becomes clear that spontaneously secreted testosterone has become insufficient to support continued normal pubertal maturation.

» A decision to start testosterone therapy can be based on the diagnosis of either biochemical or clinical hypogonadism.[2] [23]

- Low testosterone levels on early-morning testing confirm the onset of biochemical hypogonadism, which usually begins in late puberty (Tanner stage 5).[2]
- Symptoms/signs of clinical hypogonadism may occur earlier than the onset of biochemical hypogonadism. They include: *slow virilization* (i.e., stalled pubertal progress); *gynecomastia* (note that testosterone therapy can alleviate or resolve gynecomastia but is most effective

Ongoing

if started at the first appearance of breast tissue enlargement); *micropenis* (stretched length ≥2.5 standard deviations [SD] below the mean for age); *high body mass index/obesity* (the typical male pattern is to slim down and become more muscular as puberty progresses - failure of this change to occur may be an indication for treatment to start); *lethargy* (a weak indication on its own).[2]

» Do not base a decision to initiate testosterone therapy solely on rising gonadotropin (luteinizing hormone/follicle-stimulating hormone [LH/FSH]) levels.[3] [14][15]

- Gonadotropin levels will begin to rise from the start of puberty but, in isolation, this is not a sign to begin treatment if the individual has not yet developed testosterone deficiency or clinical signs of hypogonadism.
- However, in the authors' experience, all patients with rising levels of LH/FSH will have some clinical features of hypogonadism that are a sufficient indication to start testosterone therapy, albeit these may be subtle signs: for example, high fat mass/low muscle mass detected on dual-energy x-ray absorptiometry (DXA) scanning.

» An informed discussion about fertility is recommended prior to initiation of testosterone therapy in adolescence.[3]

Choice of testosterone regimen

» There are many formulations of testosterone available for administration. Options include oral, transdermal, intramuscular, intranasal, and buccal formulations, although the availability of these formulations varies between countries.[3] [39] [40] Buccal formulations are not available in the US.

- Transdermal testosterone gel is the preferred mode for managing pubertal replacement and allows for easy dose escalation.[1] [2]

» Regular monitoring is needed to ensure adherence, assess effectiveness, adjust dosing, and monitor any adverse effects.

Ongoing

- Monitoring should include regular checks of serum testosterone, gonadotropins, and hematocrit, initially at 3-6 months (depending on the testosterone formulation), then at 12 months and annually thereafter.[3] [32]

Risk of osteopenia/ osteoporosis

» The increased risk of osteopenia/osteoporosis that is associated with KS is attenuated by testosterone therapy but requires careful monitoring.[4]

- The risk of lower bone mass begins around mid-puberty, preventing the achievement of peak bone mass.[3] Osteopenia and osteoporosis have a reported prevalence of 5% to 40% and 10%, respectively, among men with KS.[1]
- Assessment of vitamin D and calcium status is recommended throughout childhood and adolescence, with DXA to evaluate bone mineral density every 2 years if vitamin D deficiency is identified.[3]

plus **fertility counseling**

Treatment recommended for ALL patients in selected patient group

» Fertility counseling is an important aspect of care for individuals with KS.

- More than 90% of individuals with KS are azoospermic. However, focal spermatogenesis may be identified, in which case techniques such as testicular sperm extraction (TESE) or microscopic testicular sperm extraction (mTESE) offer some prospect of having biological children.[2] [4]
- In the other 10% of individuals with KS, mobile spermatozoa may be found in the semen and can be cryopreserved for use in assisted reproduction.[3]

» The optimal timing for attempting sperm extraction with TESE/mTESE is unclear.[2]

- Because testicular fibrosis and hyalinization is progressive in KS, starting when gonadotropin levels begin to rise in early puberty, there is debate about whether to harvest and cryopreserve

MANAGEMENT

Ongoing

sperm as early as possible after diagnosis in adolescents and young men with KS.[3] However, there is increasing evidence that this option should not be offered to individuals ages <16 years because mTESE has lower retrieval rates for germ cells in this age group compared with those ages 16-30 years.[42]

- On balance, performing TESE/mTESE in young adulthood rather than delaying until an individual is keen to have a biological child maximizes the potential for obtaining viable sperm.[2] [3]

» Many young males with KS are emotionally less mature than their peers and the concept of fertility prediction/estimation needs careful counseling. Key points are best presented in a simple structured way, backed up by written text.[2]

- In particular, the emotional consequences of knowing they are going to be infertile needs careful consideration prior to discussion of the results of any semen analysis procedures.
- The benefit of carrying out a surgical sperm retrieval at the optimal time must be balanced against the potential psychological distress if no sperm is found.

adults

1st **multidisciplinary care ± psychological support**

» Specific treatment interventions for KS vary depending on the age at diagnosis and the severity of the phenotype. Adults with KS may have been diagnosed during adolescence or earlier in childhood, but in most cases the diagnosis is made in adulthood during evaluation for male infertility or other symptoms/signs of hypogonadism.[3] [4]

» Multidisciplinary specialist care from a team with specific expertise in KS is the ideal, particularly for patients with a severe phenotype who will benefit from input from endocrinologists, infertility specialists, psychologists, and primary care physicians.[1] [2] [4] [23]

» Social and neurocognitive challenges can persist into adulthood, often necessitating referral to a neuropsychologist.[4]

Ongoing

plus **testosterone therapy**

Treatment recommended for ALL patients in selected patient group

» Testosterone therapy is a mainstay of treatment for adult men with KS.[2] The aim is to normalize testosterone and luteinizing hormone (LH) levels to the mid-normal range, although treatment can also be guided by symptom response with the goal of reversing clinical hypogonadism.[1]

» Lifelong testosterone therapy is normally recommended to help prevent complications of hypogonadism.[1] Benefits of testosterone therapy include:[2] [3]

- Reduction of gynecomastia, although the most effective window for achieving this is when breast tissue enlargement first appears during adolescence.
- Reduced fat mass and improved muscle strength. This attenuates the increased prevalence of diabetes and cardiovascular disease among men with KS.[4]
- Improved libido and mood.

» The principles of testosterone therapy are the same as for any other man with primary hypogonadism. For more detail, see Hypogonadism in men .

- If testosterone therapy has been started during adolescence, it should be continued into adulthood.
- If KS is diagnosed in an adult man, postpone initiation of testosterone therapy if there is a plan in the near term to attempt sperm retrieval for fertility treatment.[1] [3][23] [32]

Choice of testosterone regimen

» There are many formulations of testosterone available for administration. Options include oral, transdermal, intramuscular, intranasal, and buccal formulations, although the availability of these formulations varies between countries.[3] [39] [40] Choice of testosterone regimen varies between countries. Buccal formulations are not available in the US.

- For longer-term replacement for adults, either the transdermal gel or the

Ongoing

long-acting intramuscular injection (testosterone undecanoate) tends to be best for adherence purposes.[2]

- Intramuscular or subcutaneous injection with testosterone enanthate or testosterone cypionate is also commonly used in the US. In other parts of the world, intramuscular formulations with mixed testosterone esters may be used.
- For more detail on the options for adults, see Hypogonadism in men .

» Regular monitoring is needed to ensure adherence, assess effectiveness, adjust dosing, and monitor any adverse effects.

- Monitoring should include regular checks of serum testosterone, gonadotropins, and hematocrit, initially at 3-6 months (depending on the testosterone formulation), then at 12 months and annually thereafter.[3] [32]

plus **fertility counseling ± assisted reproductive technology**

Treatment recommended for ALL patients in selected patient group

» More than 90% of individuals with KS are azoospermic.[2] [4]

- In the other 10%, mobile spermatozoa may be found in the semen and can be cryopreserved for use in assisted reproduction.[3]

Counseling for possible infertility

» Many young adult males with KS are emotionally less mature than their peers and the concept of fertility prediction/estimation needs careful counseling. Some men with KS may also have a reduced capacity to understand complex explanations so key points are best presented in a simple structured way, backed up by written text.[2]

- In particular, the emotional consequences of knowing they are going to be infertile needs careful consideration prior to discussion of the results of any semen analysis procedures.

Testicular sperm extraction

Ongoing

» Among those who are azoospermic, techniques such as testicular sperm extraction (TESE) or microscopic testicular sperm extraction (mTESE) have improved the prospects of having biological children.[2] [3]

- Focal spermatogenesis may be identified, with the possibility of attempting TESE/mTESE to harvest viable sperm for use in intracytoplasmic sperm injection (ICSI).[3]
- A meta-analysis suggested a success rate for sperm retrieval of 44% in men with KS. Age, testosterone and follicle-stimulating hormone (FSH) levels, and testicular volume were found to have no significant impact on outcome.[41]

» The optimal timing for attempting sperm extraction with TESE/mTESE is unclear.[2]

- Because testicular fibrosis and hyalinization is progressive in KS, starting when gonadotropin levels begin to rise in early puberty, there is debate about whether to harvest and cryopreserve sperm as early as possible after diagnosis in adolescents and young men with KS.[3] However, there is increasing evidence that this option should not be offered to individuals ages <16 years because mTESE has lower retrieval rates for germ cells in this age group compared with those ages 16-30 years.[42]
- On balance, performing TESE/mTESE in young adulthood rather than delaying until an individual is keen to have a biological child maximizes the potential for obtaining viable sperm.[2] [3]
- When KS is diagnosed in an adult man who has a current or potential wish for biological children, initiation of testosterone therapy should be delayed until after TESE/mTESE.[3]

» In spite of these advances in reproductive technology, use of donor sperm or adoption remains the best chance of having a child for many men with KS, although cultural factors may influence the decision for some men.[23] [32]

plus **lifestyle measures and cardiovascular disease/osteoporosis risk reduction**

Treatment recommended for ALL patients in selected patient group

» Adults with KS have a significantly increased risk of insulin resistance, obesity, metabolic syndrome, and cardiovascular disease.[3] [23]

MANAGEMENT

Ongoing

- Almost half of men with KS fulfill the criteria for metabolic syndrome compared with 10% of controls, and the reported prevalence of type 2 diabetes is 10% to 39%.[1]
- Increased insulin resistance associated with hypogonadism does not fully explain this increased risk. Poorly understood epigenetic mechanisms are also thought to be a contributory factor, hence the increased risk is only partially attenuated by testosterone therapy.[3]
- Along with testosterone therapy, lifestyle advice, regular surveillance of cardiovascular risk, and standard pharmacologic interventions to manage risk factors are all important.[2] Annual checks of weight, waist circumference, blood pressure, fasting glucose, HbA1c, and lipid profile are recommended in all adult men with KS.[3]
- See Type 2 diabetes mellitus in adults and Metabolic syndrome .

» The increased risk of osteopenia/osteoporosis requires careful monitoring, although it is attenuated by testosterone therapy.[4]

- The risk of lower bone mass begins around mid-puberty, preventing the achievement of peak bone mass.[3] Osteopenia and osteoporosis have a reported prevalence of 5% to 40% and 10%, respectively, among men with KS.[1]
- For men diagnosed as adults, a baseline dual-energy x-ray absorptiometry (DXA) and fracture risk assessment is recommended, with subsequent monitoring dependent on the individual's risk level.[3] If osteoporosis develops, it can be treated as per standard guidelines for the condition. See Osteoporosis .

» Men with KS are also at increased risk of breast cancer (approximately fourfold risk compared with non-KS males, although the lifetime risk is still low).[4]

- Breast examination to check for cancer risk is recommended in any adult with KS, initially at the point of diagnosis and thereafter on an individual basis according to risk.[3]

»

FOLLOW UP

Prognosis

Population mortality and morbidity studies suggest there is a slight but not significant lowering of life expectancy in individuals with Klinefelter syndrome (KS). The average lifespan has been found to be reduced by 1.5 to 2 years, with morbidity and mortality increased due to a wide number of conditions, including diabetes, cerebrovascular disease, and breast cancer.[43] [44] Higher rates of osteoporosis and fractures are also important to note.[4] [7]

Appropriate treatment with testosterone can alleviate the portion of excess risk that is due to conditions associated with hypergonadotropic hypogonadism, but some of the elevated risk is likely intrinsic to the chromosome aberration and therefore not corrected by testosterone treatment.[3]

The increased morbidity and mortality in individuals with KS may also be partially explained by their often lower socioeconomic status, with cohort data suggesting shorter education, higher rates of unemployment, lower average incomes, and earlier average age at retirement compared with men without KS.[1] [4][7]

It is important to note that most boys and men with KS are never diagnosed so the reported data likely reflects more severe phenotypes of the condition.

Diagnostic guidelines

International

Testosterone therapy in men with hypogonadism (https://www.endocrine.org/clinical-practice-guidelines/testosterone-therapy) [32]

Published by: Endocrine Society **Last published:** 2018

Pubertal induction and transition to adult sex hormone replacement in patients with congenital pituitary or gonadal reproductive hormone deficiency (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9066594) [37]

Published by: Endo-European Reference Network; endorsed by European Society for Pediatric Endocrinology, European Society for Endocrinology, European Academy of Andrology **Last published:** 2022

Treatment guidelines

International

Pubertal induction and transition to adult sex hormone replacement in patients with congenital pituitary or gonadal reproductive hormone deficiency (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9066594) [37]

Published by: Endo-European Reference Network; endorsed by European Society for Pediatric Endocrinology, European Society for Endocrinology, European Academy of Andrology **Last published:** 2022

European Academy of Andrology guidelines on Klinefelter syndrome (https://www.ese-hormones.org/publications/directory/?Publication+Type=Guidelines) [3]

Published by: European Academy of Andrology; endorsed by European Society of Endocrinology **Last published:** 2021

Society for Endocrinology guidelines for testosterone replacement therapy in male hypogonadism (https://www.endocrinology.org/clinical-practice/clinical-guidance/society-for-endocrinology-guidance) [23]

Published by: Society for Endocrinology **Last published:** 2021

Testosterone therapy in men with hypogonadism (https://www.endocrine.org/clinical-practice-guidelines/testosterone-therapy) [32]

Published by: Endocrine Society **Last published:** 2018

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Images

Figure 1: Prader orchidometer

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Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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