# Klinefelter's syndrome
## Management issues according to life stage

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**Males with Klinefelter's syndrome (KS) have unique health requirements, with specific issues arising during different life stages and necessitating a multidisciplinary approach. Early diagnosis and intervention in patients with KS will lead to improved developmental and physical outcomes.**

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Klinefelter's syndrome (KS) is the most common cause of primary testicular failure. The 47,XXY karyotype results from an additional X chromosome originating from either parent. The incidence of KS varies between one in every 450 to 650 men and it is estimated that over half of all cases are never diagnosed,[1,2] possibly due to the broad spectrum of symptoms and phenotype. In Australia the highest detection rates are in the 25- to 34-year-old age group, reflecting presentations for infertility evaluation.[1] Clinical features of KS are outlined in Figure 1 and the Box.[3-5] Chromosomal analysis is required for diagnosis.

Epidemiological data suggest men with KS have not only increased morbidity but also reduced life expectancy of one to two years, possibly related to delayed testosterone treatment and reduced awareness of associated medical conditions.[3,6] Men require multidisciplinary care involving the GP, paediatric and adult endocrinologist, fertility specialist and allied health team with attention to varying aspects of management through life, as summarised in Figure 2.

## Management according to stage of life

### Prenatal

Observational studies of boys and men with KS that was identified prenatally suggest that pre-emptive intervention leads to significantly better outcomes.[7,8] Only a minority of KS diagnoses are made prenatally, however, usually after amniocentesis looking for other conditions.[9] The recent availability of noninvasive prenatal testing to Australian women may improve the rate of its diagnosis.[10]

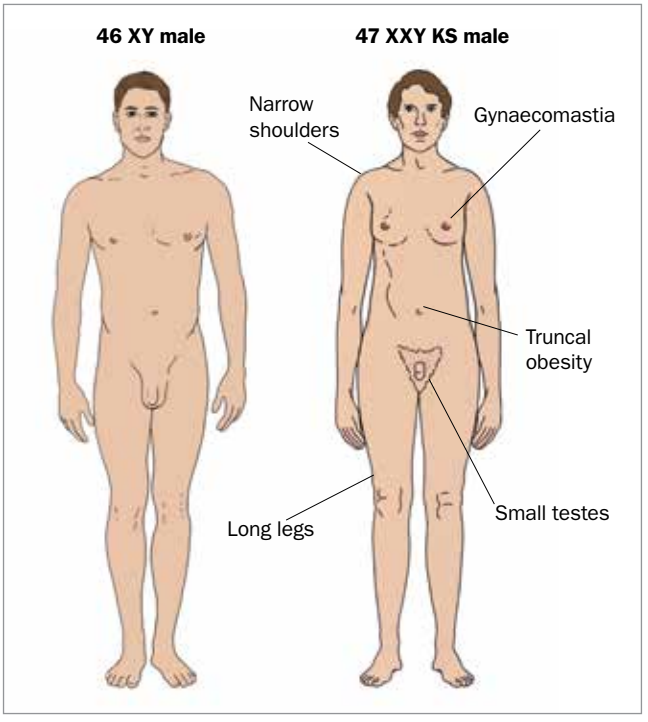



**Figure 1.** Key physical features of Klinefelter's syndrome (KS).

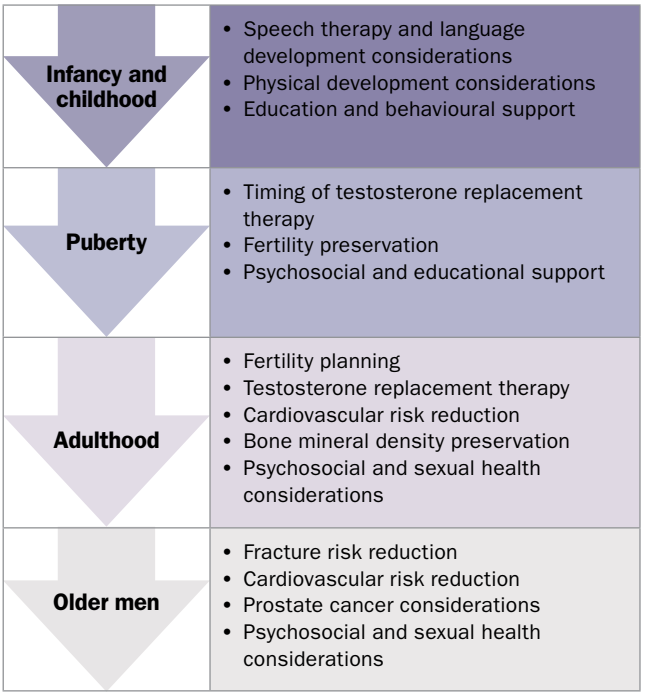



**Figure 2.** Management issues in KS represent a continuum throughout life and goals of care may differ according to life stage.

## Infancy and childhood

Male newborns and infants with KS are phenotypically normal.[11] However, congenital malformations may be increased, including cleft palate, cryptorchidism and hypospadias.[12-14]

Reduced muscle tone, gross and fine motor skills and poor co-ordination are observed from infancy and early childhood in those with KS.[15,16] Global intelligence generally falls within the average range,[15,17] but higher rates of deficits are observed in speech and language-based skills.[7,15,17,18] Distractibility and difficulty in reasoning, problem solving, planning and social integration have been described.[15,17-21] Observational data have shown that early diagnosis affords the opportunity for early implementation of appropriate speech therapy, behavioural and education support and leads to better outcomes in all domains.[7,8,22]

## Puberty and transition to adulthood

Developmental, learning and social issues continue to require attention in males with KS during puberty and the transition to adulthood, while medical management focuses on fertility preservation and the optimal time to start testosterone replacement therapy (TRT).

### *Timing of TRT initiation*

In males with KS the onset of puberty is usually spontaneous and occurs at the usual time. Testicular volume is arrested at approximately 4 to 6 mL due to damage to the seminiferous tubules (Figure 3). Timing of Leydig cell failure varies widely, with a progressive increase in levels of luteinising hormone (LH) from early puberty but with testosterone production that is at least initially sufficient for development of sexual characteristics to variable degrees.[23] An imbalance of oestrogen and testosterone levels is thought to contribute to gynaecomastia, which often emerges in puberty through to adulthood in over 50% of patients with KS.[24]

There is no evidential basis for preventative early TRT in adolescents with KS when hypoandrogenism has not occurred.[24] Annual follow up with a specialist endocrinologist from the middle teen years is warranted to determine initiation of TRT and to ensure normal completion of puberty, optimise peak bone density and prevent symptoms and long-term sequelae of androgen deficiency. TRT suppresses spermatogenesis so fertility must be considered.

### *Fertility and its preservation*

Major advances in assisted reproductive technology have made biological paternity a possibility for men with KS. As almost all men with KS are azoospermic, testicular sperm is usually the only potentially viable option. Microsurgical testicular sperm extraction (TESE) successfully retrieves sperm in 30 to 70% of men, with younger age the best predictor of success. Recovered sperm can be used with intracytoplasmic sperm injection as part of an

**KLINEFELTER'S SYNDROME: CLINICAL MANIFESTATIONS AND FREQUENCIES ACCORDING TO LIFE STAGE[3-5]**

**Infancy/early childhood**

- Delayed speech (40%), fine and gross motor skills
- Learning and problem-solving difficulties (>75%)
- Psychosocial impairment (>30%)
- Cryptorchidism (25–37%)
- Metabolic syndrome (7%)

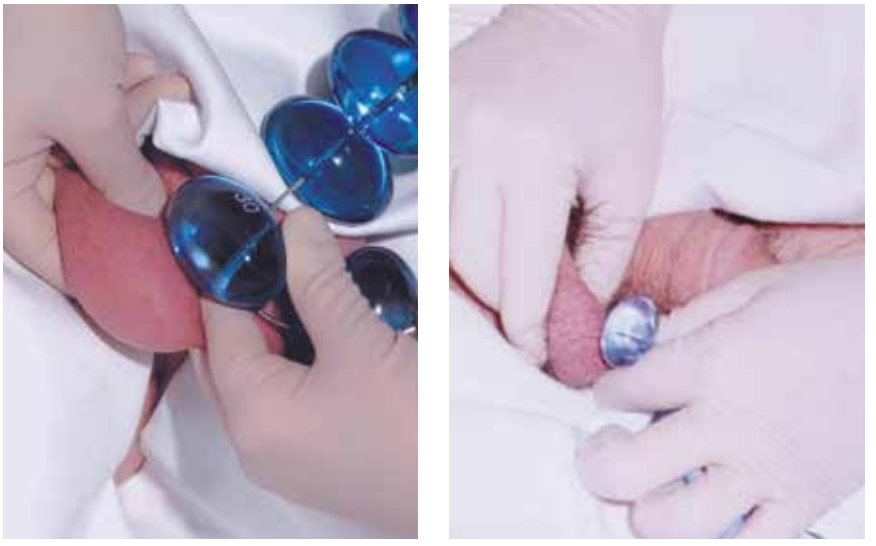
**Adolescence**

- Small firm testes (>95%)*
- Elevated gonadotropins, often FSH>LH (>95%)*
- Low-normal to low serum testosterone level (60–85%)
- Delayed or incomplete virilisation (30–80%)
- Metabolic syndrome (46%)
- Gynaecomastia (40–75%)

**Adulthood**

- Infertility (up to 99%),* majority due to non-obstructive azoospermia
- Complications of hypogonadism
  – Metabolic syndrome (up to 50%)
  – Osteopenia/osteoporosis (10–40%)
  – Sexual dysfunction
- Autoimmune disorders (SLE, type 1 diabetes) – rare
- Malignancies (breast cancer [2.5–7.5%], lung cancer, mediastinal germ cell tumours, non-Hodgkin's lymphoma) – rare but associated with higher mortality than in general population

* Cardinal features.
Abbreviations: FSH = follicle stimulating hormone; LH = luteinising hormone; SLE = systemic lupus erythmatosus.



**Figures 3a and b.** An orchidometer used to measure testicular volume. Testicular size is arrested at between 4 to 6 mL in men with Klinefelter's syndrome. a (left). A 30 mL normal testis. b (right). A 4 mL testis characteristic of Klinefelter's syndrome.

Images courtesy of Andrology Australia, www.andrologyaustralia.org

IVF cycle with pregnancy rates of approximately 20 to 25% per cycle being achieved.[25] Offspring of men with KS may be at slightly higher risk of chromosomal abnormalities, but the majority have normal chromosomal complements as their sperm arise from 46, XY spermatogonial stem cells.[25,26]

TRT is associated with suppression of gonadotropins and thus spermatogenesis, but the recovery of spermatogenesis with subsequent TRT cessation on later fertility is not well studied in men with KS. Some argue that TESE with cryopreservation should occur early and before TRT.[25] Recent, albeit limited, evidence suggesting successful TESE is possible in young adult men without significant influence of previous TRT is somewhat reassuring.[27]

## Adulthood

Management of KS is a continuum from adolescence to adulthood involving a balance between TRT and consideration of reproductive goals. In addition, surveillance for comorbidities is needed.

### *Malignancy*

There is an increased incidence of certain malignancies in men with KS, although in absolute terms they remain rare (Box).[4] The increased risk of breast cancer has been associated with a higher mortality in this group,[6,28] and, although no specific screening guidelines exist, it has been suggested that patients be educated in monthly self examination and early presentation if they detect a suspicious lump.

### *Cardiometabolic health and thrombotic risk*

A high proportion of men with KS have metabolic syndrome associated with truncal obesity, higher fat mass, dyslipidaemia and insulin resistance,[5,29,30] which can be observed from childhood.[29,30,31] The GP is well placed to perform annual screening for diabetes and of the lipid profile and to counsel patients regarding lifestyle and weight management strategies.[5]

Men with KS are at an increased risk of thromboembolism, including deep venous thrombosis and pulmonary embolus.[6,32] Very little is understood about the underlying mechanisms.[33] The effect of TRT on thrombotic risk is unknown, although avoiding excessive androgen action and polycythaemia is prudent, as is the avoidance of excessive substrate for aromatisation to oestradiol.

### *Monitoring bone health*

Patients with KS are at an increased risk of osteopenia and osteoporosis.[12,23,34] Although this is primarily related to

hypogonadism, other mechanisms are now understood to contribute, which may in part explain why TRT does not always restore bone mineral density in men with KS.[34,35] There are no fracture prevention data with the use of TRT, but detection and replacement of lowered testosterone at a younger age may improve peak bone density and reduce fracture risk.

Optimisation of vitamin D, dietary calcium and weight-bearing exercise can be advised as low cost and non-harmful preventative bone health measures despite lack of evidence as to their efficacies in patients with KS. Baseline and periodic DEXA scans are used for therapeutic monitoring and fracture risk assessment.[5] Antiresorptive therapy may be considered when clinically indicated.

### *Psychosexual health*

A substantial proportion of patients with KS exhibit from an early age attention deficit disorder, anxiety, depression, somatisation and social withdrawal.[20] Psychological distress and lowered self-esteem occur at much higher rates in men with KS than in the general population,[36] and individualised psychological or psychiatric input is warranted for those affected. Both younger and older men with KS may present for management of sexual dysfunction, including poor libido and erectile dysfunction. A recent study suggests these issues relate to hypogonadism rather than the syndrome alone.[37]

### Older men

Older men with KS require ongoing optimisation of their cardiovascular and bone health. KS carries a lower risk of prostate cancer if those affected are testosterone deficient, whereas TRT most likely restores the risk to that of the eugonadal population such that discussion of prostate cancer testing should be similarly considered, based on age and family history.[38]

## Conclusion

The health requirements of men with KS are unique with varying issues at the fore during different life stages and requiring a multidisciplinary approach. Early diagnosis and intervention leads to improved developmental and physical outcomes. Timing of TRT initiation is based on clinical symptoms and biochemical evidence of androgen deficiency. Fertility options should be considered from puberty and before commencement of testosterone therapy. Ongoing proactive monitoring for medical comorbidities into adulthood mitigates the increased morbidity and mortality of this disorder. MT

## References

A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

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