



# Klinefelter Syndrome

## The GP's role

- General practitioners should consider Klinefelter syndrome as a possible cause in male patients presenting with any relevant symptoms or signs.
- Most diagnoses of Klinefelter syndrome occur either prenatally, around the expected time of puberty or in association with infertility.
- Accurate measurement of testicular volume (using an orchidometer; Image 1) during routine physical examination would likely improve detection of Klinefelter syndrome, thereby facilitating simple, effective treatment with life-long benefit.
- GPs are ideally placed to perform clinical assessments, order laboratory investigations, refer for specialist assessment and initiation of testosterone replacement therapy, and coordinate ongoing management of Klinefelter syndrome.

## Clinical notes

Some features of Klinefelter syndrome are specific to the syndrome (e.g. behavioural and cognitive) and some features relate to the androgen deficiency (e.g. osteoporosis).

## Condition overview

- Klinefelter syndrome refers to a collection of characteristics in males caused by the presence of two or more X chromosomes.
- The most common (80-90%) karyotype of males with Klinefelter syndrome is 47,XXY. Some males with Klinefelter syndrome have more than two chromosomes, or chromosomal mosaicism<sup>1</sup>.
- Klinefelter syndrome prevalence is estimated to be 1-2 per 1000 men, with only around one quarter ever diagnosed<sup>2</sup>.
- Klinefelter syndrome is characterised by impaired testosterone production and spermatogenesis.
- Klinefelter syndrome is the most common cause of androgen deficiency in men.
- Men with Klinefelter syndrome benefit from testosterone replacement therapy<sup>3</sup>.
- Infertility is common in men with Klinefelter syndrome, due to oligi- or azoospermia, but paternity may be possible with assisted reproductive technologies using sperm collected by testicular biopsy.
- Classical features of Klinefelter syndrome (Image 2) are present to differing degrees in individuals.
- The only consistent feature of Klinefelter syndrome is small testes volume (< 4 ml)<sup>4</sup>.
- The subtle effects of Klinefelter syndrome in many men accounts for low rates of diagnosis and illustrates the importance of genital examination as part of routine clinical exams.

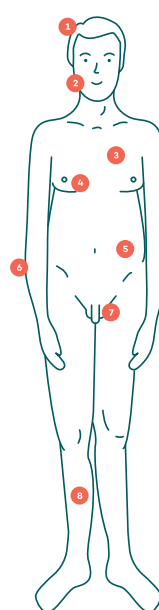


30 mL normal



4 mL Klinefelter syndrome

Image 1 – Example of 30 ml and 4 ml adult testis



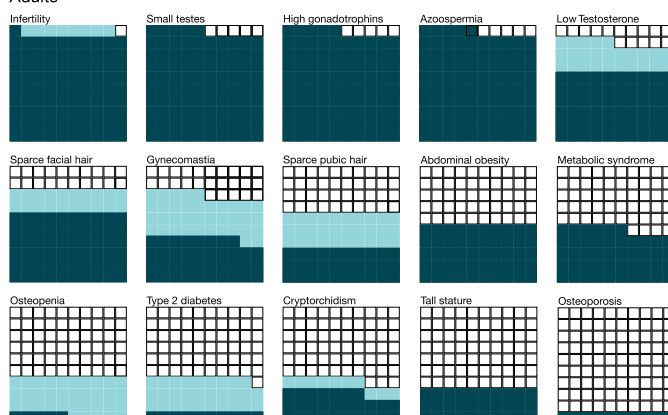
- 1 Taller than average height
- 2 Reduced facial hair
- 3 Reduced body hair
- 4 Breast development (gynecomastia)
- 5 Feminine fat distribution
- 6 Osteoporosis
- 7 Small testes (testicular atrophy)
- 8 Varicose veins

Image 2 – Clinical features of Klinefelter syndrome. Features present may be few, some or all.

### Children



### Adults



Data sourced from Groth et al., 2013 J Clin Endocrinol Metab  
Lowest reported proportion shown by dark squares  
Highest reported proportion shown by dark and light squares

Image 3 – Prevalence of Klinefelter syndrome characteristics

## Diagnosis

### Medical history

- Pubertal development (poor progression).
- Sexual function (low libido).
- Degree of virilisation.
- Psychosocial (learning, schooling and behaviour).
- Infertility.

### Examination

#### Infancy

- No hormonal features prior to puberty.
- Undescended testes.
- Rarely ambiguous genitalia.

#### Adolescence

- Small testes (< 4 mL) characteristic from mid puberty.
- Poor pubertal progression and facial, body and pubic hair relative to age.
- Gynecomastia.
- Feminine fat distribution.
- Taller than average height.
- Poor muscle development.

#### Adult

- Small testes (< 4 mL).
- Reduced facial, body and pubic hair.
- Gynecomastia.
- Feminine fat distribution and weight gain.
- Taller than average height.
- Poor muscle development.

Refer to Clinical Summary Guides 1-3

### Testicular Volume

#### Assessment of testicular volume is essential

- Testicular volume is assessed using an orchidometer.
- Normal testicular volume range:
  - Childhood 3 mL or smaller
  - Puberty 4–14 mL
  - Adulthood 15–35 mL
- Small testes < 4 mL is the only consistent feature of Klinefelter syndrome (image 2).
- The testes may start to develop in early puberty, but soon regress to < 4 mL by mid puberty.

#### Investigations

- Two morning fasting samples of serum total testosterone, taken on different mornings.
- Total serum testosterone, low or low normal from mid puberty (normal range 8–27 nmol/L).
- Serum LH, elevated from mid puberty (normal range 1–8 IU/L).
- Serum FSH, elevated from mid puberty (normal range 1–8 IU/L).
- Karyotype (47,XXY)
  - 10% mosaic 46,XY/47,XXY.

#### Other investigations

- Bone density study, DEXA (osteoporosis).
- Semen analysis if fertility is an issue (usually azoospermic).
- TFT (hypothyroidism).
- Fasting blood glucose (diabetes).

T formulation	Usual (starting) dosage	Dosage range
<b>Injections (IM)</b>		
Combined testosterone propionate Testosterone phenylpropionate Testosterone isocaproate Testosterone decanoate* Testosterone enantate*	250 mg every 2 weeks	10 to 21-day intervals
Testosterone undecanoate	1000 mg every 12 weeks following loading dose at 6 weeks (i.e., 0, 6, 18, 30 weeks)	Longer term: 8 to 16-week intervals
<b>Transdermal patch</b>		
Testosterone	5 mg applied nightly	2.5 to 5 mg daily
<b>Transdermal gel</b>		
Testosterone (1% 50 mg in 5 g sachet or pump pack dispenser; applied daily)	50 mg daily	25–100 mg daily
<b>Transdermal cream</b>		
Testosterone	100 mg daily applied to upper body 25 mg daily applied to scrotum	Up to 200 mg daily (to torso) Up to 50 mg daily (to scrotum)
<b>Oral undecanoate</b>		
Testosterone undecanoate	40 mg capsule 160 to 240 mg in 2 to 3 doses daily	80 to 240 mg daily

\*Not available on Australian Pharmaceutical Benefits Scheme (PBS).

## Management

### Testosterone replacement therapy (TRT)

- TRT is life-long and may be started from mid puberty although many boys initially virilise normally.
- Gynecomastia is an indication to start TRT.
- Teenage boys usually start on a low dose and build to full adult dose as puberty progresses.
- Even if measured T levels are normal, there is evidence that bone density is reduced in the presence of chronically raised LH levels, suggesting that TRT is indicated.
- In adults, consult with a fertility specialist (if appropriate) to develop a plan for fertility prior to TRT, as TRT will suppress spermatogenesis.

### Other treatments

- Gynecomastia may be transient, lasting one to three years.
- Adequate testosterone replacement often results in complete resolution over 12 months.
- Surgical removal, mastectomy (do not refer for early surgery as it may resolve naturally or following TRT).

### Follow-up

#### Monitoring TRT is essential

##### Prostate

- Men with Klinefelter syndrome are less likely to die from prostate cancer, and restoring testosterone levels to the normal range is likely only to return their risks to those of their eugonadal peers.
- Subject to the same advice about testing for prostate cancer as their peers (PSA).
- Exclusion of significant prostate pathology is essential for those aged > 40 years at the commencement of therapy.

#### Raising clinical awareness

Aside from cognitive and behavioural features, it is important to note that despite the following recognised disease associations with Klinefelter syndrome the absolute risk is low.

- Tumours: leukaemia, mediastinal germ cell tumours, lymphoma, teratoma and breast cancer.
- Endocrine: hypothyroidism and diabetes mellitus (Type 1 and 2, rare).
- Cardiovascular: venous ulcers and venous thromboembolic disease.
- Auto-immune: systemic lupus erythematosus (SLE) and coeliac disease.

### Referral

#### Children and adolescents

- Refer to a paediatric endocrinologist.
- Refer for educational and allied health assistance if needed.

#### Adults

- Develop a plan in consultation with an endocrinologist for:
  - Hormone deficiency
  - Infertility
  - Osteoporosis.
- Refer to a fertility specialist, as appropriate, for sperm recovery from testis (occasionally) or donor sperm.

## Infertility

Infertility is a major implication of Klinefelter syndrome<sup>1</sup>.

- Most men are azoospermic.
- Sperm are rarely found in the ejaculate but in 30–50% of cases sperm can be found in testicular biopsy tissue.
- Treatment options:
  - Intracytoplasmic Sperm Injection (ICSI) — the risk of 47,XXY offspring is low
  - Donor insemination.
- Counselling may be necessary.

Refer to Clinical Summary Guide 5: Male Infertility

## Learning and behaviour difficulties

The general intellectual ability of boys with Klinefelter syndrome is within the normal range. However, boys with Klinefelter syndrome may have:

- Difficulties with speech and reading
- Delayed motor development
- Reduced attention span
- Behavioural problems (particularly in adolescence)
- Educational and allied health assistance may be required.

## References

1. Zitzmann et al., 2020. European academy of andrology guidelines on Klinefelter Syndrome: Endorsing Organization: European Society of Endocrinology. *Andrology*
2. Crawford et al., 2017. Klinefelter syndrome. *Nursing children and young people*
3. Kanakis & Nieschlag, 2018. Klinefelter syndrome: more than hypogonadism. *Metabolism*
4. Groth, 2013. Klinefelter Syndrome - A Clinical Update. *Clinical Endocrinology and Metabolism*