Klinefelter Syndrome

Diagnosis and management

HEALTHY MALE
ANDROLOGY AUSTRALIA

Klinefelter syndrome

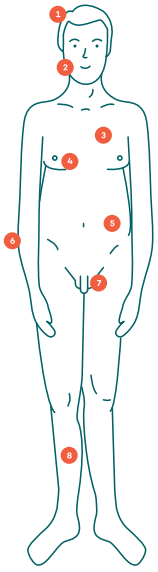
- A genetic condition affecting 1 in 550 men
- Due to the presence of an extra X chromosome (47,XXY)
- Chromosomal mosaicism (both 47,XXY and 46,XY cells) occurs in 10%
  - Usually have milder signs and symptoms, depending upon the level of mosaicism
- The most common cause of androgen deficiency
- Characterised by:
  - Impaired testosterone production (androgen deficiency)
  - Impaired spermatogenesis (azoospermia).
- Up to 70% of cases remain undiagnosed
- Classical features may be present (Image 1), however, there is a wide spectrum of signs and symptoms
- Small testes < 4 mL is the only consistent feature
- Men will benefit from life-long testosterone treatment

Clinical notes: penile development may be normal or at the lower end of the normal range.

The GP's role

- The clinical presentation may be subtle and its diagnosis overlooked unless actively considered
- Most males are diagnosed prenatally, during puberty or in association with infertility, or androgen deficiency
- The GP's role includes clinical assessment, laboratory investigation, treatment, referral and follow-up

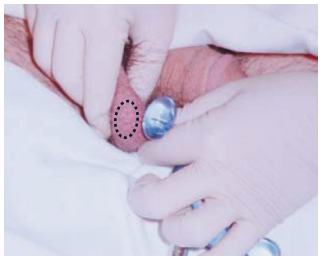
Clinical notes: the low detection rate (~30%) of Klinefelter syndrome would be improved if testicular examination became a regular part of a male physical examination.



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

Image 1 – Clinical features of Klinefelter syndrome
Features present may be few, some or all.

30 mL normal



4 mL Klinefelter syndrome

Image 2 – Example of 30 ml and 4 ml adult testis

Diagnosis

Medical history

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

Examination

Infancy

- No hormonal features prior to puberty
- Undescended testes
- Rarely ambiguous genitalia
- Occasional finding of small firm testes in childhood

Adolescence

- Small testes (< 4mL) 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 (< 4mL)
- Reduced facial, body and pubic hair
- Gynecomastia
- Feminine fat distribution (& 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)

Clinical notes: the testes may start to develop in early puberty, but soon regress to < 4mL 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)

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

Clinical notes: 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)

Clinical notes: 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, breast cancer
- Endocrine: hypothyroidism, diabetes mellitus (Type 1 and 2, rare)
- Cardiovascular: venous ulcers, venous thromboembolic disease
- Auto-immune: systemic lupus erythematosis (SLE), coeliac disease

T formulation	Usual (starting) dosage	Dosage range
Injections (IM)		
Sustanon®, Primoteston®	250 mg every 2 weeks	10 to 21-day intervals
Reandron®	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
Transdermal patch		
Androderm®	2.5 mg and 5.0 mg preps:	
5 mg applied nightly	2.5 to 5 mg daily	
Transdermal gel		
Testogel®	1%: 50 mg in 5 g sachet or pump pack dispenser; applied daily	2.5 to 10 g gel (25 mg to 100 mg T) daily
Transdermal cream		
AndroForte®5	5% (50 mg/mL): 2 mL (100 mg) applied to the torso once daily	Review levels in 1 month, up to 4 mL daily
Oral undecanoate		
Andriol Testocaps®	40 mg capsule: 160 to 240 mg in 2 to 3 doses daily	80 to 240 mg daily

* **Sustanon® is not available on the Australian Pharmaceutical Benefits Scheme (PBS)**

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).

Specialist 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

- 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

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