PIPADOR REVISION

# MRCOG Part 1 Revision Notes

## *Klinefelter and Other Sex Chromosome Aneuploidies*

CELL BIOLOGY • LECTURE 109

VISUAL EXAMINATION REVISION NOTES

*2026 Edition*

MRCOG Part 1 Revision Notes

# Lecture 109: Klinefelter and Other Sex Chromosome Aneuploidies

*Cell biology • Visual revision edition — follows Lecture 108 (Turner)*

COLOUR CODE USED THROUGHOUT THESE NOTES

| KLINEFELTER | XYY | TRIPLE X / HIGH | TURNER / CAIS | DSD / SWYER |
|---|---|---|---|---|

**LEARNING OBJECTIVES — tick off as you go**

- ☐ Know the incidence, origin and features of 47,XXY, 47,XYY and 47,XXX.
- ☐ Explain the endocrinology and fertility management of Klinefelter syndrome.
- ☐ Work up the azoospermic man genetically.
- ☐ Distinguish Swyer syndrome, complete androgen insensitivity and 46,XX males.
- ☐ Counsel after a prenatal sex chromosome finding.

## 1 Overview

**IN ONE LINE:** *Extra or missing sex chromosomes are common (together ~1 in 400–500 births), usually compatible with a normal lifespan, and often never diagnosed — they surface as infertility, tall stature, learning difficulty or amenorrhoea.*

**Sex chromosome aneuploidies — common, often mild, often never diagnosed**

| Condition | Karyotype | Incidence | Key features | Maternal age? |
|---|---|---|---|---|
| KLINEFELTER | 47,XXY | ~1 in 600 males | tall, SMALL FIRM testes, gynaecomastia, azoospermia; ↓T, ↑FSH/LH | half maternal → yes |
| XYY | 47,XYY | ~1 in 1000 males | tall; normal testes + fertility; language/learning, ADHD/autism traits | NO (paternal MII) |
| TRIPLE X | 47,XXX | ~1 in 1000 females | tall; usually normal puberty + fertility; language/learning; ↑ POI, seizures | yes (maternal) |
| TURNER | 45,X | ~1 in 2500 females | short, POI, heart/kidney (Lecture 108) | NO (paternal X lost) |
| POLYSOMIES | 49,XXXXY | rare | more X's → more severe: ID, dysmorphism, radioulnar synostosis | — |

Extra X genes are mostly silenced (X-inactivation: all X's but one are switched off), but ~15–25% of X genes ESCAPE inactivation — their extra dose (and SHOX) explains tall stature and other features.

*Figure 1. Sex chromosome aneuploidies at a glance.*

**MNEMONIC / MEMORY HOOK**

**'Extra X or Y makes you TALL; missing X makes you small'** — XXY, XYY, XXX are tall; Turner (45,X) is short (SHOX dosage).

## 2 Klinefelter Syndrome (47,XXY)

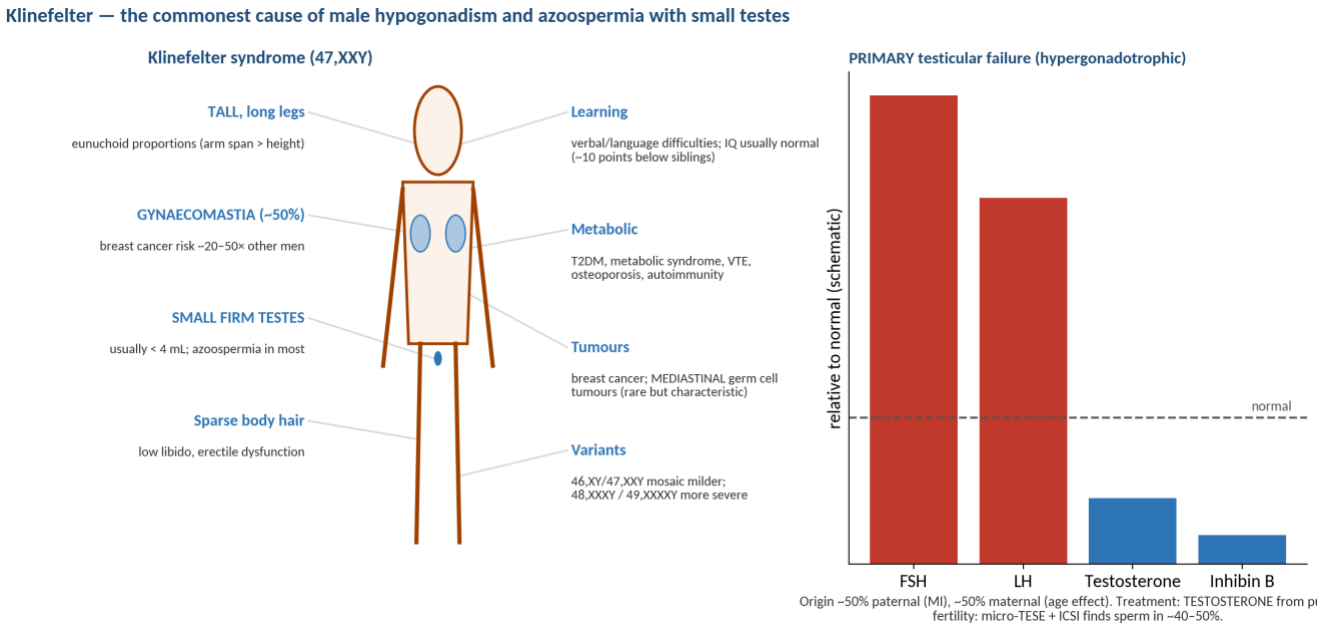



*Figure 2. Klinefelter syndrome.*

| Management | Key points |
|---|---|
| **Testosterone** | From puberty — bone density, libido, energy, body composition (does NOT restore fertility; exogenous T suppresses spermatogenesis) |
| **Fertility** | Micro-TESE + ICSI — sperm found in ~40–50%; children usually chromosomally normal (offer PND/PGT discussion); donor sperm/adoption |
| **Surveillance** | Glucose/lipids, bone density, VTE awareness, breast changes; learning and speech support in childhood |

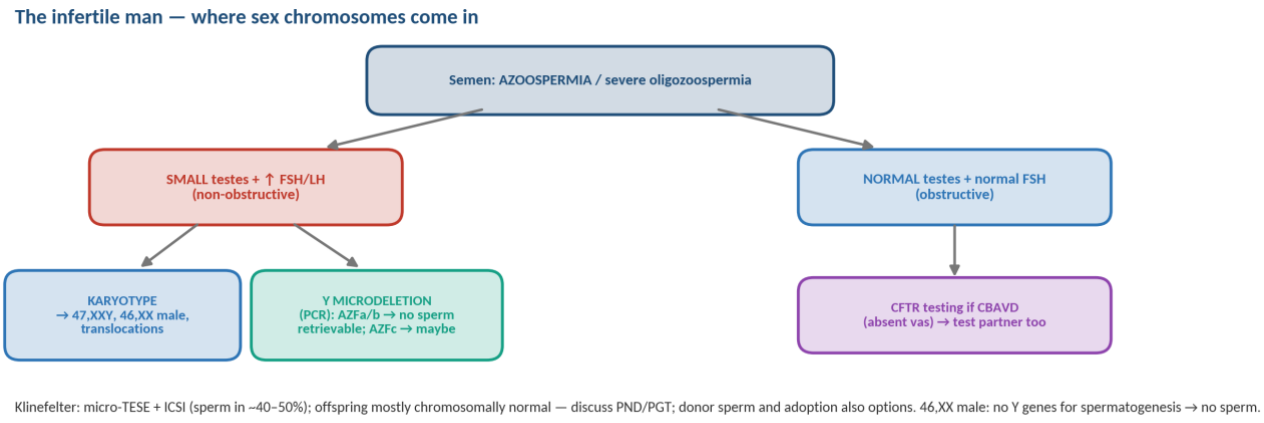



*Figure 3. Genetic work-up of the azoospermic man.*

## 3 47,XYY and 47,XXX

| | 47,XYY | 47,XXX (triple X) |
|---|---|---|
| **Incidence** | ~1 in 1000 males | ~1 in 1000 females |

| | 47,XYY | 47,XXX (triple X) |
|---|---|---|
| **Origin** | Paternal meiosis II or post-zygotic — no age effect | Mostly maternal (MI) — maternal age effect |
| **Body** | Tall (~7 cm above expected), normal face | Tall; minor features |
| **Gonads** | Normal testes; usually fertile | Normal puberty + fertility usually; ↑ POI risk |
| **Development** | Speech/learning, ADHD, autism traits; old 'criminality' link discredited | Language/learning, anxiety; ↑ seizures |
| **Variants** | 48,XYYY (rare) | 48,XXXX, 49,XXXXX — progressively more severe |

- **Dosage**: in any cell all X's but one are inactivated (XXX → two inactive X's), but ~15–25% of X genes escape — the extra active copies (incl. SHOX) explain the phenotypes. Polysomies (48,XXXY, 49,XXXXY): ID, hypogonadism, radioulnar synostosis, cryptorchidism.

## 4 Sex Reversal and DSD

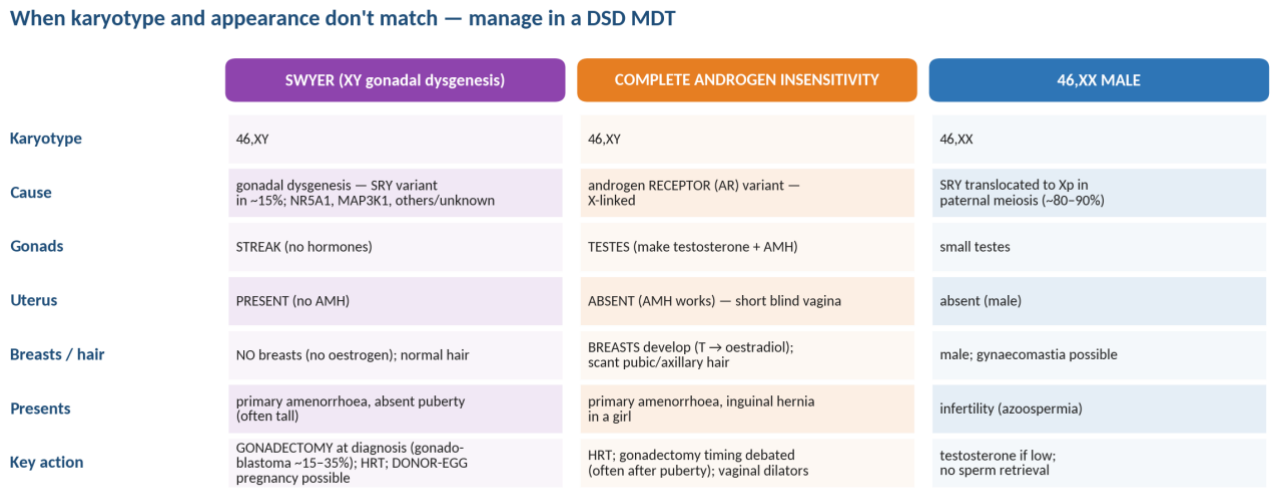



*Figure 4. Swyer vs CAIS vs 46,XX male.*

## 5 Prenatal Diagnosis

**Prenatal diagnosis of a sex chromosome aneuploidy**

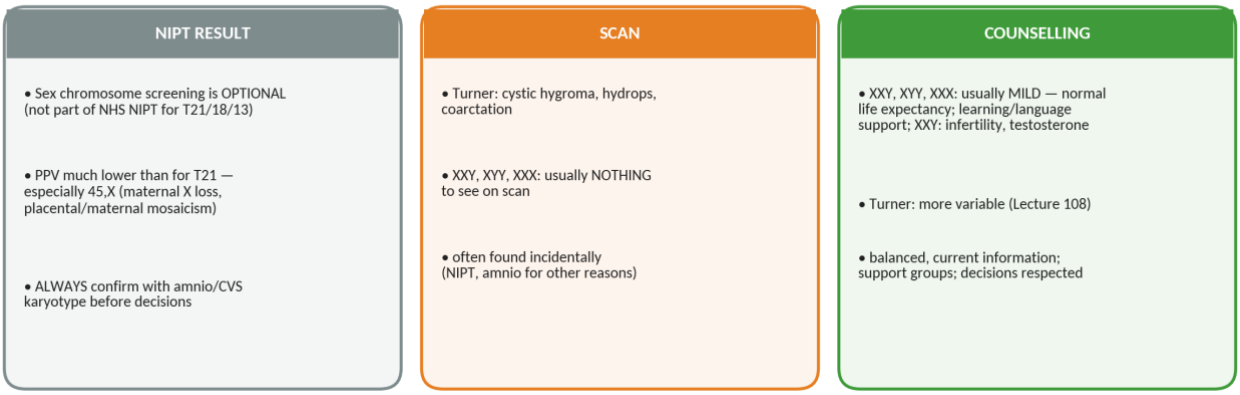



*Figure 5. Prenatal sex chromosome findings.*

★ **PEARL**

**Tall man, small firm testes, azoospermia, ↑FSH/LH, ↓testosterone → Klinefelter (karyotype). Micro-TESE-ICSI ~40–50%.**

**Tall girl, primary amenorrhoea, NO breasts, uterus present, 46,XY → Swyer → gonadectomy + HRT; donor-egg pregnancy possible.**

## 6 MRCOG Exam Pearls — Last-Minute Page

**Numbers to know**

| | | | |
|---|---|---|---|
| **1 in 600**<br>Klinefelter (males) | **1 in 1000**<br>XYY / XXX | **< 4 mL**<br>Klinefelter testes | **40–50%**<br>Micro-TESE sperm |
| **~20–50×**<br>Breast cancer (XXY) | **15–25%**<br>X genes escaping XCI | **15–35%**<br>Gonadoblastoma (Swyer) | **~15%**<br>Swyer with SRY variant |

**HIGH-YIELD CHECKLIST**

- ☐ XXY ~1/600 males; origin 50/50 paternal/maternal.
- ☐ Tall, small firm testes, gynaecomastia, azoospermia; ↑FSH/LH, ↓T, ↓inhibin B.
- ☐ Testosterone from puberty; micro-TESE-ICSI ~40–50%.
- ☐ XXY: breast cancer, mediastinal GCT, T2DM, VTE, osteoporosis.
- ☐ XYY: paternal MII, no age effect, tall, fertile.
- ☐ XXX: maternal, tall, usually fertile, ↑ POI + seizures.
- ☐ Turner and XYY: no maternal age effect.
- ☐ Azoospermia work-up: karyotype, Y microdeletion, CFTR.
- ☐ Swyer vs CAIS vs XX male (uterus? breasts?).
- ☐ NIPT SCA: optional, low PPV — confirm; usually mild phenotypes.

**Self-assessment** — cover the right-hand column

| Question | Answer |
|---|---|
| **Hormone profile in Klinefelter?** | ↑ FSH, ↑ LH, ↓ testosterone |
| **Fertility option in Klinefelter?** | Micro-TESE + ICSI |
| **Characteristic tumour in Klinefelter?** | Breast cancer; mediastinal germ cell tumour |
| **Which meiosis gives 47,XYY?** | Paternal meiosis II |
| **Which SCAs lack a maternal age effect?** | 45,X and 47,XYY |
| **POI risk is raised in…** | 47,XXX (and Turner) |
| **Uterus present in Swyer or CAIS?** | Swyer (no AMH); absent in CAIS |
| **Why gonadectomy in Swyer?** | Gonadoblastoma risk |
| **Cause of most 46,XX males?** | SRY translocated onto the X |
| **Genetic tests in azoospermia?** | Karyotype, Y microdeletion, CFTR if CBAVD |

## 7 References


- Zitzmann M et al. European Academy of Andrology guidelines on Klinefelter syndrome. Andrology 2021.
- Tartaglia NR et al. A review of trisomy X (47,XXX). Orphanet J Rare Dis 2010.
- NICE CG156. Fertility problems: assessment and treatment. 2013 (updated 2017).