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When twins don’t match: A case of sex-discordant monochorionic twins

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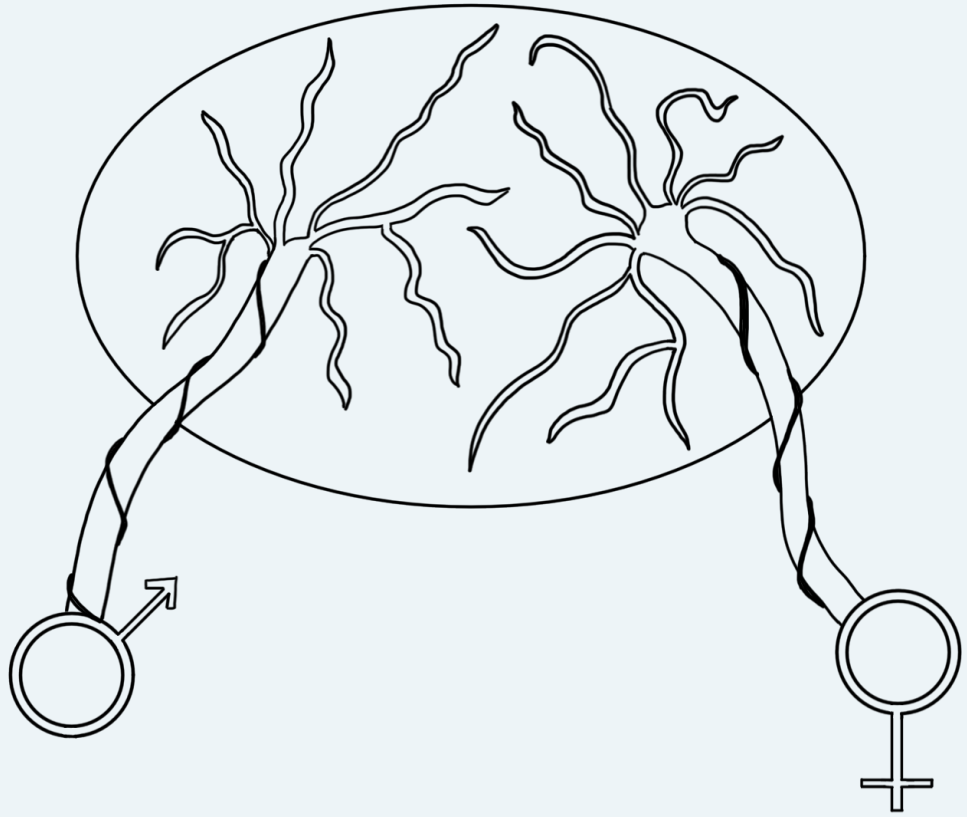

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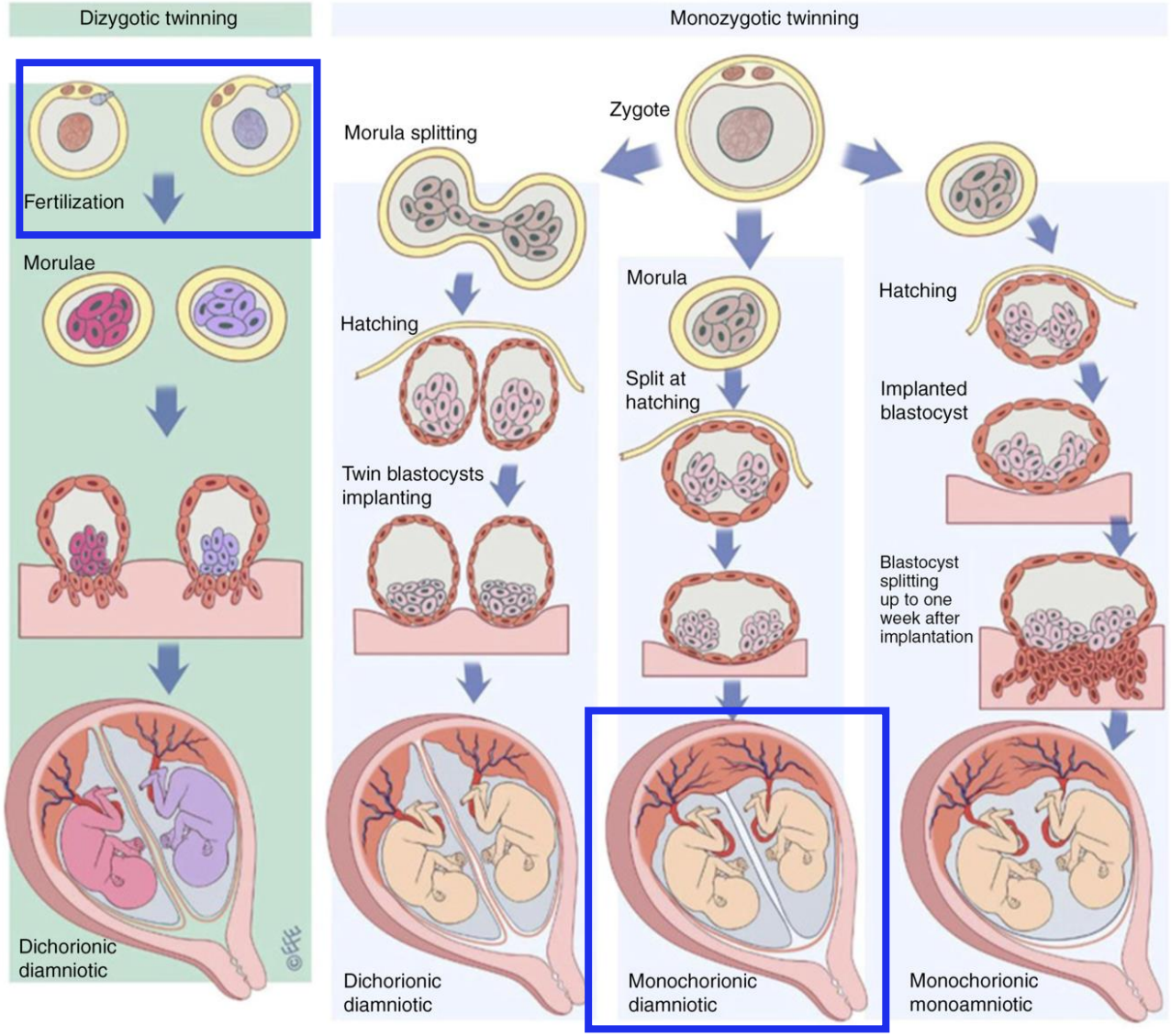
Case

- 40 year old woman, 5 years of infertility
- Conception:
  - IVF/ICSI
  - Donor oocytes
  - Dual embryo transfer
- G1P0, **MCDA** pregnancy
  - **1 boy and 1 girl**
  - Complicated by:
    - Hypertension → pre-eclampsia
    - Emergency C-section at **29+1 weeks**

Back to the basics: types of twins



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Question 1:

Why is the gender discordant in this monochorionic twin?

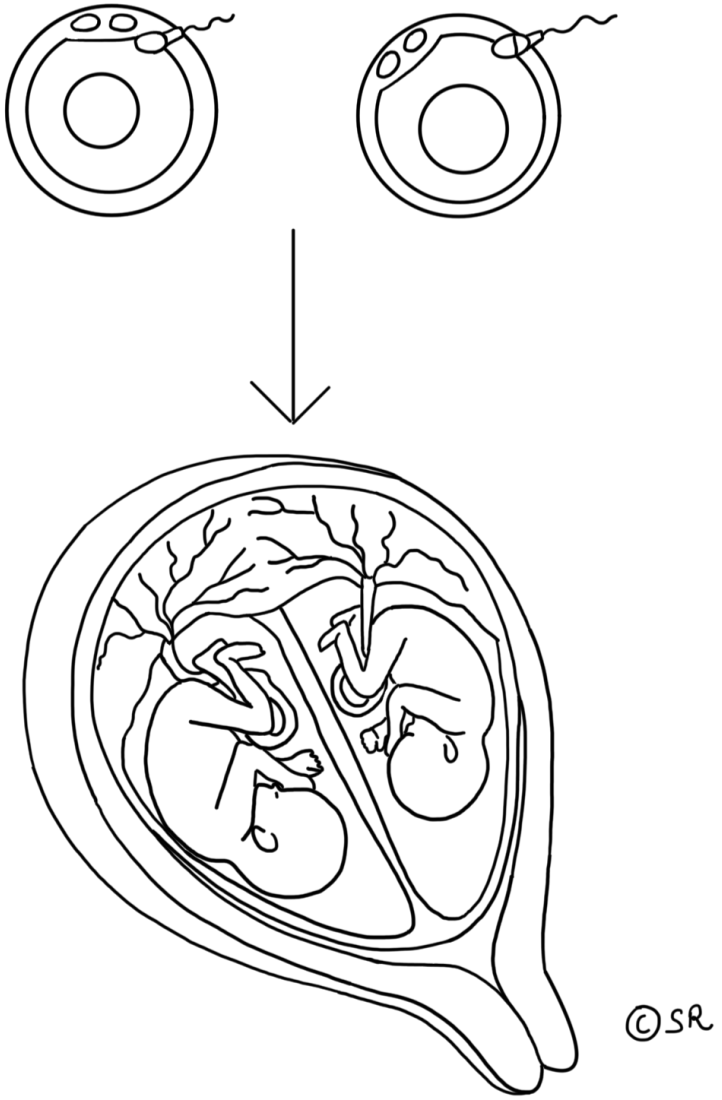
A) The gynaecologist was wrong: this is a DCDA twin.

B) This is a monochorionic dizygotic twin.

C) This is a monozygotic twin with postzygotic sex chromosome loss in one of the two fetuses.

D) This is a monozygotic twin with one of them having a disorder of sex development (DSD).

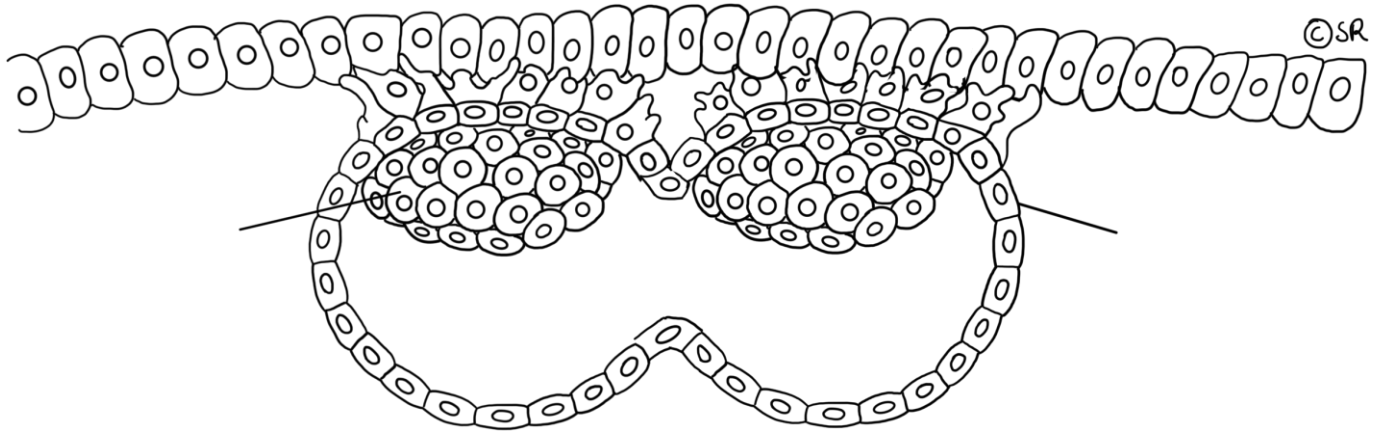
Monochorionic dizygotic twins (MCDZ)



Monochorionic dizygotic twins (MCDZ)

Conception

- **Unknown**
- Fusion of trophoblasts during early blastocyst development?
- More common in ART
  - Implantation in close proximity
  - Simultaneous embryo transfer
  - Assisted hatching



References: Peters et al. – 2017; Williams et al. – 2004; Lee et al. – 2014; Chen et al. – 2012; Rodriguez-Buritica et al. – 2014; Chen et al. – 2026

Monochorionic dizygotic twins (MCDZ)

Epidemiology

- Prevalence: ?
  - Underestimated
  - Only suspected when:
    - Discordance in phenotypic sexes → same sex MCDZ?
    - Discordance in ABO blood types
    - Congenital malformations

References: Peters et al. – 2017; Lee et al. – 2014

Monochorionic dizygotic twins (MCDZ)

Clinical consequences

- Largely **unknown**
- Prenatal consequences:
  - TTTS / TRAP / TAPS
  - (Selective) FGR
  - Congenital malformations
  - Intra-uterine fetal death (< 24 weeks)
- Postnatal consequences:
  - Mostly healthy children
  - Genital anomalies

Genital Anomalies in Sex-Discordant MCDZ Twins

- Ambiguous external genitalia female (Williams et al. 2004)
- Absence of uterus/fallopian tubes (Bogdanova et al. 2010)
- Testicular hypoplasia (Choi et al. 2013)
- Glanular hypospadias (Rodriguez-Buritica et al. 2015)

References: Peters et al. – 2017; Williams et al. – 2004; Chen et al. – 2013; Lee et al. – 2014

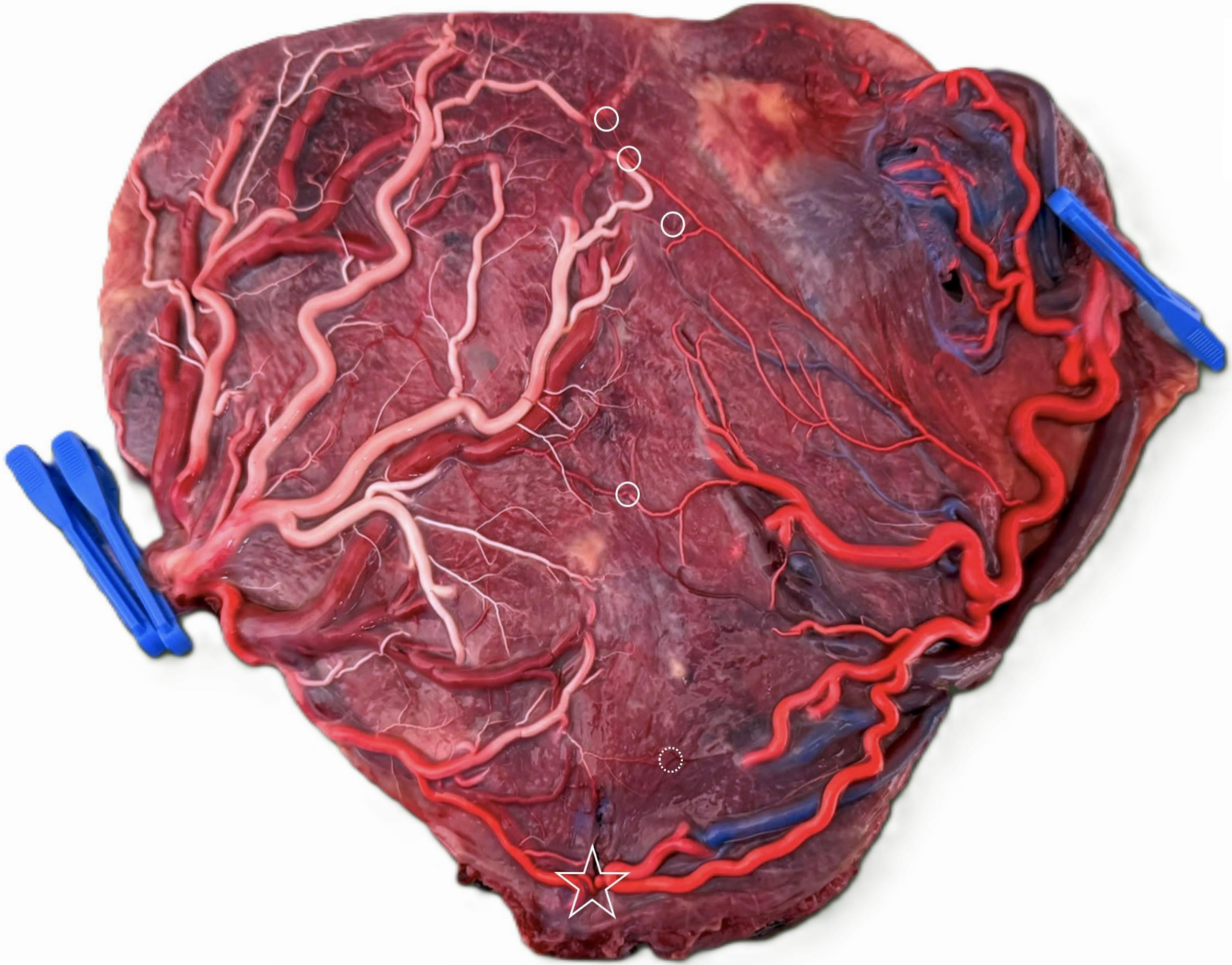
Case

Further investigations

- **Clinical examination**
  - Twin A: male phenotype
  - Twin B: female phenotype
  - No ambiguous genitalia

- **Transabdominal ultrasound of internal genitalia**
  - Boy: absence of a uterus
  - Girl: presence of a uterus

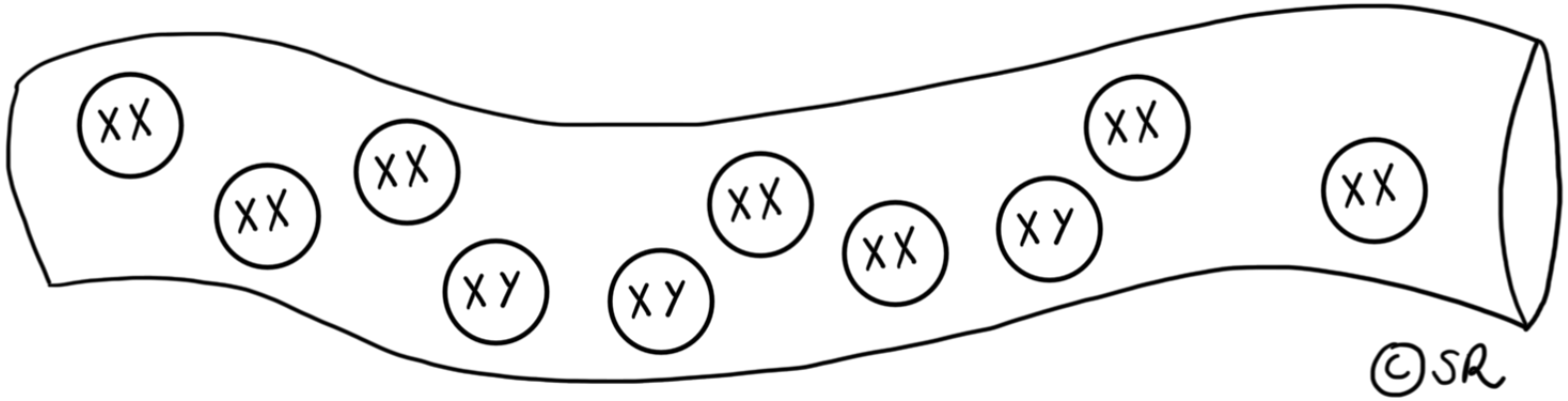
- **Pathology of the placenta**



Case

Further investigations

- **Genetic analysis**
  - Zygosity testing: dizygotic twins
  - Leukocyte culture → FISH
    - DNA pattern of **70% 46,XX and 30% 46,XY of interphases in lymphocytes**
    - Same results in both babies



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Question 2:

DNA pattern of 70% 46,XX and 30% 46,XY of interphases in lymphocytes in both babies.
What does this mean?

A) Both babies are intersex (previously called true hermaphroditism)

B) This is called mosaicism

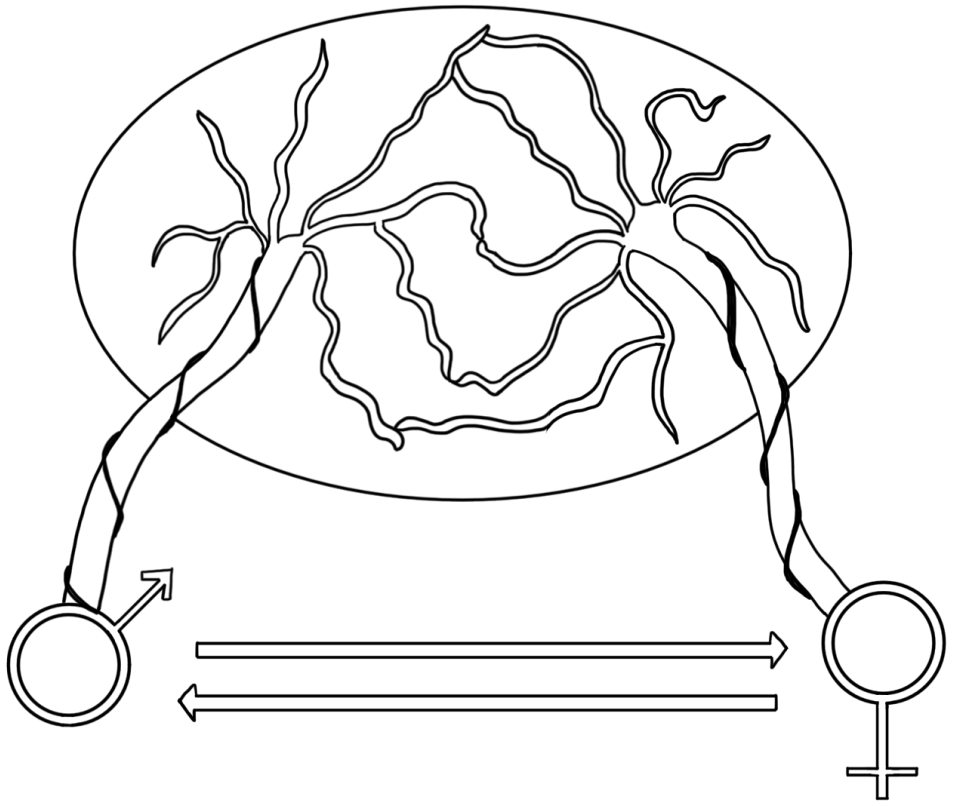
C) This is called blood chimerism

D) This is called systemic chimerism

Chimerism

What does this mean?

- Chimerism = different cell lines in one organism from **2 or more distinct zygotes**
  - >< Mosaicism = different cell lines in one organism from **a single zygote**
- Intertwin vascular anastomoses
- Shunting of haemopoietic stem cells



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References: Peters et al. – 2017; Lee et al. – 2014; Chen et al. – 2013/2026; Gilbert et al. – 2002; Walker et al. – 2007; Smeets et al. – 2013, Rodriguez-Buritica et al. – 2014

Chimerism

Blood vs. tissue chimerism

- Confined **blood** chimerism or **partial** chimerism (78.6%)
  - Shunting of haemopoietic stem cells
- **Fusion chimerism** or **whole body** chimerism (21.4%)
  - Ectopic differentiation of chimeric hematopoietic stem cells

⇒ **Differentiation by genetic tissue analysis**
- Buccal tissue
- Urine
- Gonadal tissue?

	Twin A (male)	**Twin B (female)**
Buccal tissue	99% 46,XY 1% 46,XX	100% 46,XX
Urine	Insufficient sample	77% 46,XX 23% 46,XY

References: Peters et al. – 2017; Lee et al. – 2014; Chen et al. – 2013; Gilbert et al. – 2002; Walker et al. – 2007; Smeets et al. – 2013; Chen et al. – 2026; Trombette et al – 2022

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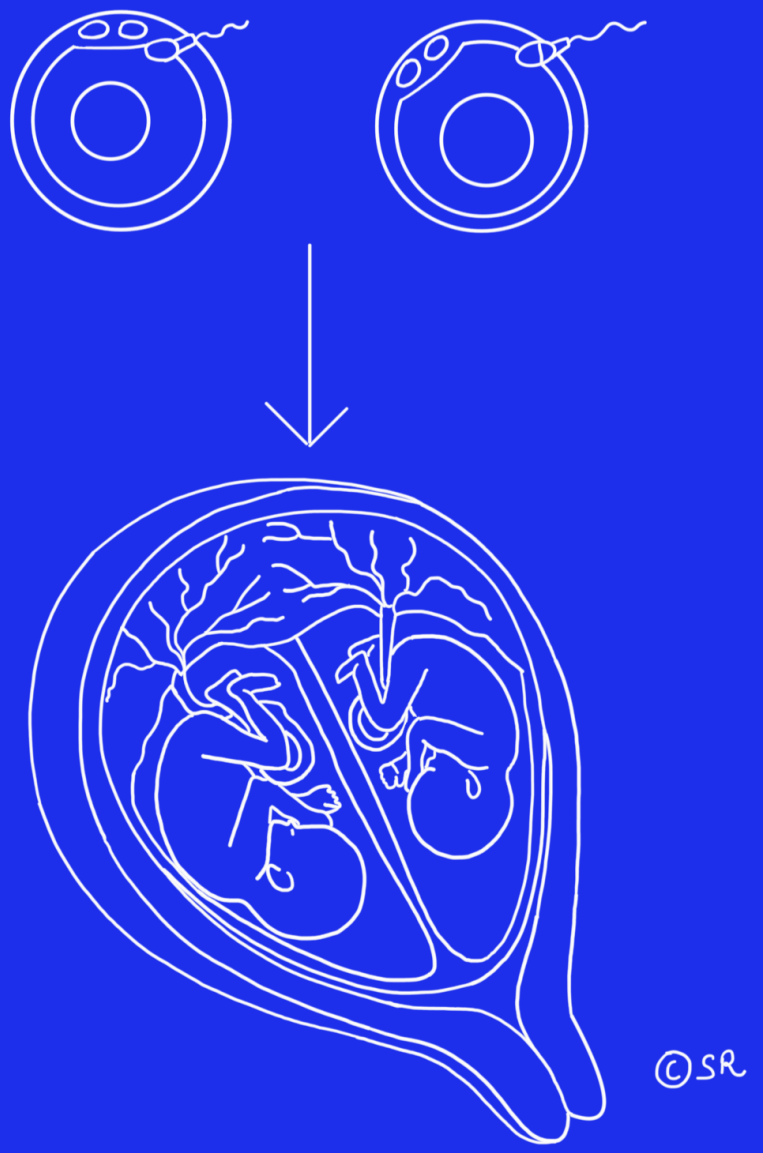
Take home message



Questions?
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