

# Male Fertility in X and Y Variations: Current State-of-the-Art and Future Implications

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# Disclosures

- None

# Klinefelter Syndrome (KS)

- First described in 1942 as an “endocrine disorder”
- Extra-X chromosome identified in 1959; re-classified as “chromosomal disorder”



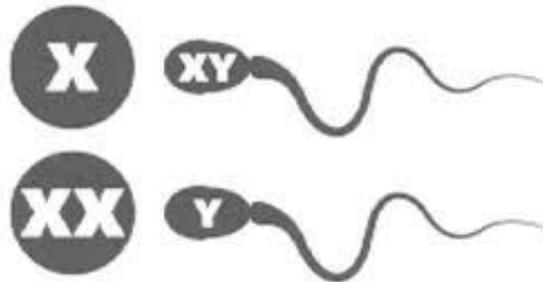
Harry F. Klinefelter, MD

# Prevalence

- 1 in 500 men
- Most common sex chromosome disorder in men
- Leading cause of male infertility

# Error in Cell Division

- Usually, a random error
- Either the egg or the sperm can have an imbalance in number of chromosomes

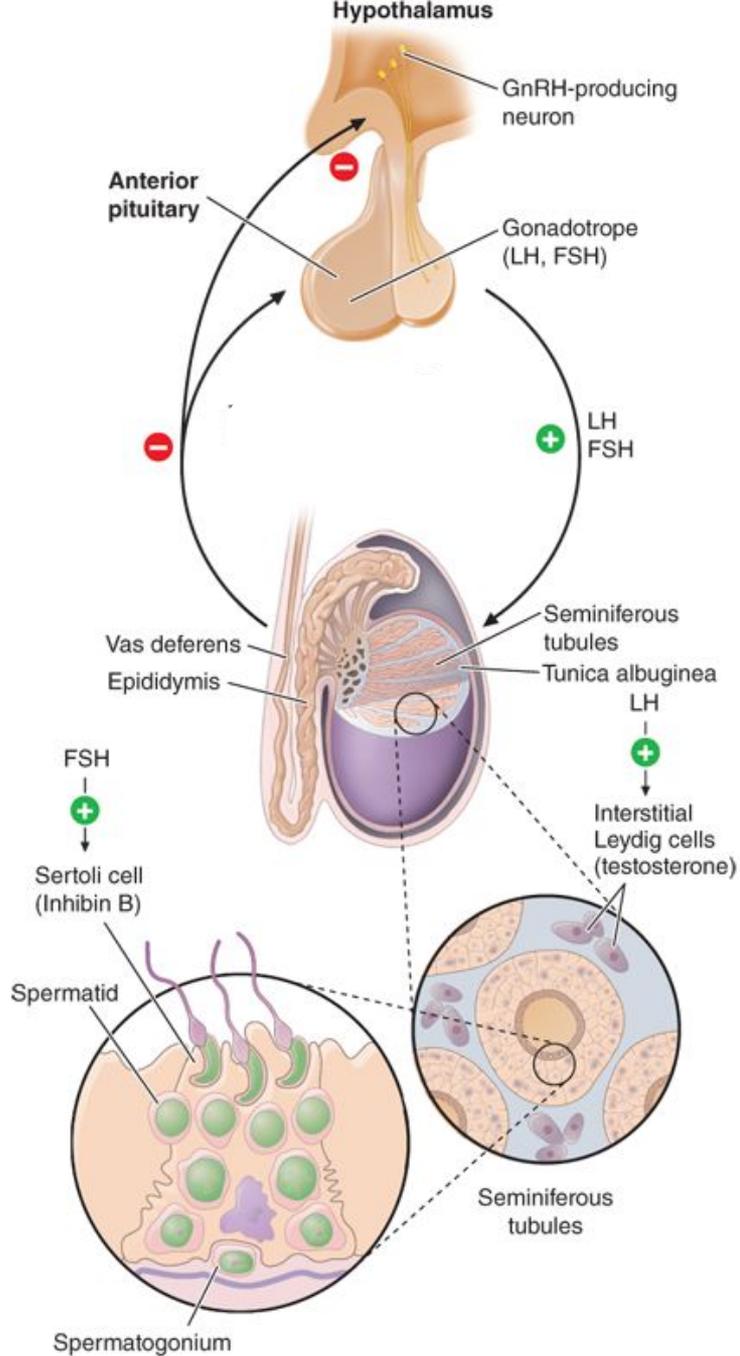


# Lots of Variability!

- 47,XXY } 80-90% of KS patients
  - Extra X chromosomes (48,XXXY, 49XXXXY etc.)
  - Mosaicism (46,XY/47,XXY)
  - Structurally abnormal X chromosome
- 10-20% of KS patients
- The “classic” KS patient is....not so classic

# Normal Testicular Function

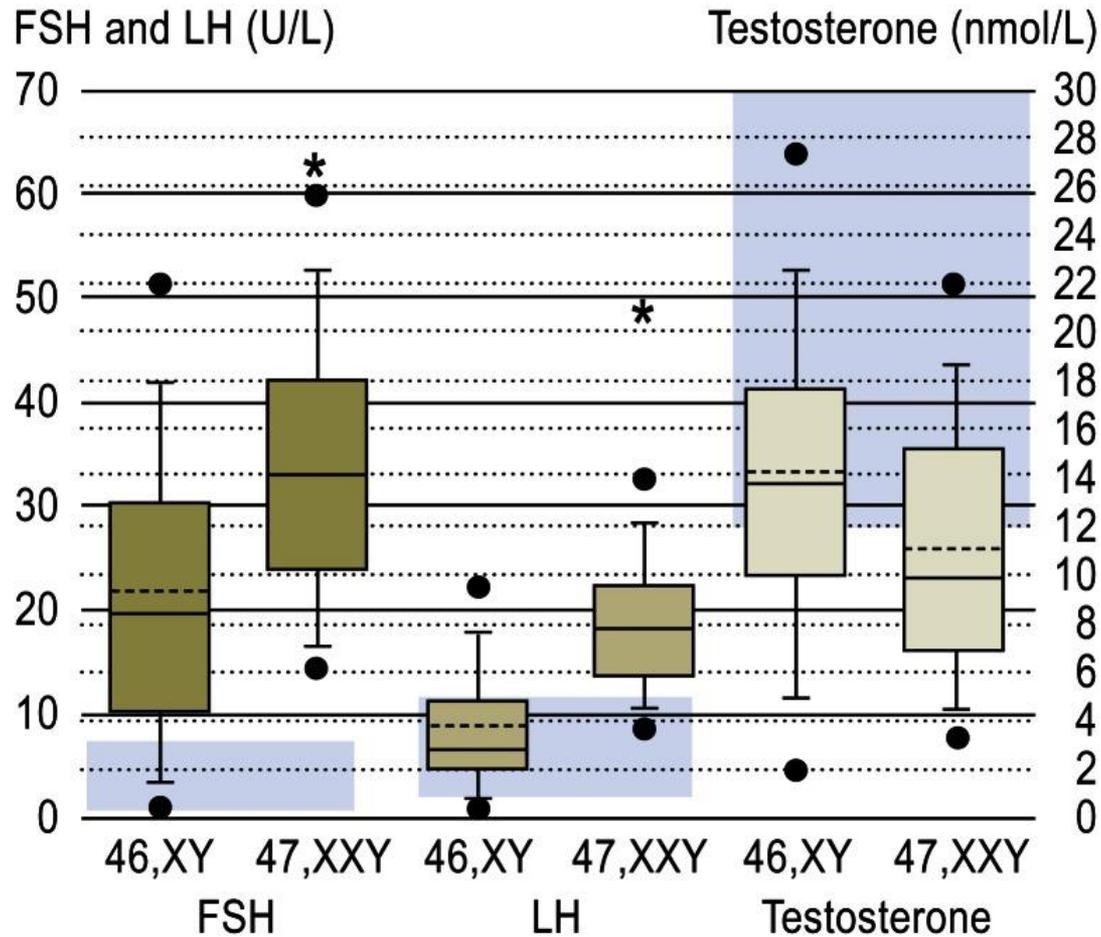
- Testosterone production
- Sperm production



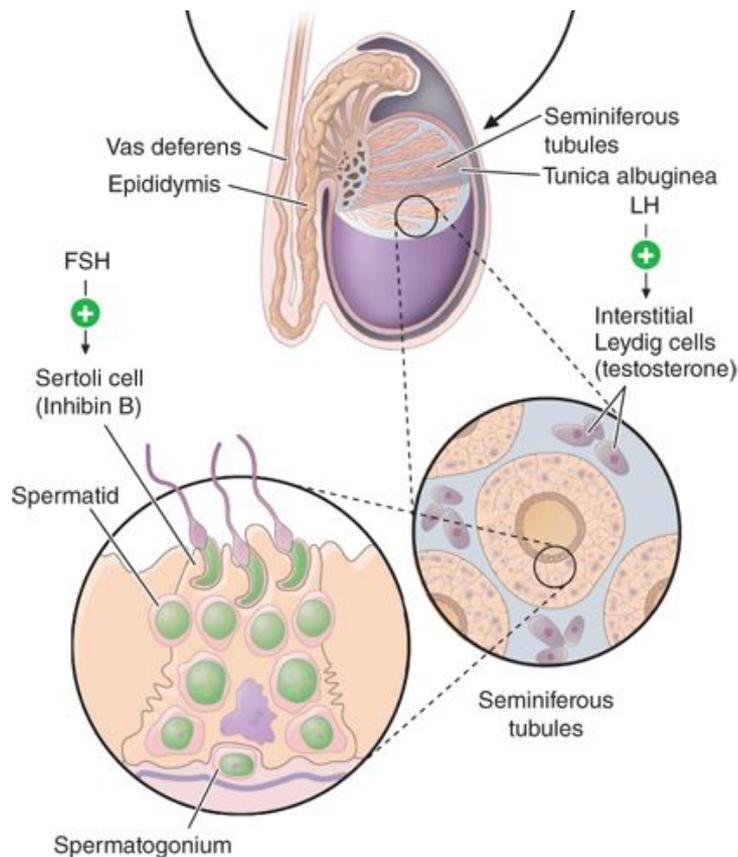
# Testosterone (T) Production

- T levels are normal in infants and pre-pubertal boys
- Most boys initiate puberty normally, but fail to progress
- T levels rise in early puberty, plateau in the low-normal range in mid-puberty, then decline

# Hormone Levels



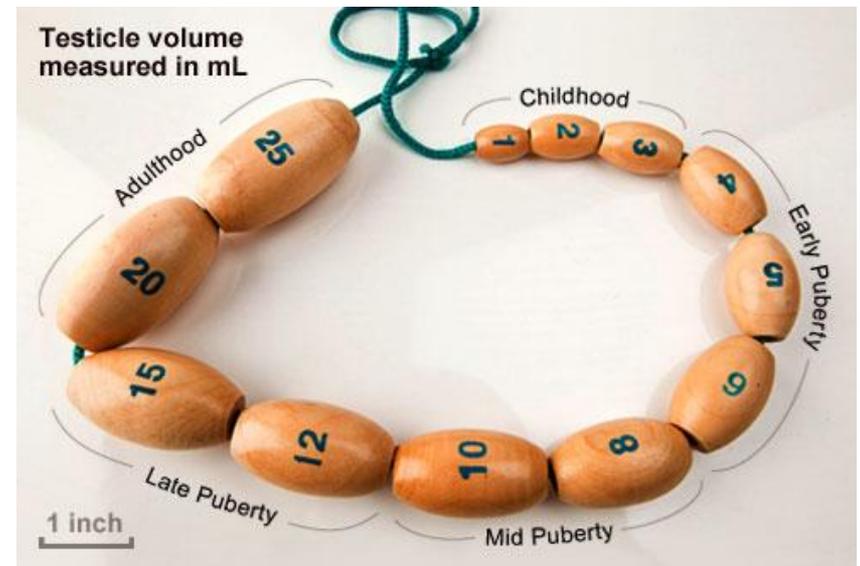
# Sperm Production



- Klinefelter syndrome
  - Germ cells do not progress normally to produce sperm
  - Seminiferous tubes become scarred
  - Rare areas of sperm production may be possible

# Testicular Size

- Boys with KS have smaller testes compared to their peers
- Testicular growth briefly increases after the onset of puberty to mid-puberty, then declines



# Puberty: A Critical Time

- Decline in testicular function begins shortly after entering puberty
- This is the time to consider testosterone therapy
- This is also the time to think fertility preservation

# Testosterone Therapy (TRT)

- Testosterone supplementation is helpful because testosterone plays many important roles:
  - Promotes growth
  - Increases muscle mass
  - Preserves bone density
  - Allows development of secondary sexual characteristics
  - Has positive psychological benefits

# But...

- Testosterone supplementation *can* harm sperm production
- We don't have a complete understanding of this effect

# TRT and Sperm Production

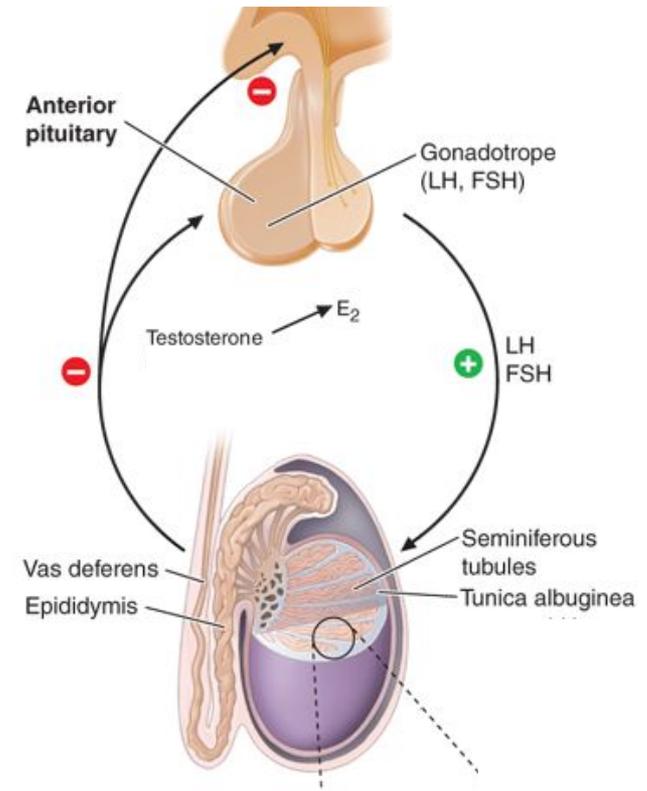
- Effect of testosterone supplementation on sperm production may be variable:
  - Initiation of therapy
  - Duration of therapy
  - Type of formulation

# Options

- Use non-testosterone based hormone therapies
- Address fertility preservation before starting testosterone therapy

# Options

- Use non-testosterone based hormone therapies
  - hCG
  - Clomiphene citrate
  - anastrozole



# Options

- Address fertility preservation before starting testosterone therapy
  - Ejaculated semen sample
  - Surgical sperm retrieval
  - Testicular tissue cryopreservation



# Fertility Outcomes

- Natural conception
- Intrauterine insemination (IUI)
- In vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) - most common



# Fertility Outcomes

- Success rate of surgical sperm retrieval: 28-69% (average 51%)
- Predictors of successful sperm retrieval: age, pre-operative serum testosterone level
- Surgically retrieved sperm must be used with IVF/ICSI

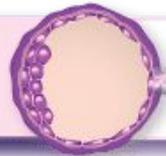
# Fertility Outcomes

- Higher risk of sperm chromosomal abnormalities
- Pre-implantation genetic screening is recommended
- Majority of children born to fathers with KS have been healthy



## How Preimplantation Genetic Screening (PGS) Works

1



A small sample of cells are removed from the outside layer of a blastocyst embryo.

2



The cells that have been removed from each embryo are loaded into a small tube and sent to the reference laboratory for Next Generation Sequencing.

3



The cells are analyzed to verify that all 23 sets of chromosome pairs are identified to confirm the embryo is genetically normal.

4



Based on the genetic results, you and your medical team will select which embryo will be transferred.

# Summary

- Paternity is possible
- Fertility potential should be discussed in early adolescence, before starting testosterone therapy
- Research is ongoing to further expand reproductive options for patients with KS

# THANK YOU

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