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 “chromosomonal disorder”
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 \[80-90\% \text{ of KS patients}\]
- Extra X chromosomes (48,XXXY, 49XXXXY etc.)
- Mosaicism (46,XY/47,XXY)
- Structurally abnormal X chromosome

\[10-20\% \text{ of KS patients}\]

- 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

Wikstrom et al, 2007
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
  - anastrazole
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
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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