Thinking About Starting Testosterone for XXY/XXYY/XXXY

Shanlee Davis, MD, MSCS
Pediatric Endocrinologist, eXtraordinarY Kids Clinic
University of Colorado School of Medicine
Section of Pediatric Endocrinology, Children’s Hospital Colorado
Disclosures

• No relevant disclosures
Outline

• Basics of Puberty and Hormones
• Puberty & Hormones in XXY/XXXY/XXXXY
• When (and why) to start testosterone
• Frequently Asked Questions
• Infant and other pre-pubertal testosterone
  • 2pm today in Columbia

• Formulations of testosterone
  • 2pm today in Oxford

• Fertility Preservation
  • RIGHT NOW in Harvard

• Non-testosterone medication management
  • 10am tomorrow in Yale
Puberty: a time of change

PUBERTY is the process of physical changes involved when a child’s body matures into an adult body.

**First sign?** testicular enlargement

**When?** Starts 11-12 years old (anywhere 9-14 years is normal)

**How long?** ~5 years

**Why?** Hormones
Hormones 101

A HORMONE is a message sent from one part of the body to another.

At the start of puberty: the brain “turns on” the system
The pituitary gland releases LH and FSH
LH talks to the cells in the testes that produce testosterone
FSH talks to the cells in the testes that make the testes grow and support germ cell (sperm) development
Testosterone Effects

**SKIN**
- Acne
- Body & facial hair
- Pubic hair
- Balding

**BRAIN**
- Mood, memory, executive function, sex drive

**VOICE BOX**
- Voice deepening

**GENITALS**
- Penile growth
- Erections
- Sperm production

**BONE**
- Linear growth
- Growth plate closure
- Bone strength

**MUSCLE**
- Mass and strength
- Less fat tissue

**ORGANS**
- Increase red blood cells
- Protein synthesis
A closer look in the testes

XY Male Testis

Testes with an extra X

Germ cells
Leydig cells
Sertoli cells

germ cells
leighdig cells

Scarring
Problem in the testes

In XXY/XXYY

FSH $\uparrow$ 1 year after puberty onset
LH $\uparrow$ 2 years after puberty onset
Testosterone Levels

- Normal range of testosterone for 46,XY males
- Testosterone range in XXY/XXYY/XXXY

![Graph showing testosterone levels over age]

**Axes:**
- Y-axis: Testosterone
- X-axis: Age (approximate)
Puberty in XXY/XXYY/XXXY

- Pubic hair occurs before testicular enlargement in over half (average age 11.5)
- Testicular enlargement is minimal (max 5-8 mL), often decreases later to 2-4 mL
- Less body hair
- Less muscle bulk
- Taller stature
- More gynecomastia?
When to start testosterone?

• Not yet any evidence-based or even consensus guidelines

• Considering the boy’s age, pubertal development, mental and physical health, and blood work – not **just** based on a blood level

• Not cookie-cutter and input from the parents (and ideally the child) is helpful
When to start testosterone?

Different Approaches:

A: Pre-pubertal or immediately pubertal. All measurable hormones normal (RESEARCH).

B: Rising LH, T may still be within the normal range.

C: Testosterone levels below the normal range (and falling).

D: Low T + clinical signs of testosterone deficiency: gynecomastia, stalled puberty, fatigue, osteoporosis, poor sexual function.
Our Practice

- Endocrinology evaluation at 10-11 years of age or first sign of puberty – build a relationship
- Physical Examination
- Bone age x-ray
- Blood tests of hormones
  - Every ~6 months

LH above the upper limit of normal for pubertal stage or consistently rising we consider testosterone supplementation
FAQ: How do we give T?

- There are many formulations of T on the market
- < 18 years, our choices are more limited
  - Testosterone shots (IM or SQ)
  - Testosterone gel
- Pros and cons → individualization
- Experience from two great guys
FAQ: What are the side-effects?

- Local skin reactions / allergies (preservatives)
- Acne
- Bone age advancement / fusion of growth plates
- Clotting or bleeding issues; increased hematocrit
- Mood changes or aggression
- Preoccupation with sex, frequent erections, priapism
- Testosterone can be a drug of abuse
- FDA warning heart attacks/death – old men

Our goal is always to NORMALIZE testosterone concentrations NOT to exceed normal levels
FAQ: Does T reduce fertility outcomes?

Giving T: ↓ LH →
↓ intratesticular testosterone →
↓ spermatogenesis

BUT, this doesn’t seem to be permanent...right away

<table>
<thead>
<tr>
<th>Ages 15-24 years</th>
<th>Ages 24-35 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young group</td>
<td>Adult group</td>
</tr>
<tr>
<td>TESE + rate (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6/10 (60.0)</td>
<td>7/15 (46.2)</td>
</tr>
<tr>
<td>3/7 (42.9)</td>
<td>7/9 (77.8)</td>
</tr>
<tr>
<td>9/17 (52.9)</td>
<td>14/24 (59.1)</td>
</tr>
<tr>
<td>13/25 (52.2)</td>
<td>10/16 (62.5)</td>
</tr>
<tr>
<td>23/41 (56.4)</td>
<td></td>
</tr>
</tbody>
</table>

Plotton et al, TESE in Young vs Adult Nonmosaic 47,XXY JCEM, 2015
FAQ: Does T reduce fertility outcomes?

My approach (right now):
• ~>14 years old (new diagnosis, etc), discuss with family, offer referral to repro endo if desired
• ~<14 years old, do not delay testosterone treatment if needed
• Continue fertility discussions
FAQ: Once T is started, can it ever be stopped?

- YES. It does not have to be a permanent decision
- I encourage the patient to be involved in the discussion
- “Trials” are perfectly fine
- May have to stop if considering attempt at sperm retrieval
FAQ: Does every guy with XXY/XXXY/XXYY need T?

• “Need” is hard to define
• Universally, testes do not function normally
• Almost all will have elevated LH levels, but not all will have low testosterone levels
• Most will benefit from supplementary T
Limitations & Future Directions

- We have so little evidence-based research on when, why, and how to start testosterone in boys with XXY/XXXY/XXYY
- More research to come to help us!
- THANK YOU to the boys and families who participate in important research!!!
Summary

• The decision of when to start testosterone should involve the patient, parents, and the physician

• It may include all of the following
  • Growth and pubertal exam
  • Laboratory measures (LH, FSH, T)
  • Mental & physical health considerations
  • Patient and family preferences

• Our goal is to replace without causing side effects or exceeding normal values

• Advocate for yourself/child
Acknowledgements

Mathew & Kyler

eXtraordinarY Kids Clinic Team
Nicole Tartaglia, MD, MS
Susan Howell, MS, MBA, CGC
Tanea Tanda
Lisa Cordeiro, MS
Rich Boada, PhD
Jen Janusz, PsyD
Rebecca Wilson, PsyD
Jackie Frazier, MA, SLP
Syd Martin, OT-R
Sarah McSwegin, LSW
Philip Zeitler, MD, PhD
questions