HORMONES IN XXY, XXYY AND XXXY

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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
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

**ORGANS**
- Increase red blood cells
- Protein synthesis

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

9 yo XY Male Testis
- Germ cells
- Leydig cells
- Sertoli cells

9 yo XXY Male Testis
- Germ cells
- Leydig cells
- Scarring
Problem in the testes

In XXY/XXYY

FSH ↑ 1 year after puberty onset
LH ↑ 2 years after puberty onset
Testosterone Levels

Normal range of testosterone for 46,XY males

Testosterone range in XXY/XXYY/XXXY
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
FAQ: When to start testosterone?

No consensus guidelines for XXY

Endocrine Society Hypogonadism Guidelines
Low T + clinical signs of testosterone deficiency

pre-pubertal or early pubertal
All measurable hormones normal (RESEARCH)

Rising LH, T still within the normal range

LH high + low T (or falling T)

Serum Testosterone

Infancy  Childhood  Adolescence  Adulthood

XY  XXY
Our Practice

- Endocrinology evaluation at ~10 yrs or first sign of puberty – **build a relationship**
- Physical Examination
- Bone age x-ray
- LH, FSH, T
  - Every ~6 months

LH above the upper limit of normal for pubertal stage or consistently rising we consider testosterone supplementation
Supplemental Testosterone

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

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

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

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

**MUSCLE**
Mass and strength
Less fat tissue

**VOICE BOX**
Voice deepening

**ORGANS**
Increase red blood cells
Protein synthesis
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
FAQ: What is the best formulation/dose?

- One small study on 1% gel in XXY
  - Start 1 pump daily → sometimes too much
  - Titrate serum levels, exam, symptoms

- Weekly subcutaneous injections
  - Start at 20-30 mg/week
  - Titrate serum levels (trough), exam, symptoms

- Monthly IM injections
  - Start 100-150 mg/month
  - Titrate up based on exam, symptoms (max 200 q2 wks)

- Patches aren’t my first choice

- Other formulations too potent

Rogol et al, J Adolesc Health 2014
Davis, Rogol, Ross, EMCNA 2015
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 every guy with XXY 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
  • Bone density
• Encourage trials (can come off)
• Individualize therapy with parents and patient
FAQ: Does T worsen behavior?

• No evidence implicating T treatment to worsened behavior in XXY (if kept in the normal range)
• Adolescence is a time when psychiatric conditions develop and behavior worsens (for all)
• Start low & go slow if concerns
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 preservation
FAQ: Does T reduce fertility outcomes?

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

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

| Table 3. Positive TESE Rate According to Age Group and Previous T Treatment |
|---------------------------------|------------|-------------|--------|
| TESE + rate (%)                | Yes       | No          | Total  |
| Young group                    |           |             |        |
| Ages 15-24 years               | 6/10 (60.0) | 7/15 (46.2) | 13/25 (52.2) |
| Ages 24-35 years               | 3/7 (42.9)  | 7/9 (77.8)  | 10/16 (62.5) |
| Adult group                    | 9/17 (52.9) | 14/24 (59.1) | 23/41 (56.4) |
| Total                           |           |             |        |

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

Successful testicular sperm retrieval in adolescents with Klinefelter syndrome treated with at least 1 year of topical testosterone and aromatase inhibitor

Akanksha Mehta, M.D., Alexander Bolyakov, M.Sc., Jordan Roosma, Peter N. Schlegel, M.D., and Darius A. Paduch, M.D., Ph.D.
Department of Urology, Weill Cornell Medical College, New York, New York

Our approach (right now):
- ~>14 years old (new diagnosis, etc), discuss with family, offer referral to repro team if desired
- ~<14 years old, do not delay testosterone treatment if needed
- Continue fertility discussions

Mehta et al, Andrology, 2015
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
# Cardiometabolic Screening in XXY

## (My Approach)

<table>
<thead>
<tr>
<th>Screening</th>
<th>When to get it</th>
<th>What to know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height &amp; Weight</td>
<td>Every visit (at least annually)</td>
<td>Plot on growth curves including BMI, trend is most important</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Annually &gt; 3 years old</td>
<td>Blood pressure norms depend on sex, age, and height</td>
</tr>
<tr>
<td>LDL, HDL, triglycerides</td>
<td>At 9-11 years old in all, then every 1-3 years</td>
<td>Cholesterol (lipids) screening, best done when fasting</td>
</tr>
<tr>
<td>HbA1C</td>
<td>Annually if obese &gt; 10 years old, as needed for symptoms/risk</td>
<td>Diabetes screening; Measures of blood sugar over the last 3 months</td>
</tr>
<tr>
<td>AST, ALT</td>
<td>Every 1-3 years starting in puberty</td>
<td>Liver function tests, screening for fatty liver disease</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Depends on diet/history</td>
<td>Low in many people, may or may not have consequences</td>
</tr>
</tbody>
</table>
Resource for Providers

Advances in Pediatrics 63 (2016) 15–46

ADVANCES IN PEDIATRICS

Advances in the Interdisciplinary Care of Children with Klinefelter Syndrome

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questions