Thinking About Starting Testosterone for XXY/XXYY/XXXY

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Disclosures

- No relevant disclosures

Outline

- Basics of Puberty and Hormones
- Puberty & Hormones in XXY/XXXY/XXYY
- When (and why) to start testosterone
- Frequently Asked Questions

Not Covered Here

- 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

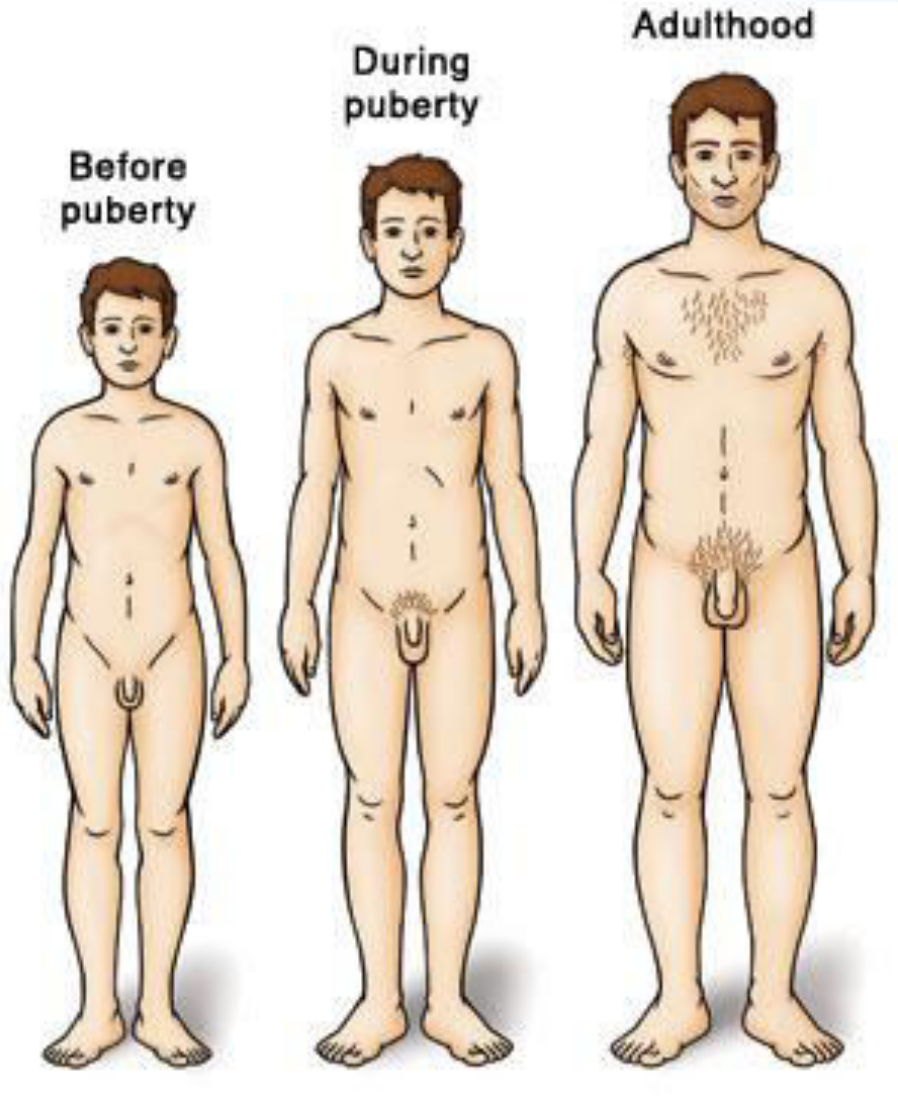
PUBERTY is the process of physical changes involved when a child's body matures into an adult body

First sign? testicular enlargement

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

How long? ~5 years

Why? Hormones



Hormones 101

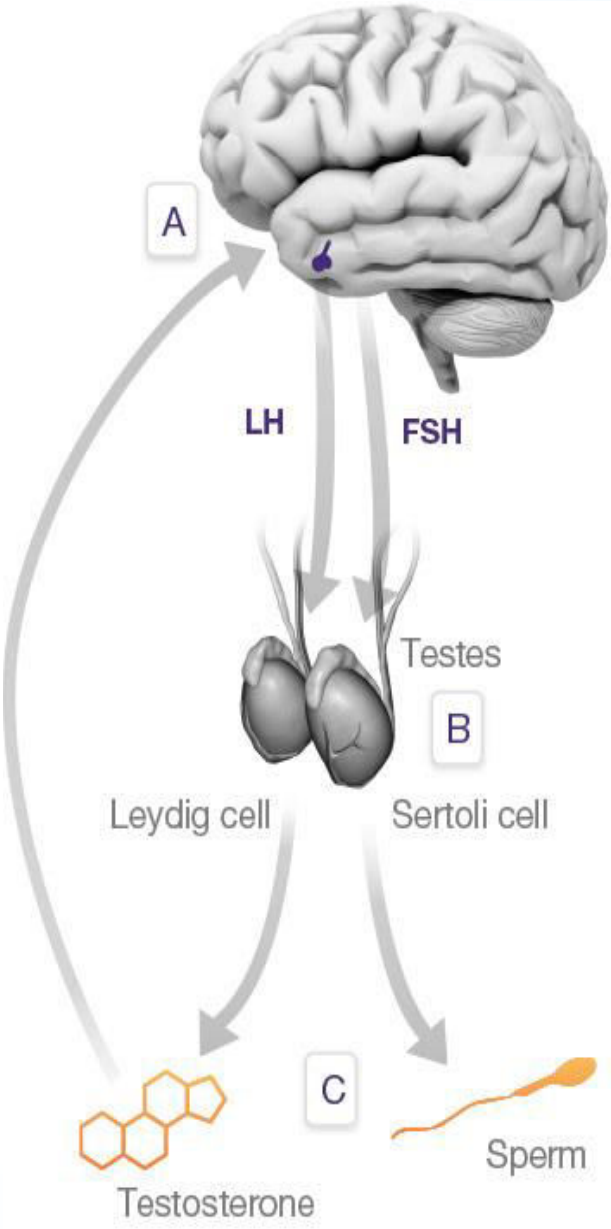
A HORMONE is a message sent from one part of the body to another.

At the start of puberty: the brain "turns on" the system

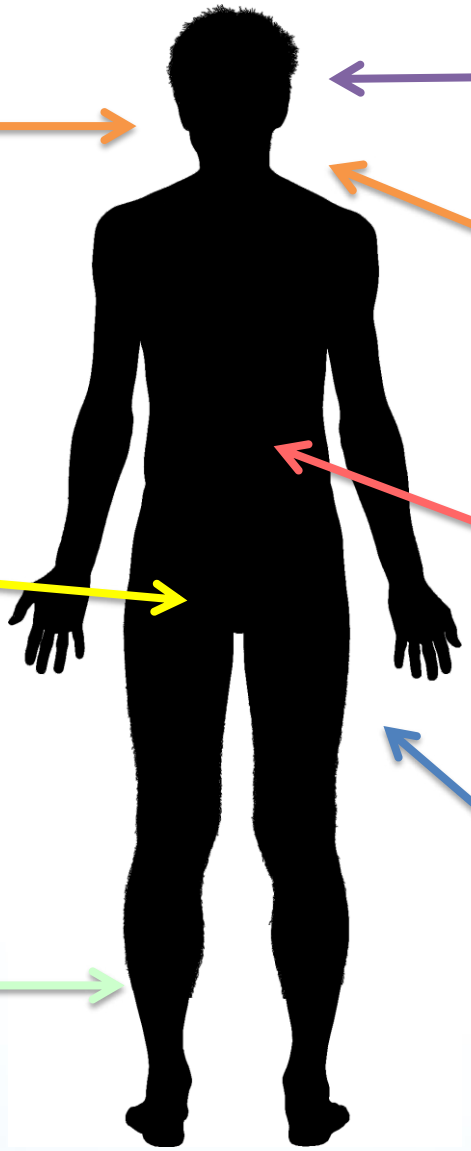
The pituitary gland releases LH and FSH

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

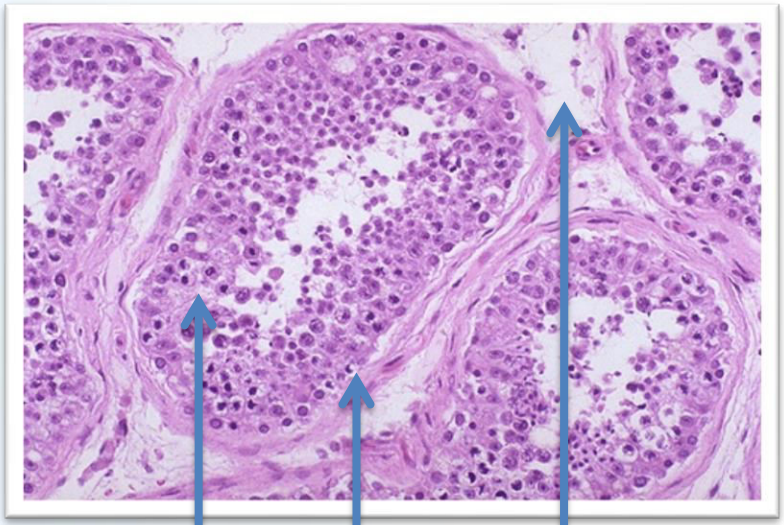
ORGANS
Increase red blood cells
Protein synthesis

BONE
Linear growth
Growth plate closure
Bone strength

MUSCLE
Mass and strength
Less fat tissue

A closer look in the testes

XY Male Testis

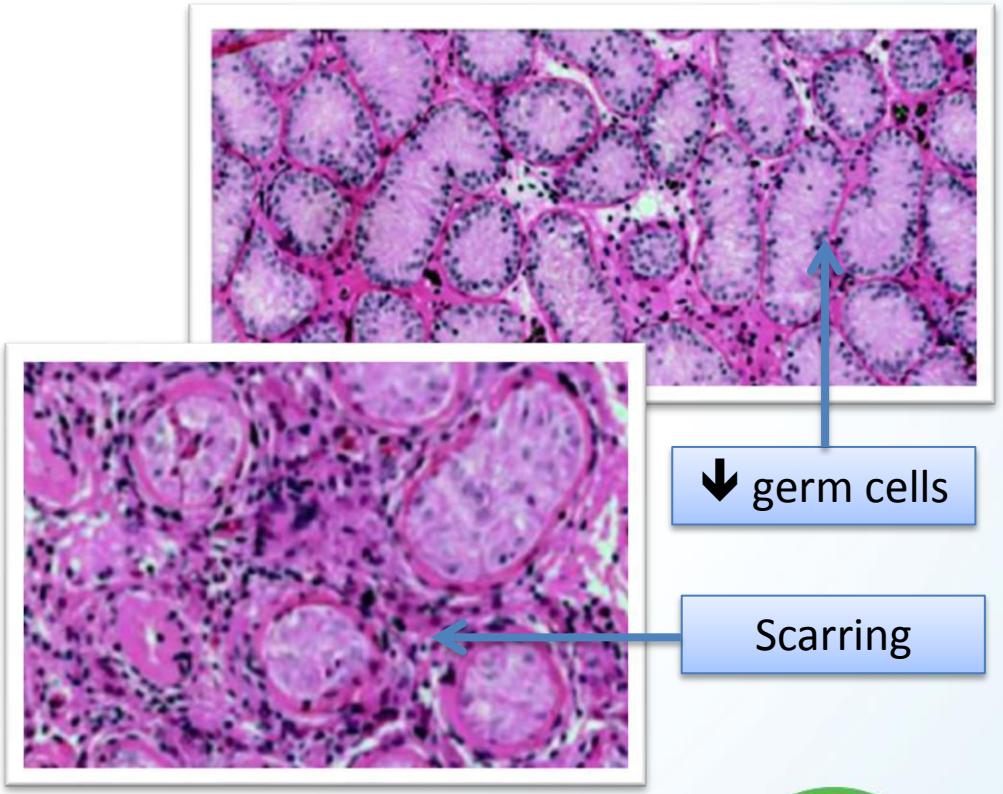


Germ cells

Leydig cells

Sertoli cells

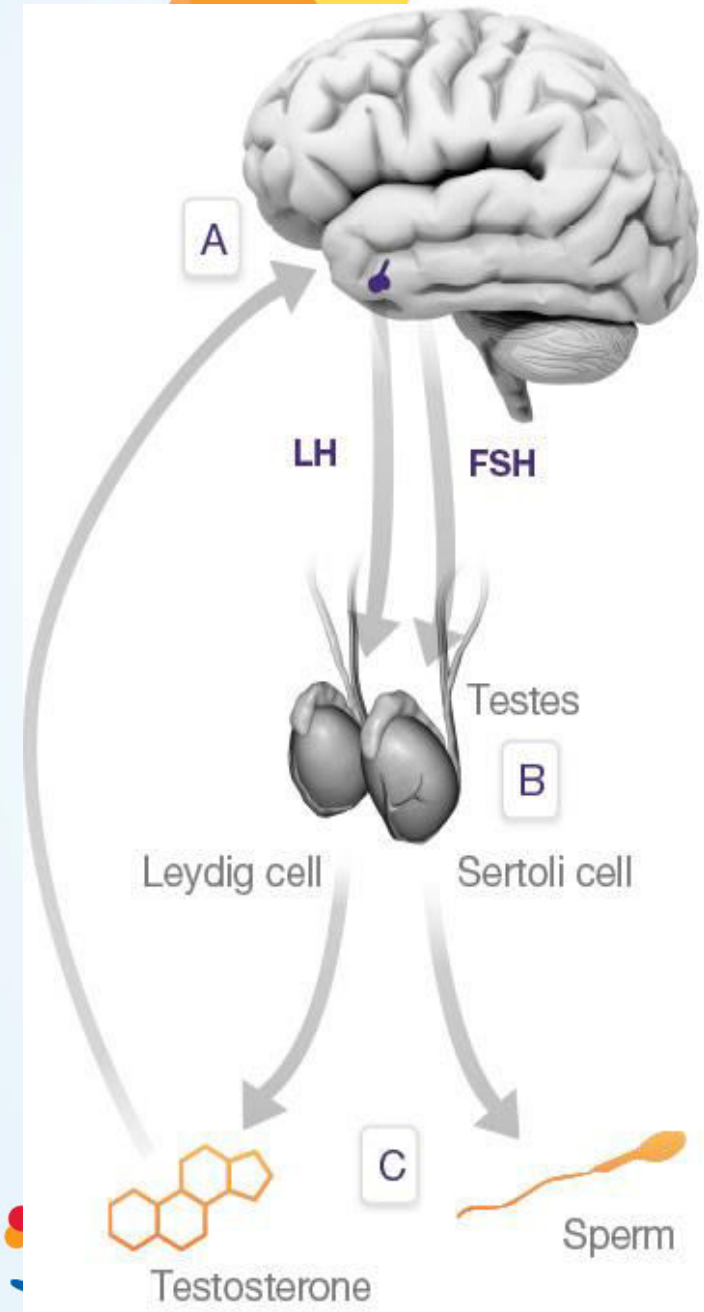
Testes with an extra X

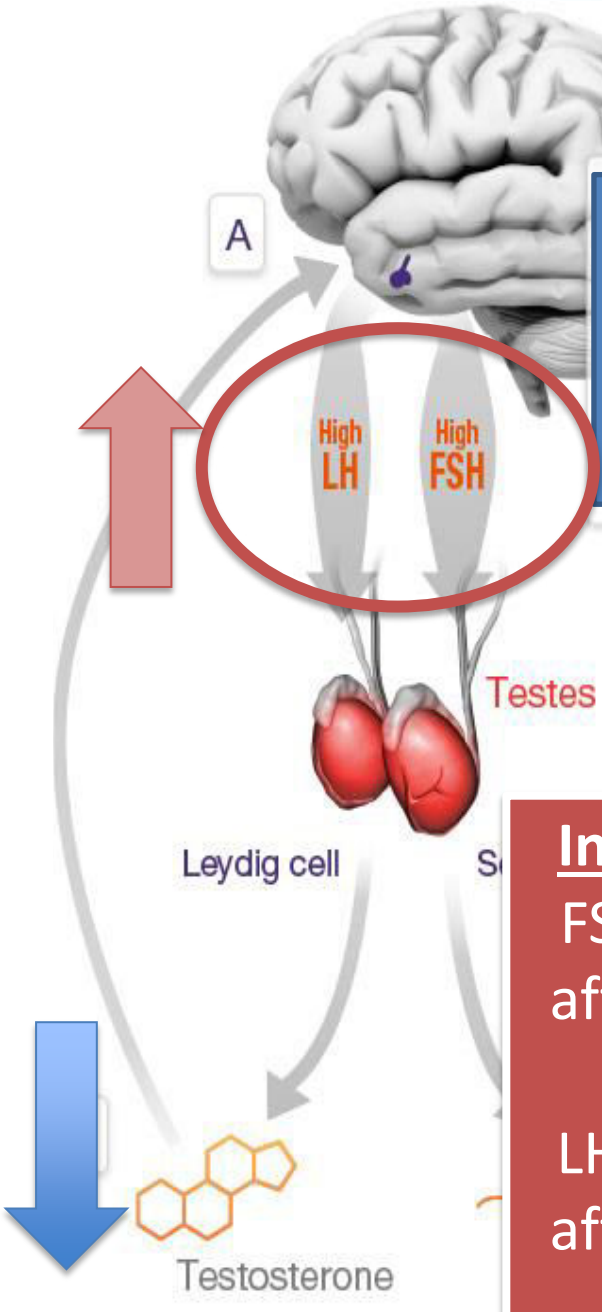


↓ germ cells

Scarring

↑ leydig cells





Problem in the testes

In XXY/XXYY

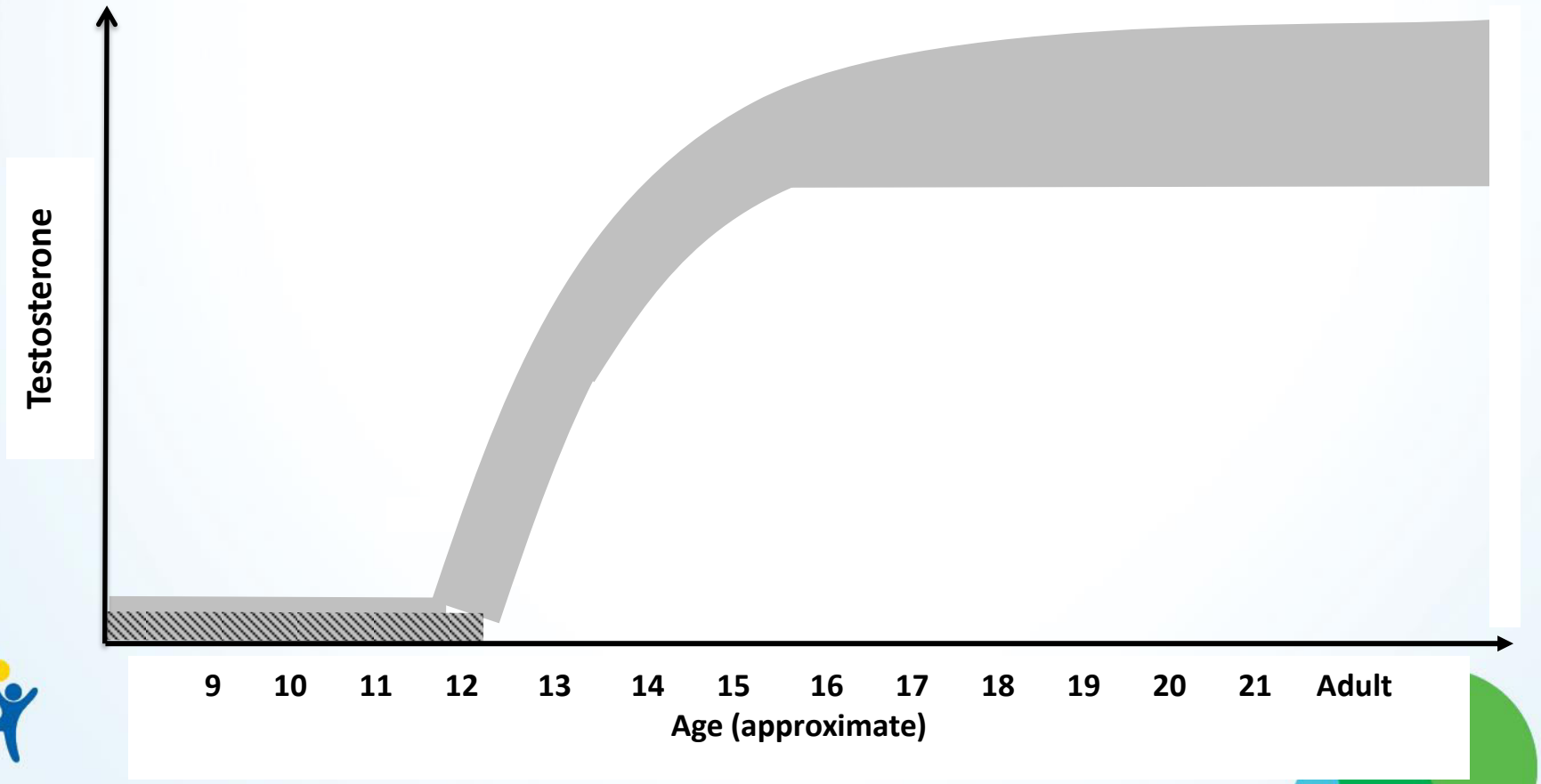
FSH ⇧1 year after puberty onset

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**

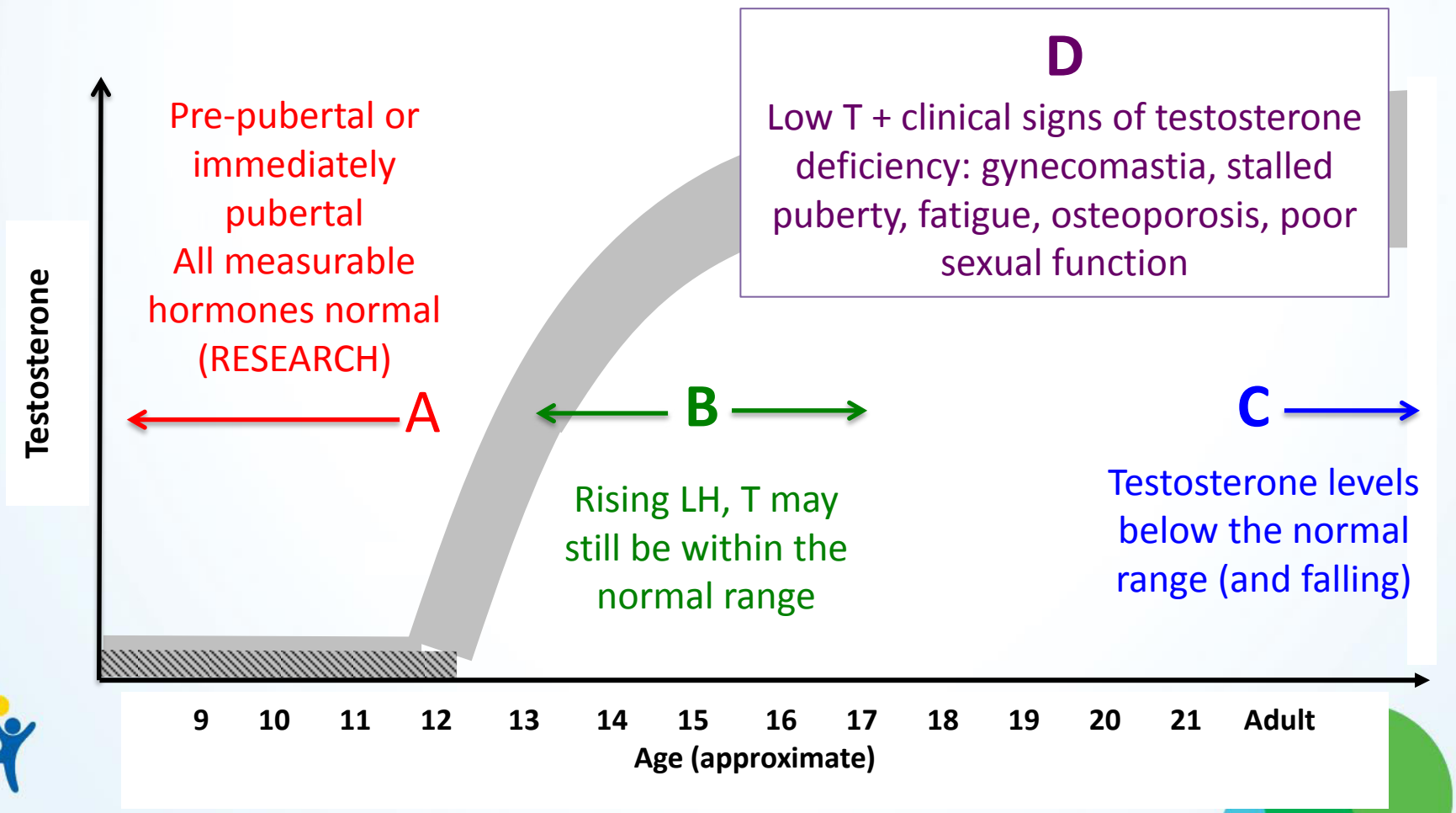
- Pubic hair occurs before testicular enlargement in over half (average age 11.5)
- Testicular enlargement is minimal (max 5-8 mL), often decreases later to 2-4 mL
- Less body hair
- Less muscle bulk
- Taller stature
- More gynecomastia?

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 <u>just</u> 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:

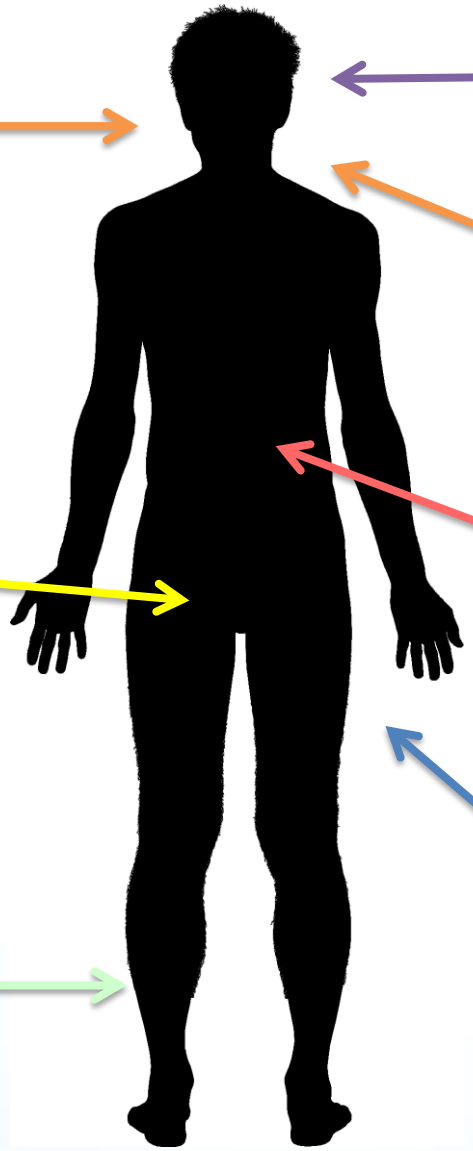


Our Practice

- 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

Supplemental Testosterone



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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 3. Positive TESE Rate According to Age Group and Previous T Treatment

		Previous T Treatment		
	TESE + rate (%)	Yes	No	Total
Ages 15-24 years →	Young group	6/10 (60.0)	7/15 (46.2)	13/25 (52.2)
Ages 24-35 years →	Adult group	3/7 (42.9)	7/9 (77.8)	10/16 (62.5)
	Total	9/17 (52.9)	14/24 (59.1)	23/41 (56.4)

Plotton et al, TESE in Young vs Adult Nonmosaic 47,XXY JCEM, 2015

FAQ: Does T reduce fertility outcomes?

ORIGINAL ARTICLE: ANDROLOGY

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

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

Patient characteristics and success of sperm retrieval.

Patient	Age at TESE (y)	Testis volume (cm3)	Duration of hormone therapy (mo)	Total T (ng/dL)		LH (mIU/mL)		FSH (mIU/mL)		Sperm retrieved
				Base	Pre-op	Base	Pre-op	Base	Pre-op	
1	14	3	15	161	345	1.8	12.1	17.6	58.6	Yes
2	14	2.5	40	40	253	2.9	17.3	8.3	74.5	No
3	16	10	14	214	990	12	7.4	23	20.2	Yes
4	15	5.5	34	251	895	1.9	8.6	8.1	16.7	Yes
5	15	2.5	22	210	873	20.4	16.5	47.3	40.1	Yes
6	14	6	12	57	126	1.0	6.3	2.4	31.1	No
7	16	2	12	179	746	25.1	24.6	40.7	27.9	Yes
8	22	2.5	>60	350	744	19	46.2	34.6	45.0	Yes
9	14	1	30	226	513	0.6	4.8	1.4	4.7	Yes
10	15	3.4	35	236	513	0.4	4.1	1.2	15.3	No

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

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questions