Management of Permanent Hypogonadism in Boys

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Disclosures

- Y-MC was a medical advisory board member for Endo Pharmaceuticals.
- SBS has nothing to disclose.

- This presentation will discuss off-label use of medications.

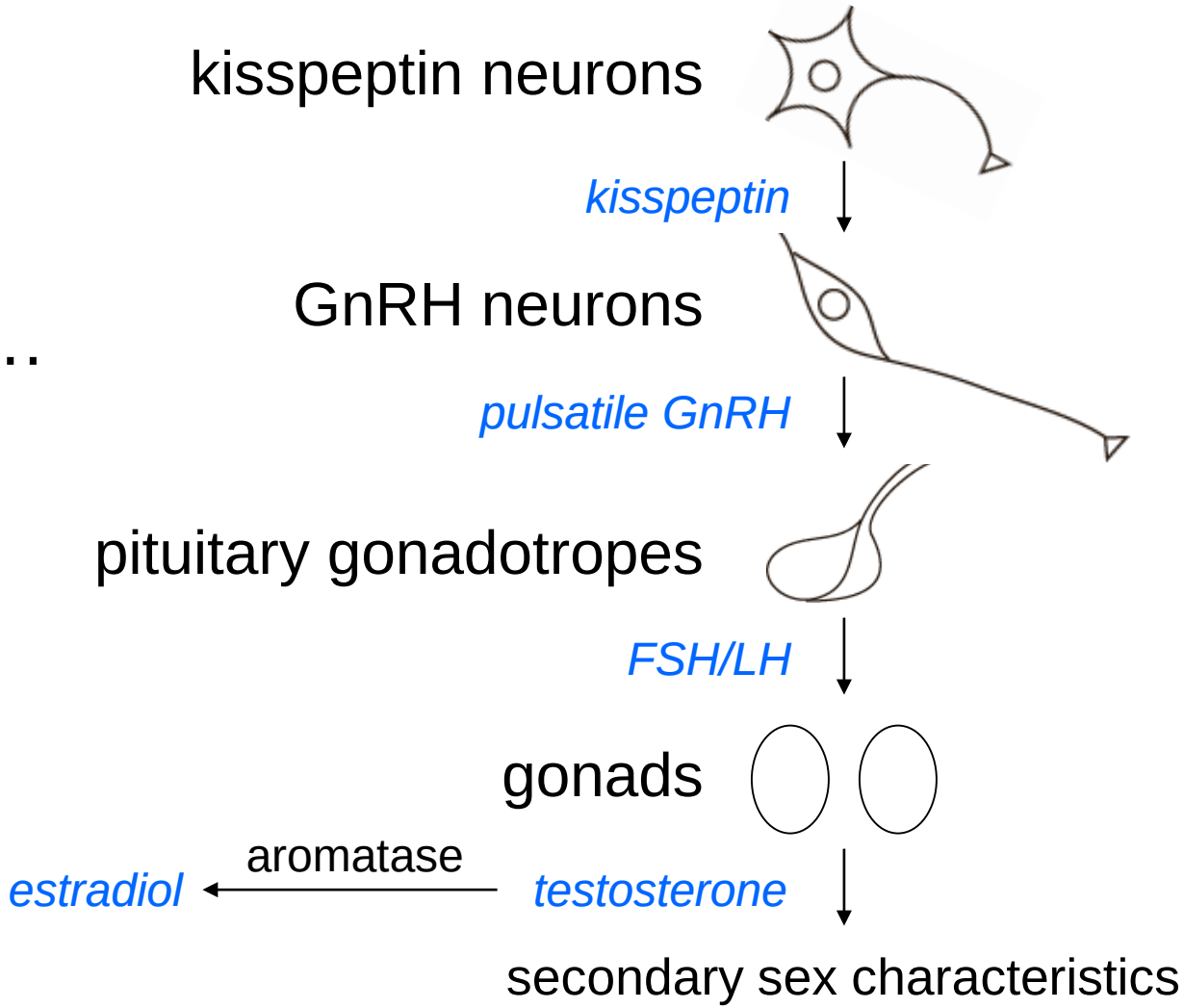
Outline

- Review of male reproductive endocrine physiology
- Causes of hypogonadism in boys
- Diagnosis of permanent hypogonadism
- Management of permanent hypogonadism

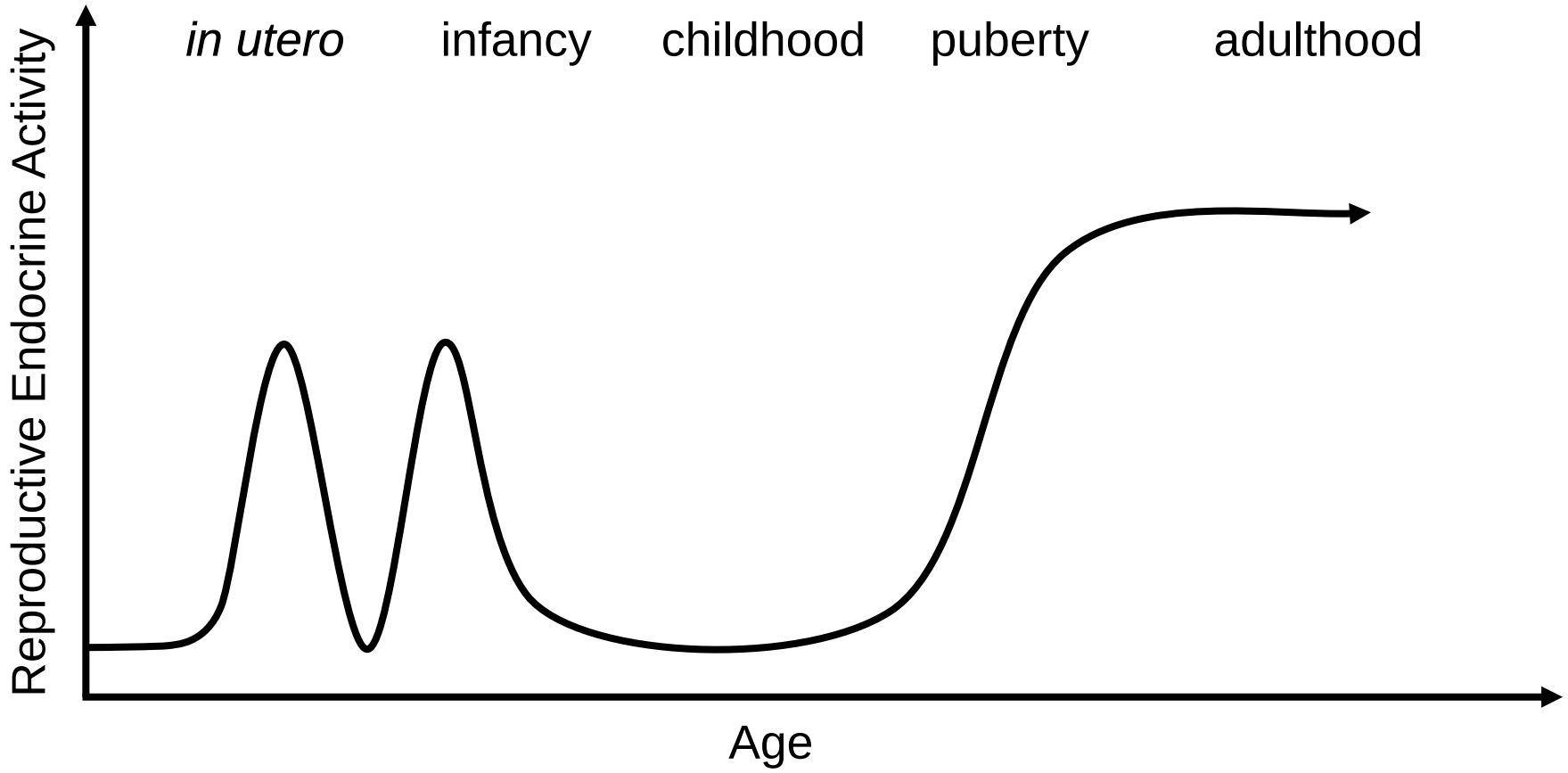
Reproductive Endocrine Physiology

Male Reproductive Endocrine Physiology

The
Hypothalamic
Pituitary
Gonadal axis…

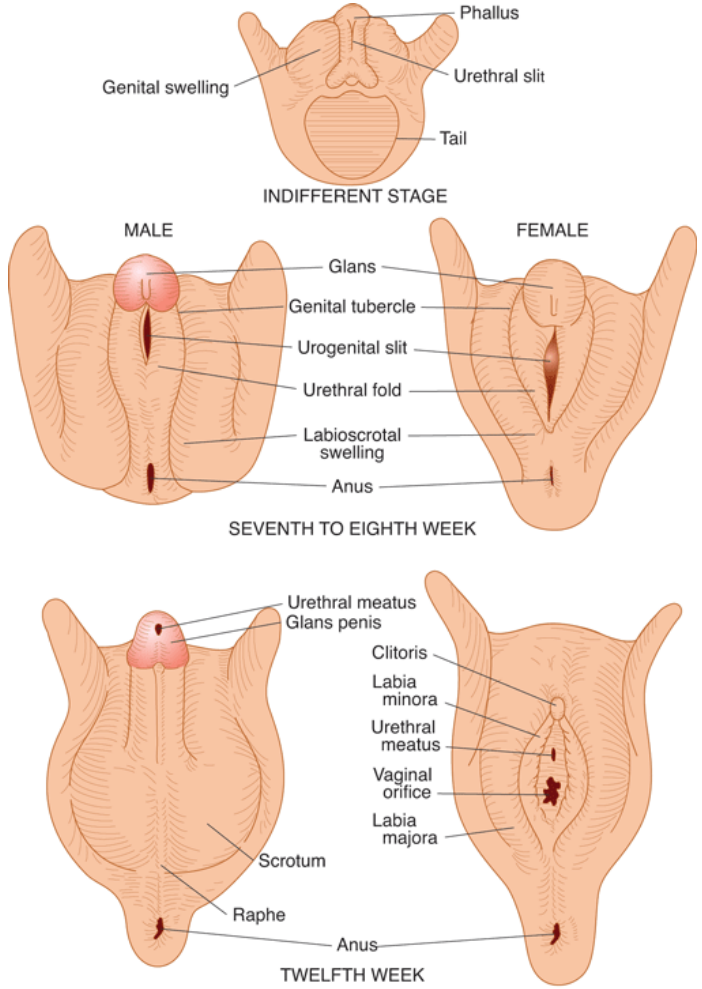


Reproductive Endocrine Function Across the Life Cycle



Androgen Effects: Fetal Development

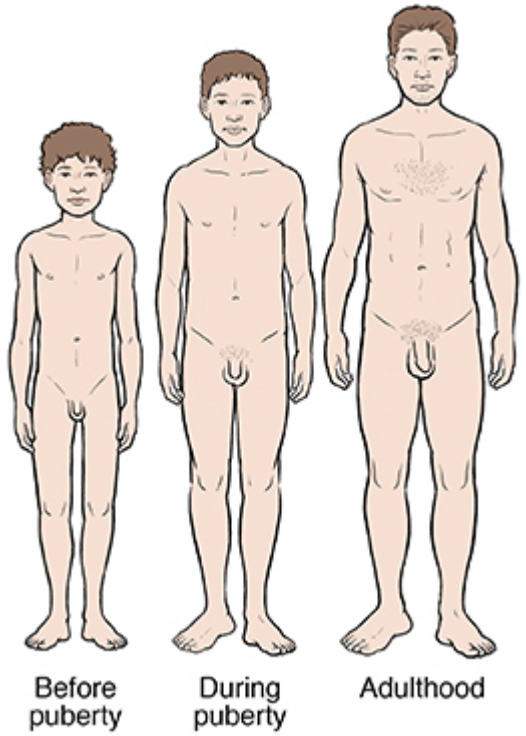
- First trimester
  - Virilization of the external genitalia
  - Stabilization of internal male genital structures (Wolffian duct-derived)
- Second and third trimesters
  - Testicular descent from inguinal ring to scrotum
  - Growth of penis
- Also has effects on the brain



http://www.accessmedicine.ca/search/searchAMResultImg.aspx?rootterm=sex+differentiation&rootID=28735&searchType=1

Androgen Effects: Pediatric Years

- Minipuberty: Role of testosterone unclear
- Childhood: Very low-level testosterone production, unclear whether physiologically significant
- Puberty
  - Hair growth
  - Voice deepening
  - Growth acceleration
  - Genital development
  - Increased muscle



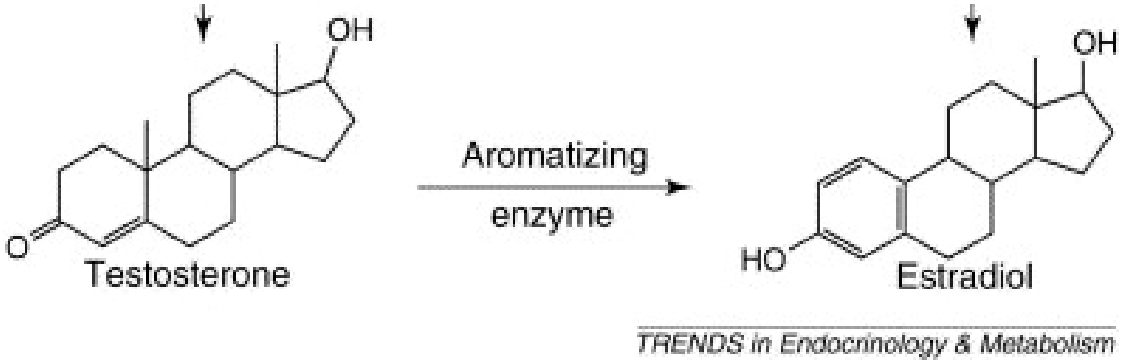
Saint Luke's Health System

Androgen Effects: Adulthood

- Maintenance of:
  - Libido
  - Erectile function
  - Muscle mass and strength

Indirect Effects Through Estradiol

- Testosterone converted to estradiol by aromatase
- Estrogen effects:
  - In puberty and adolescence:
    - Pubertal growth acceleration
    - Maturation of growth plates
    - Acceleration of bone mineralization
  - In adulthood
    - Maintenance of bone mineralization



Brodie, Trends Endocrinol Metab 2002;13:P61

Causes of Testosterone Deficiency in Boys

Causes of Delayed Puberty in Boys

Typically permanent causes

1. Primary testicular insufficiency
2. Persistent/permanent hypogonadotropic hypogonadism
   - 2a. Hypothalamic/pituitary pathology
   - 2b. Idiopathic hypogonadotropic hypogonadism (IHH)

Self-limited or reversible causes

3. Constitutional delay
4. Functional hypogonadotropic hypogonadism

Causes of Primary Testicular Insufficiency

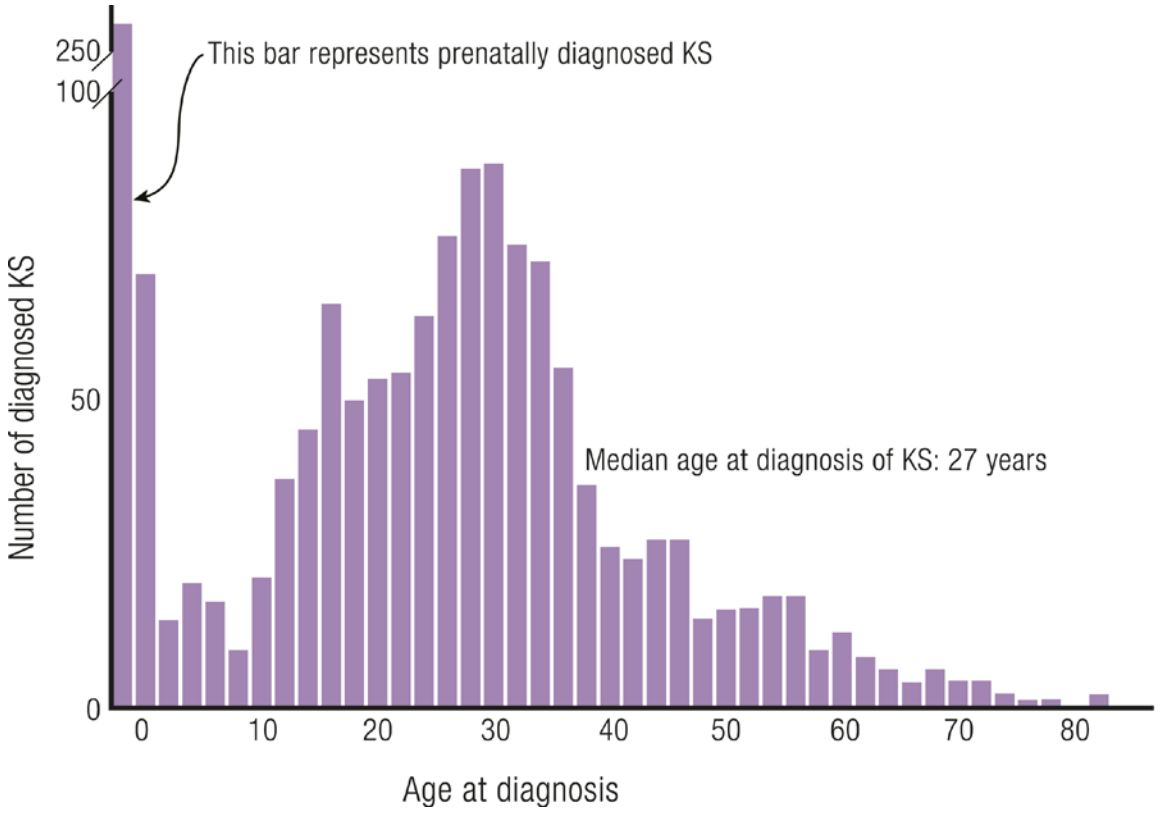
- Congenital
  - Klinefelter syndrome
  - Congenital anorchia, testicular regression syndrome
  - Certain disorders of sex development (DSD, a.k.a. intersex conditions)
- Acquired
  - Chemotherapy (alkylating agents)
  - Radiation
  - Mumps
  - Bilateral trauma, torsion
  - Surgical removal

Klinefelter Syndrome

- Presence of Y chromosome and two or more X chromosomes
  - Classically 47,XXY, but also 48,XXXY; 48,XXYY; 46,XY/47,XXY; etc.
- Clinical features – highly variable
  - Smaller penis
  - Tall stature
  - Learning, social, and psychiatric issues
  - Gynecomastia
  - Increased risk for features of metabolic syndrome
  - Testicular insufficiency, typically starting mid-puberty or later

Diagnosis of Klinefelter Syndrome

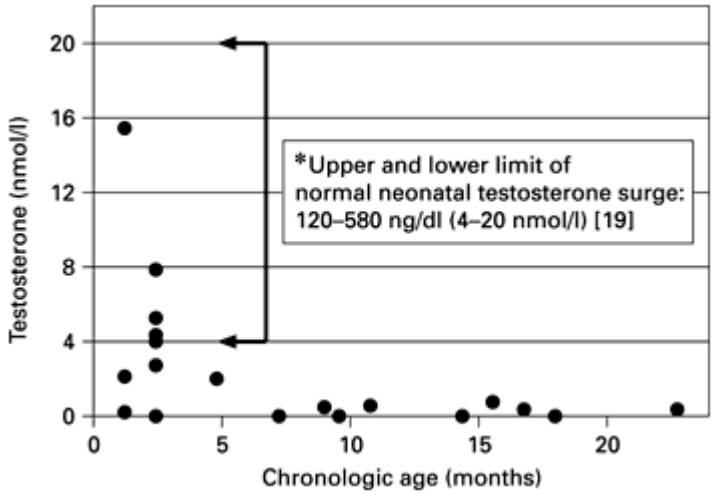
- Prevalence ~1:600 live male births
- Historically underdiagnosed and often diagnosed late
- Early diagnosis increasing with increased availability of noninvasive prenatal screening



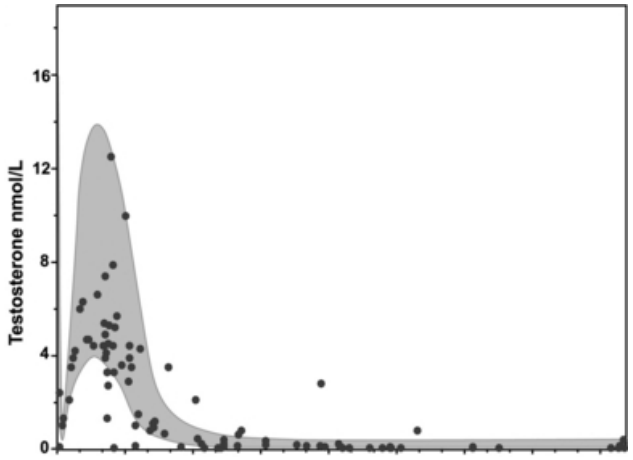
Gravholt et al. Endocr Rev 2018;39:389-423

Hypogonadism in Klinefelter Syndrome

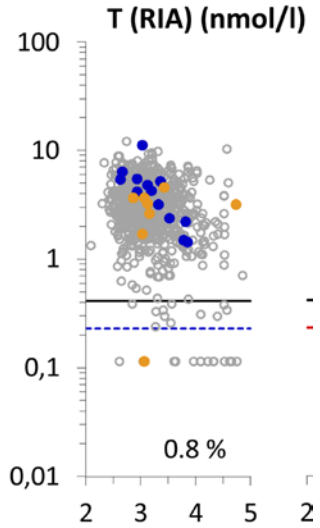
- Puberty typically starts at a typical time
- Primary hypogonadism emerges in late adolescence or early adulthood
  - Inconsistent evidence of testicular insufficiency in infancy and childhood



Ross et al. Horm Res 2005;64:39



Lahlou et al. Acta Paediatr 2011;100:824



Johannsen et al. JCEM 2018;103:3028

Testicular Regression Syndrome

- XY chromosomes, male external genitalia, absence of testes
- Pathophysiology
  - Testes must have functioned in first trimester to virilize external genitalia
  - Loss must have occurred during second or third trimester
  - Cause of testicular loss unclear
    - Possibly bilateral torsion, at least in some cases
- Rare: incidence ~1:20,000 boys Brauner R, et al. PLoS One. 2011;6:e23292;
Bernasconi S, et al. Horm Res. 1992;37 Suppl 3:50-4.
- Diagnosed by labs (high FSH, LH; low testosterone, AMH)
  - Karyotype, exploratory laparoscopy sometimes done

Intersex Conditions, also called DSD

- DSD = “Disorders/Differences of sex development”
  - “Congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical” Lee et al. Pediatrics 2006;118:e448
  - Nomenclature contentious
    - “Intersex” has come in and out of favor with some
- DSD conditions potentially associated with male hypogonadism:
  - XY partial testicular dysgenesis
  - XY disorders of androgen synthesis or action
  - XX testicular/ovotesticular DSD
  - Y chromosome mosaicism/chimerism resulting in gonadal dysgenesis and/or ovotesticular DSD
- Rare conditions; precise prevalence unclear for many
- Testicular insufficiency inherent
  - Also, gonadectomy may be performed if high risk of germ-cell tumor

Acquired Primary Hypogonadism in Boys

- Chemotherapy (particularly alkylating agents)
- Radiation
  - Direct radiation to testes can cause primary hypogonadism
  - Radiation of hypothalamus/pituitary can cause secondary hypogonadism
- Infections (e.g., mumps orchitis)
- Bilateral injury (e.g., torsion)
- Bilateral orchiectomy, e.g., for tumor treatment or prophylaxis

Congenital Hypopituitarism

- Combined Pituitary Hormone Deficiency (CPHD)
  - Mutations in transcription factors such as HESX1, PROP1, POU1F1, LHX3, LHX4, GLI2 and SOX3
  - Phenotype may consist of isolated hypopituitarism, or more complex disorders such as septo-optic dysplasia (SOD) and holoprosencephaly
  - Deficiencies of GH, TSH, LH, FSH, prolactin, and occasionally ACTH
  - May present with micropenis and cryptorchidism, neonatal hypoglycemia, features of hypothyroidism, or growth failure in early childhood
  - Affected individuals can have absent/delayed sexual development and infertility

Acquired Hypopituitarism

- Hypothalamic/pituitary tumors or other masses
- Surgery of hypothalamic/pituitary region
- Cranial irradiation
- Traumatic brain injury
- Invasive/inflammatory/infectious causes, such as:
  - Langerhans cell histiocytosis
  - Lymphocytic hypophysitis
  - Tuberculosis

Idiopathic Hypogonadotropic Hypogonadism

- Idiopathic hypogonadotropic hypogonadism (IHH) and Kallmann Syndrome (IHH + anosmia)
- Mutations in genes that affect GnRH neuronal migration or GnRH synthesis/secretion/signaling
- Deficiency of GnRH-induced LH secretion
- Phenotype may consist of isolated hypogonadotropism, or more complex disorders such as CHARGE syndrome, cerebellar ataxia
- Most ascertained due absent/delayed secondary sexual development
  - Some boys recognized in infancy due to micropenis and/or cryptorchidism

Constitutional Delay

- Self-limited delay in pubertal onset
  - Puberty does start, but late
- By definition, affects 2-3% of children
  - Often associated with slower childhood growth
  - Common reason for pediatric endocrine consultation
- Largely considered a benign developmental variant
  - But may have lasting effects on height, bone mineral density, psychosocial outcomes

Bramswig et al. J Pediatr 1990;117:886; Crowne et al. Arch Dis Child 1990;65:1109; Albanese and Stanhope Eur J Pediatr 1993;152:293; Wehkalampi et al. Horm Res 2007;68:99; Finkelstein et al. NEJM 1992;326:600; Lubushitsky et al. J Nucl Med 1998;39:104; Bertelloni et al. JCEM 1998;83:4280; Yap et al. JCEM 2004;89:4306; Darelid et al. J Bone Miner Res 2012;27:2198; Duke et al. J Pediatr 1982;100:633; Graber et al. J Am Acad Child Adolesc Psychiatry 1997;36:1768; Graber et al. J Am Acad Child Adolesc Psychiatry 2004;43:718

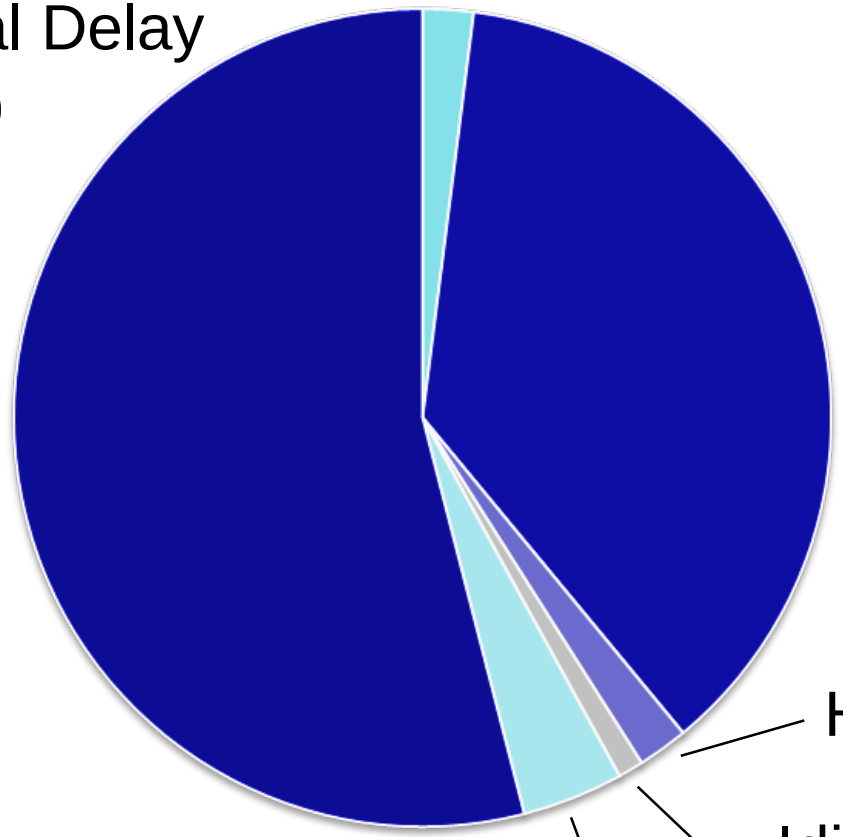
Functional Hypogonadotropic Hypogonadism

- Normal physiologic response of HPG axis to stress
- Stressors can include
  - Chronic illness/inflammation
    - Inflammatory bowel disease
    - Celiac disease
  - Undernutrition
  - Excessive exercise

Hormones and Drugs

- Hormones that suppress the HPG axis
  - Prolactin
  - Glucocorticoids
  - Sex steroids (through negative feedback)
- Drugs
  - Glucocorticoids
  - Opiates

Causes of Delayed Puberty
(Boston Children's Hospital 2000-2015, 920 Boys)



Hypergonadotropic Hypogonadism (2%)

Constitutional Delay (54%)

Functional Hypogonadotropic Hypogonadism (37%)

Hypothalamic/Pituitary Pathology (2%)

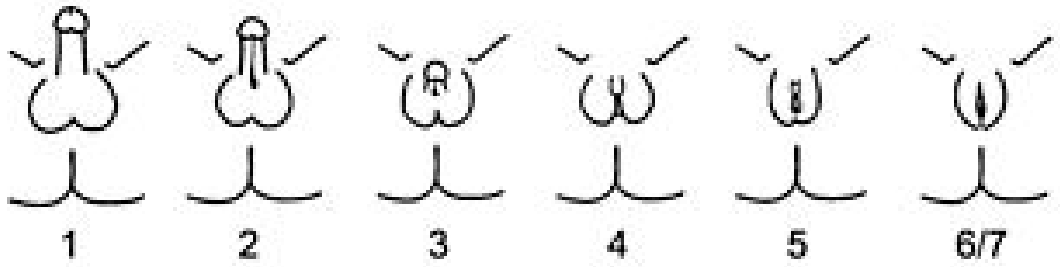
Idiopathic Hypogonadotropic Hypogonadism (1%)

Other Syndromic Causes (4%)

Diagnosis of Hypogonadism

Clinical Features of Prenatal Hypogonadism

- Hypogonadism present during first trimester
  - Atypical development of external genitalia
    - Hypospadias
    - Incomplete scrotal development
    - Ambiguous genitalia



- Hypogonadism during second/third trimesters
  - Undescended/incompletely descended testes (cryptorchidism)
  - Micropenis

Clinical Features of Infant Hypogonadism

- Postnatal HPG axis activation important for penile and testicular growth

  Kuiri-Hanninen et al. J Clin Endocrinol Metab, 2011;96:98

  - Penile length and growth positively correlated to serum testosterone

    Boas et al. Eur J Endocrinol 2006;154:125

  - Testosterone deficiency in infants (even in patients with normal genitalia at birth) can cause progressively impaired development (*i.e.*, lack of penile growth and involution of the scrotum)

    Main et al., J Clin Endocrinol Metab 2000;85:4905

Clinical Features of Adolescent and Adult Hypogonadism

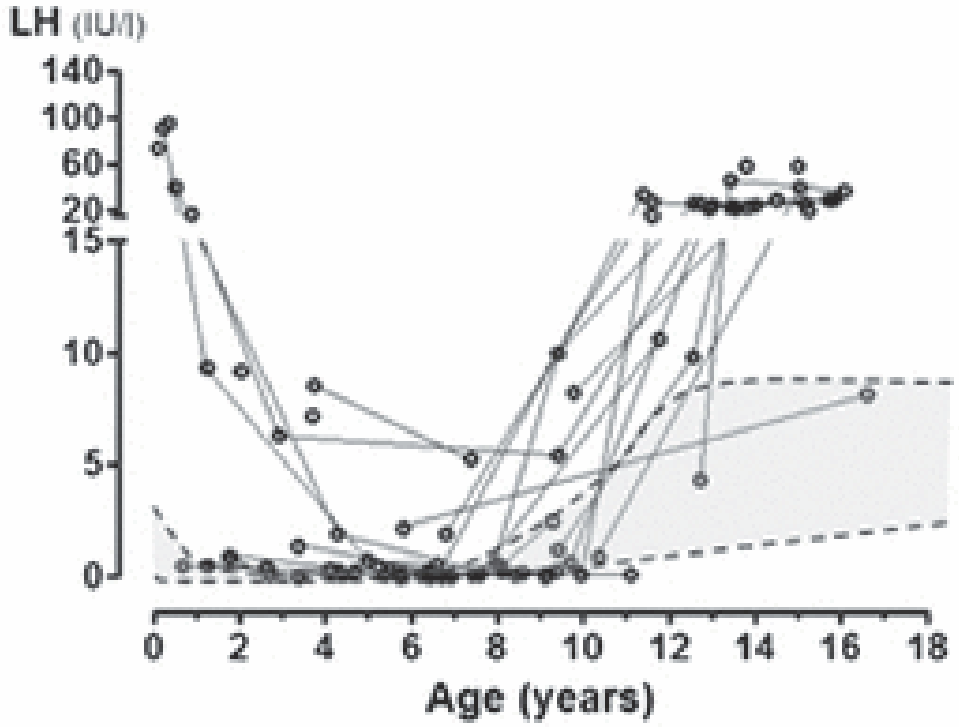
- Hypogonadism during adolescence
  - Absence of pubertal onset (and absence of pubertal growth spurt)
  - Delayed pubertal onset
  - Partial pubertal development that stalls
- Hypogonadism during adulthood
  - Loss of libido
  - Erectile dysfunction
  - Loss of muscle strength/mass
  - Decreased sense of well-being
  - Infertility

Laboratory Findings

- At times when HPG axis is active (minipuberty, adolescence, adulthood)
  - Primary testicular insufficiency:
    - Low testicular products (testosterone, AMH, inhibin B)
    - Elevated gonadotropins (FSH, LH) due to loss of negative feedback
  - Hypogonadotropic hypogonadism:
    - Low testosterone (and often low AMH and inhibin B)
    - Low or inappropriately normal gonadotropins

Laboratory Findings in Prepubertal Boys

- Primary testicular insufficiency
  - May see low AMH (if Sertoli cells are affected)
  - May see elevated gonadotropins
- Hypogonadotropic states
  - Difficult to diagnose, much less distinguish between underlying causes



Grinspon et al. Clin Endocrinol 2012 ;76:698

IHH vs. Constitutional Delay

IHH

- delayed puberty
- other diagnoses excluded
- low sex steroids
- low gonadotropins
- failure to achieve normal reproductive endocrine activity by cutoff age (18 y commonly used)

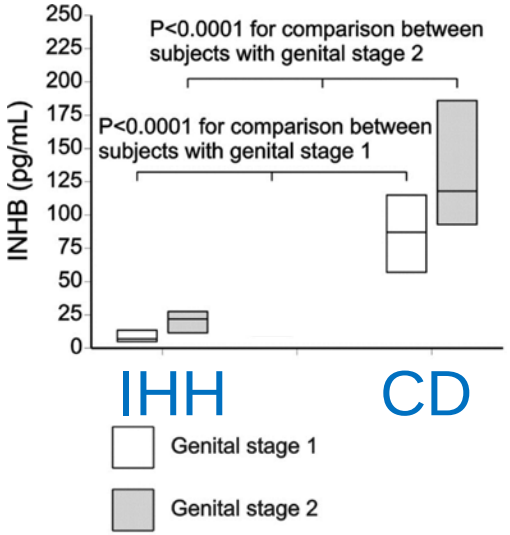
Constitutional Delay

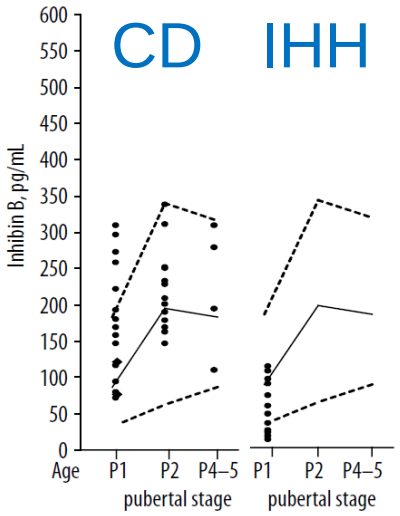
- delayed puberty
- other diagnoses excluded
- low sex steroids
- low gonadotropins
- puberty achieved spontaneously (but late), before cutoff age

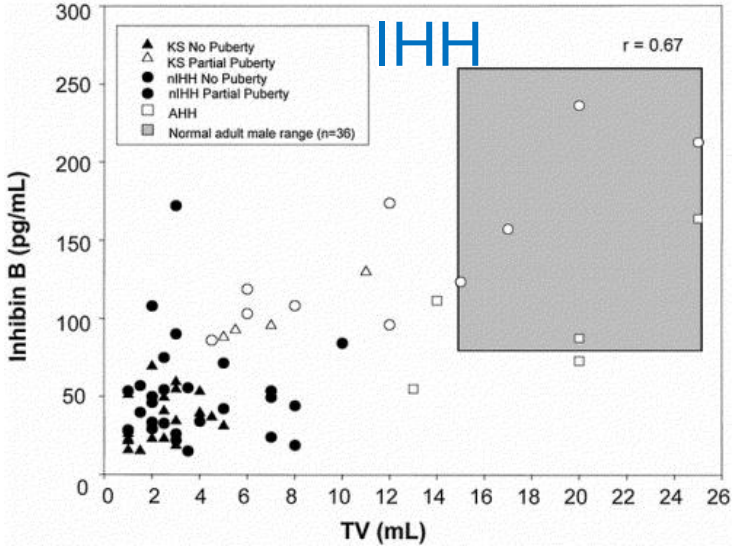
- Both are currently retrospective diagnoses.
- Prognosis differs, as does pathophysiology (?)

Laboratory Tests to Distinguish CDP from IHH

- Tests that have been studied:
  - LH (first-morning, overnight, GnRH/GnRHa-stimulated)
  - hCG-stimulated testosterone
  - Inhibin B, AMH
- None is fully sensitive or specific Harrington and Palmert JCEM 2012;97:3056



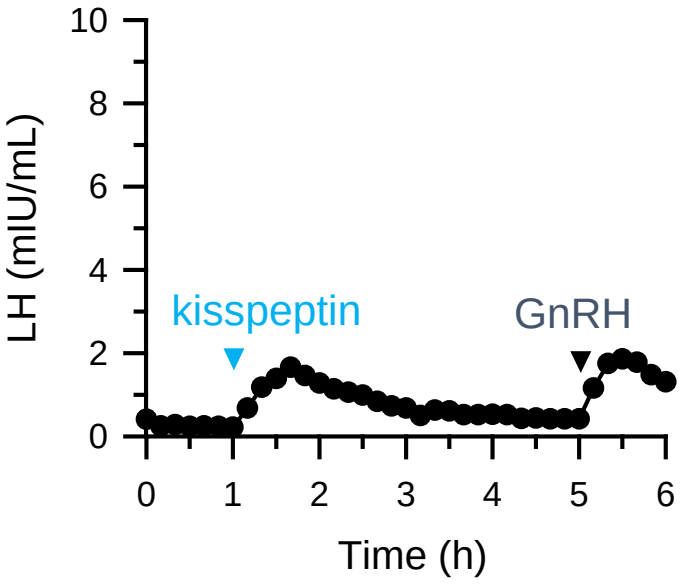




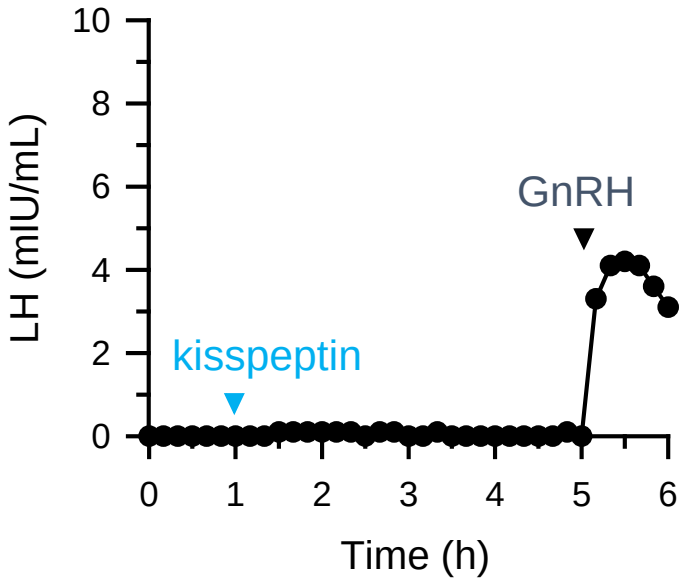
Coutant et al. J Clin Endocrinol Metab 2010;95:5225. Adan et al. Med Sci Monit 2010;16: CR511. Pitteloud et al. J Clin Endocrinol Metab 2002;87:4128

Kisspeptin-Stimulation Test

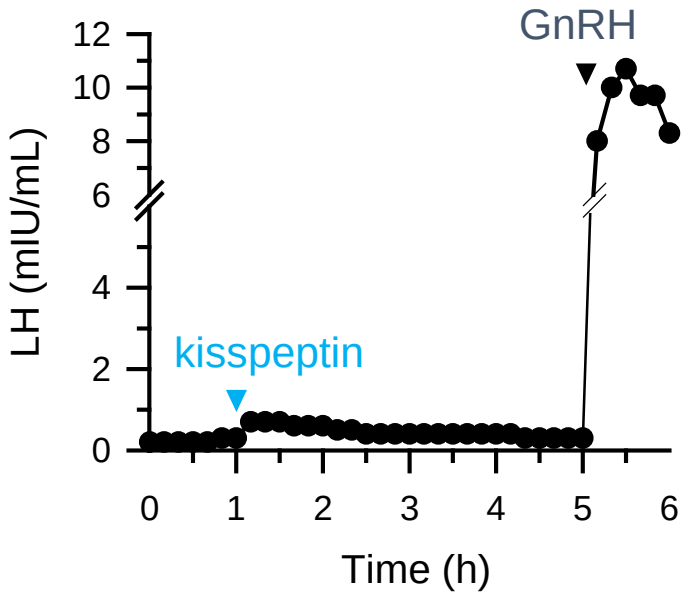
Responders (N = 7)



Non-Responders (N = 7)



Intermediate Responder (N = 1)



Chan et al. JCI Insight 2018;3:e99109

- Awaiting final diagnoses
- Accurate prospective diagnosis likely to require integrated assessment of clinical features, functional testing, genetic testing

Management of Persistent Hypogonadism in Boys

Formulations
Injected

- Testosterone esters (enanthate, cypionate, also undecanoate)
- Mainstay of treatment in pediatric population
  - Dose easily titratable
  - No concerns about cross-contamination of others
  - Intermittent dosing can be convenient
- Only forms approved for pediatric use
  - T cypionate: Hypogonadism
  - T enanthate: Hypogonadism, delayed puberty

Formulations
Oral

- When administered orally, testosterone is subject to significant metabolism in the gastrointestinal tract and in the liver

Hartiata, Physiol Rev 1973; 53:496; Synder, Ann. Rev Med 1984; 35:207

- Testosterone undecanoate recently approved for treatment of men with hypogonadism

Formulations
Transdermal

- Goal is to achieve plasma levels in the range of normal endogenous production of 3-10 mg over 24 h
- Trans-scrotal patches achieved testosterone levels ≥ 400 ng/ml in hypogonadal subjects in less than 4 h, with dose-dependent increases depending on patch size. Findlay et al. J Clin Endocrinol Metab 1987;64:266
- Transdermal patches cause skin irritation, leading to discontinuation in ~10%
  - Irritation can be prevented by topical corticosteroids Wilson et al. Clin Therap 1998;20:299
- Transdermal gel difficult to titrate for small doses

Formulations
Other

- Rarely used in pediatrics:
  - Buccal patches
  - Subcutaneous pellets

Monitoring Therapy
Lessons from Adult Care

- Improvement in hypogonadal signs and symptoms occur at different times for different organ systems.
- Upon starting T:

Finding	**Time to Improvement**
Serum testosterone	3 months
Fat/lean mass	6 months
Hematocrit	3 months
Prostate volume	6 months
Energy, sexual function	3 months
Bone	6 mo (max 2 y)

Snyder et al. J Clin Endocrinol Metab 2000;85:2670
Hackett et al., Int J Clin Pract 2014;68:203

Monitoring Therapy
Lessons from Adult Care

- Improvement in hypogonadal signs and symptoms occur at different doses for different organ systems.
- Healthy men given GnRH analog to suppress endogenous gonadal steroid production
  - Also given testosterone 1% transdermal gel at various doses

Finding	Daily Dose of Gel to Prevent	Mediated by Estradiol?
↑ % body fat	5 g (average serum T 485 ng/dL)	Partially
↑ Subcutaneous fat	5 g	Partially
↑ Intraabdominal fat	5 g	Completely
↓ Lean mass	2.5 g (average serum T 367 ng/dL)	No
↓ Leg-press strength	1.25 to 2.5 g (average serum T 231-367 ng/dL)	No

Finkelstein et al. NEJM 2013;369:1011

Upon Starting Testosterone in Men *Parameters to Be Monitored*

- Assessment of the amount and distribution of body hair (including beard growth and pubic hair)
- Presence of acanthosis nigricans
- Presence and degree of breast enlargement
- Size and consistency of the testes
- Abnormalities in the scrotum and size
- Appearance of the penis, presence of subcutaneous plaque
- Weight, height, body mass index (BMI) and waist circumference

Hermanns-Le T, Am J Clin Dermatol 2004; Saad F, Curr Diabetes Rev 2012; Corona G, Best Pract Res Clin Endocrinol Metab 2011; Corona G, J Endocrinol Invest 2011; Bhasin S, J Clin Endocrinol Metab 2010

Concerns
Adult Men

- An increased incidence of prostate events and hematocrit values >50% was flagged in a meta-analysis of intramuscular, oral and transdermal delivery; there was no evidence that testosterone therapy increases prostate cancer
- Boxed warning for increase in cardiovascular risk

Treatment of Permanent Hypogonadism in Boys – *When to Start Pubertal Induction?*

- No consensus or guidelines
- Hypergonadotropic hypogonadism:
  - Can base on rising gonadotropins
- Hypogonadotropic hypogonadism:
  - No method to tell when puberty “would have started”
  - Factors to consider:
    - Population averages
    - Family history of pubertal timing
    - Psychosocial factors

Treatment of Permanent Hypogonadism in Boys – *What Dose to Start?*

- Starting with too high a dose may cause overly rapid skeletal maturation
- Studies did not find bone-age advancement with doses ranging from 33 mg to 200 mg every 3-4 weeks for 3 to 20 months

  Albanese and Stanhope, J Pediatr 1995;126:54; Rosenfeld et al. Pediatrics 1982;69:681; Zachmann et al. Helv Paediatr Acta 1987;42:21; Wilson et al. Am J Dis Child 1988;142:96; Gregory et al. Clin Endocrinol 1992;37:207; Buyukgebiz A, Horm Res 1995;44 Suppl 3:32; Bergada and Bergada, J Pediatr Endocrinol Metab 1995;8:117; Arrigo et al. J Pediatr Endocrinol Metab 1996;9:511; Soliman et al. Metabolism 1995;44:1013

- Typical starting dose is testosterone enanthate/cypionate 25-50 mg monthly Palmert and Dunkel, N Engl J Med 2012;366:433
  - Some but not all monitor serum testosterone
  - Safety labs rarely followed

Treatment of Permanent Hypogonadism in Boys – *How Fast to Advance Doses?*

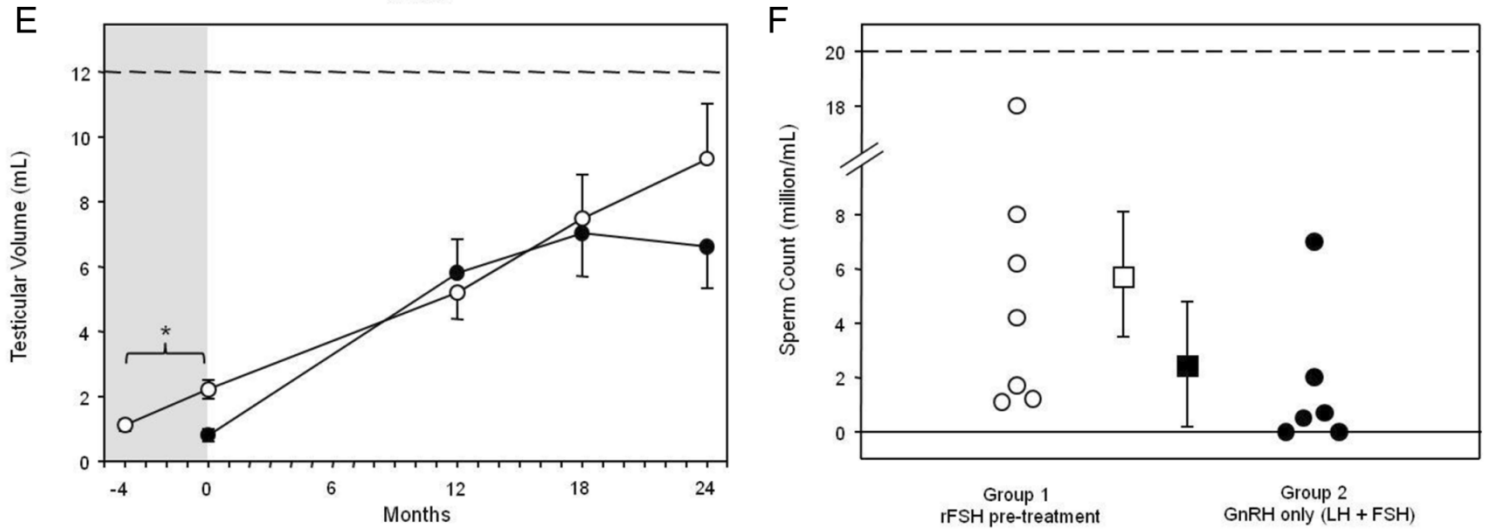
- Dosing increased by ~2x every ~6 months
  - Dose or frequency may be increased
  - Achieve adult doses over about 2 years
- Primarily based on growth and skeletal maturation
  - May also consider rate of appearance of secondary sex characteristics, sexual drive and function
- Serum testosterone followed by some but not all
- Safety labs rarely followed
  - Replacement felt to be physiologic

Hypogonadotropic Hypogonadism *Considerations for Therapy*

- Because defect is localized to the brain/pituitary, hypogonadotropic patients can use fertility therapies to stimulate their own Leydig cell complement to make testosterone and their Sertoli cells to support spermatogenesis
- Traditionally, testosterone has been used for pubertal induction
  - When seeking fertility, transitioned to gonadotropins/GnRH
- Little data regarding whether this treatment sequence optimizes future testicular function

Hypogonadotropic Hypogonadism *Questions*

- Are testes more responsive to fertility therapy (gonadotropins, GnRH) when treatment is initiated at younger ages?
- Does testosterone therapy do harm to the testes?
  - Success at spermatogenesis induction impaired by prior testosterone use in one study (Liu et al. JCEM 2009;94:801) but not another (Pitteloud et al. JCEM 2002;87:4128)
  - Pretreatment with FSH may improve fertility induction with GnRH



Dwyer et al. J Clin Endocrinol Metab 2013;98:E1790

Timing of Treatment for Klinefelter Syndrome

- No consensus or guidelines
- Goals of care: complete pubertal growth; induce secondary sex characteristics; improve bone health, sexual function, cardiovascular health (?), psychosocial outcomes (?)
- Potential ages/indications for treatment
  - Frankly low testosterone and symptoms of hypogonadism
  - Low-normal testosterone, elevated LH, and symptoms of hypogonadism and/or arrest of pubertal development
  - Elevated LH alone
  - At first signs of puberty
  - Before puberty
  - In infancy

Prepubertal Androgen Treatment for Klinefelter Syndrome

- Randomized, double-blind, placebo-controlled trial of 2 years of oxandrolone (nonaromatizable anabolic steroid) in prepubertal boys with Klinefelter syndrome, ages 4-12 y
- Oxandrolone treatment resulted in:
  - Lower % body fat (0.29 SDS vs. 0.81 SDS in controls)
  - Lower triglycerides (64 mg/dL vs. 84 mg/dL)
  - Lower HDL cholesterol (35 mg/dL vs. 49 mg/dL) Davis et al. J Clin Endocrinol Metab 2017;102:176
  - Modest improvements in some measures of motor function, anxiety/depression, social/interpersonal problems Ross et al. J Pediatr 2017;185:193
  - More advanced bone age (by 0.7 years)
  - Earlier gonadarche, with 23% having onset <9 years (precocious)

Davis et al. J Clin Endocrinol Metab 2018;103:3449

Infant Testosterone Treatment for Klinefelter Syndrome

- Observational studies demonstrate better neurodevelopmental outcomes in boys treated with testosterone in infancy
  - Nonrandomized design susceptible to confounding
- Pilot randomized control trial Davis, ENDO 2019
  - Boys with Klinefelter treated with placebo had higher fat mass and lower lean body mass compared to age-matched norms
  - Boys with Klinefelter treated with testosterone indistinguishable from age-matched norms
- Given uncertainty in whether infant boys with Klinefelter syndrome have testosterone insufficiency, unclear if testosterone treatment is physiologic or pharmacologic

Other Potential Uses of Testosterone in Boys

Constitutional Delay

- Approved indication for testosterone enanthate
- Induce secondary sex characteristics, pubertal growth spurt
- “Insurance policy” in case of IHH
- May accelerate onset of endogenous puberty

	Control (N = 50)		Testosterone (N = 148)	
	Baseline	After 1 Yr	Baseline	After 1 Yr
GV (cm/yr)	4.8 ± 0.1	6.1 ± 0.1	4.6 ± 0.1	11.5 ± 0.4*
Tanner stage	1.4 ± 0.05	1.8 ± 0.05	1.6 ± 0.04	2.6 ± 0.06*
Testicular diameter (cm)	2.4 ± 0.05 (~4 mL)	2.7 ± 0.04 (~5 mL)	2.6 ± 0.05 (~5 mL)	3.5 ± 0.05* (~10 mL)

Soliman et al. Metabolism 1995;44:1013

Transgender Youth

- Off-label use
- Individuals with XX chromosomes (designated a female sex at birth) and a masculine gender identity
- Testosterone used to induce male secondary sex characteristics
  - Endocrine Society guidelines recommend treatment starting at 16 y, and acknowledge that earlier treatment may be appropriate
  - Many centers starting at age 13-14 y
- Demand for care at gender centers increasing rapidly
  - Growth most rapid in patients designated female at birth
  - Many seeking testosterone treatment (but not all)

Infant Micropenis

- In boys with micropenis secondary to congenital hypogonadism, 1 or 2 short courses of testosterone in infancy and childhood augment penile size into the normal range for age
- Replacement therapy at of puberty results in an adult-size penis within 2 SD of the mean Bin-Abbas et al. J Pediatr 1999; 134:579

Enhancement of Athletic Performance

- Illicit use
- CDC 2017 Youth Risk Behavior Survey: 3.3% of boys and 2.4% of girls reported use of anabolic steroids
- DEA: “For purposes of illegal use there are several sources; the most common illegal source is from smuggling steroids into the United States from other countries such as Mexico and European countries…. Less often steroids found in the illicit market are diverted from legitimate sources (e.g. thefts or inappropriate prescribing) or produced in clandestine laboratories.”