Pediatric Endocrinology for the General Pediatrician

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OUR LADY OF THE LAKE CHILDREN’S HOSPITAL

BATON ROUGE, LA

Disclosures

- I have no relevant financial relationships with commercial interest to disclose.
- I will be discussing medications that have FDA approved uses in children

Purpose

- Address some common endocrine issues seen by pediatricians
- Often involves these questions:
  - Should I screen for this and how?
  - How should I interpret this lab?
  - When should I be concerned and refer?
  - What can I handle myself?
- We'll also have some fun today with Kahoot!
  - Go to www.kahoot.it on your phone, tablet, or laptop
  - Await for further instructions

Question 1

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Common Referrals

Total Referrals Jan-June 2016	352	
Short stature	72	20%
Diabetes/abnormal glucose/abnormal insulin	60	17%
early puberty/adrenarche	54	15%
Abnormal thyroid test	45	13%
Total of the Top 4 Referrals	231	66%

Short stature

Question 2

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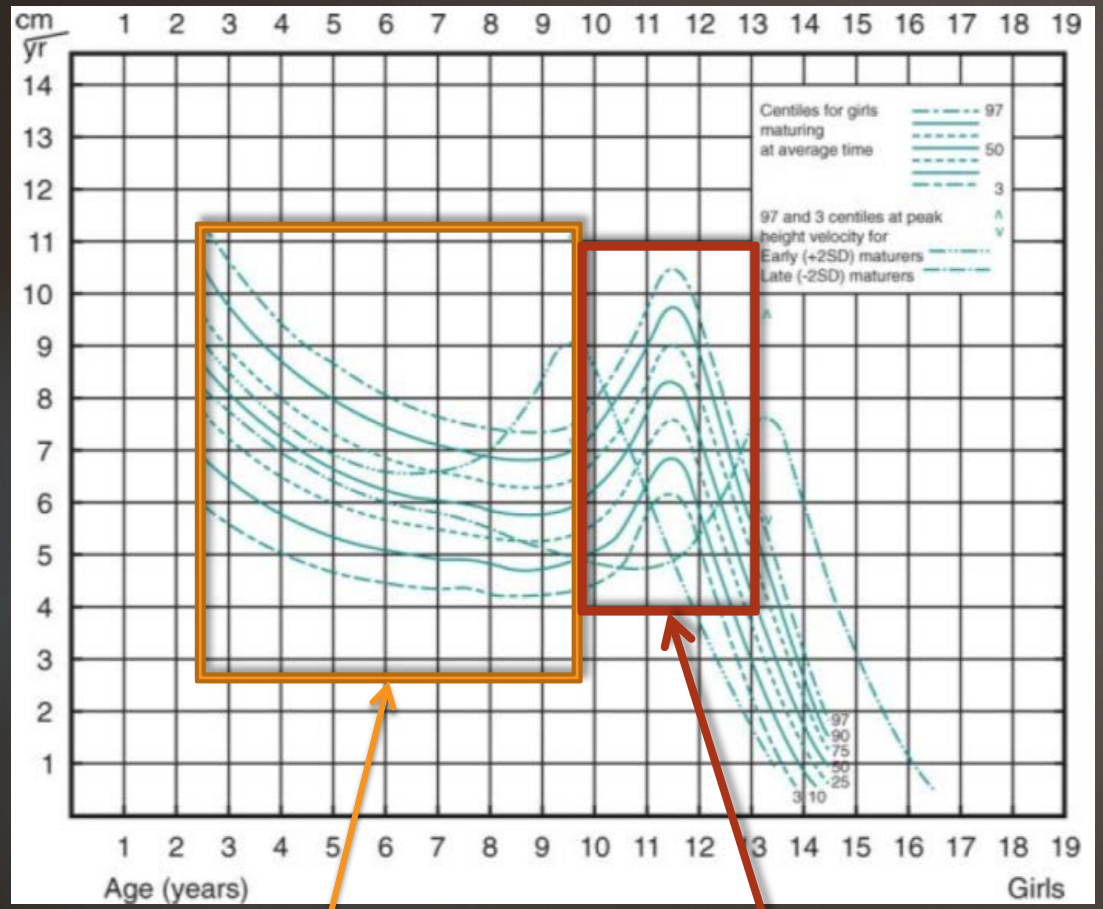
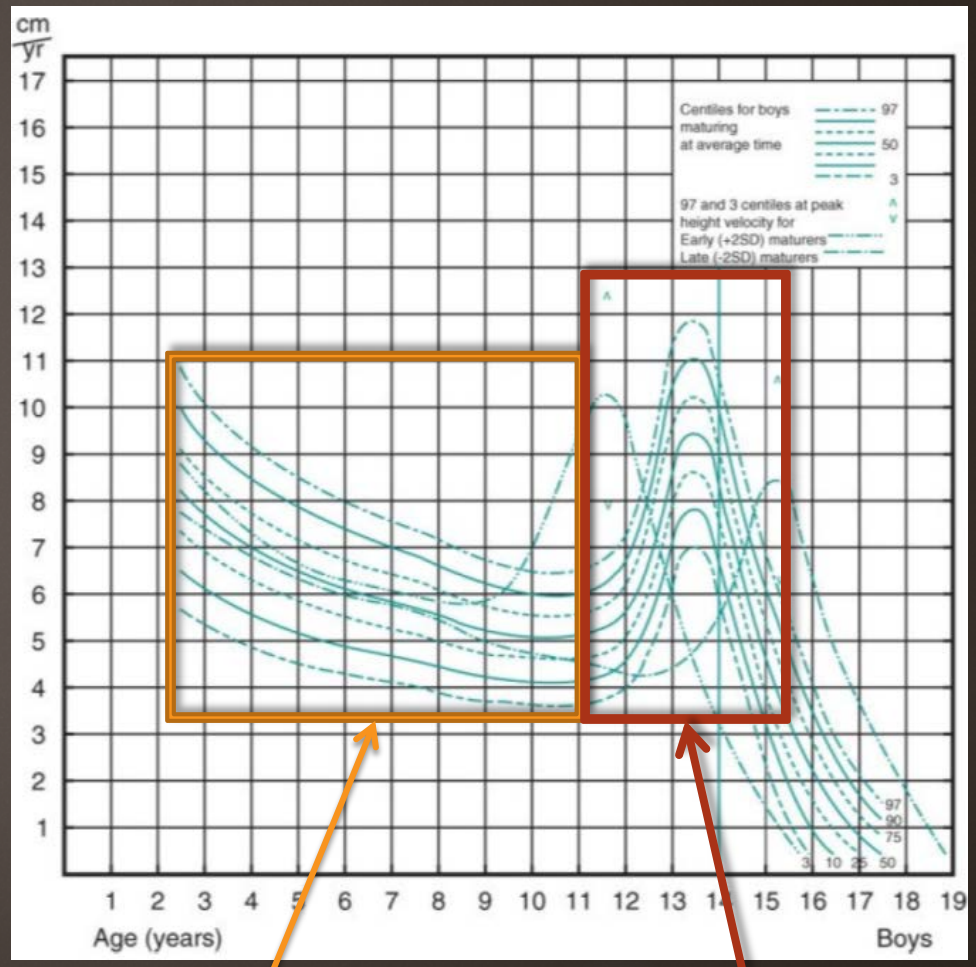
Short stature

- Short stature definition: Length or height either < 3% or < -2 SD from the mean for age and gender
  - Basically, 3% of all children are short
  - GH deficiency incidence is about 1 in 3500 children
- Most short stature are due to normal variations of growth
  - Constitutional delay
  - Familial short stature
- Most short stature not growth failure
  - How is their growth trending – growth velocity
  - A single plot well tell you very little of a child's growth

Short Stature: It's velocity that counts



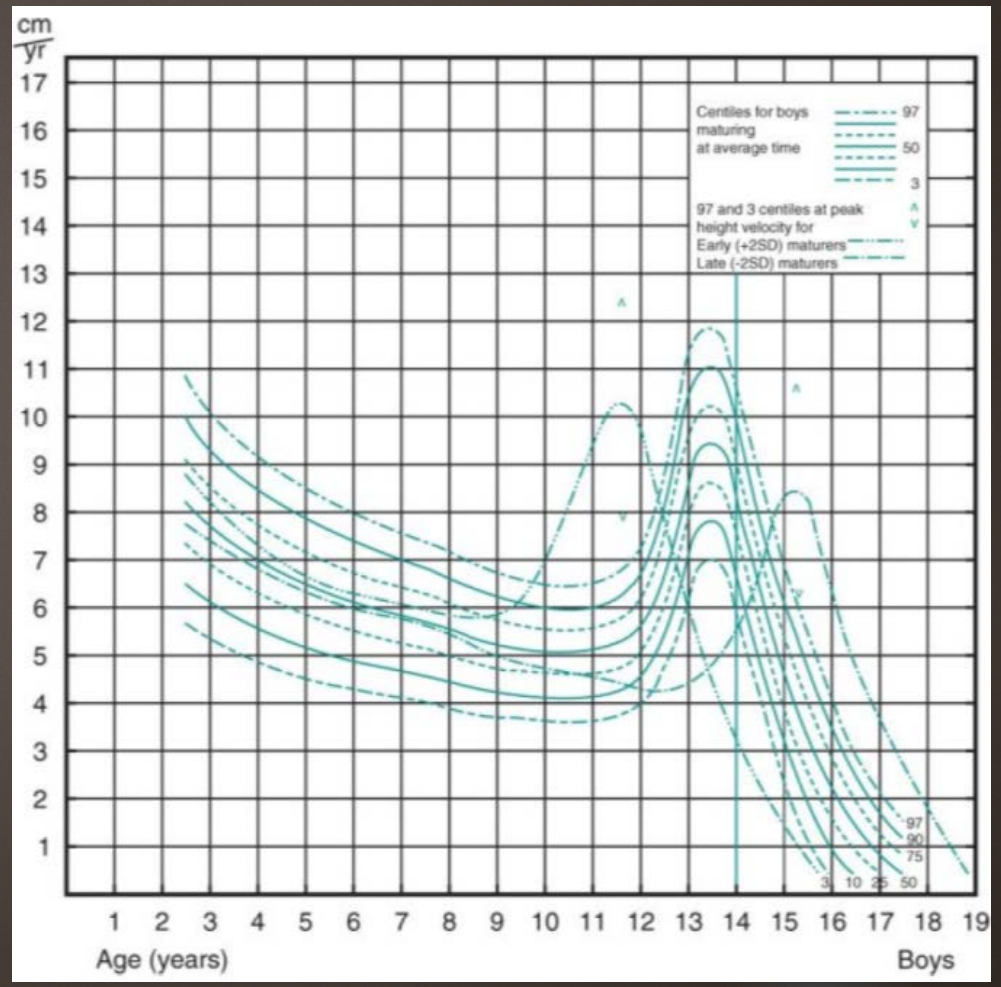
GV = 4-7 cm/yr GV = 6-10 cm/yr



GV = 4-7 cm/yr GV = 7-12 cm/yr

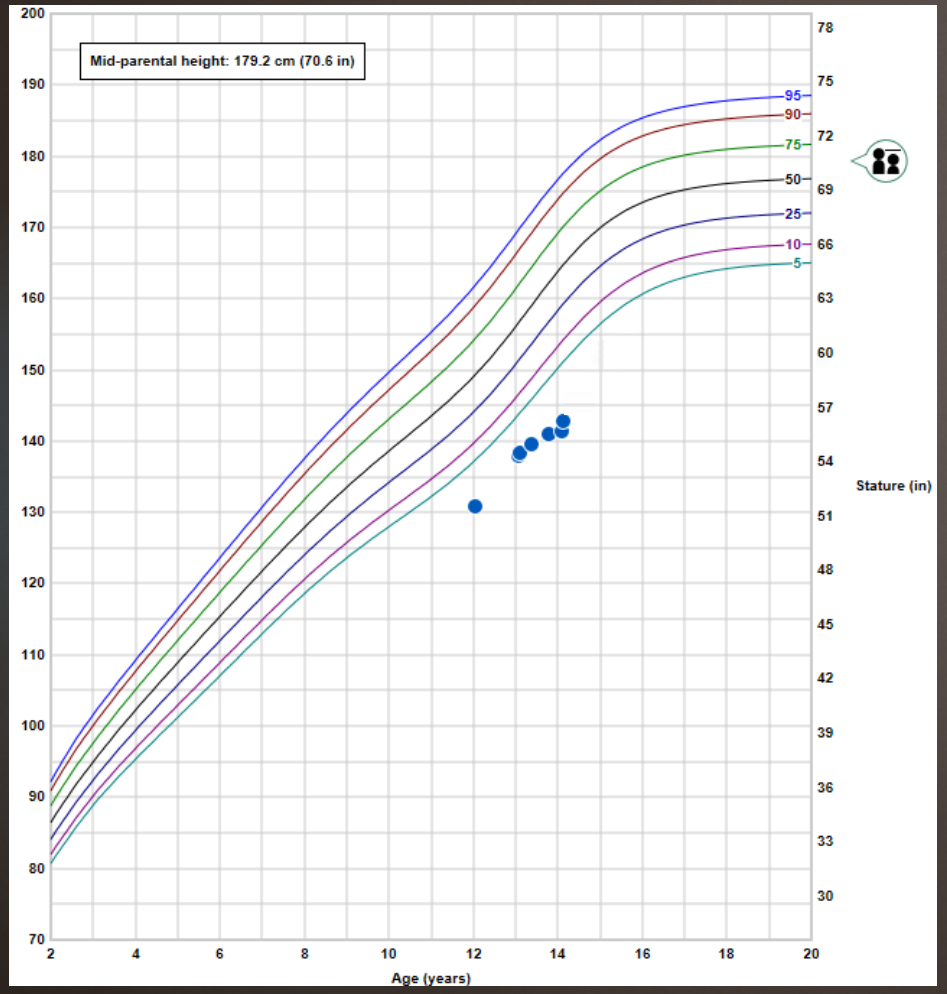
Short Stature: keep parents and puberty in context

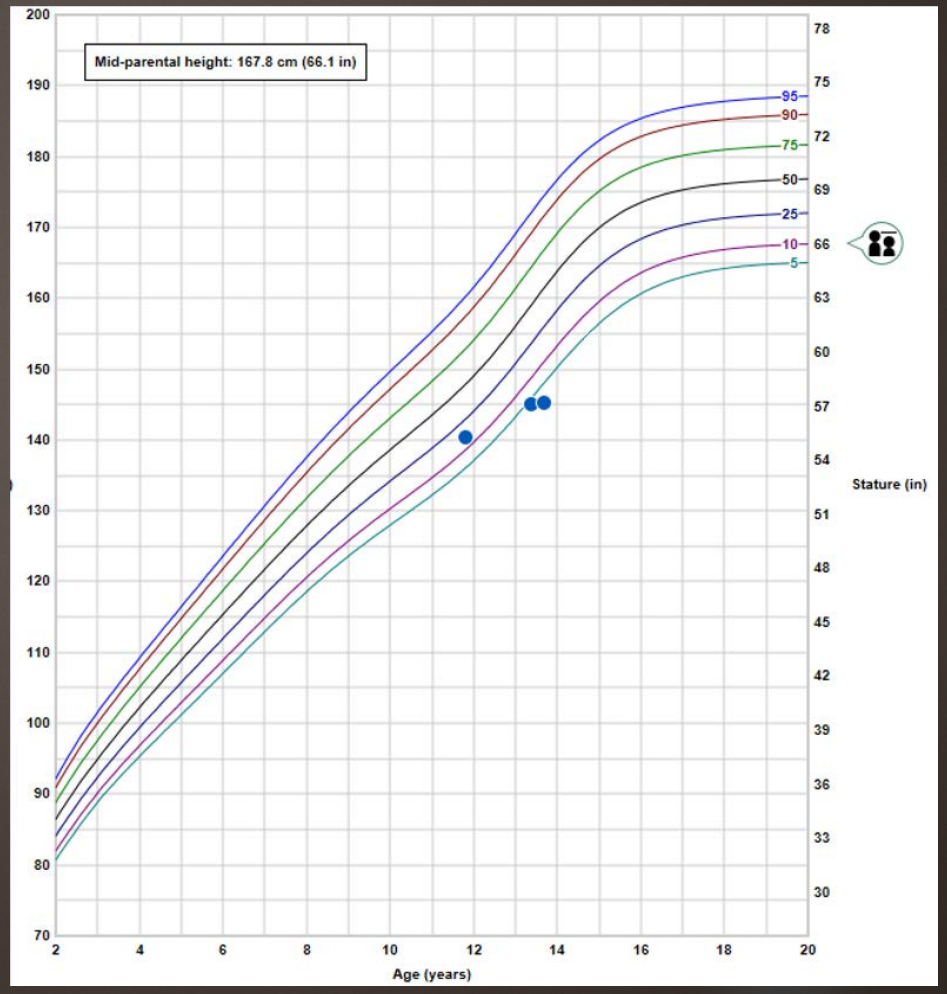
- Always calculate a mid-parental height
  - + or -5 inches for parent of opposite sex, then take the average
- Kids have a growth nadir just prior to puberty
- The nadir and peak velocity are dependent on pubertal timing and progression
- Important to look at velocities in context of puberty



Is this growth failure?

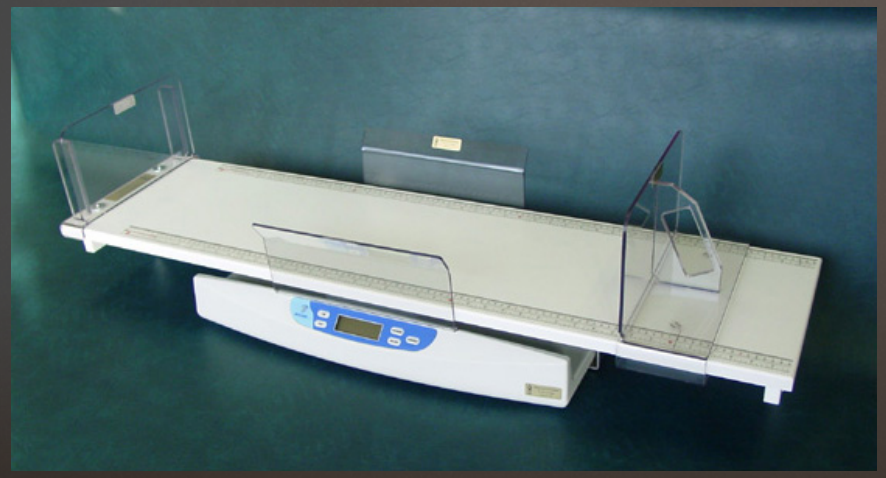
Probably not – they were just prepubertal





Short stature: measurements

- Stadiometer is best in measuring heights
  - Infant version for length
  - Child version preferably secured to the wall
- Avoid floppy arm stadiometers
- Remove shoes and move/remove pony tails, bows, etc…
- Avoid measuring on exam paper if all possible



Question 3

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Weight vs. Height

Height more severely effected

- Endocrine disorders
- Syndromes and skeletal dysplasias
- Idiopathic short stature
- Normal variants

Weight more severely effected

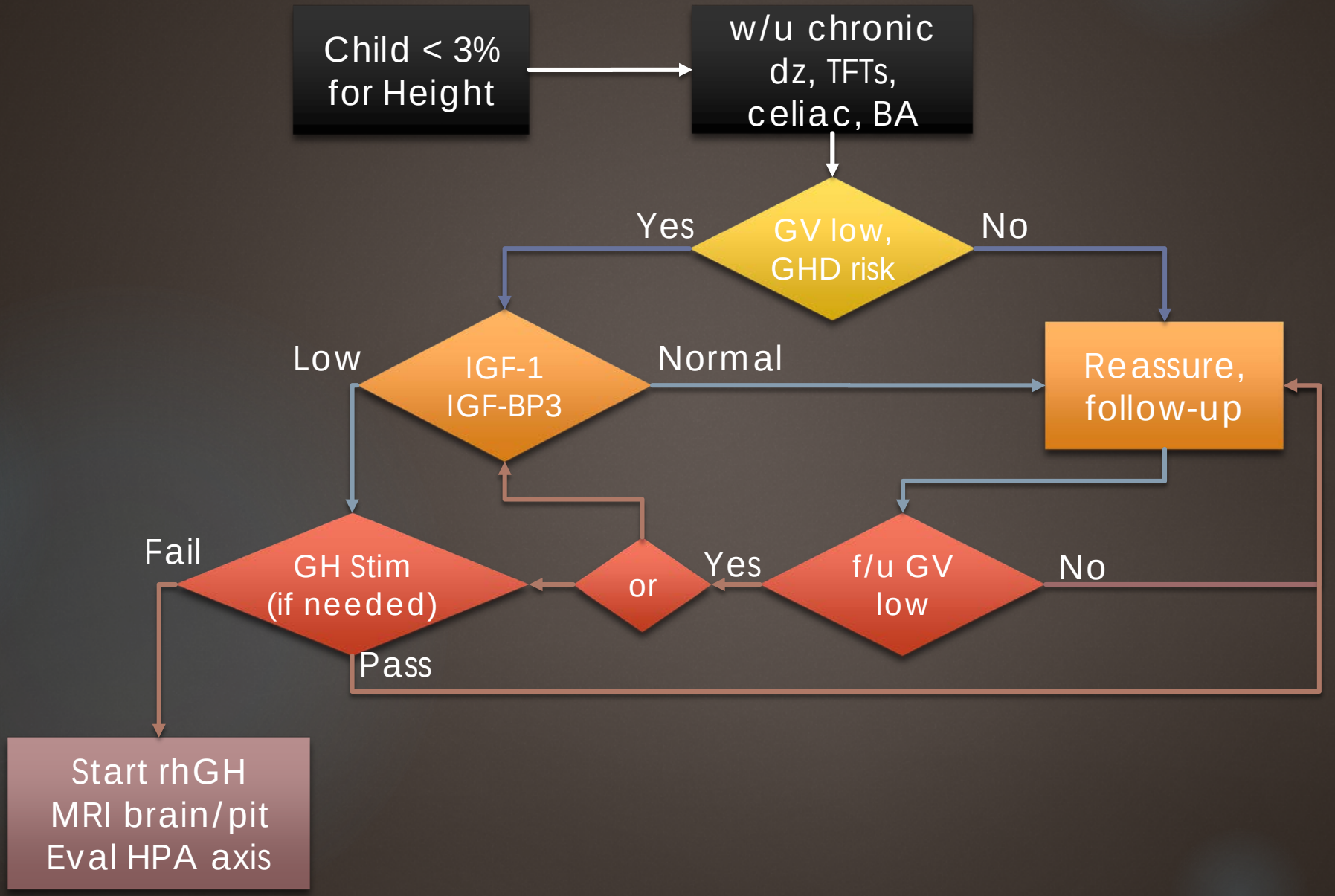
- Nutrition
- Malabsorption
- Chronic diseases
- Variation of normal (thin families)

Failure to thrive (weight worse than height) is not a typical growth pattern of endocrine disorders

Short Stature: should I work them up?

- Discern variation of normal growth versus growth failure
  - If normal velocity and otherwise healthy, then only a bone age is required
    - A delayed bone age can reassure a family and avoid an unnecessary work up
  - If velocity is consistently low, consider a further evaluation
    - Remember to keep puberty in context where appropriate
- To what extent should I work a kid up?
  - H&P findings may provide clues for a like a chronic disease
  - In addition to bone age, check thyroid, renal function, and celiac disease
  - Screening of GH function with IGF-1 and IGF-BP3
    - Interpretation is tricky – maybe leave it up to a ped endo
    - Never measure a random GH level – it's useless

GH deficiency Decision Tree



Question 4

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Indications for rhGH therapy

- Current FDA indications
  - Growth hormone deficiency (regardless of etiology)
  - Small of Gestational age and no catch-up growth by 3 years
  - Turner Syndrome and *SHOX* deficiency
  - Prader-Willi syndrome
    - Caution with sleep apnea
  - Noonan Syndrome
  - Chronic renal failure
  - Idiopathic Short Stature
    - Not covered by insurance
    - Results are modest at best – maybe 1-2 inches of additional growth

When not to use rhGH

- Constitutional delay, familial short stature, or cosmetic purposes
  - They have no deficiency of GH
  - Most influences of growth and final stature are not GH dependent
- Chronic conditions and syndromes without an FDA indication
  - Investigational use is seen in many conditions
  - However, many are not proven and are not covered by insurance
- Contraindications to therapy
  - Malignancies (absolute if active, relative if at high risk), pseudotumor cerebri
- When you refer a child, be very clear or the uses and limitations of rhGH therapy

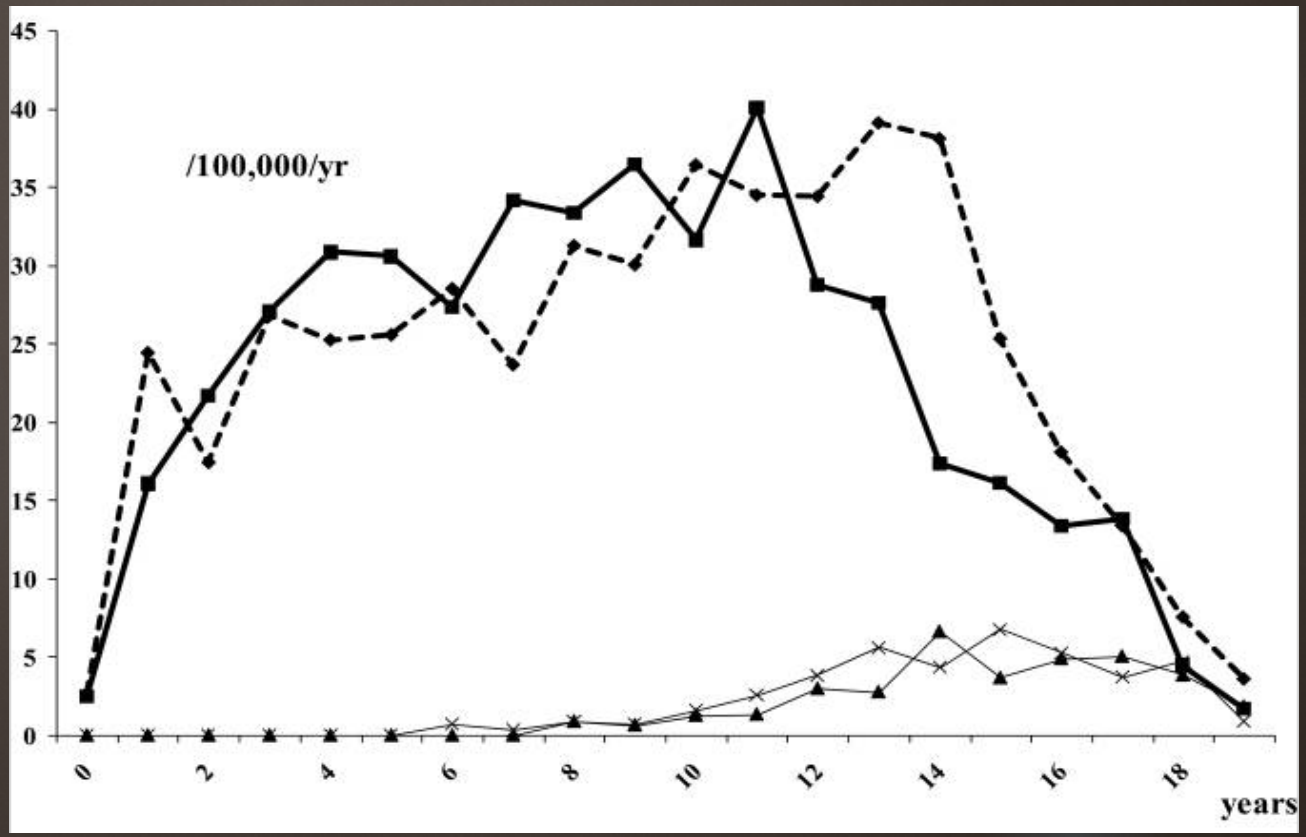
rhGH Therapy

- Benefits
  - Often obvious increase in linear growth, greatest in the 1st year
  - Most cases, duration of therapy is until growth plate fusion
- Risks
  - Pseudotumor cerebri
  - SCFE
  - Tumor risk?
    - No association with leukemias
    - Relative contraindication in children with malignancy risk
  - Diabetes? Only if at risk or have pre-diabetes
  - Caution with Prader-Willi and sleep apnea

Screening diabetes in asymptomatic children

Who gets diabetes?

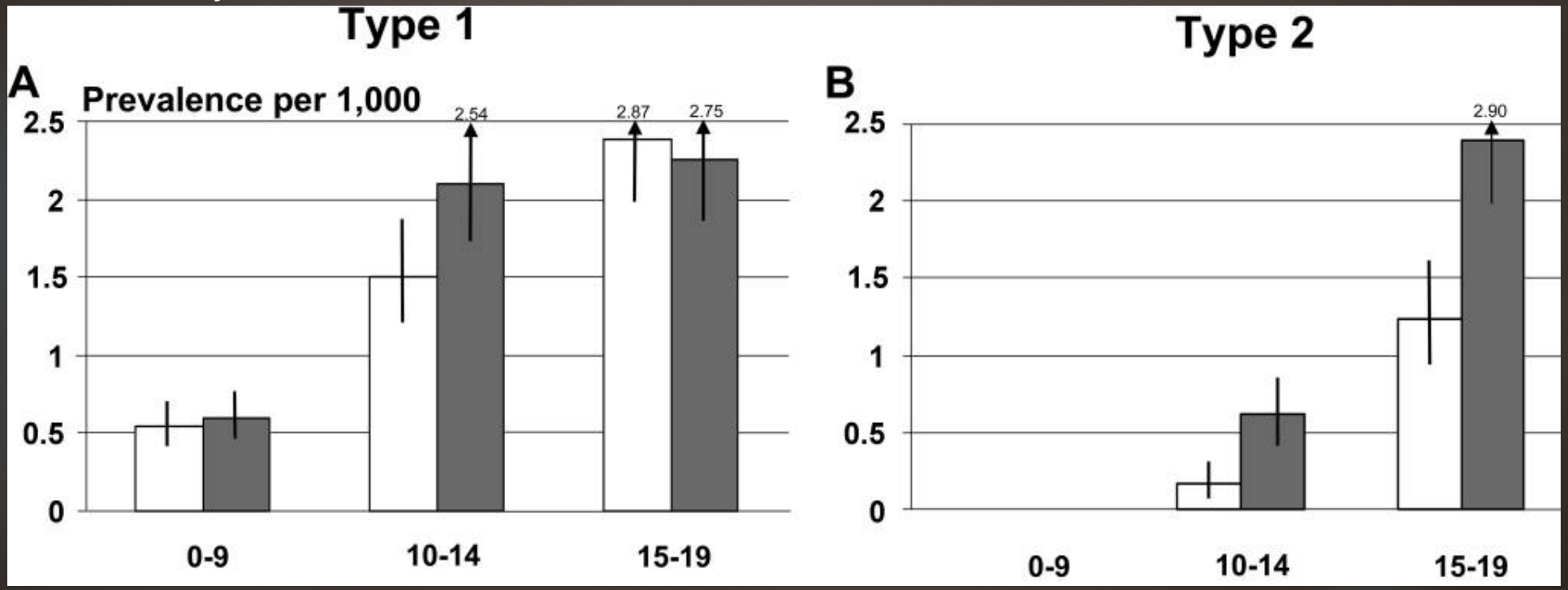
- Diabetes incidence In non-Hispanic white children
- Thick lines – Type I
  - Solid – males
  - Dotted - females
- Thin lines – Type II
  - X – males
  - ▲ – females



Imperatore, G., et al. *Diabetes Care.* 2012 ;35(12):2515-20.

Who gets diabetes?

- Diabetes prevalence in African American children
  - White bars – males
  - Grey bars – females



Imperatore, G., et al. *Diabetes Care.* 2012 ;35(12):2515-20.

Who should we screen?

- If symptomatic for diabetes, a child of any age should be screened
  - Polyuria and polydipsia
  - Unexplained fatigue or weight loss
  - Most kids who present with symptomatic diabetes have T1D
- However, many children with early T2D have no symptoms
  - Less than 10% of T2D presents as DKA
  - Many do not report polyuria/polydipsia at diagnosis of T2D
  - T2D screening is usually in asymptomatic children and based on risk

Rewers, A., et al. *Pediatrics.* 2008 May;121(5):e1258-66.

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Who should we screen?

- If asymptomatic, only screen in overweight children
  - BMI > 85% for age and sex
  - Weight > 120% of ideal for height
- And they should have 2 or more risk factors
  - 1st or 2nd degree relative with type 2 diabetes
  - Ethnicity – All except non-Hispanic white
  - Signs or risk of insulin resistance (acanthosis, PCOS, HTN, dyslipidemia, history of SGA)
  - Gestational diabetes

ADA. (2013). Standards of Medical Care in Diabetes - 2013. *Diabetes Care*, S11-S66

Who should we screen?

- Start screening at age 10 or at puberty
  - Rescreen every 3 years
- Current issues with screening criteria
  - Type 2 diabetes can occur in children under 10 years, so consider screening younger kids if many risk factors
  - NAFLD is not listed, but this is often from insulin resistance
  - Screening every 3 years seems too long
  - Dyslipidemia is not well defined, but authors likely want to be all inclusive

ADA. (2013). Standards of Medical Care in Diabetes - 2013. *Diabetes Care*, S11-S66

Should we screen for T1D?

- Widespread clinical screening of asymptomatic children is not recommended
- Screening 1st degree relatives of T1D should be considered
  - Best done in a clinical study – TrialNet: www.diabetestrialnet.org
    - Screened through T1D antibody testing
  - If positive, need counseling on their risk and symptoms of diabetes
    - Provide opportunities to enroll in prevention studies

ADA. (2013). Standards of Medical Care in Diabetes - 2013. *Diabetes Care*, S11-S66

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How should we screen?

- Single blood glucose measurement – fasting or random
- Oral glucose tolerance testing (OGTT)
- Glycated hemoglobin (HbA1c)

Single blood glucose

- If fasting, a simple an inexpensive test
  - Pre-diabetes: FBG > 100 mg/dL
  - Diabetes: FBG > 126 or random BG > 200
- Problems with single glucose
  - Take caution if acute illness – stress hyperglycemia
    - If 300 or greater, then more likely diabetes
  - Reproducibility issues, especially with capillary glucose
    - If symptomatic for diabetes, then false positive rate is lower
  - In pre-diabetes, high BG's are usually post-prandial and not fasting

ADA. (2013). Standards of Medical Care in Diabetes - 2013. *Diabetes Care*, S11-S66
Inzucchi, S. *NEJM*. 2012 Aug; 367:542-550

Glucose tolerance testing

- A “gold standard” in diabetes testing
  - ADA cutoffs for diabetes and pre-diabetes
  - Greater sensitivity than fasting or random blood glucose
- Pre-diabetes (either/or)
  - fasting hyperglycemia (FH): FBG > 100
  - impaired glucose tolerance (IGT): 2 hour BG > 140
- Diabetes
  - Fasting > 126, or any measures > 200

ADA. (2013). Standards of Medical Care in Diabetes - 2013. *Diabetes Care*, S11-S66
Inzucchi, S. *NEJM*. 2012 Aug; 367:542-550

Glucose tolerance testing pitfalls

- Should be venous samples after an 8 hour fast
- Needs to be in the well state
  - Stress hyperglycemia
- Reproducibility errors
- Added time and expense with OGTTs
  - Testing on a different day if not fasting
  - Requires 2-3 hours of sampling

ADA. (2013). Standards of Medical Care in Diabetes - 2013. *Diabetes Care*, S11-S66
Inzucchi, S. *NEJM*. 2012 Aug; 367:542-550

HbA1c testing

- Nonenzymatic glycation of hemoglobin
  - Estimate of average glucose over the last 3 months
  - Accurate by standardized assays
- Advantages
  - No fasting required
  - Can be in the well or ill state
- Disadvantages
  - False values in altered red cell turnover
  - Assay interference by hemoglobin variants http://www.ngsp.org/interf.asp
  - Differences in glycation between ethnicities

ADA. (2013). Standards of Medical Care in Diabetes - 2013. *Diabetes Care*, S11-S66
Inzucchi, S. *NEJM*. 2012 Aug; 367:542-550

What not to measure

- Urine Glucose
- Serum Insulin

Urine Glucose

- Glucosuria occurs when BG is above 180
  - Would only pick up children with uncontrolled diabetes
- False positive if benign renal glucosuria
  - Genetic defect of SGLT2 (*SLC5A2* gene)
- Only get a urinalysis if checking for ketones

Question 7

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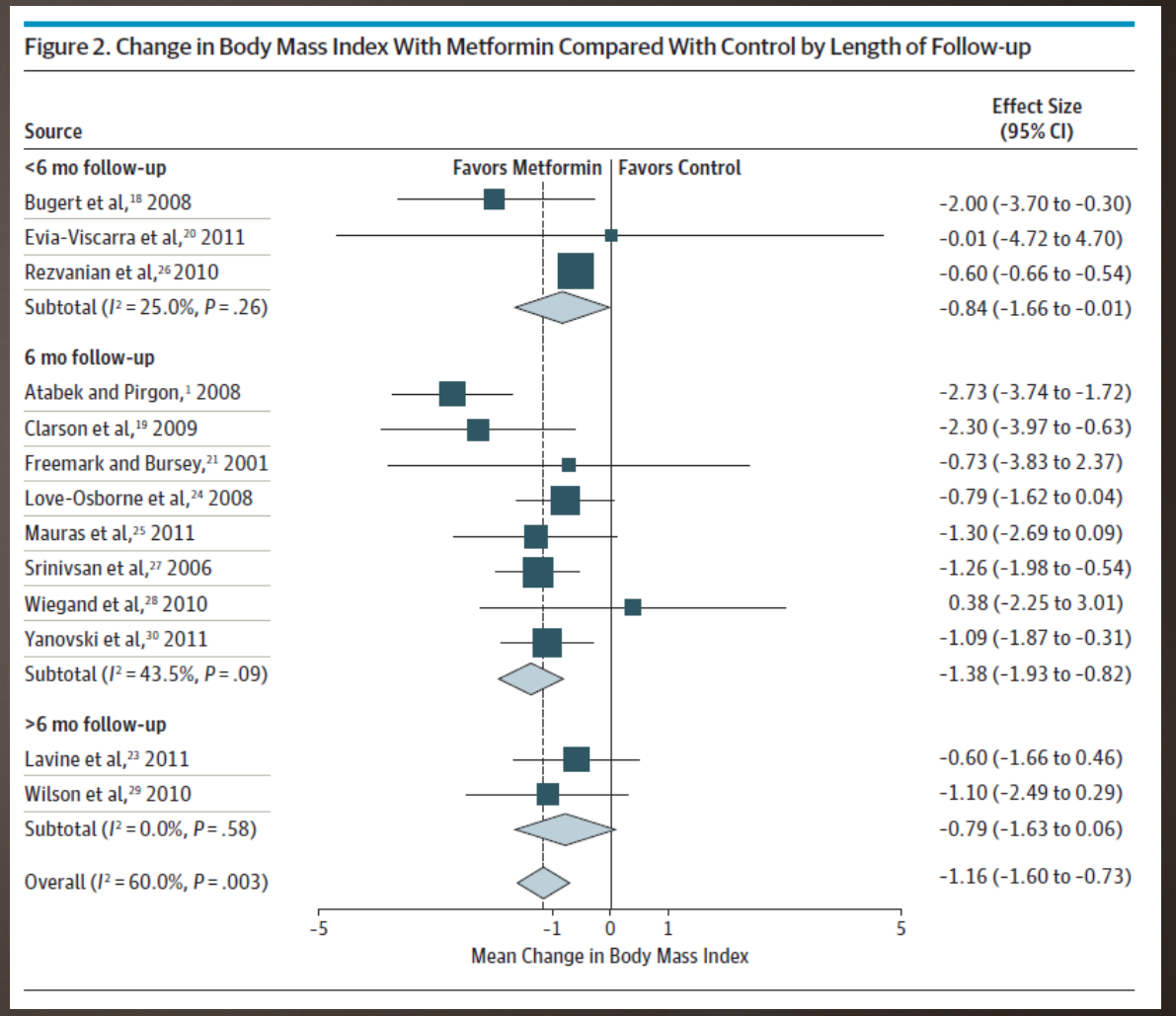
Insulin measurements

- Children with insulin resistance by definition will have elevations in serum insulin
- However, insulin measures are unreliable in children
  - Differences in pubertal status, ethnicity, and other genetic factors
  - Puberty causes a natural degree of insulin resistance
  - No risk prediction for diabetes in children
    - Insulin measures may be elevated in early type II diabetes, then low with beta cell burnout
- Insulin is not part of diagnostic testing for diabetes
  - Avoid measuring insulin as part of screening and diagnosis

Arslanian SA, et al. *JCEM*. 87:1555–1559
Levy-Marchal, et al. *JCEM.* 2010, 95(12):5189–5198

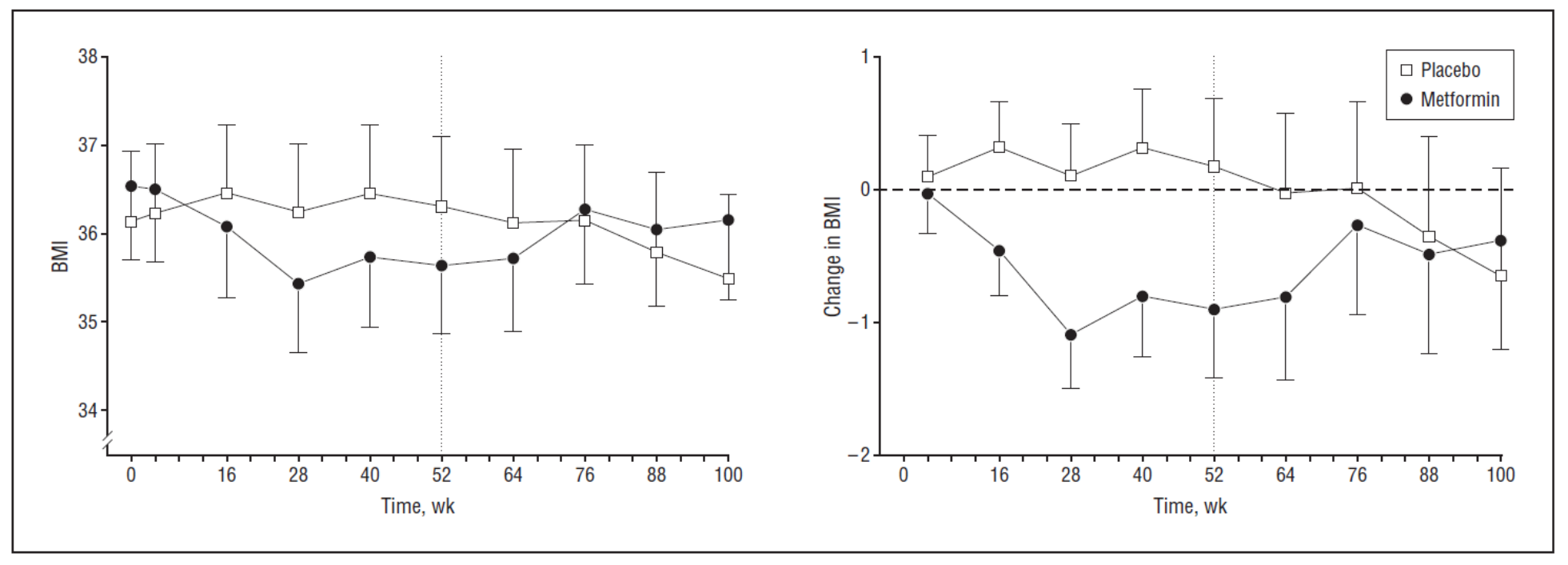
Metformin for non-diabetic obese kids

- Treatment of insulin resistance is primarily by lifestyle modifications
- Metformin use in non-diabetic obese children is controversial
  - Modest benefits in children with severe obesity (BMI > 35 kg/m^2)
  - Reduction of BMI by 1-1.5 kg/m^2 or about 3 kg of weight (3.6% greater BMI change than lifestyle alone)
  - No change in lipids or markers or insulin resistance
  - The effect stops once the metformin is stopped



GPRN. Arch Pediatr Adolesc Med. 2010 February ; 164(2): 116–123.
McDonagh MS, et al. JAMA Pediatr. 2014 Feb;168(2):178-84.

Metformin for non-diabetic obese kids



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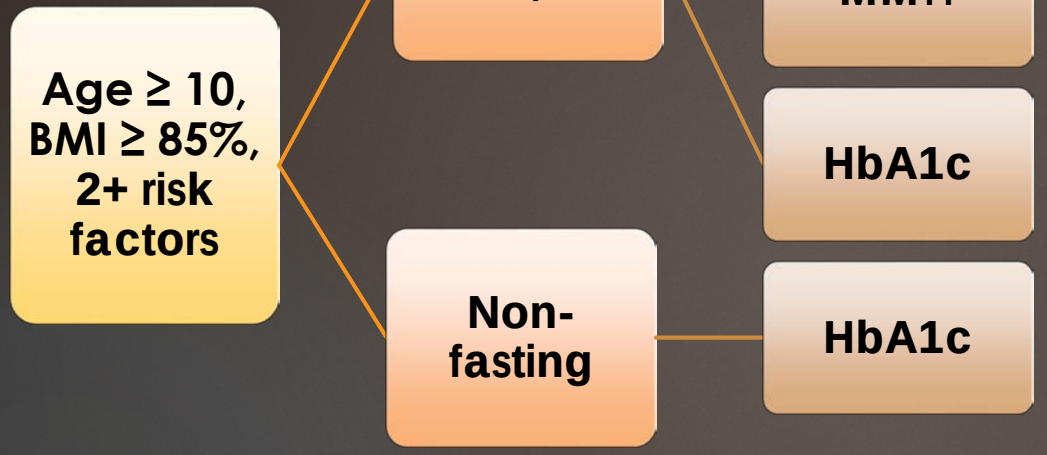
Diabetes screening in asymptomatic children



Risk factors

1. 1° or 2 ° relative w/ DM2
2. Ethnicity: AA, HA, API, AI
3. Signs of insulin resistance (PCOS, acanthosis,, HTN, dyslipidemia, SGA)
4. Gestational DM

OGTT = Oral Glucose Tolerance Test

After 8+ hr fast, check venous FBG
drink 1.75g/kg glucola max 75g
check venous 1 & 2 hour BG

MMTT = Mixed Meal Tolerance Test

After 8+ hr fast, check fasting BG, eats regular meal, check 2 hour BG
POC testing – less accurate

Normal	Pre-diabetes	Diabetes
BG fasting < 100	FBG 100-125 or	FBG ≥ 126 or
2 hour < 140	2 hr BG 140-199 or	2 hr BR ≥ 200 or
HbA1c < 5.7%	HbA1c 5.7-6.4%	HbA1c ≥ 6.5%
Lifestyle changes	Consider referral	Peds Endo referral

ADA. (2013). Standards of Medical Care in Diabetes - 2013. *Diabetes Care*, S11-S66

Early puberty

Question 8

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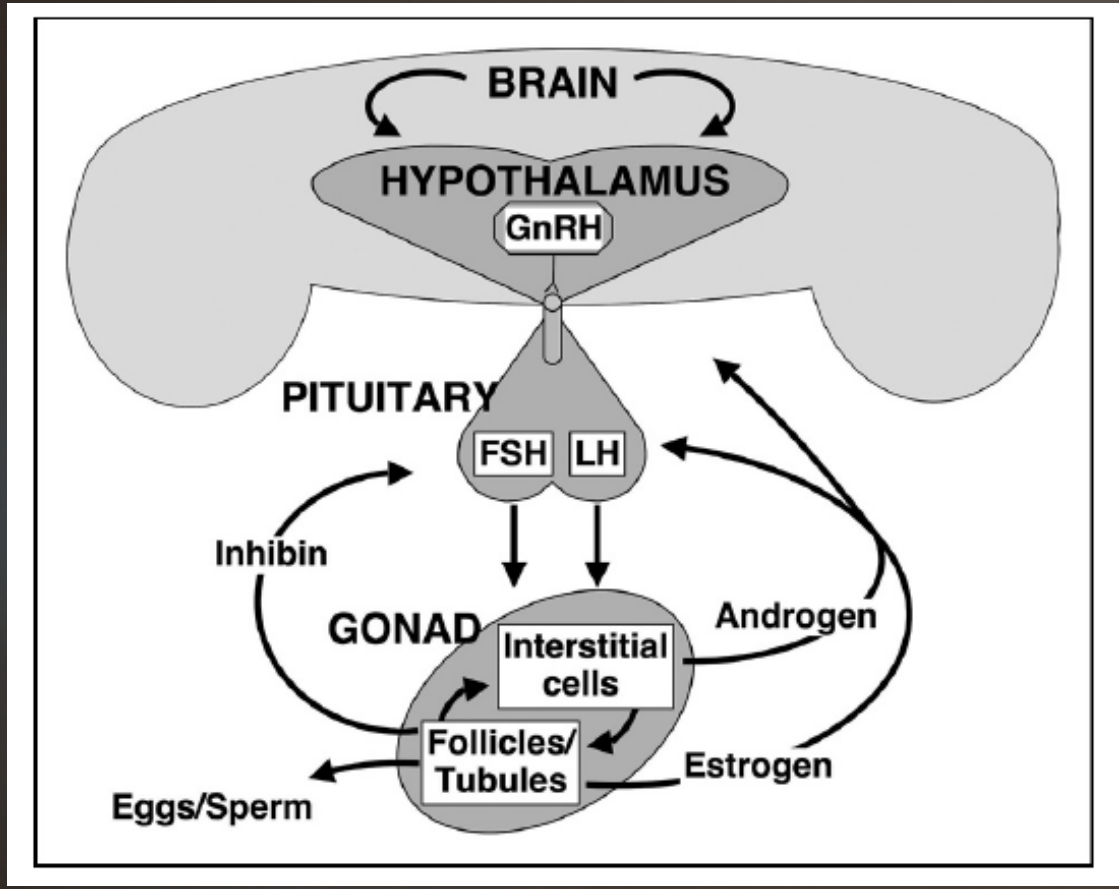
Endocrine basis of puberty



- Hypothalamic-pituitary-gonadal (HPG) Axis
  - Pulsatile release of GnRH
  - LH stimulates androgen production by Lydeg (male) and Thecal (female) cells
  - FSH stimulates gamete production (egg recruitment, sperm), inhibin B, and aromatization of androgens (female)
  - Inhibin B and gonadal sex hormones provide feedback inhibition

Bordini and Rosenfeld. *PIR*. 2011.

Endocrine basis of puberty

- HPG Axis is active in 3 phases of childhood
  - Fetal – established during the 1st trimester. In males, it is critical in the 2nd and 3rd trimester for phallic growth and the inguinal-scrotal phase of testicular descent
  - Early infancy, AKA mini-puberty: a normal surge of gonadotropins at 3-12 mos
  - Puberty
- In between Mini-puberty and true puberty, the HPG axis is mostly dormant
  - CNS inhibiting GnRH pulsitility
  - All LH production ceases
  - FSH levels fall to low (but not undetectable) levels – small FSH production can lead to ovarian follicles in pre-puberty (which is normal)

Endocrine basis of puberty

- Adrenarche (or pubarche)
  - Sexual hair, along with some body odor and acne
    - Body odor or acne alone is not adrenarche
  - A re-onset of androgen production from the adrenal cortex
    - *In utero*, the fetal zone of the cortex produces large amounts of DHEAS – provides placental estrogen. It then regresses in the first few post-natal months
    - Zona reticularis increases adrenal androgen production in mid-childhood
    - Primarily produces DHEAS (a pro-androgen), but also androstenedione and small amounts of testosterone
  - Usually coincides with true puberty, but it is independent of the HPG axis

Endocrine basis of puberty

- Regulation of pubertal onset
  - Removal of inhibition by the CNS
    - Increasing stimulation by glutamate and kisspeptin
    - Less inhibition by GABA and endorphins
  - Gradually less sensitivity to negative feedback by sex steroids
- Factors that influence pubertal timing
  - Genetics determines about half of timing variation
  - Ethnicity
  - Endocrine disruptors
  - Other somatic stimuli – nutrition (anorexia, obesity), GH-IGF1 axis, thyroid function, leptin, etc…

Question 9

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Define Puberty

- When does it normally occur?
  - Girls = 8-13 years
    - Some populations may have lower limits of normal at 7 or 7.5 years
  - Boys = 9-13 years
- What physical change best defines puberty?
  - Girls = thelarche
  - Boys = testicular enlargement
- Does thelarche mean that a girl is definitely in puberty?
  - Not definitely, but it's certainly possible, maybe even likely.
- Does testicular growth mean that a boy is definitely in puberty?
  - Yes, absolutely!

Define Puberty

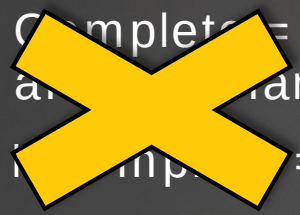
- What's wrong with too soon?
  - Early growth plate closure leading to shorter adult stature
  - Early menses and its effect on the girl's (and at times the parents') psyche
- What's wrong with too late?
  - Insufficient bone accrual in adolescence leading to osteoporosis
  - Infertility in some instances
  - Psychological impact of a pre-pubertal state

More Definitions

- What is thelarche?
  - Breast buds: firm nodule under the nipple and areola – an eraser head
  - Fat is mushy. It does not mean thelarche
- What is adrenarche (aka pubarche)?
  - Sexual hair: Coarse hairs on the mons, labia, and axillae
    - Not fine, downy hairs
    - Not hair on the forearms or legs
  - Body odor and acne – often seen (or smelled) with adrenarche, but you need the sexual hair as well
  - Does adrenarche = puberty?
    - NO!

Even More Definitions

- What are we talking about when we say central or peripheral?
  - Central – induction of puberty from the HPG axis
  - Peripheral – a different source of puberty, not from the HPG axis
- What about complete or incomplete?
  - Complete = both thelarche and adrenarche or both testicular enlargement and pubarche
  - Incomplete = basically is a another way of saying adrenarche
- What does “hormonal” mean?
  - I don’t know
  - Emotional lability, risk taking behavior, oppositional defiance, and conflict are not necessarily signs of puberty



Please avoid: Neither term is accurate

Other exam notes

- You must palpate! Not just inspect!
  - Breast tissue is firm, whereas fat is mushy
  - Testicular size in volume is the best indicator in boys
    - Phallic size varies and can be obscured by obesity
    - Use of on orchidometer may be needed. 4 ml or greater is c/w puberty
- Remember – pubic hair alone does not mean puberty!
  - What looks like Tanner 2 hair could actually be generalized hypertrichosis
  - Tanner 3 hair is more specific to sexual hair, but in isolation is still adrenarche, not puberty.

Normal puberty: sex hormone functions

Estrogen

- Endometrial growth, cervical mucus
- Thelarche
- Growth Spurt
- Bone mass accrual
- Growth plate closure
- Lipogenesis and lower body fat distribution

Androgen

- Sexual hair, sebaceous gland secretions
- Growth spurt
- Bone mass accrual (but likely by paracrine aromatization to estrogens)
- Wider bones and larynx
- Lipolysis (except visceral fat)
- Muscular development

Variation of normal puberty

- 15% of pediatric female office visits present with a chief complaint of premature thelarche or adrenarche
  - Most are in isolation, and thelarche may regress
  - May be related to obesity, functional ovarian cysts that involute, or exposure (lavender & tea tree oils)
- Isolated premature adrenarche
  - Usually is benign, and at times mild elevations of DHEAS are seen
  - Can be a precursor to PCOS or rarely a virilizing disorder
  - Usually just close observation and a bone age is indicated. Rapid progression, advanced bone age, clitoral growth, and other pubertal changes may warrant a ped endo evaluation

Herman-Giddens ME, Slora EJ, Wasserman RC, et al. *Pediatrics*. 1997

Precocious Puberty

- Evidence of pubertal changes before the expected age of puberty
  - Suspected by history and physical
    - Boys – testicular enlargement
    - Girls – thelarche
  - Confirmed by biochemical testing
  - Usually occurs in early school age: 5-7 years in girls, 5-8 years in boys
    - Don't confuse mini-puberty for true puberty – minimal thelarche or adrenarche in infants is usually normal.
- Two categories
  - Central
  - Peripheral

Question 10

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Central Precocious puberty

- Early activation of the HPG axis
- Five times more common in females
  - Idiopathic in 90% of girls and 50% of boys
  - Other causes are typically CNS lesions, rarely genetic mutations
- Risk factors for CPP
  - Past insults to the CNS can lead to CPP – lack of GnRH inhibition
  - Obesity
  - Exposures to endocrine disruptors (controversial)
  - Genetic syndromes, such as NF1
  - Inadequately treated peripheral puberty disorder

Question 11

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Peripheral Precocious Puberty

- AKA Gonadotropin independent precocious puberty
- Exogenous exposures
- Virilizing or feminizing masses
  - Adrenal or gonadal tumors
  - HCG secreting tumors
- CAH (although no thelarche in females, but rather ambiguous genitalia)
- Genetic syndromes
  - McCune-Albright – GNAS activation of many hormone receptors, including LH
  - Male-limited precocious puberty (formerly testotoxicosis) – Constituent LH receptor activation
- Severe thyroid disease – either hypo- or hyper-
- If prolonged and untreated, these conditions could eventually lead to CPP

Evaluation of Early Puberty

- Thorough H&P
  - Timing and progression of pubertal changes
  - Risk factors for CPP
    - prior CNS insults, seizure d/o
    - Symptoms to suggest an intracranial mass – headaches, vomiting, etc…
    - Low or high thyroid symptoms
  - Accurate anthropometrics and calculating a height velocity (if prior measures)
    - Height acceleration suggests a pubertal growth spurt
  - SMR staging…with palpation!
  - Neuro exam

Lab Evaluation of Precocious Puberty

- When in doubt, get a bone age!
  - A normal bone age is often reassuring and suggests that the adrenarche or thelarche is benign
- Biochemical tests
  - If minimal adrenarche or thelarche, just get a bone age
  - If still concerned (more pronounced thelarche, testes > 4 mL) and/or advanced bone age
    - Measure LH and testosterone or estradiol
    - FSH not very helpful
    - TFTs and serum βHCG to rule out some peripheral causes

Question 11

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Lab Evaluation of Precocious Puberty

- Pure adrenarche with advanced bone age is not puberty, but consider an adrenal disorder like CAH.
  - Best to probably defer to the ped endo on what to measure
- What about an advanced bone age but normal labs?
  - Not all advanced bone ages are concerning
  - Some advanced bone ages correct with time
  - Isolated advanced bone age can indicate constitutional advancement
    - Tall for age but parents of normal stature
    - Puberty on the early side of normal
    - Reach final height at a younger age
    - Their bone age predicts normal stature as an adult

Lab Evaluation of Precocious Puberty

- Pubertal hormone values are much lower in children
  - Requires ultrasensitive assays
  - Use labs that report pediatric ranges
- Some local labs can measure LH & FSH at low levels
  - Clue is decimal points – if 1 or less, don't use it
- Other sex hormones should be measured at a reference lab
  - May need to defer to ped endo
- First morning samples are a little more accurate, but no need to fast

Diagnosis of Precocious Puberty

- LH of 0.20 mIU/mL or above is diagnostic for CPP
  - A random LH by 3rd gen assay is over 80% sensitive in picking up CPP
  - Estradiol or testosterone occasionally elevated to pubertal ranges
    - Estradiol > 15 pg/mL in girls
    - Testosterone > 10 ng/dL in boys
- Peripheral causes: Low LH and FSH, but sex hormones often very high
- If bone age is advanced but labs are pre-pubertal, consider 2nd tier tests is still concerned for CPP
  - Leuprolide (GnRH) stimulation testing
    - Stimulated LH and sex hormone Increases sens and spec to > 95%
    - Requires ped endo
  - Pelvic Ultrasound

Conclusions

- Most short kids do not have a growth disorder
  - Keep puberty and family height into context
- Target diabetes screening based on risk
  - Diagnosis based on blood glucose and/or A1c, not insulin
- Pubic hair does not mean puberty
- When in doubt, get a bone age!

And the winner is...

KAHOOT

Thanks!

ANY QUESTIONS?