GROWTH & DEVELOPMENT ISSUES IN THALASSEMIA

UCSF Benioff Children's Hospital Oakland

Northern California Comprehensive Thalassemia Center

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DISCLOSURES

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- I have no actual or potential conflict of interest in relation to this program/presentation.

ENDO 101

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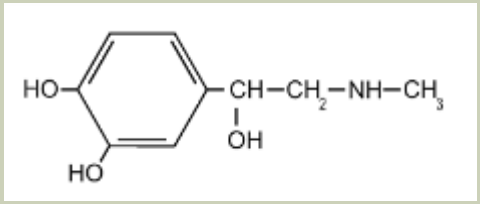
- Hormones are made in one area of the body and act somewhere else

ENDO 101

- Hormones are made in one area of the body and act somewhere else

Amines



e.g. Epinephrine

Proteins

e.g. Insulin

Steroids

e.g. testosterone

IRON OVERLOAD RECAP

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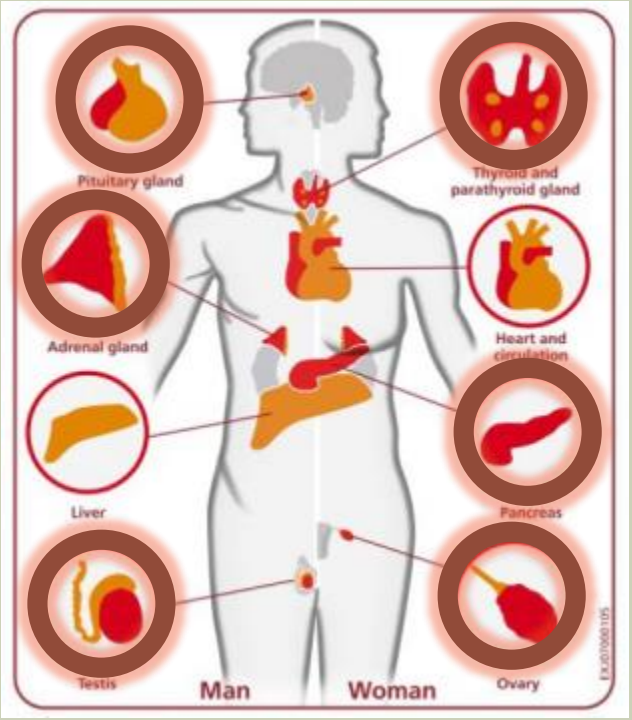
- Iron is typically bound to transferrin
- Excess iron leads to increased unbound iron (NTBI) circulation of molecules toxic to cells
- Low red blood cell counts can cause chronic low oxygen delivery to cells and worsen the toxicity
- Certain tissues are more susceptible to excess unbound iron



INCIDENCE/PREVALENCE

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Endo. Problem (% in both sexes)	Cyprus (n=436)	Greece (n=262)	Italy (n=1861)	North America (n=262)	Iran (n=220)	Turkey (n=252)
Hypogonadism	35.2	42	49	42	35	50
Diabetes mellitus	9.4	5	4.9	5	8.7	9.3
Short stature/GHD	35	32	-/12.4	32/3	39.3	-/10
Hypothyroidism	5.9	4	6.2	4	7.7	29
Hypo-parathyroidism	1.2	4	3.6	4	7.6	4

Thalassemia News 2001, page 12

- 34.7% had biochemical adrenal insufficiency (Soliman A, et al, 2013)

ENDOCRINOLOGY AND YOU…

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- Among 316 regularly transfused patients older 10 years old across Europe (Wonke B, et al., 2001)
  - 56% were seen by an endocrinologist
    - 42% of the 56% were seen at least annually
- Among 96 patients in the Middle East (De Sanctis V, et al., 2012)
  - 62.4% never saw an endocrinologist
  - 34% seen yearly
  - 3.6% seen every 2 years or less

HORMONES AT RISK

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- Pituitary
  - Growth Hormone
  - TSH Hormone
  - Gonadotrophins
  - Adrenocorticotrophic Hormone (ACTH)
- Thyroid Glands
  - Thyroid hormone
- Adrenal Glands
  - Cortisol
- Gonads
  - Testosterone
  - Estrogen
- Parathyroid Glands
  - Parathyroid (PTH) hormone
- Pancreas
  - Insulin

GROWTH HORMONE AXIS AND IGF-1

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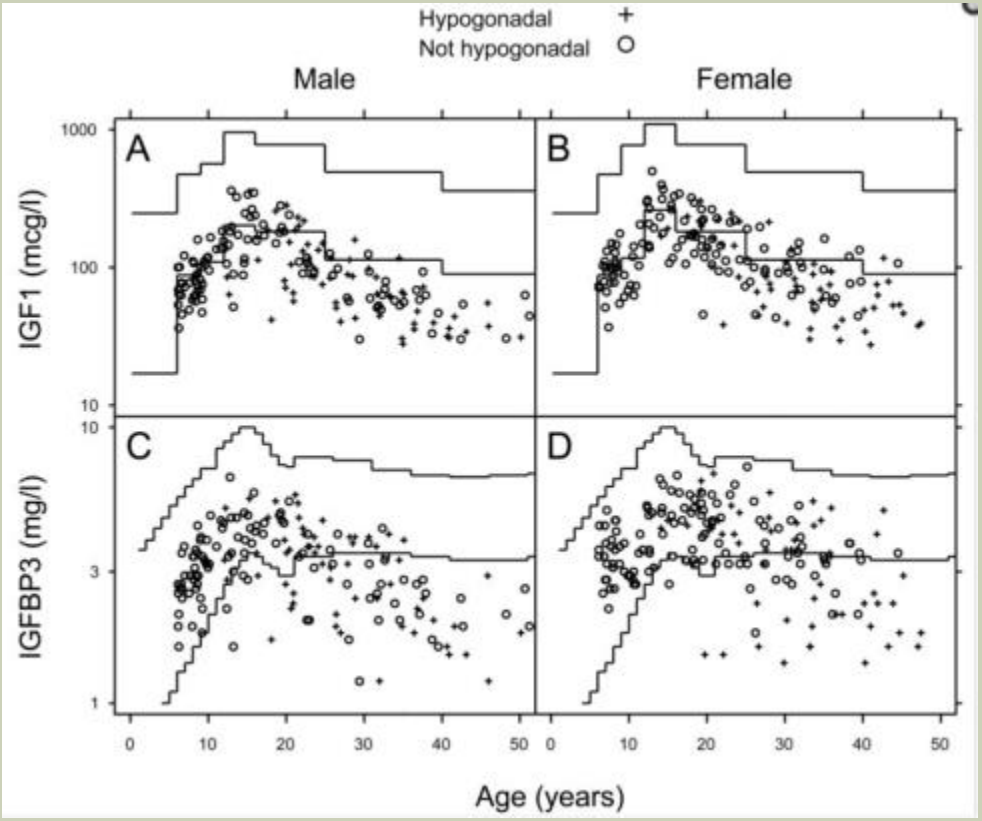
- 361 subjects
- 71% of all patients had levels below normal
- By age
  - 6-11 yr → 57.7%
  - 12-19 yr → 56.8%
  - > 20 yr → 83.3%
- 25% of those < 20 yr were below the 3%ile for height
- 28.5% of those > 20 yr were below the 3%ile for height
- As a group the Δ from MPTH was -4.3 cm ± 7.4 cm



Vogiatzi MG, et al., Br J Haemotol 2009

SO WHO HAS "SHORT STATURE"?

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- > 2 SD (ie < 2.3%ile) below the mean for age, gender, and population group

BUT "WHO'S" CURVE IS IT ANYWAY

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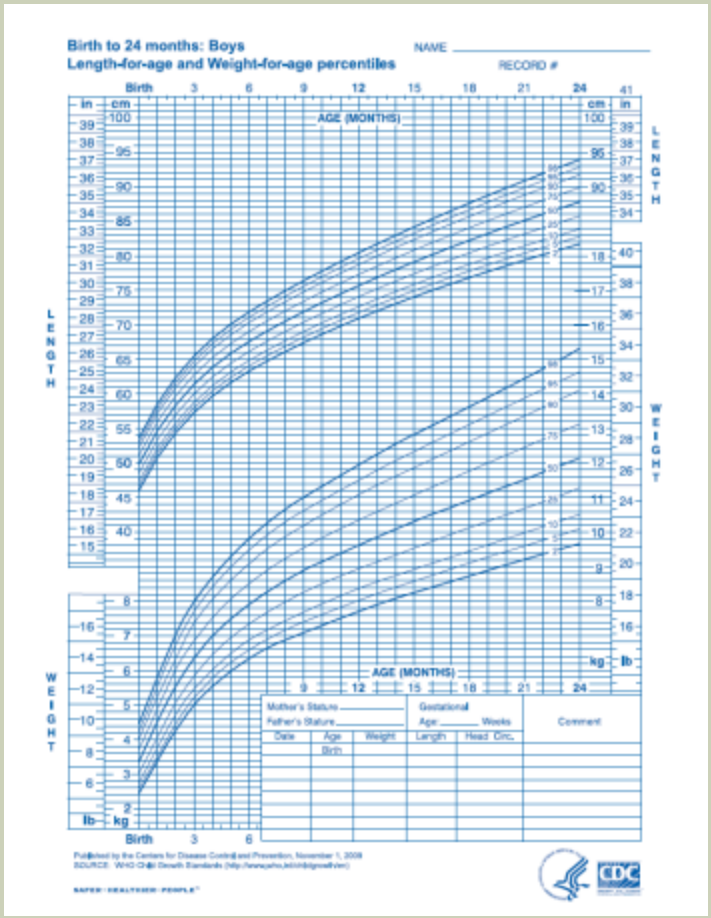
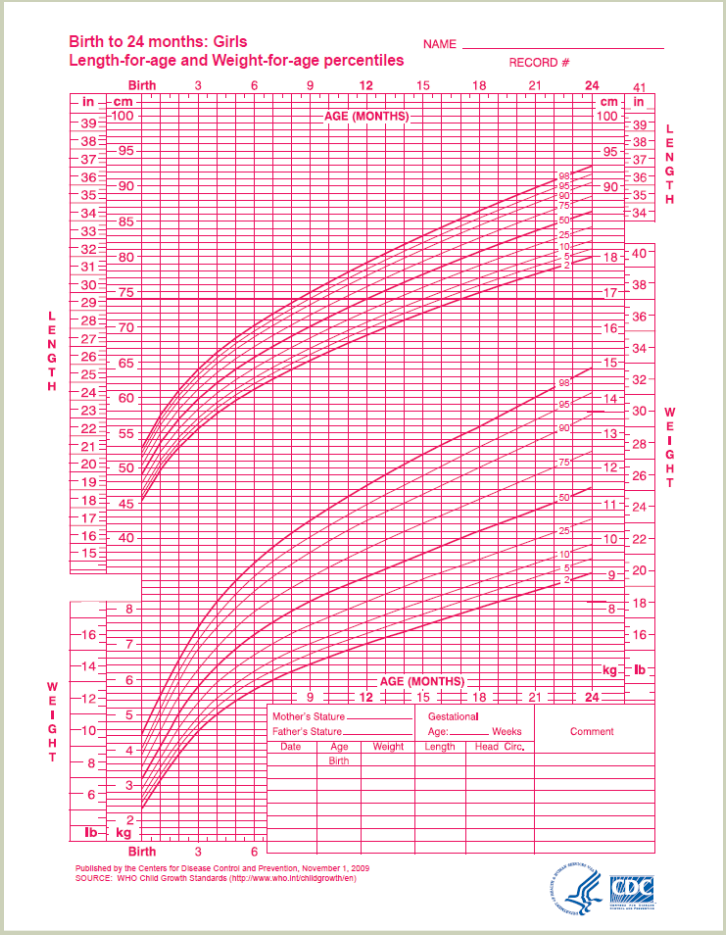
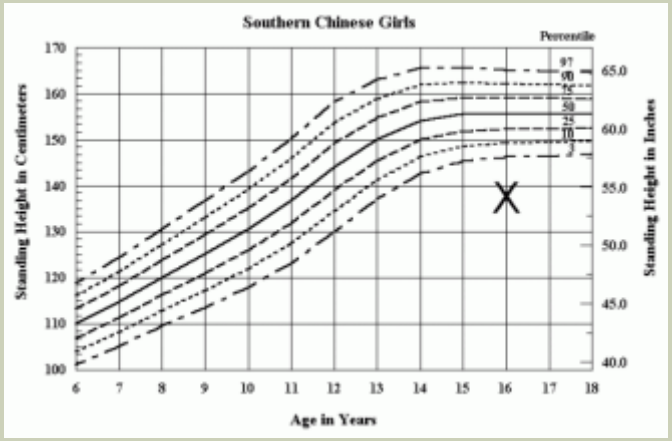
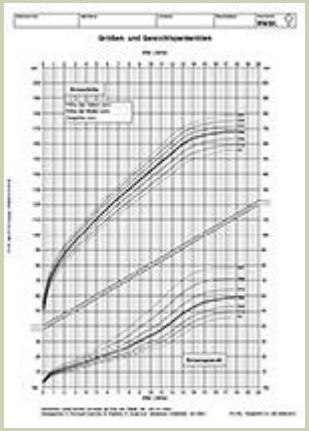


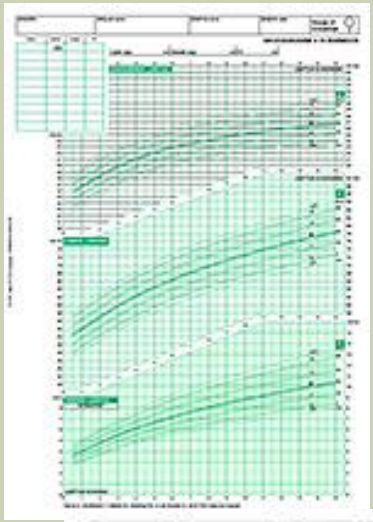




Southern China



Germany



Netherlands

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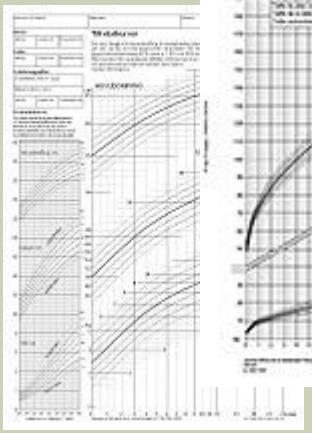
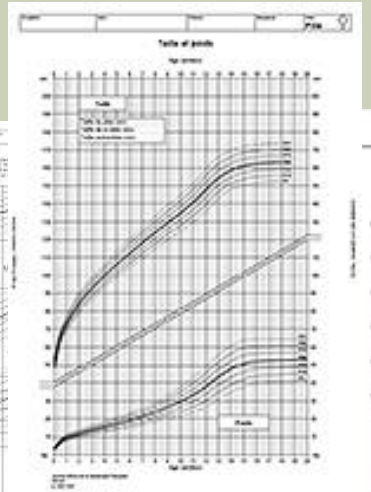
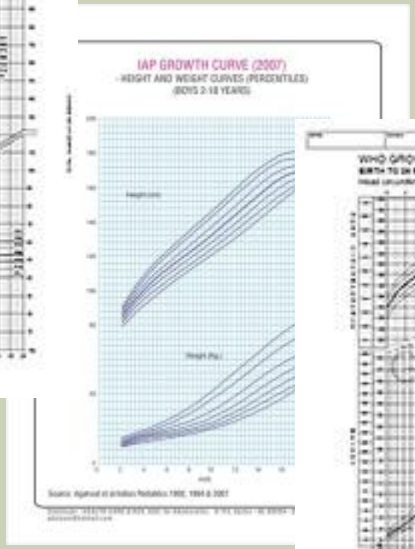


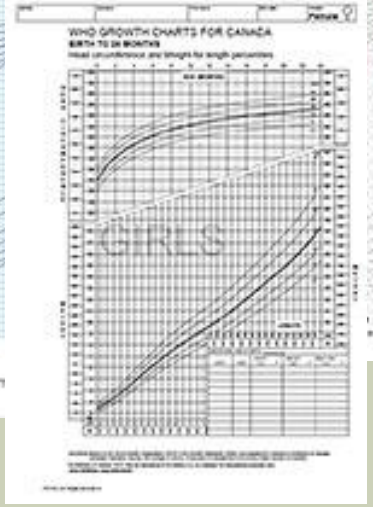
Sweden



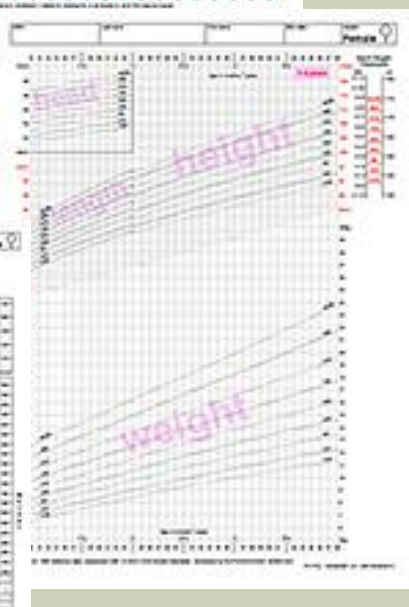
France



India

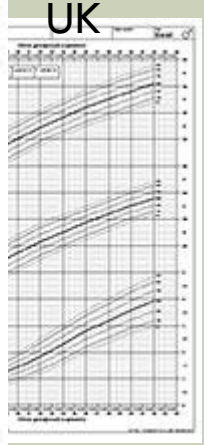


Canada



Romania

UK



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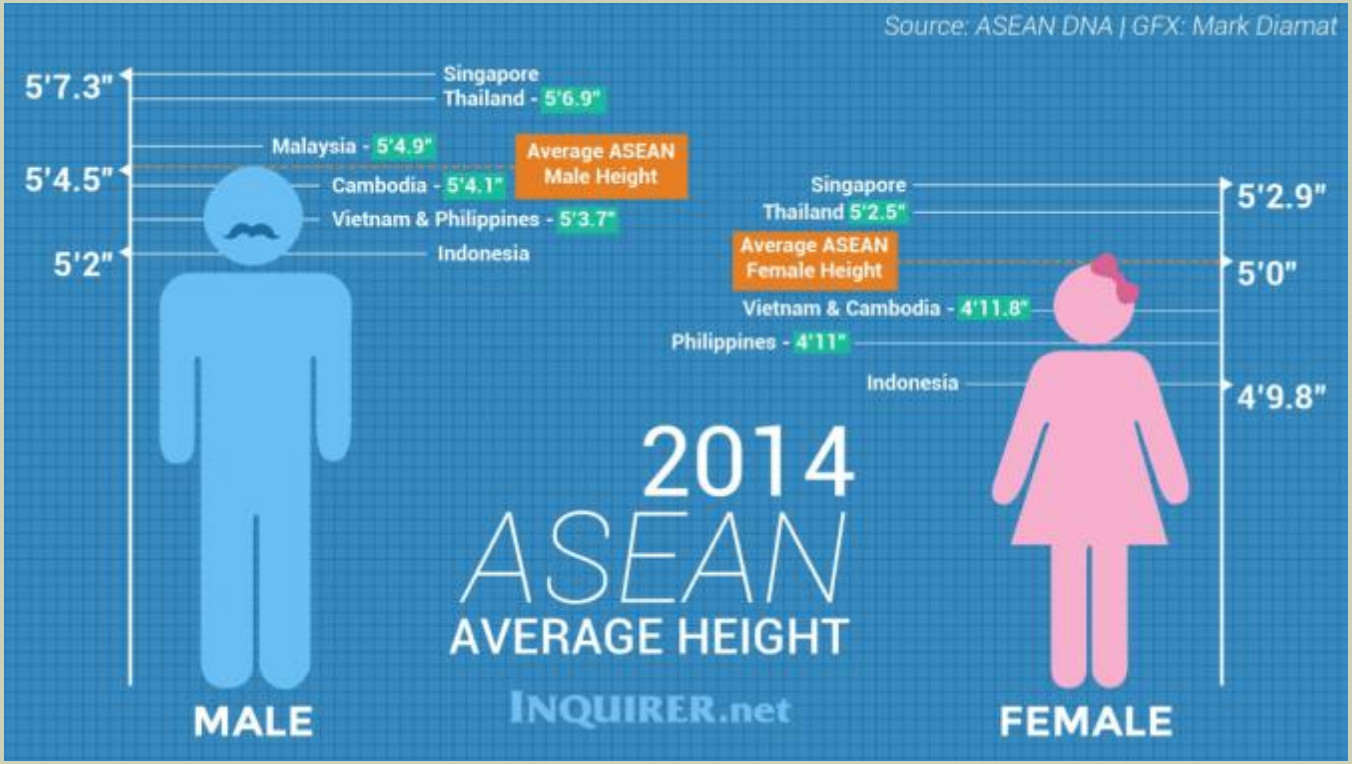

IT'S ALL "RELATIVE"…

- Mid-parental target height (MPTH)

$$\frac{\text{Mom's height} + \text{Dad's height}}{2}$$

+ 2 ½"

- 2 ½"

GROWTH FAILURE

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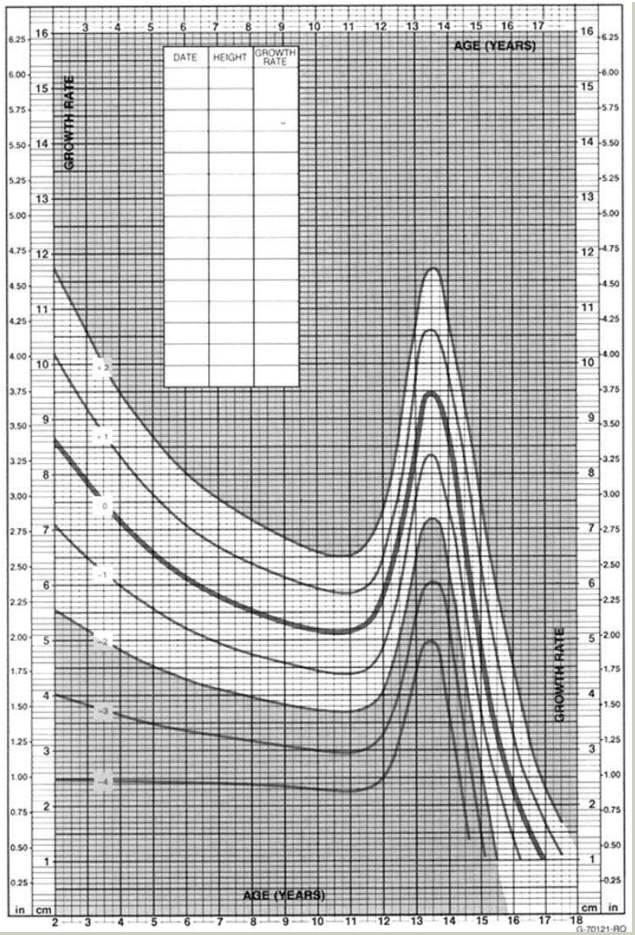
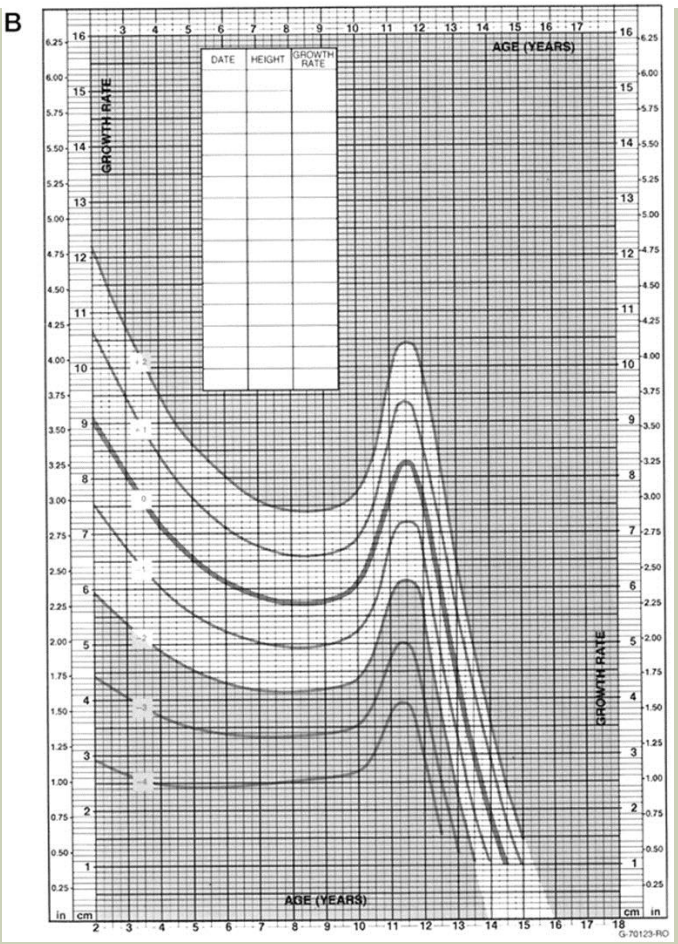
A



Boys

B



Girls

Tanner JM, Davies PSW (1985). J Pediatr **107**:317–329

THE GROWTH CHART AS A VITAL SIGN

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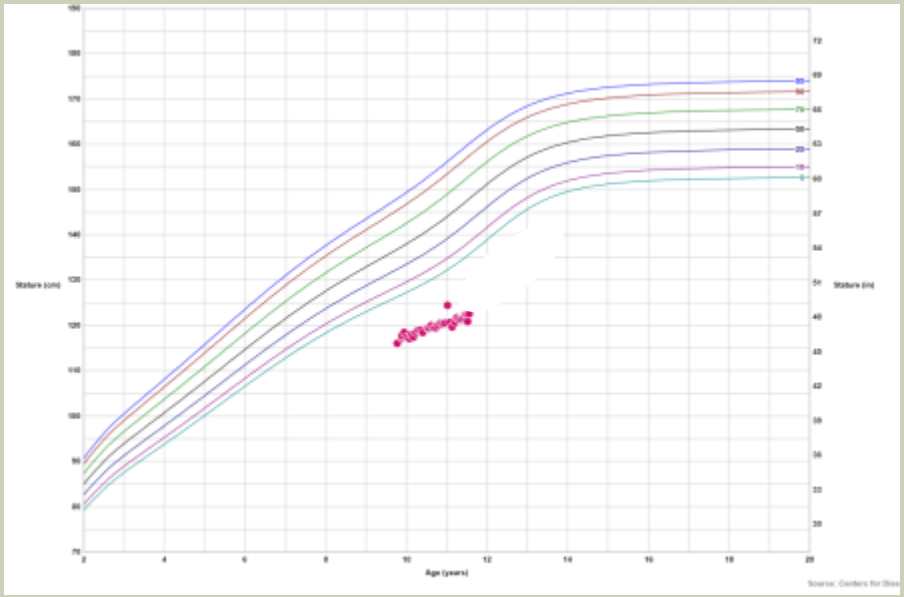

THE DIFFERENTIAL OF SHORT STATURE

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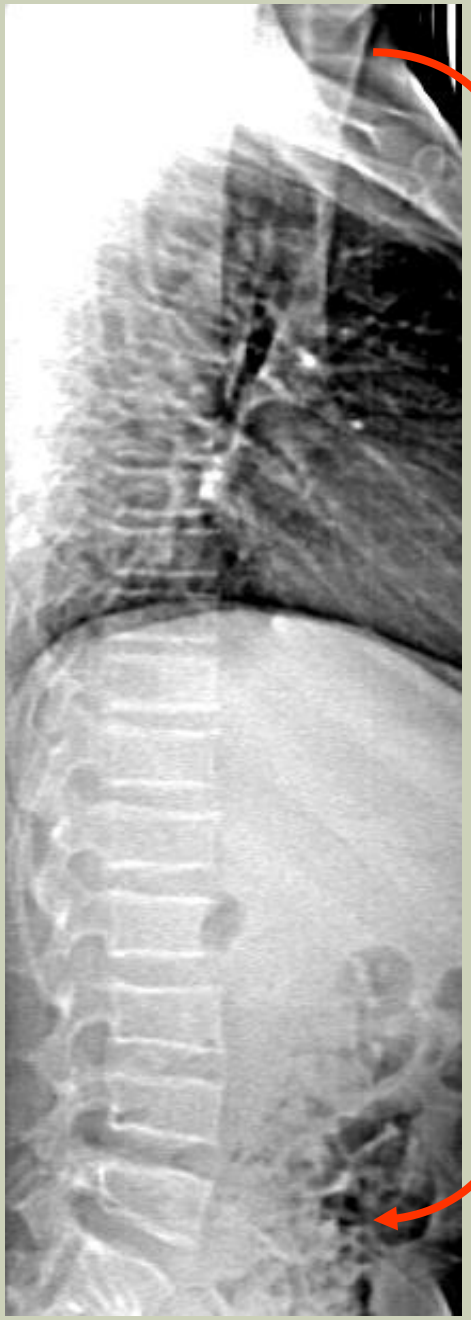
- Genetic
  - Familial
  - Constitutional delay
- Endocrinologic
  - GH deficiency
    - Hypopituitarism
  - GH resistance
    - Small for gestational age
    - ~15% will have growth failure
  - Hypothyroidism
  - Cortisol excess
  - Bone Disease
  - Diabetes
  - Premature epiphyseal closure
    - Precocious puberty
    - Non-classical adrenal hyperplasia

→

- Cardiac
- Pulmonary
- Gastrointestinal/Nutritional
  - E.g celiac
  - Zn, Vit D, carotenoids, retinol BP
- Renal
- Conditions of chronic inflammation
- Psychosocial Stress
- Hematologic
  - Anemia
  - Iron toxic to bone formation
- Medications
  - Chelator



31 year-old

Male

Asian

ß-Thal major

Overall truncal shortening

Flattened vertebrae

Secondary to chelation toxicity?

Healthy Control

GROWTH HORMONE (GH) DEFICIENCY

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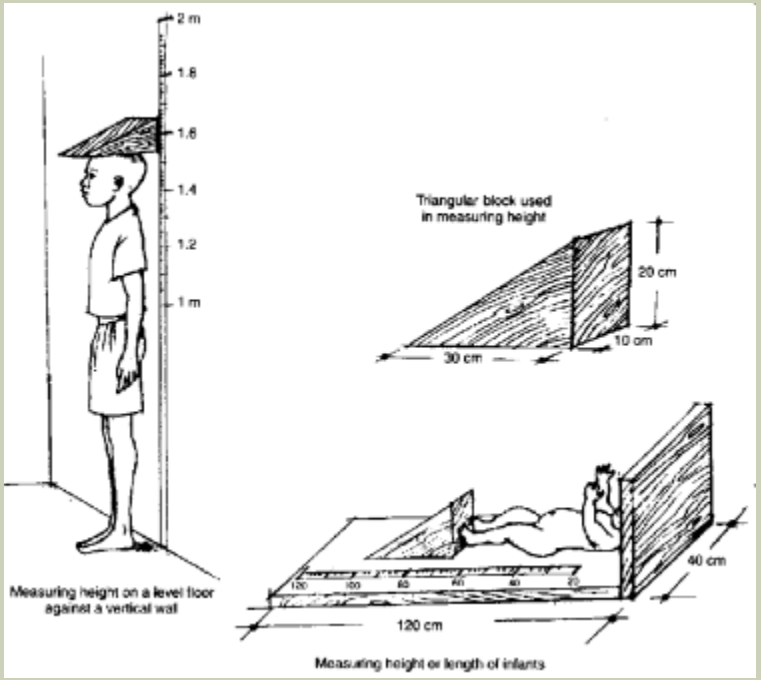
- Clinical Monitoring
  - Calculate mid-parental target height
  - Accurate measurements; calculate height velocity
  - Nutrition assessment
  - Appropriate growth charts
  - Evaluating pubertal status



GROWTH HORMONE (GH) DEFICIENCY

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- Laboratory/Radiological Monitoring (start at 9 yo or earlier)
  - Serum TSH, Free T4, IGF-1*, IGFBP-3, CMP, UA
  - GH Stimulation test +/- priming
  - Bone age
  - Head MRI
- Red Flags (earlier this is addressed the better!)
  - Height < 3%ile or 2 SD below the mean
  - Falling height velocity
  - 1 SD below the mid-parental target height

ANATOMY OF A GROWTH CURVE

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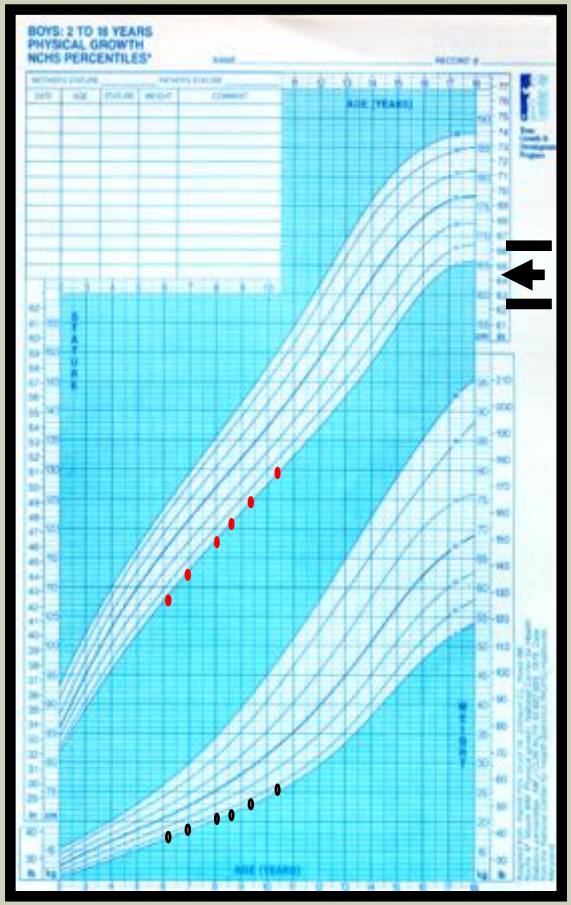
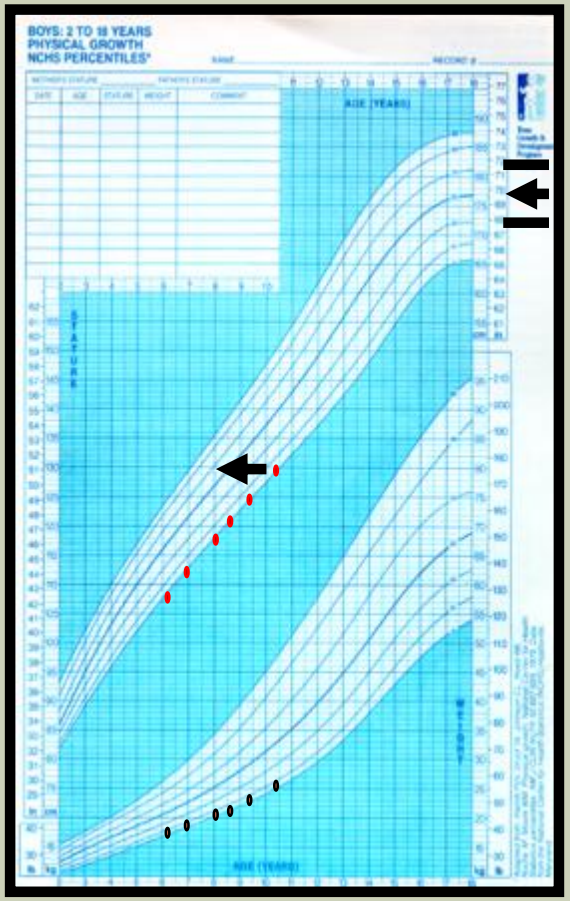
FAMILIAL SHORT STATURE



CONSTITUTIONAL DELAY



GH DEFICIENCY TREATMENT

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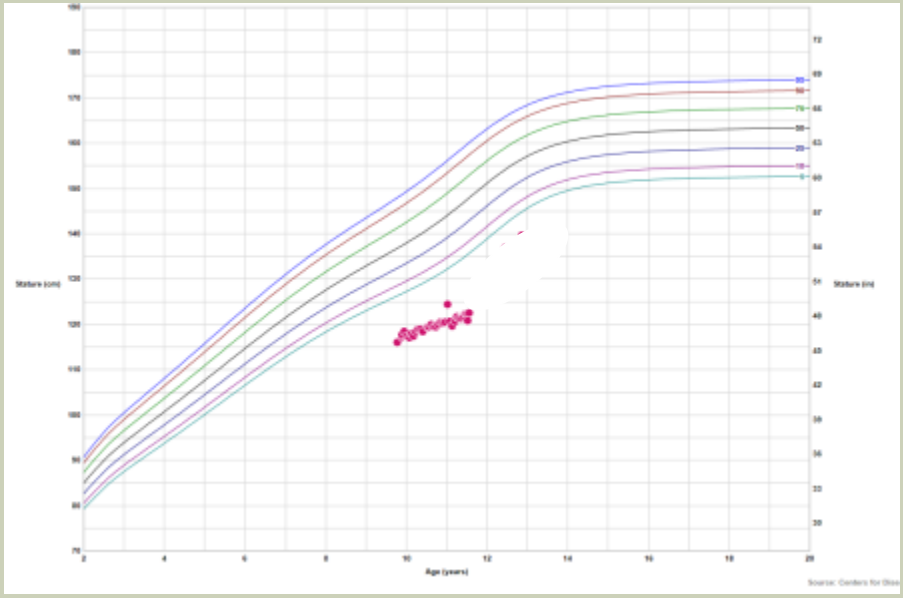
Adopted Chinese Female with transfusion dependent Beta Thalassemia and failed GH stimulation test



GH DEFICIENCY TREATMENT

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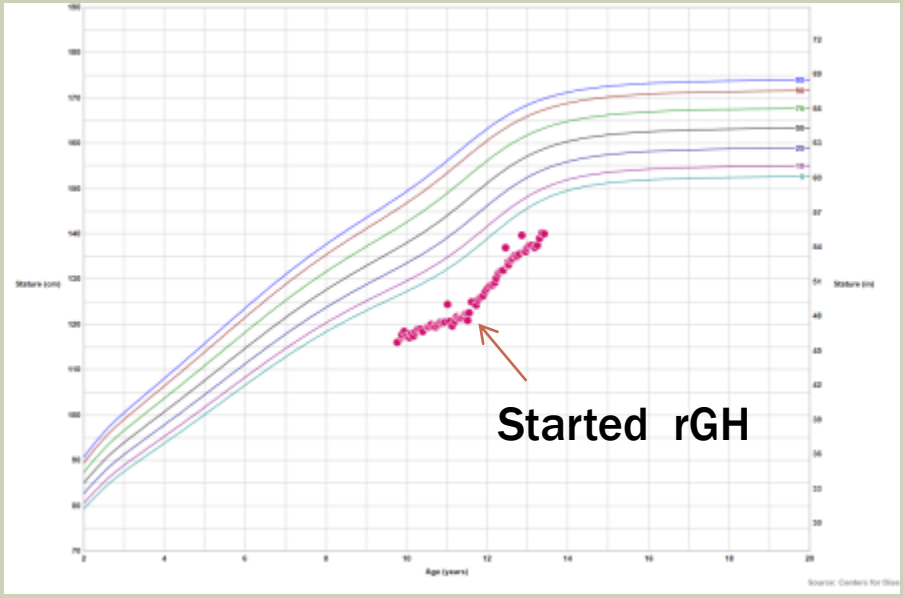
- GH given as daily SQ injections
- Dose titrated based on quarterly IGF-1 and IGFBP-3 levels (relative to pubertal status)
- Earlier the better
- Assess cortisol deficiency prior to treatment
- Continues until height vel < 2 cm/year or growth plates close (around 16 yo in boys and 15 yo in girls)
- **rGH may still have a role in adults with GHD**
- Side effects (rare)
  - Insulin resistance/diabetes mellitus
  - Accelerated growth of body parts
  - Slipped capital femoral epiphyses
  - Pseudotumor cerebri
    - Headaches
    - Vision impairment (double vision, increased blind spots)
    - Instability
- Role of GH replacement in adults
- rIGF-1 ? Aromatase inhibitors?

Adopted Chinese Female with transfusion dependent Beta Thalassemia and failed GH stimulation test



HYPOTHYROIDISM

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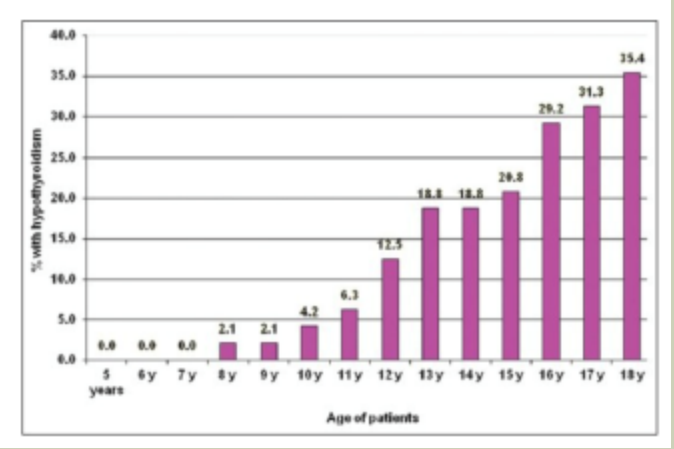
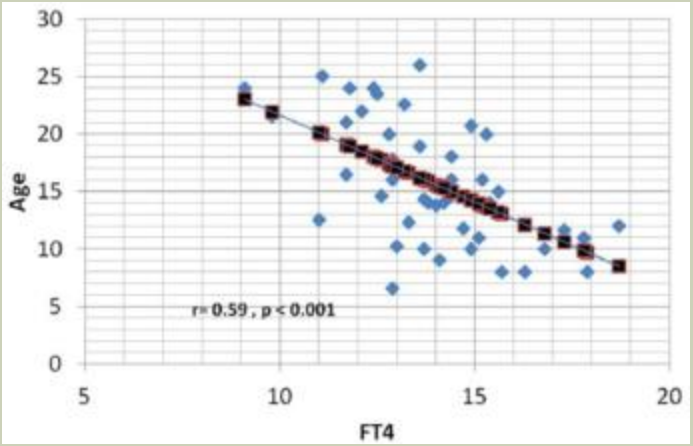
- Clinical Monitoring
  - Poor height velocity
  - Weight gain
  - Low energy
  - Cold intolerance
  - Dry skin
  - constipation
- Laboratory Monitoring (start at 9 yo or earlier)
  - Annual TSH and FT4



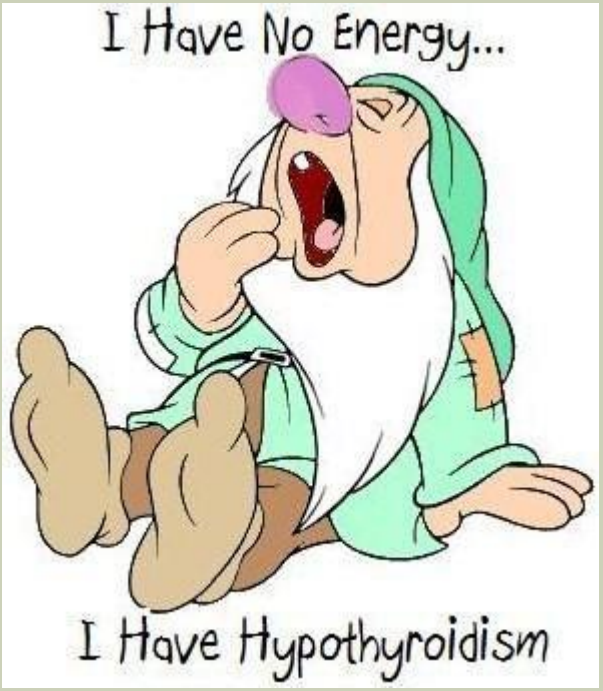


n = 48 patients with thal major

Soliman A, IJEM, 2013

HYPOTHYROIDISM TREATMENT

- Daily levothyroxine pill
  - Take 30 minutes apart from food
  - Try to take the same time of day
  - Long half life (don't stress about missed doses)
- Medications that effect the thyroid axis
  - Lithium
  - Depakote
  - Risperdal
  - Amiodarone



HYPOGONADISM

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- Clinical Monitoring
  - > 20 year old 52.4% female; 60% male
  - < 20 year old 14.3% female; 25.5 % male (Vogiatzi, 2009)
  - Tanner stage every 6 months starting at 10 yo
    - Delayed puberty
      - Absence of breast development by 13 years old in girls
      - Absence of testicular enlargement by 14 years old in boys
    - Arrested development for > 1 year
  - Poor height velocity
  - Damage to the ovaries is rare in adolescence but more likely at 25-30 years of age

HYPOGONADISM

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- Laboratory/Radiological Monitoring
  - Usually not looked at until after 12 yo
  - LH, FSH, estrogen/testosterone (may need a GnRH stimulation test)
  - Head MRI with small cuts of the hypothalamic pituitary axis with and without contrast at 7 yo (Noetzli L, et al., 2011)?
  - Bone age
  - Pelvic u/s

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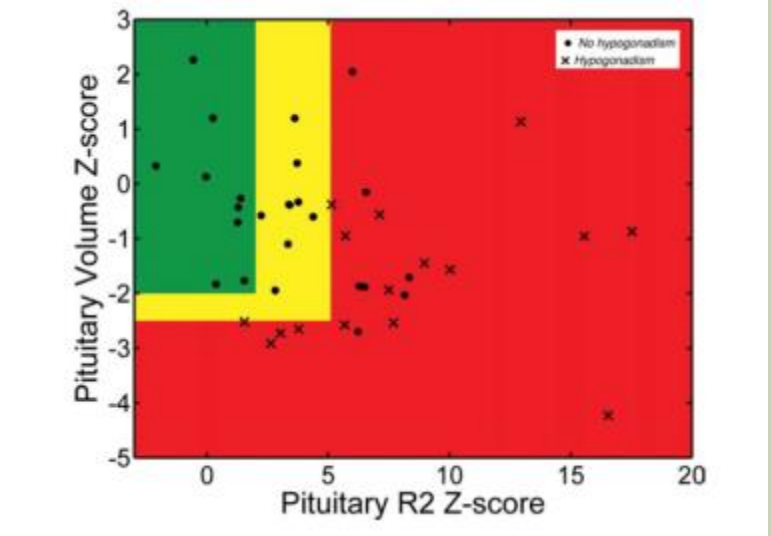
n = 56, 25 female, 47 TM, 5 TI



(Noetzli L et al., 2011)

HYPOGONADISM TREATMENT

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- Boys
  - Induction of puberty with low dose testosterone
    - 50-100 mg IM q 4 weeks x 3 months
  - Androgen replacement
    - Shots vs gels vs patches
- Girls
  - Induction of puberty with estrogen patches (Vivelle Dot Matrix)
  - Estrogen replacement
    - OCP's
    - Patch with Provera (fewer side effects)
- Role of cryopreservation for both males and females.
- Use of antioxidants?
  - Vitamins C, E, Folic acid
  - Se, β-carotens, Zinc,
  - CoQ10, L-Carnitine, Gluthatione

HYPOPARATHYROIDISM/BONE DISEASE

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- Clinical Monitoring
  - Tetany
  - Muscle cramping
  - History of fractures
  - Paraesthesias
  - Seizures
  - Cardiac failure
- Laboratory/Radiological monitoring (typically doesn't present until after 16, but screen early, start at 9 yo)
  - Ca (with albumin), Phosphorus, PTH
  - 25(OH) vitamin D and 1,25 (OH)2 vitamin D
  - Osteocalcin, c-terminal telopeptides, deoxypyridinolines
  - Urine ca/cr
  - DEXA scan (start at 10-12 yo and every 1-2 years thereafter)
  - AP and Lateral spine films
- Treatment
  - Vitamin D3, calcium, calcitriol

ADRENAL INSUFFICIENCY

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- Clinical Monitoring
  - Can be primary or central or both
  - Typically asymptomatic and adrenal crisis is rare
  - Symptoms
    - Muscle weakness
    - Lack of energy
    - Arthralgias
    - Weight loss/anorexia
- Laboratory monitoring (assess every 1-2 years) is still under investigation
  - 8 am cortisol (> 10 mcg/dL unlikely; < 4.2 very likely) and ACTH
  - ACTH stimulation test (low dose)
    - Beware of OCP's
    - Any value > 18 mcg/dL (> 16 mcg/dL)
    - Delta of 10 mcg/dL
  - Glucagon stimulation test

ADRENAL INSUFFICIENCY TREATMENT

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- Hydrocortisone (cortef) 3 x day by mouth
- May just need for stress
- Avoid prednisone and decadron in growing children
- Maintenance and stress dose
  - Stress dose is triple the daily dose
- IM hydrocortisone

DIABETES MELLITUS

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- Clinical monitoring
  - Seen after 10 yo
  - Polyuria, polydipsia, nocturia, polyphagia, weight loss
  - Poor growth
  - Ketoacidosis is rare
- Laboratory monitoring
  - OGTT performed starting at 10 years old every 2 years then annually after 16 yo
    - 2 hour BG between 140 and 200 mg/dL is pre-diabetes
    - 2 hour BG > 200 mg/dL is diabetes
  - Fructosamine

DIABETES MELLITUS TREATMENT

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- SQ Insulin
  - Shots vs pump
- BG monitoring
  - Meters (check 4x a day and/or continuous glucose sensors)
- Optimizing chelation particularly in early stages of diabetes
- Nutrition
- Oral agents?
  - Metformin
- Diabetes complications are less frequent compared to those with type 1 and type 2 diabetes

TAKE HOME MESSAGES

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- Growth charts are invaluable
- Bone ages keep it real
- Find a pediatric endocrinologist, even if they are not local
- All hormone problems can be treated
- Hormone deficiencies should be managed throughout childhood (and adulthood)
- New generation of patients
- Be proactive
- Chelate
- Chelate
- Chelate
- But not too much

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Many thanks to my mentors and colleagues

Dr. Elliott Vichinsky
Dr. Ashutosh Lal
Dr. Sylvia Titi Singer
Dr. Marcela Weyhmiller
Dr. Ellen Fung

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Thank You for your Time