26th Annual General Pediatric Review & Self-Assessment

Nicklaus Children's Hospital

ENDOCRINOLOGY

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Disclosure of Relevant Relationship

Dr. Diaz has not had (in the past 24 months) any relevant conflicts of interest or relevant financial relationship with the manufacturers of products or services that will be discussed in this CME activity or in his presentation.

Dr. Diaz will support this presentation and clinical recommendations with the "best available evidence" from medical literature.

Dr. Diaz does not intend to discuss an unapproved/investigative use of a commercial product/device in this presentation.

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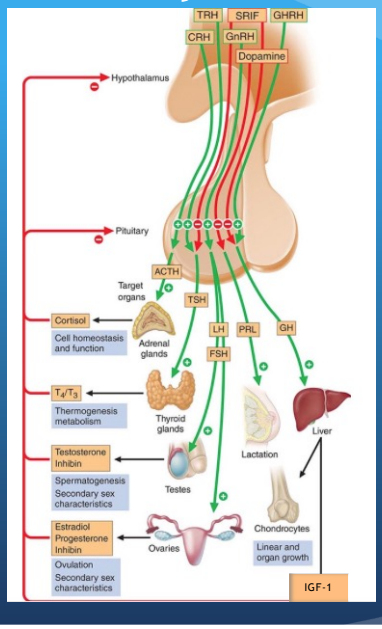
Pituitary Gland

Inhibitory hormones:
SRIF: Somatostatin
Dopamine



iKnowledge, Jameson

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Hypopituitarism

- Congenital defects with hypopituitarism
  - Midfacial anomalies: solitary incisor, cleft lip or palate (4% growth hormone deficiency)
  - Empty sella syndrome: congenital or secondary to surgery or radiation. Craniopharyngioma most common tumor to cause it
  - Ectopic pituitary gland: Isolated growth hormone deficiency or panhypopituitarism

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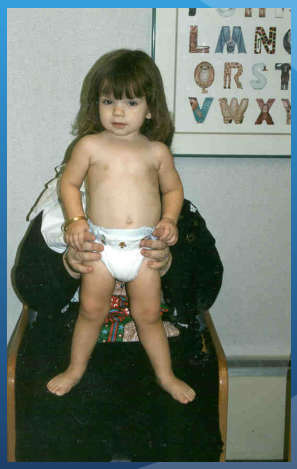
Clinical Signs of Classical GH Deficiency

- Infancy
  - Hypoglycemia
  - Micropenis
  - Prolonged jaundice
- Childhood
  - Growth deceleration after 2 years of age
  - "Cherubic" facial appearance
  - Delayed dentition
  - Retained "baby fat"
  - Central adiposity; "ripply" abdominal fat
  - Delayed gross motor development
- Teen years
  - Delayed puberty
  - Young appearance for age



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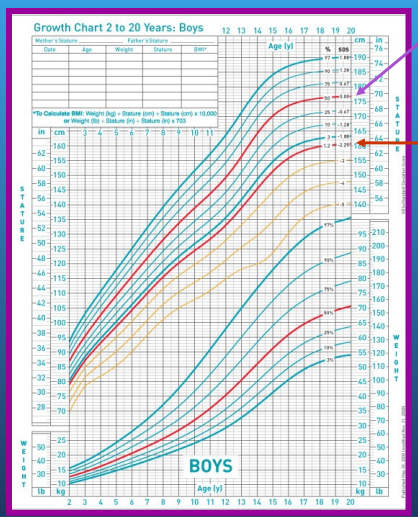
Short Stature



Average US adult heights:
Male 5' 9.4"
Female 5' 4.2"

-2.0 SDS adult heights:
Male 5' 3.6"
Female 4' 11.1"

(1 SD = ~3")

Short stature = below –2 SDS

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Short Stature Standard Initial Laboratory Investigations

- Chemistry
- Blood count, CRP or sedimentation rate
- Thyroid function tests
- Antibodies for celiac disease
- IGF-I, IGFBP-3. Do not order random growth hormone
- Karyotype for girls (and boys when indicated clinically)

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Causes of short stature

Non-pathogenic (most common)
Constitutional delay of growth and puberty
Familial short stature (males are 5 inches taller than females on average)
Nutritional

Intrauterine growth restriction
Syndromic—e.g., Silver-Russell syndrome (large head, triangular face, clinodactyly of the 5th digits.
Non-syndromic

Systemic disorders
GI (celiac or IBD), cardiovascular disease, renal, respiratory, neurological, psychosocial

Chromosomal and genetic causes
Turner, Noonan, Down syndrome, Skeletal dysplasias, Seckel, Prader-Willi, Rothmund-Thompson, Leri-Weill, Progeria, mucopolysaccharidoses

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Causes of Short Stature

Endocrine causes

- Growth hormone deficiency (GHD); isolated or combined with other pituitary hormone deficiencies

- Hypothyroidism
  - Short with a goiter
  - Precocious puberty (Van-Wyk-Grumbach syndrome) (bone age is delayed in precocious puberty)

- Glucocorticoid excess (Cushing disease/syndrome):
  - Decreased growth velocity and obesity with hyperglycemia and/or hypertension

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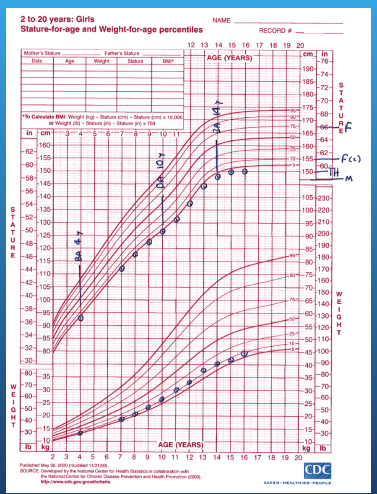
Familial Short Stature



- Remember women are 5 in shorter than men
- Normal growth velocity
- No dysmorphism
- Bone age and chronological age are similar

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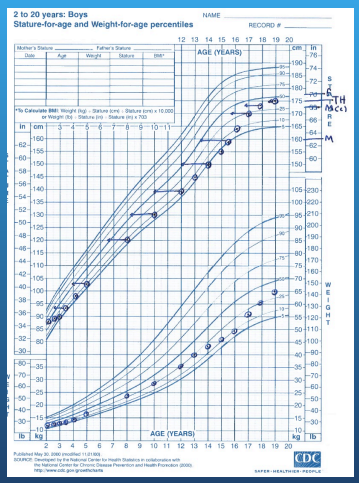
Constitutional Growth Delay



- One parent was a late bloomer (autosomal dominant)
- Drop off the growth chart during first 3 years of life
- Delayed bone age
- Normal growth velocity after age 3-4 years

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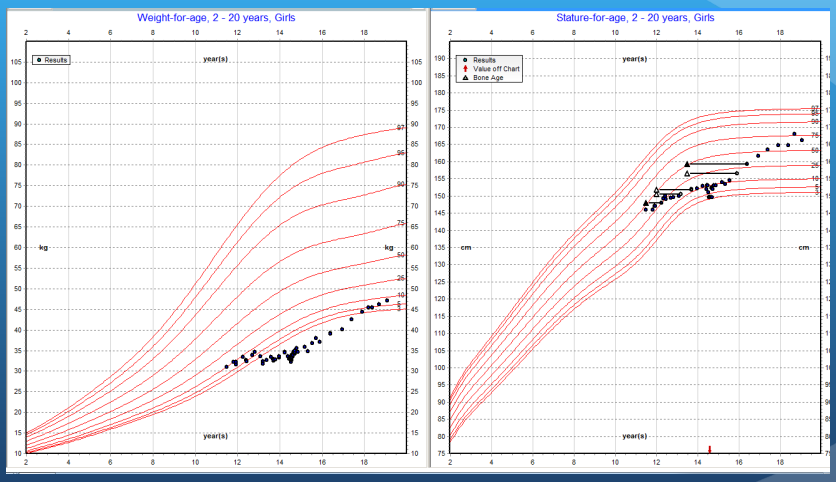
Anorexia Nervosa/Crohn Disease



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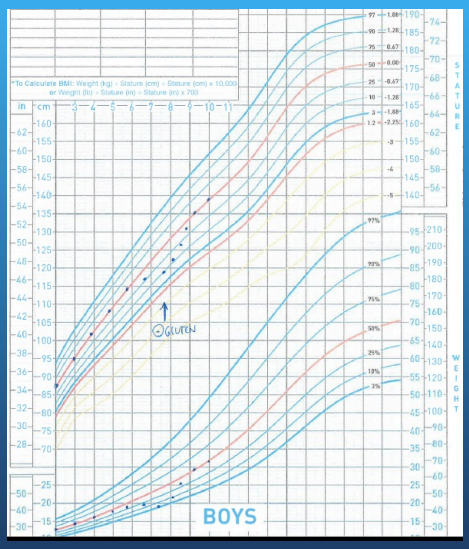
Patient with Celiac Disease or Other GI Problem/Anorexia



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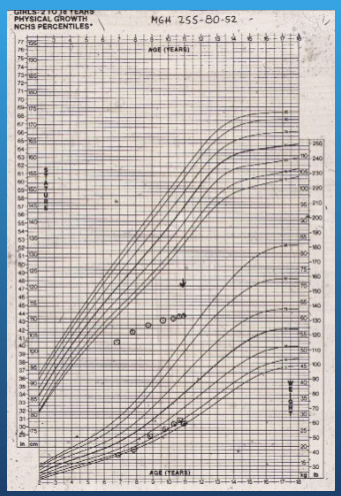
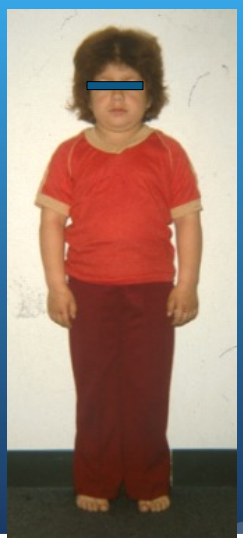
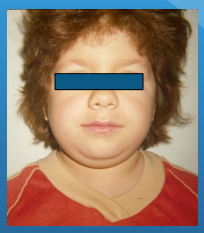
Secondary Growth Disorders (Hypothyroidism). GHD. If obesity: Cushing disease







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Treatment of Growth Hormone Deficiency

- Recombinant human growth hormone (hCG) 0.18-0.3 mg/kg/week SQ 7 days a week
- Continue until growth velocity < 1 inch per year and bone age >14 years in girl and >16 years in boys
- Side effects to monitor:
  - Slipped capital femoral epiphysis (SCFE)
  - Pseudotumor cerebri
  - Transient carbohydrate intolerance
  - Transient hypothyroidism
  - Scoliosis

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FDA Approved Indications for Growth Hormone Therapy

- Growth hormone deficiency (GHD)
- Idiopathic short stature (ISS)
  - Normal GH production, below 2.25 SD, and predicted adult height <2 SD below the mean
- Chronic renal insufficiency
- Turner syndrome and SHOX gene deficiency
- Prader-Willi syndrome (sleep studies before starting GH)
- Small for gestational age (SGA) if not caught up by 2 years
- Noonan syndrome
- Adults with GHD or AIDS-wasting syndrome

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Hyperpituitarism

- Primary overproduction of pituitary hormones is rare in children
  - Prolactinoma: headaches, amenorrhea, and galactorrhea. Visual field defects. Tx: cabergoline and bromocriptine
  - Gigantism and Acromegaly: coarse facies, large hands and feet. Hypogonadism is common. No GH suppression with glucose administration. Tx: surgery, somatostatin analogs, or pegvisomant (GH receptor antagonist)
  - Cushing disease: poor growth, obesitiy, hyperglycemia, purple striae, buffalo hump. Tx: surgery

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Temporal Sequence of Puberty (Girls)

- Thelarche (mean age 9-10 AA girls, 10-11 white girls)
- Pubarche: pubic hair (10.5-11.5 years)
- Growth spurt (11-12 years)
- Menarche (average age 12.5-13 years)
- After menarche girls grow 2-4 more inches

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Temporal Sequence of Puberty (Boys)

- Gonadarche (testicular volume >3 cc and testicular length >2.5 cc) and scrotal thinning (11-12 years)
- Pubarche: pubic hair (11.5-12.5 years)
- Growth spurt: peak between bone ages 12 and 14 years
- Spermarche at 13.5 years
- Change in voice (13.9 years)
- Facial and underarm hair

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Definition of Precocious Puberty

Girls:

- Breast development: < 8 years
- Menarche before age <9-10 years
- Pubic Hair: < 8 years

Boys:

- Testes > 2.5 cm length (>3 cc vol) before age 9 years
- Pubic hair before age 9 years

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Precocious Puberty

- Gonadotropin-dependent (Central)
- 4/5 of patients with PP
  - Idiopathic 60-90%
  - Between four to eight times more common in girls than boys
- In boys PP 30% have a pathologic cause: CNS pathology: order a brain MRI
- Precocious puberty occurs in 1-2,000/10,000 children.

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Precocious Puberty Etiology

GnRH independent (Peripheral-always abnormal)

- Adrenal Causes : congenital adrenal hyperplasia, cortical tumors
- Gonadal Cause
  - McCune-Albright Syndrome (Isosexual)
    - Polyostotic fibrous dysplasia
    - Cafe au lait spots
    - Precocious Puberty
    - Associated with Hyperthyroidism, Cushing's Syndrome, acromegaly, rickets, etc
  - Tumor (Isosexual or Contrasexual): testicular asymmetry or mass

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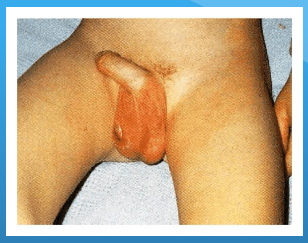
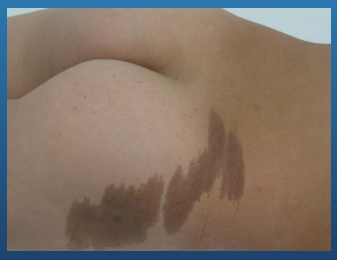
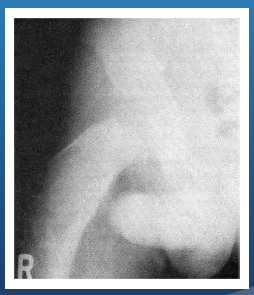
McCune-Albright Syndrome







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Precocious Puberty Etiology

Partial Sexual Development Causes

- Benign Premature Thelarche (first 6 months is almost always benign. Usually resolves by 2 years of age)
- Benign Premature Adrenarche (h/o SGA or obesity)
  - Isolated pubic hair (pubarche) develops under age 7-8 years in girls or 9 in boys
  - Apocrine axillary body odor

Normal growth velocity and bone age

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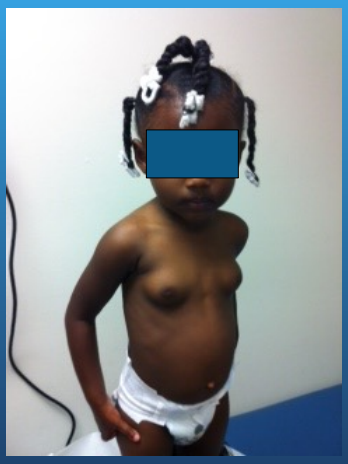
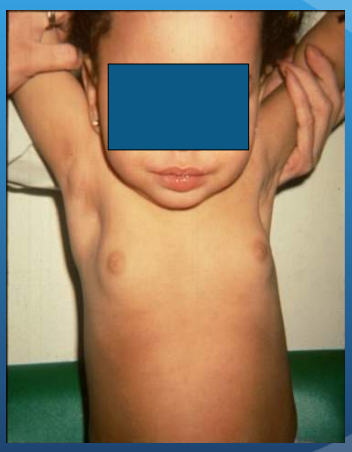
Premature Thelarche





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Evaluation of Precocious Puberty

- Clinical history and physical (family history)
  - Testicular volume and scrotal thinning
  - Estrogenized vaginal mucosa: pink color
- Exogenous Sex Hormone sources
  - Androgens and Anabolic steroid
  - Oral Contraceptives
  - Estrogen or placental containing hair products
    - Common use in African American girls
    - Associated with breast or pubic hair development
- Paternal use of androgens (gels)
- Evaluate growth chart: growth acceleration
- Obtain a left wrist x-ray for bone age

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Laboratory Test for Precocious Puberty Evaluation

- LH (central puberty >0.3 IU/L) and FSH
- Estradiol Level (in girls)
- Dehydroepiandrostendione (DHEA) + DHEA-Sulfate
- Testosterone Level (in boys)
- Thyroid Stimulating Hormone (TSH)
- Boys: Human Chorionic Gonadotropin (HCG)
  - Screen for gonadotropin secreting tumor
- Consider GnRH Stimulation Test

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Classification of Delayed Puberty and Sexual Infantilism

- Hypergonadotropic hypogonadism (high FSH)
  - Males
    - The syndrome of seminiferous tubular dysgenesis (Klinefelter syndrome): 1 in 500/1,000 newborn males. 47XXY (meiotic nondisjunction of an X chromosome during gametogenesis)
    - Other forms of primary gonadal failure
      - Chemotherapy
      - Radiation therapy
      - Testicular steroid biosynthetic defects
      - Sertoli-only syndrome
      - LH receptor mutation
      - Anorchia and cryptorchidism
    - Trauma/surgery
    - Noonan syndrome

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Classification of Delayed Puberty and Sexual Infantilism

- Hypergonadotropic hypogonadism (high FSH)
  - Females
    - The syndrome of gonadal dysgenesis (Turner syndrome)
    - XX and XY gonadal dysgenesis
    - Aromatase deficiency
    - Other forms of primary ovarian failure
      - Chemotherapy/Radiation therapy
      - Autoimmune oophoritis
      - Trauma/surgery

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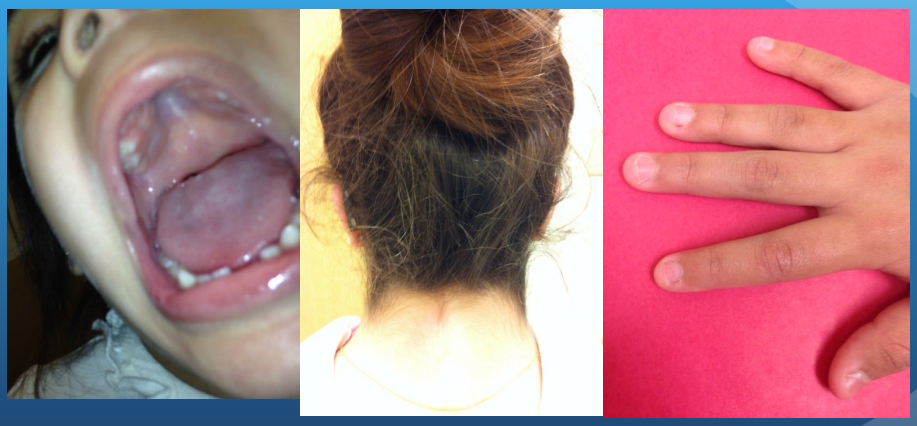
Turner Syndrome



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Classification of Delayed Puberty and Sexual Infantilism

- Secondary Hypogonadism
  - Hypopituitarism: congenital or acquired lesions in hypothalamus or pituitary gland
  - Isolated deficiency of gonadotropins (males with micropenis: <2.5 cm)
    - With anosmia/hyposmia: Kallmann syndrome (kidney US)
    - Hypogonadotropic hypogonadism with olfaction
- Prader-Willi syndrome
- Laurence-Moon-Biedl/Bardet-Biedl syndrome: retinitis pigmentosa, obesity, low IQ, polydactyly, hypogonadism

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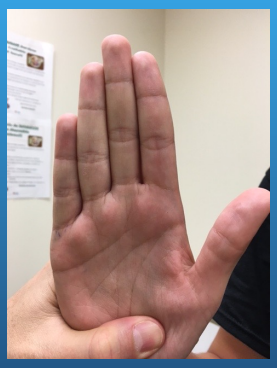
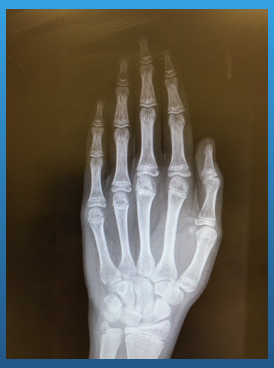
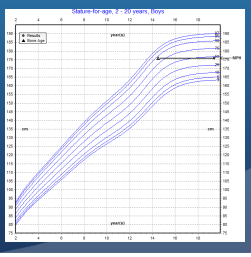
19 y/o Boy with Kallmann Syndrome







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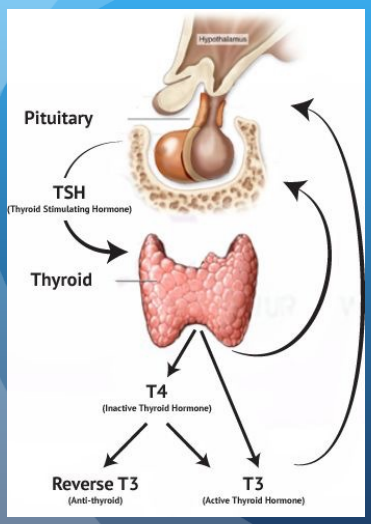
Thyroid Physiology



- At birth ➔ TSH surge (peaks at 12 hours)
- Peak of T4 and T3 during the first day of life
- Newborn screening >48 hours
- Thyroid-binding globulin (TBG): one of the carrier proteins for thyroid hormone
  - ↑TBG (high T4): OCP, pregnancy, tamoxifen, clofibrate, narcotics, hepatitis
  - ↓TBG: androgens, glucocorticoids, nephrotic syndrome and TBG deficiency (X-linked)

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Evaluation of Congenital Hypothyroidism (CH)

- Newborn screening:
  - 2-5 days of life
  - T4 with "reflex" TSH, initial TSH (misses central hypothyroidism and CH in premature infants), combined T4/TSH
- Obtain confirmatory serum thyroid function tests before treatment is started
- TSH between 9 and 25 mU/L and normal T4/fT4 can wait to start treatment (first year of life TSH is normal up to 8-10 mU/L)
- Low total T4 with normal TSH in a boy: TBG deficiency (1:3,000)
- Thyroid radionuclide scan (does not show a gland if TBII) and/or a thyroid US may be performed. Do not wait for results to start treatment

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Congenital Hypothyroidism

- 1 in 2,500 newborns
- 2 x more common in girls than in boys
- Thyroid dysgenesis
  - Most common cause of congenital hypothyroidism
  - Includes agenesis, hypoplasia and ectopy
  - Most sporadic but few familial
  - May be associated with cardiac (ASD, VSD, and pulmonary stenosis) and kidney defects (order a renal US)
  - All infants with CH should undergo screening hearing test (20% neurosensory hearing deficit)

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Other Causes of Congenital Hypothyroidism

- Dyshormogenesis
  - Any step of the process of thyroid hormone production
  - All autosomal recessive
  - Goiter: also if mother was treated with PTU
  - Elevated thyroglobulin level
- TBII (TSH receptor blocking antibodies) or mother treated with PTU: transient: maternal h/o thyroid disease
- Central Hypothyroidism (1:30,000-50,000)
  - Associated with midline defects, birth trauma, other pituitary deficiencies
  - TSH may be low, normal, or slightly elevated (TRH deficiency)
  - TSH becomes undetectable once LT4 treatment is started

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Clinical Manifestations of Congenital Hypothyroidism

- Increased Birth Weight
- Increased Head Circumference, large fontanel
- Lethargy, slow movement, hypotonia
- Hoarse cry
- Feeding problems, constipation
- Macroglossia
- Umbilical hernia
- Dry skin
- Hypothermia
- Prolonged jaundice
- Absence of knee epiphyses
- Anemia
- Edema
- Bradycardia

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Note the hypotonic posture, coarse facial features, and umbilical hernia.

Close-up of the face of the same infant. Note the macroglossia.

The infant a few months after starting LT4

Same infant a few months after starting LT4

Images from emedicine.medscape.com/article/919758-media

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Congenital Hypothyroidism

- Early treatment with the appropriate dose protects IQ
- Treat with sodium-L-thyroxine (levothyroxine = LT4) 10-15 mcg/kg/day (only crushed tablets. Do not mix with soy milk or iron)
- Check TSH and FT4 1-2 weeks after treatment started, then every 1-2 months the first 6 months

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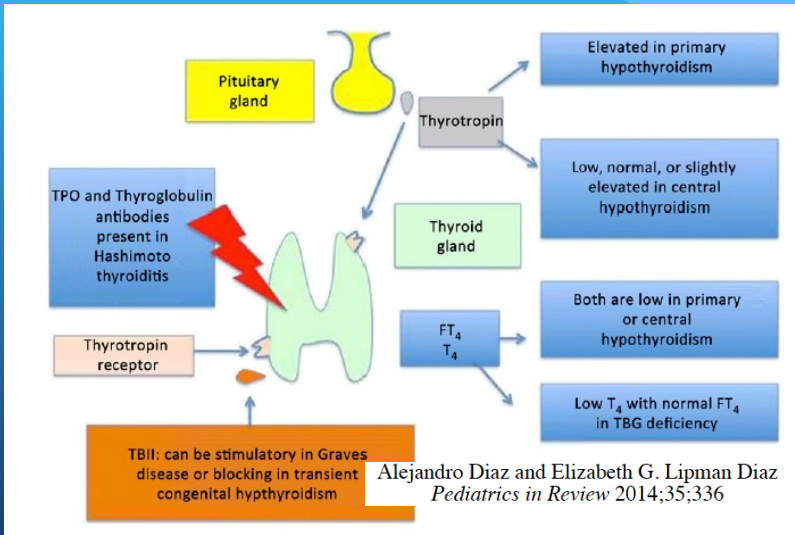
Pathogenesis of Hypothyroidism



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Chronic Lymphocytic or Hashimoto Thyroiditis

- Females >> males. Also in Down, Turner, and Klinefelter syndrome
- Thyroid peroxidase antibodies (TPO) and/or anti-thyroglobulin (ATG) are positive
- Goiter = enlarged and firm thyroid (most children with Hashimoto are euthyroid)
- If hypothyroidism: dry skin, fall of the growth chart, slow return phase of deep tendon reflexes, jaundice, SCFE, somnolence, constipation, cold intolerance
- Higher risk of celiac disease, T1DM and other autoimmune disorders

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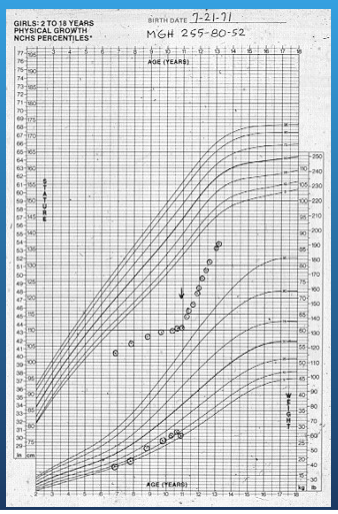
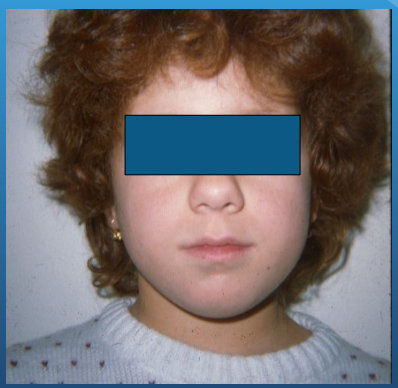
Secondary Growth Disorders: Hypothyroidism





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Hypothyroidism

- Treatment:
  - Levothyroxine (LT4) 1-2 mcg/kg/day
  - Repeat TFTs in 4-6 weeks to determine if the dose of LT4 needs to be adjusted, then q 6 months
- If Hashimoto with normal thyroid function tests
  - TFTs every 6-12 months
- Sick euthyroid syndrome or non-thyroidal illness
  - Mild: normal TSH, and T4 with ↓T3 ↑reverse T3 (rT3)
  - Moderate: normal TSH, ↓T4, T3, & ↑rT3
  - Severe: low TSH, T4, T3, & ↑rT3 (high mortality)
  - No treatment needed

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Thyroiditis

- Subacute (de Quervain) thyroiditis
  - Self-limited inflammation of the thyroid after an URI
  - Fever and thyroid gland tenderness. ↑ ESR
  - Initial signs/symptoms of hyperthyroidism
  - Followed by a prolonged period of hypothyroidism
  - Whole illness lasts from 2 to 9 months without residual thyroid problem
  - Treatment with analgesics or, if severe, prednisone
- Suppurative thyroiditis
  - Bacterial infection: Staph aureus, Strep pyogeneis, Pneumococcus
  - Associated with embryologic remnant or a left pyriform sinus tract, which is diagnosed by telescopic hypopharyngoscopy
  - Last 2-4 weeks

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Thyroid Nodule

- Rare in children (<1%)
- If present: 20-26% malignancy
- Evaluation:
  - Check TSH:
    - If ↓, do a thyroid scan. If "hot" nodule → less likely to be cancer
    - If ↑ or normal, do a thyroid US
  - If nodule >1 cm or suspicious for malignancy → fine-needle aspiration biopsy (FNAB)
- FNAB:
  - Indeterminate or positive → surgery
  - Benign → just follow
  - Nondiagnostic → follow or do surgery

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Thyroid Cancer

- Most common thyroid cancer: papillary/follicular (good prognosis)
- Risk factors
  - H/o radiation to the neck or head
  - Solitary nodule >1 cm with fixed, hard, and/or irregular borders
  - Family h/o mutiple endocrine neoplasia (MEN)
  - Rapidly growing nodule that is firm or hard
  - Satellite lymph nodes
  - Horseness or dysphagia
- Medullary thyroid cancer (MTC): parafollicular or C cells (calcitonin)
- MEN 2A and 2B: MTC, pheochromocytoma, hyperparathyrodism (2A), mucosal neuromas (2B)
  - Prophylactic thyroidectomy according to *RET* mutation

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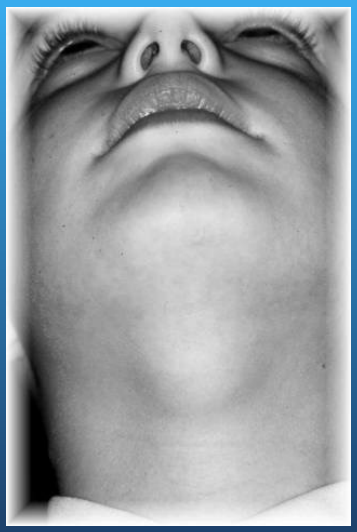
Thyroglossal Duct Cyst



- Round midline mass in the neck that moves when patient swallows
- Risk of infection and/or malignancy
- Thyroid scan to determine if the cyst contains all the thyroid tissue
- Surgery vs. observation
- Surgery preferred for risk of malignancy

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Hyperthyroidism (Graves Disease)

- Most common cause of hyperthyroidism in pediatrics
- More common in girls
- Eye manifestations and dermatopathy: rare in children
- Cause by TSH receptor-stimulating antibodies: TSI or TBII
- Symptoms: Nervousness, palpitations, increase appetite, nocturia, and muscle weakness
- Signs: tachycardia, goiter, widened pulse pressure, tremor, ↑ perspiration, and rapid tendon reflex relaxation times

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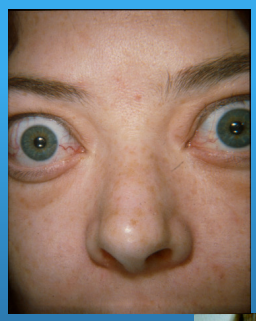

Graves Disease

- Labs: ↓TSH, ↑T4-T3, + TSI/TBII, + TPO-ATG abs.
- Treatment:
  - Beta blocker to decrease symptoms/signs
  - Medical: methimazole (MMI). NO PTU
    - 50% complete remission
  - Radioactive Iodine (5% relapse. Most will have permanent hypothyroidism)
  - Surgical (younger children)

    (post-op hypothyroidism, hypoparathyroidism, recurrent laryngeal nerve damage)

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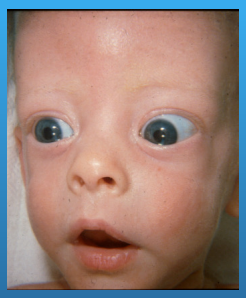

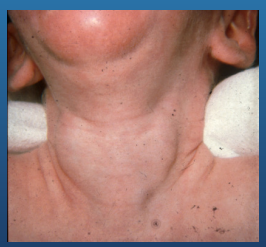

Congenital Graves Disease

- Mother with h/o hyperthyroidism even with hypothyroidism at the time of delivery (h/o) RAI
- Transplacental transmission of TSI
- Increased fetal heart rate and fetal movements (treatment in utero with PTU)
- IUGR/SGA
- Tachycardia, goiter, irritability, flushing. Rarely: thrombocytopenia, liver and cardiac dysfunction
- Signs/symptoms can appear after a week of age. Resolves after 3-12 weeks
- Tx: 5% iodine or 10% potassium iodide 1 drop q 8 hs, MMI 0.5-1 mg/kg/day q 8 hs, propanolol 1-2 mg/kg/day q 6-12 hs

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Hypoparathyroidism

Hypocalcemia and hyperphosphatemia with low intact PTH (iPTH)

- Congenital
  - Transient neonatal
  - Dysgenesis/agenesis of the parathyroid glands
    - Isolated
    - Deletion 22q11 syndrome (DiGeorge): conotruncal anomalies
- Insensitivity to PTH
  - Pseudohypoparathyroidism (Types IA, IB, and II): high iPTH with low Ca and high Phos

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Hypoparathyroidism

- Acquired
  - Autoimmune polyglandular syndrome type I (AIRE gene)
    - Adrenal insufficiency and mucocutaneous candidiasis
  - Post surgical (thyroid cancer), radiation destruction
  - Infiltrative (iron or copper deposition; granulomatosis or neoplastic invation; amyloidosis, sarcoidosis
  - Maternal hyperparathyroidism (mother's calcium level)
  - Hypomagnesemia (mother with h/o diabetes)

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Hypocalcemia (Etiology)

- Hypocalcemia with hyperphosphatemia
  - With low iPTH: hypoparathyroidism
  - With high iPTH: pseudohypoparathyroidism: often with obesity, mild hypothyroidism and short 4th metacarpals bones
- Hypocalcemia with hypophosphatemia
  - Vitamin D deficiency (usually with high iPTH and high alkaline phosphatase)

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Etiologic Classification of Rickets

- Mainly due to calcium/phosphate deficiency
  - Deficiency rickets
    - Vit D deficiency: nutritional /medications: AA infant exclusively breast fed without vit D supplementation/Anticonvulsants
    - Calcium deficiency
  - Defects in Vit D metabolism or action
    - Vit D dependency type I (AR, absence of hydroxylase)
    - Hereditary Vit D resistant rickets (formerly Vit D dependency type II) (Vit D receptor defect)

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Etiologic Classification of Rickets

- Mainly due to phosphorus deficiency
  - X-linked hypophosphatemic rickets (XLH): X-linked dominant: women also affected
  - AD hypophosphatemic rickets
  - Tumor induced osteomalacia (TIO)
  - Hereditary Hypophosphatemic rickets with hypercalciuria
  - Renal tubular defects
- Alkaline phosphatase deficiency
  - Hypophosphasia: teeth loss, fractures, short stature

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Familial Hypophosphatemic Rickets

- X-linked dominant (*PHEX* mutation) or autosomal dominant
- Most common for of inherited rickets in the developed world
- Reduced reabsorption of phosphate in the nephron
- Bowing of the lower extremities, inadequate dental enamel and tooth decay
- Low phosphate, normal Ca and normal iPTH. High urine phosphate
- Tx:
  - Oral phosphate supplements (4-5 times a day) and calcitriol
  - Berosumab-twza: monoclonal antibody anti FGF23

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Hypercalcemia

- Calcium >10.5 mg/dL (check albumin)
- Symptoms:
  - Neonatal: GER, lethargy, failure to thrive
  - Nausea, vomiting, anorexia, constipation, weight loss, lethargy, weakness, inability to concentrate, depression
- Signs:
  - Band keratopathy of the margins of the cornea
  - Short QTc interval on ECG
  - Hypertension, hypercalciuria, nephrolithiasis, pancreatitis and peptic ulcer disease

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Causes of Hypercalcemia

Condition	Serum Ca	Serum Phos	Alk phos	iPTH	Vit D25	Vit D1,25	Other
1ary hyperparathyroidism	↑	↓	↑	↑ for Ca	↔	↔↑	
Fam. Hypocalciuric hypercalcemia	↑	↔↑↓	↔↑	↔↑	↔	↔	↓ uCa
Hypercalcemia of malignancy	↑	↔↓	↑	↓	↔	↔	↑PTHrP
Hypervitaminosis D	↑	↔↓	↔↓	↓	↑	↔↑	
Renal insuff. and 2ndary hyperparathyroidism	↓	↔↑	↔↑	↑	↔	↓	
↑ 1^{α}-hydroxylation of vit D25	↑	↔	↔	↔	↔	↑	Granulomatous disease or neoplasm
Immobilization	↑	↔↓	↑	↔	↔	↔	
Hyperthyroidism	↑		↔	↓	↔	↔↓	
Adrenal insufficiency	↑		↔	↓	↔	↔↓	
Hypervitaminosis A	↑		↔	↓	↔	↔↓	

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Adrenal Insufficiency

Primary adrenal insufficiency:

- Congenital adrenal hyperplasia (CAH) (most common cause in children)
- Autoimmune adrenalitis (Addison disease): 21-hydroxylase antibodies (most common cause in adults)
- Autoimmune polyglandular syndromes (types I and II)
- Infectious: tuberculosis, fungal, HIV, meningococcemia
- Adrenal hemorrhage or infarction
- Congenital adrenal hypoplasia (*DAX1* gene on Xp21)
- Adrenoleukodystrophy (high levels of very long fatty acids)
- Unresponsiveness to ACTH

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Adrenal Insufficiency

- Secondary adrenal insufficiency (central) (normal electrolytes, blood pressure, and not hyperpigmentation)
  - Withdrawal from glucocorticoid therapy (hypoglycemia) (most common cause of adrenal insufficiency in North America)
  - Hypopituitarism
  - Isolated ACTH deficiency
  - Hypothalamic tumors (craniopharyngioma): hypoglycemia, hypotension, diabetes insipidus
  - Irradiation of the central nervous system

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Clinical Features at Presentation of Adrenal Insufficiency

- Anorexia, apathy and confusion
- Fatigue, weakness, nausea and vomiting
- Hypoglycemia
- Only in primary adrenal insufficiency: Hyponatremia, hyperkalemia, elevated plasma renin activity, hypovolemia and tachycardia, postural hypotension, and salt craving

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Clinical Features at Presentation of Adrenal Insufficiency

- Features of acute insufficiency (adrenal crisis)
  - Abdominal pain
  - Fever
- Features of chronic insufficiency (Addison disease)
  - Decreased pubic and axillary hair
  - Diarrhea, weight loss
  - Hyperpigmentation
  - Small heart on radiograph, low voltage ECG

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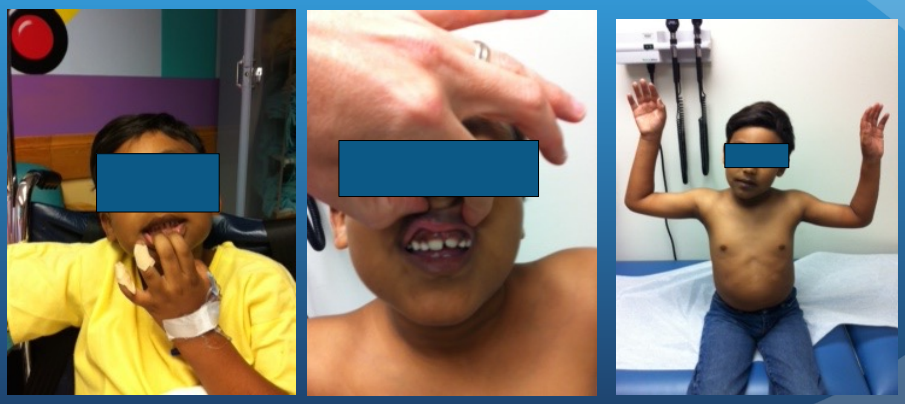
Primary Adrenal Insufficiency (Adrenoleukodystrophy)



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Treatment of Addison Disease

- Crisis (hypovolemia/hypotension): fluid replacement (isotonic fluids), hydrocortisone (50-100 mg/m2) one dose IV/IM and then 100 mg/m2/day divided every 6 hours until clinically well
- Maintenance: hydrocortisone (10-15 mg/m2/day) + fludrocortisone 0.1 mg daily
- Stress dose in case of febrile illness: double or triple maintenance

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Congenital Adrenal Hyperplasia

- Congenital adrenal hyperplasia (CAH): Most common cause of female virilization
- 21-Hydroxylase deficiency: ↑ 17OHP (newborn screening)
  - 95% of all causes of CAH
  - Mutations of *CYP21A2* (active gene).
  - ¾ of CAH are salt wasting (boys: when not diagnosed with newborn screening presenting with hyponatremia, hyperkalemia, and shock)
  - ⅓ of CAH simple virilizing (female ambiguous, males with peripheral precocious puberty)

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Congenital Adrenal Hyperplasia

- CYP21: Laboratory findings: ↓Na, ↑K, ↑17OHP, ↓cortisol
- Treatment
  - Crisis (hypovolemia/hypotension): fluid replacement, hydrocortisone (50-100 mg/m2)
  - Maintenance: hydrocortisone (10-15 mg/m2/day) + fludrocortisone + NaCL

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Congenital Adrenal Hyperplasia

- If positive newborn screening for CAH:
  - first test to order: electrolytes.
  - And repeat 17OHP levels
- Non-classical 21OH deficiency CAH (1:1000) presents with premature pubarche and/or apocrine body odor in children (advanced bone age); PCO-like with high androgens in teenager girls

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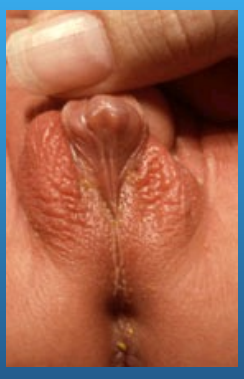
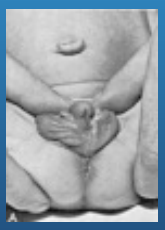
Congenital Adrenal Hyperplasia



"Male" newborn with bilateral cryptorchidism: order a pelvic US

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Cushing Syndrome

- Excess of exogenous (most common) or endogenous glucocorticoids
- ACTH independent (Cushing syndrome)
  - In infants: functioning adrenocortical tumors (usually malignant)
  - Primary pigmented nodular adrenocortical disease (part of the Carney complex: AD, blue nevi, cardiac and skin myxomas, and precocious puberty in boys)
- ACTH dependent (Cushing disease)
  - Most due to pituitary microadenomas
  - Ectopic ACTH production
- Laboratory:
  - 24-hour urinary free cortisol and midnight cortisol
  - Dexamethasone suppression test: a dose at 11 PM. Early cortisol should be <5 ug/dL
- Treatment:
  - If benign cortical adenoma: unilateral adrenalectomy
  - Pituitary adenoma: transsphenoidal microsurgery

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Patient with Iatrogenic Cushing Syndrome (triamcinolone injections)

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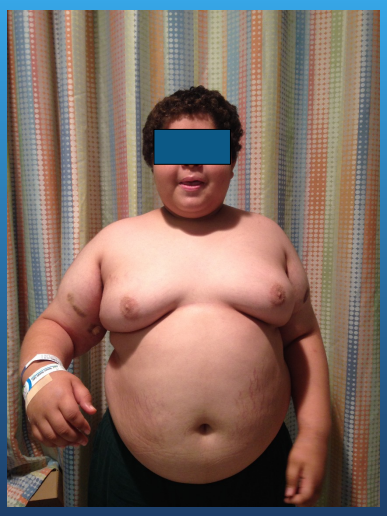
Cushing Syndrome)



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Excess Mineralocorticoid Secretion

- Primary hyperaldosteronism (rare)
  - Hypertension, hypokalemia, and low renin
  - Conn syndrome:
    - Adrenal adenoma: unilateral mainly affecting girls
      - Treatment: surgery
    - Bilateral micronodular adrenocortical hyperplasia: older children and mainly in boys
      - Treatment: spironolactone
  - Glucocorticoid suppressible aldosteronism
    - ACTH-dependent autosomal dominant
    - Treated with glucocorticoids

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Pheochromocytoma

- Catecholamine-secreting tumor from the chomaffin cells
- Typically from the adrenal medulla
- Paraganglyomas: same but from the abdominal sympathetic chain near the aorta, periadrenal area, bladder, ureteres, thorax, or neck
- In children between ages of 6 and 14 years
- Seen in NF, von Hippel-Lindau disease, familial paraganglioma syndrome, and as part of MEN-2A and 2B syndromes

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Pheochromocytoma

- Signs/symptoms: sustained hypertension, headaches, dizziness, abd pain, and palpitations.
- Laboratory: free plasma metanephrines or 24-hs total urine catecholamines (+ if >300 mcg)
- Most pheos seen on US, CT or MRI of adrenals
- Paragangliomas: ^{131}I-metaiodobenzylguanidine
- Treatment:
  - Removal of the tumor
  - Preoperatively: both alpha- and beta-blockers

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Disorders of Sex Development (DSD)

- 46, XX DSDs: gonads are ovaries, and internal genitalia are female, but external genitalia virilized
  - CAH: 21-OH and 11-OH defects (most common cause)
  - Maternal with tumor producing testosterone from adrenals or ovaries (e.g. Krukenberg tumor)
  - Exposure to androgens or progestins can cause virilization in female infants
    - If mother exposed during 8-13 weeks of gestation = labial fusion
    - If exposure >13 weeks = clitoral enlargement

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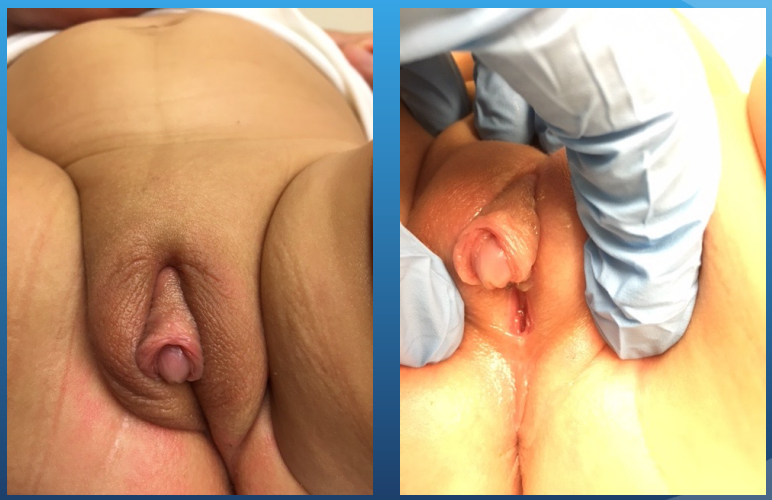
46XX Girl With Androgenization Due Maternal Androgens



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Disorders of Sex Development (DSD)

- 46, XY DSD: external genitalia are not completely virilized, are ambiguous, or completely female
  - 46, XY DSD due to defects in testicular differentiation
  - 46, XY DSD due to defects in testicular hormones
  - 46, XY DSD due to defects in androgen action
    - 5-Alpha-Reductase deficiency: ↓ dihydrotestosterone (DHT) (necessary for the development of external genitalia). Virilization at puberty. Should be raise as males
    - Androgen insensitivity syndrome: most common cause of 46,XY DSD
      - Defects in the androgen receptor (X-linked)

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Type I Diabetes Mellitus

- Incidence: 1/350-1/500 children/adolescents
- Autoimmune disorder: antibodies found in 90% of cases (GAD-65, ICA-512, insulin autoantibodies, and ZnT8)
- Presentation: polyuria, polydipsia, secondary enuresis, weight loss
- HLA type association: HLA-DR3 & DR4: sibling shares 1 haplotype risk 5-7%, both 12-20%, identical twins 30-50%

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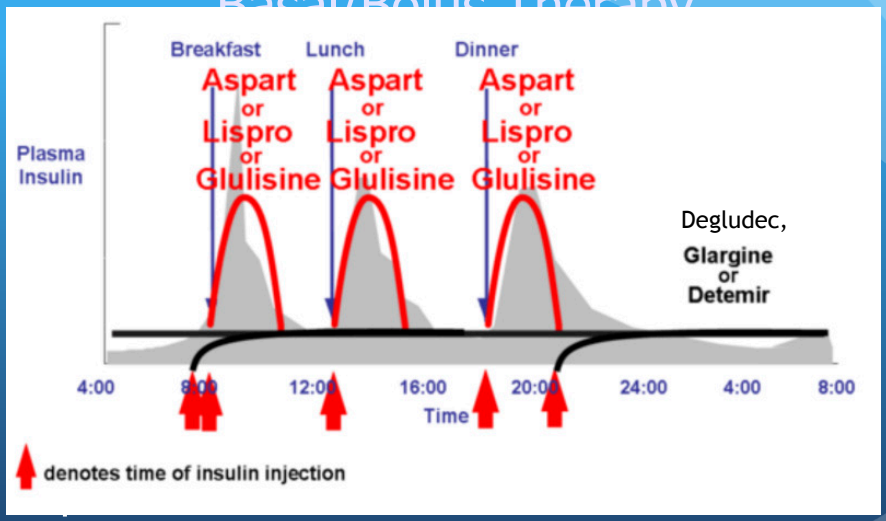
Basal/Bolus Therapy



Lantus

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Type I Diabetes Mellitus

- Most children require less insulin in the first few days after diagnosis but this is temporary (Honeymoon period)
- HbA1C is the best objective tool to determine control
- When children are sick they may need different doses of insulin, they should have glucose evaluated more often (variable glucose readings)
- Self-administration of insulin encourage by age 10 years
- Dawn phenomenon: increased blood glucose (BG) between 4 and 7 AM (peak of cortisol)
- Somogyi effect: increased early AM BG secondary to midnight hypoglycemia (contraregulatory hormones)

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Type I Diabetes Mellitus

- Risk for thyroiditis ~ 20%
- Risk for Addison's ~1% (hyperpigmentation, tireness, hypoglycemia)
- Risk for Celiac disease ~ 7-8%
- Poorly controlled T1DM: retinopathy, kidney disease, neuropathy, increased CV risk

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Screening of Patients with T1DM

- Urine microalbumin: at puberty or >10 years, after 5 years of diagnosis, if normal, annually (target <30 mg/g)
- Ophtalmologic exam: at puberty or >11 years of age, after 3-5 years. If normal every 2 years
- Neuropathy: foot pulses, vibration, monofilament: at puberty or >10 years, after 5 years.
- Fasting lipids:
  - Soon after diagnosis (glycemic control) and > 2 years of age
  - If LDL <100 mg/dL: repeat between 9-11 years
  - If LDL <100 repeat every 3 years
- Celiac disease: at diagnosis, within 2 years, and at 5 years
- Thyroid: soon after diagnosis and every 1-2 years if negative antibodies

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Diabetic Ketoacidosis (DKA)

- Definition:
  - Blood glucose > 200 mg/dl (11 mmol/L)
  - Venous pH < 7.3 and/or HCO3 < 15 mmol/L
  - There is associated glycosuria, ketonuria, and ketonemia
- Management of mild/moderate DKA
  - If patient with glucose >250 mg/dL or not feeling well, check urine ketones; if moderate/large and able to drink (without vomiting), give short-acting insulin; if unable to drink, should be taken to the closest ED

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Diagnosis of T2DM

1. HbA1C ≥ 6.5%; or
2. Fasting (8 hours) plasma glucose ≥ 126 mg/dL; or
3. 2-hour plasma glucose ≥ 200 mg/dL during an OGTT (order if impaired fasting glucose or mildly elevated HbA1C; or
4. A random plasma glucose ≥ 200 mg/dL with symptoms of hyperglycemia

(In the absence of unequivocal hyperglycemia, criteria 1-3 should be confirmed by repeat testing)

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Screening for Complications in Children with T2DM

- Urine microalbumin at diagnosis and then yearly
- Lipid profile as soon as metabolically stable and yearly
- Retinal exam at diagnosis and yearly
- Transaminases for non-alcoholic fatty liver at diagnosis and yearly
- Blood pressure at every visit
- Obstructive sleep apnea at diagnosis and every visit

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Treatment of T2DM

- Lifestyle modification and metformin
- If presentation in DKA, random glucose >250 mg/dL and/or HbA1C >9% start insulin
- Evaluate for comorbidities once glucose levels have been stabilized

86

Mature Onset Diabetes of the Youth (MODY)

- Several hereditary (autosomal dominant) forms of diabetes (1-2% of patients with diabetes)
- Mild to moderate hyperglycemia: usually diagnosed by accident during routine laboratory evaluation
- Absence of obesity or other risk factors for T2DM
- MODY 2: glucokinase (*GCK* gene). 30-70% cases. No treatment needed
- MODY 3: HNF1α mutation. 30-70% cases. Tx: sulfonylureas

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Neonatal Hypoglycemia

- Signs/symptoms: apnea, bradycardia, tachypnea, cyanosis, abnormal cry, hypothermia, hypotonia, jitteriness, and seizures
  - Neurodevelopmental deficit if hypoglycemia > 5 days
- AAP recommends glucose >40 mg/dL in the first 4 hs of life
- >45 mg/dL between 4 and 48 hs of life, >60 md/dL >48 hs

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Glucose Screening in Neonates

- At risk infants:
  - Within 60 min of life when suspecting hyperinsulinemia (e.g. maternal poorly control diabetes)
  - Before the second feeding or 2-4 hs of life if other at-risk groups (SGA)
  - Continue monitoring before feedings until at least 3 satisfactory numbers (>45 mg/dL)
  - For hypoglycemia >48 hs: urgent investigation
  - For persistent hypoglycemia do a "safety" fast for 6-8 hours before discharge. Glucose should be >60 mg/dL

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Classification of Hypoglycemia in Neonates

- Neonatal transient hypoglycemia
  - Associated with inadequate substrate or immature enzymes
    - Prematurity
    - Normal newborn
  - Transient hyperinsulinism
    - SGA, discordant twin, birth asphyxia, or infant of toxemic mother

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Classification of Hypoglycemia in Neonates cont.

Persistent hypoglycemia:

- Hormonal disorders
  - Hyperinsulinism (low glucose, insulin >2 uIU/mL, no ketones)
  - Counter-regulatory hormone deficiency
  - Glycogenolysis disorders
  - Gluconeogenesis disorders
  - Lypolysis disorders
  - Fatty acid oxidation disorders

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Evaluation of Neonatal Hypoglycemia

- Maternal history and complete physical examination
- Any glucose value < 60 mg/dL should be verified in the clinical laboratory
- If plasma glucose < 50 mg/dL and asymptomatic neonate with delayed feedings → give oral glucose/milk
- If no response or relapse → draw blood for critical sample

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Critical Sample (If Plasma Glucose <55 mg/dL)

- Should be taken prior to correction of glucose
  - Glucose
  - Insulin and C-peptide
  - Beta-hydroxybutirate
  - Free fatty acids
  - Lactate
  - Cortisol
  - Growth hormone
- May be taken after correction of glucose
  - Plasma or blood spot acylcarnitines
  - Plasma amino acids
  - Ammonia
  - Urea and electrolytes
  - Liver function tests
- First urine passes after episode
  - Ketone bodies
  - Organic acids

Ghosh, Arch Dis Child 2015

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Causes of Hypoglycemia in the Infant and Child

- Idiopathic ketotic hypoglycemia
- Hyperinsulinism
- Growth hormone or adrenal insufficiency
- Defects of glycogen synthesis and degradation
- Defects of gluconeogenesis
- Defects of fatty acid oxidation and ketogenesis
- Liver disease
- Late dumping (alimentary hypoglycemia) h/o g-tube or Nissen fundoplication
- Infections
- Drugs: insulin, sulfonylureas, beta-blockers, alcohol, quinine
- Reactive hypoglycemia

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Idiopathic Ketotic Hypoglycemia

- Hypoglycemia after a period of caloric deprivation
- Most common cause of hypoglycemia in childhood: 18 mo to 5 yr (cease by 7 yr)
- After a fast of 10-16 hours
- Intercurrent illness (e.g., URI)
- Avoid prolonged fasting: frequent meals, uncooked cornstarch

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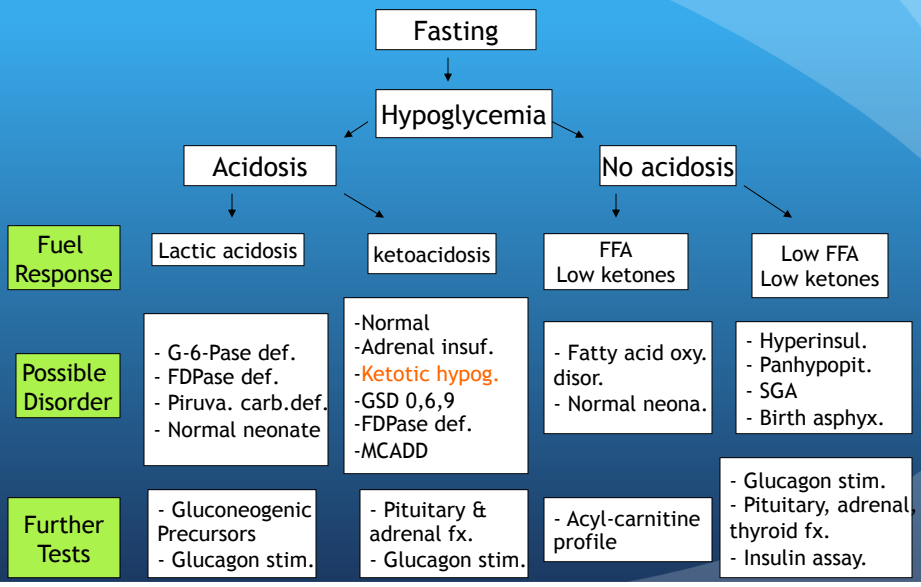
Algorithmic Approach to Hypoglycemia



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Emergency Treatment of Hypoglycemia

- Once critical sample has been obtained:
  - Bolus 2 cc/kg of D10% over 1min
  - Followed by IVF → 4-8 mg/kg/min (D10%)
  - Check glucose level 15 min after bolus
  - If hypoglycemia recurs → bolus 5 cc/kg and increase infusion by 25-50%

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Obesity

- Annual and symptom-based screening for comorbidities:
  - T2DM, HTN, dyslipidemia, OSA, NAFLD, depression
- Bariatric surgery indications:
  - BMI >40 kg/m2 with mild comorbidities or >35 kg/m2 with significant, extreme comorbidities.
  - Extreme obesity and comorbidities persist despite compliance with LMT program
  - Psychological evaluation confirms stability and competence of family unit
  - Demonstrate ability to adhere to principles of healthy dietary and activity habit
  - Experience surgeon and plan for long-term patient care afterwards

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