

ENDOCRINE DISORDERS 18

GENERAL APPROACH

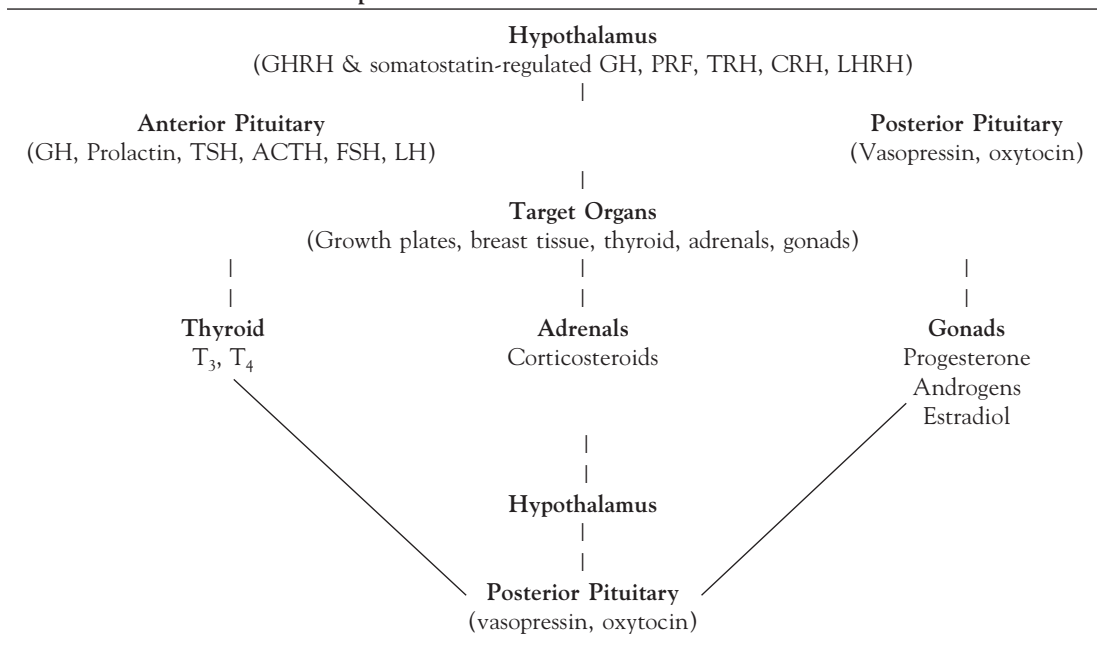
- The endocrine, or hormonal system, is a secretory feedback system that involves control of different metabolic functions of the body
- Multiple organs and tissues can be affected by dysfunctions in any endocrine gland in the body
- Disorders of the endocrine system can manifest their effects immediately or gradually over several days to months
- Hormone secretion is regulated by neural stimuli, negative feedback—a change in the body triggering the release of a hormone—and endocrine regulation—a hormone from one gland controlling another gland
- Hormones are divided into the following categories:
 - Proteins, e.g., growth hormone, prolactin, insulin, and parathyroid hormone
 - Glycoproteins, e.g., FSH, LH, and TSH
 - Polypeptides, e.g., TRH, oxytocin, ADH, calcitonin, glucagon, and somatostatin
 - Amino acid derivatives, e.g., epinephrine, norepinephrine, thyroxine, and melatonin
 - Lipids/steroids, e.g., estrogens, progestins, testosterone, mineralocorticoids, and glucocorticoids
 - Fatty acids, e.g., prostaglandins and leukotrienes
- Overall endocrine problems are not common in children; the primary disorders seen are short stature, diabetes mellitus and hypothyroidism
- Growth parameters—height and weight—are an integral component in the evaluation of possible endocrine abnormalities and should be measured in centimeters, kilograms for greater accuracy
- Abnormal findings need to be re-checked and re-plotted on the growth chart before an extensive evaluation is obtained
- Overall, a growth rate of less than 4.5 cm per year at any age is abnormal
- Specific rates of age groups are as follows:
 - Newborn to one year of age—anything less than 11 cm per year is abnormal
 - 1–2 years—anything less than 7–8 cm/yr is abnormal
 - 2–3 years—anything less than 5–7 cm/yr is abnormal
 - Childhood—anything less than 4.5 cm/yr is abnormal
 - Puberty—anything less than 5.5–6.5 cm/yr is abnormal
 - Ranges reflect different texts
- At 2 years of age, a child is approximately one half of his/her adult height
- Target height for children is approximately:
 - Boys—add both parents' heights, divide by 2, add 13 cm
 - Girls—same, only subtract 13 cm
- Bone age is an important diagnostic study in endocrine disorders and is usually obtained from the left hand/wrist

- Disorders associated with delayed bone age include hypothyroidism, growth hormone deficiency, chronic illness and accelerated bone age may be seen with certain types of tumors and precocious puberty
- Normal bone age is seen with normal variants such as genetic short stature or a few pathological conditions such as rickets
- Bone age necessary to calculate eventual height potential
- As a general rule, short stature accompanied by inadequate weight is usually due to a nutritional or gastrointestinal problem; whereas short stature accompanied by excessive weight—for height—is often due to an endocrine disorder
- Presenting symptoms of an endocrine disorder may vary according to age, e.g., young children with diabetes mellitus often present with acute onset of ketoacidosis; whereas older teens may present with more adult-like symptoms—fatigue, polyuria)
- Any child presenting with vague symptoms of lethargy, change in appetite and GI symptoms, with or without the presence of weight loss, should have a urine dip to check for glucose, particularly if the child is obese
- Endocrine disorders affect children differently at different ages
- Hypothyroidism in an infant can have profound and irreversible effects; it is the number one preventable cause of mental retardation in infants and is a true endocrine emergency. Onset in an older children will not cause the same level of severity.
- Gender differences may play a role in the etiology of the same disorder. Precocious puberty in females is often due to a benign etiology; whereas in males 50% occur secondary to a tumor

Definitions

- GHRH—growth hormone-releasing hormone
- GH—growth hormone
- PRF—Prolactin-releasing factor

Table 18-1: The Endocrine Loop



- TRH—Thyroid stimulating hormone-releasing hormone or Thyrotropin-releasing hormone
- CRH—Corticotropin-releasing hormone
- LHRH—Luteinizing hormone-releasing hormone
- TSH—Thyroid-stimulating hormone
- ACTH—Adrenocorticotrophic hormone or Corticotropin
- FSH—Follicle stimulating hormone
- LH—Luteinizing hormone
- T₃—Triiodothyronine
- T₄—Thyroxine
- ADH—Antidiuretic hormone

NEWBORN ALTERATIONS

Hypoglycemia

Description

- Blood glucose level <40 mg/dL in term or pre-term infant at <24 hours of age or <45 mg/dL after 24 hrs of age

Etiology

- Hyperinsulinism, particularly in newborns whose mothers had gestational diabetes or diabetes mellitus—about 40% chance of developing hypoglycemia; also caused by rare disorders such as Beckwith-Wiedemann syndrome and nesidioblastosis
- Decreased hepatic glycogen stores and total body fat due to intrauterine malnutrition particularly in infants with intrauterine growth retardation (IUGR) and premature infants
- Metabolic needs > calories supplied + substrate stores in very ill or immature infants; highest risk in low birth weight infants with respiratory distress syndrome (RDS), perinatal asphyxia, polycythemia, hypothermia, systemic infections, and congestive heart failure (CHF) and cyanotic congenital heart disease (CHD)
- Metabolic defects such as galactosemia, glycogen storage disease, and maple syrup urine disease
- Maternal medications—beta sympathomimetics or propranolol
- Most common of all the causes are infants of diabetic mothers and small for gestational age (SGA)

Incidence and Demographics

- Varies with method and timing of feeding, population, and the definition
- Occurs between 1 and 3 per 1000 live births, including about 5–15% of infants with IUGR
- After treatment, recurs in 10–15% of infants

Risk Factors

- Small for gestational age (SGA)—highest risk
- Prematurity
- Infants who experienced conditions associated with acute distress such as hypoxia, hypothermia, or RDS
- Smaller of a twin
- Large for gestational age (LGA)

Prevention and Screening

- Decreased incidence with early feeding
- In high-risk newborns, check serum glucose level within one hour of birth, then Q1–2 hours for the first 6–8 hours, then Q4–6 hours until 24 hours old. If serum glucose is normal, feed high-risk newborns Q2–3 hours for 24 hours, starting at 1–3 hours after birth.
- If the newborn is unable to tolerate oral or gavage feedings or if asymptomatic hypoglycemia occurs, administer IV glucose at 4 mg/kg/minute

Assessment

History

- Newborn—history of prematurity, SGA, LGA, low APGAR scores, asphyxia, hypothermia
- Postnatal—delayed feedings, infection, polycythemia, drug withdrawal, hypocalcemia
- Maternal history of diabetes, glucose infusion during pregnancy, toxemia

Physical

- Some infants may have no symptoms
- If symptomatic, onset of symptoms may be a few hours to a week after birth and include:
 - Jitteriness
 - Convulsions
 - Episodic cyanosis
 - Episodic apnea or tachypnea
 - High-pitched cry
 - Lethargy
 - Poor feeding
 - Diaphoresis
 - Pallor
 - Hypothermia
 - Hypotonia
 - Possible cardiac arrest
 - Exaggerated Moro reflex
 - Abnormal eye movement

Diagnostic Studies

- Serum glucose level:
 - <35 mg/dL at 1–3 hrs old
 - <40 mg/dL 3–24 hrs old
 - <45 mg/dL >24 hours
 - Normally declines after birth until 1–3 hours of age, then increases to normal levels
- In high-risk infants, obtain serum glucose per schedule noted above

Differential Diagnosis

- Asymptomatic transient neonatal hypoglycemia
- Neonatal hyperinsulinism
- Nesidioblastosis
- Islet cell adenomas
- Galactosemia
- Glycogen storage disease
- Tyrosinemia
- Maple syrup urine disease
- Leucine sensitivity
- Drug withdrawal
- Sepsis
- CNS anomalies
- CHD
- Congenital adrenal hyperplasia
- Panhypopituitarism
- Infant of diabetic mother
- G6PD
- Fructose intolerance

Management

Nonpharmacologic Treatment

- Oral or gavage feed high-risk infants with normal serum glucose within 1–3 hours of birth, then every 2–3 hours for 24–48 hours
- Monitor for signs and symptoms of hypoglycemia
- Surgical treatment of nesidioblastosis and islet cell adenomas

Pharmacologic Treatment

- If feedings are not tolerated in a normoglycemic, high-risk neonate, administer IV glucose at 4 mg/kg/min
- Absence of convulsions in a hypoglycemic newborn, administer 200 mg/kg of 10% glucose IV bolus over 1 min
- Presence of convulsions in a hypoglycemic newborn, administer 400 mg/kg of 10% glucose IV bolus over 1 min
- After initial IV glucose bolus in a hypoglycemic newborn, continue glucose infusion at 8 mg/kg/min; if hypoglycemia persists or recurs, increase glucose to 15–20% solution; if hypoglycemia still persists (e.g., in congenital adrenal hyperplasia), consider prednisone at 1 mg/kg/day or hydrocortisone at 2.5 mg/kg/6hrs. After obtaining serum glucose levels >40 mg/dL, wean therapy over several days to a week.

- If hypoglycemia unresponsive to the above regimen, consider diazoxide, somatostatin, and epinephrine

When to Consult, Refer, Hospitalize

- Refer to a pediatric endocrinologist if hypoglycemia persists despite treatments described above

Special Considerations

- Nesidioblastosis and islet cell adenomas will require surgery
- Beckwith syndrome: macroglossia, mild microcephaly, omphalocele, risk of endocrine gland tumors, severe hypoglycemia, which may last for several months with a poor prognosis, visceromegaly (liver and kidney)
- Severe hypoglycemia may be seen in very high birth weight infants, occasionally with pancreatic hyperplasia

Follow-up

- Monitor for attainment of developmental milestones as intellect can be affected by hypoglycemia, especially in low-birth weight infants and infants of diabetic mothers

Hypocalcemia

Description

- Serum calcium level below normal values (see Table 18-2)
- 2 groups
 - Early hypocalcemia—occurs during the first 48–72 hours of life, primarily before adequate oral intake of milk
 - Late hypocalcemia—occurs in full-term healthy infants about 5–7 days of age

Etiology

- Early onset—idiopathic, associated with low birth weight, sepsis, and prematurity in the infant; hypercalcemia, diabetes mellitus, and vitamin D deficiency in the mother
- Late onset—causes include phosphorus overload (usually from using unmodified cow's milk which has six times the amount of phosphorus as human milk), hypoparathyroidism, hypomagnesemia, renal failure, and intestinal malabsorption

Incidence and Demographics

- Uncommon in healthy term infants
- High incidence of early hypocalcemia in premature infants
- Occurs in both premature and full-term infants with intake of unmodified cow's milk

Risk Factors

- Prematurity
- Inadequate maternal intake of vitamin D
- Increased serum calcium level of the fetus causing hypoparathyroidism

Table 18-2: Normal Serum Calcium Levels

	Total Serum Calcium		Ionized Calcium	
	Mg/dL	Mmol/L	Mg/dL	Mmol/L
Premature infants	<7.2	<1.8	<5.2	<1.3
Full-term infants	<8.0	<2.0	<4.0	<1.0
Children and adolescents	<8.7	<2.2	<4.6	<1.2

Adapted from Hochberg Z, Tiosano D (2004). Disorders of Mineral Metabolism in Pescovitz OH, Eugster EA (Eds). *Pediatric Endocrinology Mechanisms, Manifestations and Management*. Lippincott Williams & Wilkins: Philadelphia.

- IUGR
- Infants of diabetic mothers (50% develop early neonatal hypocalcemia)
- Hyperbilirubinemia treated with exchange transfusion and/or phototherapy
- Anoxia
- Use of unmodified cow's milk
- Low glomerular filtration rate of the newborn
- Maternal hyperparathyroidism
- Syndromes—certain syndromes such as DiGeorge syndrome is associated with hypocalcemia

Prevention and Screening

- Adequate prenatal vitamin D intake
- Breast-feeding decreases the risk of hypocalcemia
- Encourage adequate intake of breast milk or formula in the first 36 hours of life
- No use of unmodified cow's milk before 6 months of age; preferably until 12 months of life

Assessment

History

- Inadequate prenatal vitamin D intake
- Maternal DM
- Maternal hyperparathyroidism
- Prolonged delivery
- Prematurity
- SGA
- Intake of cow's milk

Physical

- Jitteriness and seizures are the major manifestations
- Irritability
- Muscle twitches
- Signs of sepsis (e.g., poor feeding, vomiting, lethargy)
- Prolonged Q-T interval; QRS and ST changes
- Laryngospasm (stridor) with apnea and cyanosis
- High-pitched cry
- Note: Chvostek sign is common in normal newborns and is not a reliable sign of tetany

Diagnostic Studies

- Serum calcium <7 mg/dL confirms (levels <7.5 mg/dL suggest the disorder and should be repeated)
- EKG: prolonged Q-T interval
- Elevated serum phosphate level
- Possible low magnesium
- Normal BUN (High BUN with a high phosphate may be indicative of renal disease)

Differential Diagnosis

EARLY:

- | | |
|--|------------------------|
| • Prematurity | • Cerebral edema |
| • Maternal diabetes | • Anoxia |
| • Preeclampsia | • Injury |
| • RDS | • Vitamin D deficiency |
| • Severe renal dysfunction | • DiGeorge syndrome |
| • Severe Congenital Hypoparathyroidism | |

LATE:

- | | |
|--------------------------------|----------------------------------|
| • Cow's Milk Hyperphosphatemia | • Less severe hypoparathyroidism |
| • Maternal hypercalcemia | |

Management

Nonpharmacologic Treatment

- Encourage breast-feeding (low in phosphorus) or formula feeding. If unable to breast feed and formula feeding is unaffordable, may try evaporated milk (formula for mixing in Chapter 3—Nutrition)

Pharmacologic Treatment

- With mild hypocalcemia, no treatment may be needed
- With convulsions, administer 2 ml/kg of 10% calcium gluconate IV
- Oral elemental calcium may be given every 4-6 hours

How Long to Treat

- Gradually wean calcium supplements once serum calcium has normalized
- Calcium levels usually return to normal within a few hours if treated IV or up to 1–2 weeks if untreated

When to Consult, Refer, Hospitalize

- Patient must be hospitalized until convulsions have resolved, calcium levels have normalized, and treatment has been safely weaned
- Refer mothers to WIC (women, infants and children) programs to allow for formula feeding if unaffordable

Special Considerations

- Serum phosphate levels can be elevated in normal newborns fed cow's milk
- If poor response is noted to treatment, consider congenital hypoparathyroidism or vitamin D deficiency

Follow-up

- Continue to monitor calcium and phosphorus levels as treatment is weaned
- With recurrent hypocalcemia, despite adequate therapy, consider congenital absence of the parathyroids. In this case, vitamin D supplementation is required. Continue to monitor serum calcium levels, and adjust vitamin D doses accordingly (especially as patient grows).

DISORDERS OF THE THYROID

Hypothyroidism—Congenital

Description

- Decreased secretion of sufficient quantities of thyroid hormone that is present at birth or a defect in thyroid hormone receptor activity

Etiology

- Most common causes are dysgenesis of thyroid (80%), ectopic thyroid gland (5%), dyshormonogenesis (ineffective synthesis or utilization of thyroid hormone; 10%) or maternal factors (5%)
- Transient hypothyroidism is related primarily to maternal factors, particularly thyroid disease, use of thyroid medications, and iodine. Newborns at risk include those exposed to maternal antithyroid antibodies and antithyroid medications, high doses of thyroid hormone, maternal iodine deficiency, use of products with iodine (e.g., cough medications) and ingestion of goitrogens (e.g., cabbage, soybeans).
- Congenital hypopituitarism—associated with CNS malformations and midline cranial defects

Incidence and Demographics

- Occurs in 1 in 3500–4000 live births worldwide
- More common in individuals of Far Eastern or Hispanic descent (1:2000)
- Less common in individuals of European (1:5500) and African descent (1:10,000)

- Male: female ratio is 1:2–3
- Most common cause of preventable mental retardation

Risk Factors

- Maternal autoimmune thyroid disease with fetal exposure to antithyroid drugs
- Fetal or newborn exposure to excessive amounts of iodine
- Down syndrome
- History of abdominal irradiation during pregnancy

Prevention and Screening

- Monitor patients with the above risk factors
- Most cases of congenital hypothyroidism are detected on mandatory newborn screening tests.
Note: 5–10% false negative rate.
- Thyroid dysfunction detected on a newborn screen needs to be confirmed by thyroid function tests from a venous sample

Assessment

History

- No specific abnormalities at birth; may be asymptomatic up to 3–4 months of age
- May have history of large birth weight
- Symptoms may include:
 - Persistent jaundice
 - Lethargy/somnolence
 - Constipation
 - Prolonged gestation
 - Poor feeding
 - Increased birth weight
- Review mother's history for hypothyroidism

Physical

- Jaundice
- Cool, mottled extremities
- Enlarged tongue
- Large fontanelles
- Goiter
- Hoarse cry
- Hypothermia
- Umbilical hernia
- Dry skin
- Untreated: leads to facial edema, hirsute forehead, growth delays, mental retardation and cretinism

Diagnostic Studies

- Newborn screening test (done in all states—most states screen with a T_4 and follow with a TSH if T_4 was low): If thyroxine $<7 \mu\text{g/dL}$ and/or TSH $>50 \mu\text{U/ml}$, confirm with thyroid function tests from venous sample; possible elevation in TSH if drawn prior to 48 hours of age. Values are normally higher in the first few weeks of life; TSH between 20–40 $\mu\text{U/ml}$ borderline and requires repeating. (Values may differ depending on reference)
- Thyroid scan not routinely obtained but must be done before therapy started; can demonstrate aplasia, ectopic or underdeveloped thyroid or poor uptake

Differential Diagnosis

- Cerebral palsy
- Transient hypothyroidism
- Down syndrome
- Hypopituitarism
- Mucopolysaccharidoses

Management

Pharmacologic Treatment

- Congenital hypothyroidism is a true endocrine emergency; goal is to begin therapy by 14 days of life
- Initially, L-thyroxin 10–15 $\mu\text{g/kg/day}$ PO (usually 25–50 $\mu\text{g/day}$) Crush tablets, mix with small amount of liquid (milk recommended)
- Recheck thyroid function test (TFT) within 2–3 weeks. Goal is to raise T_4 to upper half and decrease TSH $\sim 1 \text{ mU/L}$. TSH may not decrease to normal levels for several months, despite a normal T_4

- If T_4 is not at high end of normal in 2–3 weeks, increase dose by 12.5 μg , and recheck studies at age 3 months, at which time TSH should also be normal. After this, titrate dose by 12.5 to 25 $\mu\text{g}/\text{day}$ until TSH normalizes.
- Ensure that T_4 and TSH monitored per recommendations of endocrinologist and all results shared with health care team members

How Long to Treat

- Usually lifelong
- May consider stopping L-thyroxin at 3 years and reevaluate 4–6 weeks later in an infant with suspected hypothyroidism of prematurity
- Test T_4 and TSH after at least 1 month of no therapy

When to Consult, Refer, Hospitalize

- Refer to endocrinologist for ongoing management
- Hospitalization is not usually required

Special Considerations

- T_4 may be normally low and TSH high in premature infants
- Soy-based formula, ferrous sulfate and aluminum hydroxide antacids may interfere with absorption of L-thyroxine
- 12% of infants with hypothyroidism have other congenital anomalies (PDA, ASD)

Follow-up

- Excellent prognosis if treatment was started in the first four weeks of life; frequent follow up 1st 3 years of life
- Poor growth or persistently low T_4 and high TSH may indicate underdosing of L-thyroxin or noncompliance with treatment regimen
- Monitor development closely as mild learning disabilities, memory and attentional problems (not associated with hyperactivity) may occur.
- Refer for hearing evaluation at 3–5 years
- Family may have a significant financial burden due to the cost of repeated lab tests and medication. Web site support: www.magicfoundation.org

Acquired Hypothyroidism—Hashimoto Thyroiditis

Description

- Inadequate amount of thyroid hormone; most common cause outside newborn period is Hashimoto's thyroiditis
- Characterized by various clinical manifestations (dependant on age and severity) and low free T_4 and increased TSH

Etiology

- Autoimmune disorder
- Characterized by chronic lymphocytic infiltration of the thyroid gland
- Genetic susceptibility

Incidence and Demographics

- Estimated prevalence 1 in 500–1,000 school-age children
- Male: female ratio 1:4–7
- Can occur prior to age 3 years, but usually occurs after age 6 with peak from 8–15 yrs

Risk Factors

- Genetic predisposition (30–40% have a family history of thyroid disease)
- Presence of antithyroid antibodies
- Presence of other autoimmune conditions, particularly insulin dependent diabetes mellitus and Addison disease; less commonly pernicious anemia

- Increased incidence in patients with specific chromosomal abnormalities such as Down, Turner, Klinefelter, or Noonan syndromes

Prevention and Screening

- Retest children with Down syndrome at age 3 months and periodically thereafter
- Screen those with other autoimmune diseases yearly, particularly Type 1 diabetes

Assessment

History

- Family history of thyroid disease
- Poor growth—“not outgrowing clothes”
- Learning disabilities or declining performance on schoolwork
- Fatigue
- Constipation
- Weight gain secondary to myxedema; not usually obese
- Cold intolerance
- Dry skin and thinning of the hair
- Delayed dentition
- Unexplained hypoglycemia in child with Type 1 diabetes
- Delayed puberty and menstrual abnormalities are common in the adolescent
- Obtain information about medications and food that may interfere with thyroid function. Alone, these foods and medications do not cause a problem but in the person with marginal thyroid functioning, may have an effect. Medications include sulfonylureas, INH, and preparations that contain iodine (some cold/cough medications). Foods that can be a problem include cabbage, turnips, kale (contain goitrogenic factors) and soybeans which increase the loss of thyroid hormone.

Physical

- Dull facial expression
- Cool skin
- Puffy eyes
- Enlarged, firm, nontender goiter—may have a “cobblestone” feel
- Delayed relaxation of deep tendon reflexes
- Muscle weakness
- Short stature
- Bradycardia
- Delayed dentition

Diagnostic Studies

- Decreased free T_4 (FT_4), T_4 , and T_3 with an increase in TSH
- Elevated antimicrosomal and antithyroglobulin antibodies (>80% of persons); antithyroid hormones may be found in normal people and those with other autoimmune disorders
- Combination of decreased T_4 , increased TSH with the presence of antibodies is supportive of the diagnosis
- Mild anemia is usually present (normochromic, normocytic)
- Bone age (if short stature is an issue) is delayed in proportion to delay in linear growth

Differential Diagnosis

- Endemic goiter
- Anemia
- Hypothalamic or pituitary disease
- Thyroid hormone resistance
- TBG deficiency (rare)

Management

Nonpharmacologic Treatment

- Avoid medications/food that may contribute to the problem

Pharmacologic Treatment

- L-thyroxin at 2–5 µg/kg/day for children older than 3 years (dose depends on age); recheck T₄ and TSH at one month and titrate to maintain normal levels

How Long to Treat

- Usually lifelong
- Complete remission may occur in about 30% of children (usually in 5–6 years); reassess yearly

When to Consult, Refer, Hospitalize

- Refer to endocrinologist
- Hospitalization is not usually required

Special Considerations

- Slight elevations of the TSH with a normal FT₄ do not require immediate treatment with L-thyroxin, but periodic evaluation is recommended

Follow-up

- Follow up at regular times for assessment of growth, sexual development, thyroid function tests and possibly bone age. Antibody levels fluctuate, usually persist for long periods of time; therefore not used for follow-up.
- Patients receiving L-thyroxin will resume growth at a faster than normal rate initially
- Measure T₄ and TSH levels at one month and 1–2 times per year
- Excellent prognosis with adequate treatment; counsel patients/family about potential need for lifelong treatment
- Adolescent girls should be educated about necessity of euthyroid state if considering pregnancy

Hyperthyroidism (Grave's Disease)

Description

- Excess synthesis and secretion of thyroid hormone; also known as thyrotoxicosis
- >90% are due to Graves disease, an autoimmune disorder (the focus of this section)
- Subacute thyroiditis occurs after a viral illness (usually URI); causes inflammation of the thyroid with tenderness; self-limited but needs evaluation; uncommon
- Neonatal Grave's disease—transplacental antibody transfer from mothers with Grave's disease; potentially life threatening, but rare

Etiology

- Autoimmune disease—production of antibodies (immunoglobins) against the thyroid; different antibodies than in hypothyroidism and act differently. In Grave's disease, develop antibodies known as thyroid stimulating immunoglobulin (TSI) that stimulate receptors which result in accelerated thyroid cell function
- Genetic susceptibility
- Theorized to be a combination of genetic susceptibility together with environmental influences (e.g., stress, infection) that result in antibody formation that attack the thyroid gland

Incidence and Demographics

- Occurrence increases with age with a peak in adolescence (12–14 yrs) and adulthood
- Female predominance with 4.8:1 ratio
- Significantly less frequent than hypothyroidism (accounts for about 10–15% of thyroid problems)

Risk Factors

- Family history of thyroid disease (about 60%)
- Environmental triggers (e.g., stress, infection)
- Asian descent

Prevention and Screening

- No known prevention
- In the presence of symptoms, obtain thyroid function tests

Assessment

History

- Gradual onset of symptoms:
 - Irritability
 - Marked mood swings
 - Decline in school performance (mind racing, difficulty concentrating)
 - Palpitations
 - Emotional lability
 - Increased appetite with weight loss
 - Insomnia
 - Heat intolerance
 - Increased urination
 - Diarrhea
 - Precocious or delayed puberty
 - Menstrual irregularities
- Family history of thyroid disease

Physical

- Enlarged thyroid (90%)—smooth, nontender, diffuse, firm goiter, possible audible bruit: presence of tenderness would suggest infection
- Exophthalmos: symptoms may include lid lag and staring
- May have linear growth acceleration but weight loss
- Tachycardia and widened pulse pressure (from systolic hypertension)
- Systolic murmur due to mitral regurgitation
- Tremor—fine tremor of hands
- Muscle weakness
- Shortened relaxation phase of deep tendon reflexes
- Diaphoresis (excessive)
- Thyroid storm (rare in children): acute onset of hyperthermia, severe tachycardia, and irritability; can progress to delirium, coma, and death

Diagnostic Studies

- Elevated T_4 , T_3 , free T_4 , and free T_3
- TSH low or undetectable
- Presence of TSH-receptor stimulating antibodies (TSI) in about 90% of children
- Bone age may be accelerated (congruent with increase in height)
- Cholesterol levels are usually low
- Thyroid scans or ultrasound should be performed if a nodule is suspected; occasionally needle biopsy done

Differential Diagnosis

- Infection
- Anxiety
- Thyrotoxic phase of Hashimoto thyroiditis
- Hormone ingestion
- Tumors of the pituitary or thyroid
- Plummer disease
- Hypercalcemia
- McCune-Albright syndrome

Management

Nonpharmacologic Treatment

- Education of parents about thyroid disease and side effects of medication
- Treatment may not be necessary in mild cases but then close follow-up is important
- Encourage a diet with increased calories, carbohydrates and vitamin B_1

Pharmacologic Treatment

- Antithyroid medications: first line treatments, inhibits thyroid hormone synthesis which decreases thyroid hormone levels but do not treat the underlying cause (autoimmune process); 65–95% effective:
 - Methimazole (MMI): 0.5–1.0 mg/kg/day
 - Propylthiouracil (PTU): 5–10 mg/kg/day (maximum 450 mg) divided every 8 hours
 - Common side effects: rash (most common), gastrointestinal discomfort, agranulocytosis (need to check WBC stat in febrile child), hepatitis (need to monitor liver function studies) and lupus-like syndrome (resolves if medication discontinued)
 - May not see clinical response for 2–3 weeks
 - In refractory children, complete suppression with provision of synthetic thyroid hormone supplementation may occasionally be necessary
- Beta-blockers are used in conjunction with antithyroid medications for 4–6 weeks to block the symptoms of thyrotoxicosis (e.g., tachycardia and tremors)
 - Propranolol (never used in an asthmatic child)
 - Atenolol
- Ablative dose of radioactive Iodine (I-131)—usually given as a one-time dose (but may need to repeat); used for adolescents who have completed their growth spurt. Closely follow child as suppression may not occur for 4–6 months.
- Rarely thyroidectomy may be necessary for some patients

How Long to Treat

- In a minority of children, adequate pharmacologic suppression for 1–3 years may lead to an ability to discontinue suppressive medications. Continue to follow laboratory and clinical status
- Beta-blockers are used until T_4 and T_3 levels are under control (usually about six weeks) and child is experiencing clinical response

When to Consult, Refer, Hospitalize

- Refer all cases to an endocrinologist
- Thyroid storm, a medical emergency, requires immediate treatment including potential hospitalization
- Ophthalmology referral—about 3–5% of patients develop severe eye problems (e.g., eye muscle dysfunction and optic neuropathy)

Special Considerations

- Consider a multivitamin with calcium, Vit. D to help prevent osteoporosis during the period of hyperthyroidism
- Antihistamines, cold medicines may exacerbate hyperthyroid symptoms particularly nervousness, tachycardia
- Depression may occur after successful treatment

Follow-up

- Follow up with an endocrinologist
- If treated with antithyroid drugs:
 - Check T_3 and free T_4 level after 4 weeks of treatment, then periodically based on results
 - Check WBC for neutropenia after the first several weeks at regular intervals and most importantly if patient develops a fever
 - Check liver function tests (LFTs) every 3–6 months

Expected Course

- Beta blockers (e.g., propranolol)—immediate decrease in sympathetic symptoms
- Antithyroid medications—successful in 65–95% of patients; normal T_3 and T_4 levels in about 4–6 weeks but needs continued treatment

- Remissions are common (approximately 25% after 2 years and 50% by 4.5 years) but relapses occur in approximately 40–60% of children

Complications

- Thyrotoxicosis may cause life threatening arrhythmias
- Chronic long term hyperthyroidism may result in osteoporosis

Diabetes Mellitus (DM)

Description

- A disease exhibited by hyperglycemia related to defects in insulin secretion, insulin action, or both; disruption in energy storage and metabolism; untreated, can lead to ketoacidosis, shock, and death

Etiology

- Type 1, now known as Autoimmune Type 1 diabetes mellitus; formerly known as insulin-dependent diabetes mellitus or juvenile-onset diabetes
 - Most common in children though the proportion of new onset cases of DM that are type 1 has decreased as the incidence of type 2 has risen at alarming rates; higher incidence in Caucasians
 - Beta-cell destruction: the result of an autoimmune response to environmental triggers (e.g., viruses) in a genetically susceptible host
 - Absence of insulin—requires exogenous insulin
 - Usually presents with acute onset of symptoms; ketoacidosis is common
- Type 2 (formerly known as non-insulin dependent diabetes mellitus or adult onset diabetes)
 - Typically seen in adolescence; more common if obese and/or African American.
 - Usually the result of long-term insulin excess and insulin resistance
 - Insulin resistance is not overcome with insulin administration
 - Gradual onset of symptoms
- Maturity onset diabetes in youth (MODY)
 - Inherited disorder (strong family history) with characteristics of both Type 1 and Type 2 diabetes (more Type 2); sometimes called Type 3 diabetes
 - Impaired insulin secretion but not total absence
 - Variable degrees of insulin resistance
 - No antibodies as seen in Type 1
 - Onset before age 25 years; begins with mild to moderate hyperglycemia (no ketoacidosis) which may progressively worsen
- More common in Caucasians

Incidence and Demographics

- Overall (all types)—occurs in about 5% of the population; incidence is increasing
- Type 1 diabetes mellitus—1–2/1,000 children; incidence increases with age to 1 in 350 by age 16 (peaks in adolescence)
- About 30,000 new cases of Type 1 diabetes mellitus are diagnosed each year
- More common in Northern Europeans/Caucasians
- Historically, 90–95% of diabetes in children is Type 1. However, the incidence of Type 2 diabetes is increasing dramatically, particularly in some inner city populations, secondary to the epidemic of obesity and insulin resistance in adolescents and younger. Metabolic syndrome, manifested by hypertension, hyperlipidemia, obesity and insulin resistance, becoming epidemic. (See Chapter 9 discussion of hypertension, hyperlipidemia)

Risk Factors

- Genetic predisposition for all types
- Obesity (>20% over ideal body weight) for Type 2 diabetes mellitus
- Down syndrome—higher incidence

- Type 2 DM is more common in children of African American, Mexican American, or Native American descent

Prevention and Screening

- Maintaining ideal body weight, balanced diet and regular exercise may prevent the onset of Type 2 DM
- Screen blood glucose level in the presence of symptoms
- Children with Type 1 risk factors need fasting blood sugar every 2 yrs starting at age 10 or onset of puberty

Assessment

History

- Onset of symptoms: more acute with Type 1 and ketoacidosis is common; gradual onset is more characteristic of other types
- Symptoms:
 - Polyuria, polydipsia, polyphagia
 - Nocturia
 - Weight loss with Type 1; not noted with Type 2
 - Fatigue and malaise
 - Possibly blurred vision
 - Changes in school performance or behavior
 - May be precipitated by an acute stressor or illness
 - Females may develop candida vulvovaginitis
- Family history of diabetes mellitus
- Nutritional history

Physical

- Type 1
 - Typically, no visible abnormalities
 - With diabetic ketoacidosis (DKA):
 - Dehydration
 - Kussmaul breathing (slow, labored)
 - Confusion/disorientation; coma (severe)
 - Lethargy
 - Acetone (fruity) breath
- Type 2
 - BMI >85% for age
 - Acanthosis nigrans

Diagnostic Studies

- A random or 2 hour postprandial blood glucose level > or equal to 200 (and confirmed with second test); glucose tolerance test not routinely obtained OR fasting blood glucose >126–140 mg/dL on two occasions
- Glycosuria and ketonuria (latter may not be present with Type 2)
- Measurement of anti-islet, anti-insulin antibodies (positive in >90% with Type 1)
- Hemoglobin A1C (to evaluate blood glucose status over the previous 2–3 months)
- In DKA: Immediate hospital admission to resolve ketosis and minimize incidence of fluid to the brain with other tests (such as electrolytes, calcium, phosphate, pH, BUN, and creatinine)
- Always check a urine dip in children presenting with vague symptoms

Differential Diagnosis

POLYURIA

- Urinary tract infection
- Renal glucosuria
- Diabetes insipidus
- Hypercalcemia

DKA

- Sepsis
- Acute abdomen
- Pneumonia
- Salicylate poisoning

WEIGHT LOSS/FATIGUE

- Chronic illness

HYPERGLYCEMIA

- Use of high-dose oral steroids, e.g. lupus exacerbation
- Stress related (e.g., trauma)

Management

Nonpharmacologic Treatment

- Patient education in regard to general management of DM:
 - Pathophysiology
 - Importance of maintaining adequate control in order to prevent acute and chronic complications
 - Basic skills (Insulin administration, blood glucose monitoring)
 - Symptoms and management of hypo- and hyperglycemia
 - Signs and management of DKA
 - Adjusting insulin and diet for exercise, growth, and illness
- Use a multidisciplinary approach to help work with the patient and the family. Team should include the patient, parents, primary care provider, endocrinologist, diabetes nurse specialist, and dietician.
- Keep a log of diet, blood sugars, and insulin doses
- Check blood glucose before each meal and at bedtime
- Regular exercise regimen 25 minutes daily
- Consistent timing and amount of meals
- Usual caloric requirement:
 - Infants and preschool children: 1,000 calories + 100 calories/year of life
 - School-aged children: 65 calories/kg of ideal body weight
 - Puberty: initially, increased caloric need, followed by a decrease to 35 calories/kg of ideal body weight as growth is completed
- Balanced source of calories: 55% from carbohydrates, 30% from fats, and 15% from protein
- Arrange diet around patient and family's food preferences to help promote compliance
- Keep a source of calories (simple sugar) readily available during physical activity or while driving. For example, tube of cake icing, 4 oz. of juice, or sugared soda
- Wear a Medic-Alert bracelet or necklace
- Educate in regard to symptoms of hypoglycemia (e.g., trembling, diaphoresis, tachycardia, lethargy, mental status changes, seizures, and coma) due to inadequate oral intake, increased exercise without adequate increase in caloric intake, and excess insulin
- Treat hypoglycemia with 15 grams of fast-acting carbohydrates (e.g., 4 oz of juice or sugared soda), wait 10 minutes and check glucose. If <80, repeat carbohydrate dose

Pharmacologic Treatment

- Goal of control: preprandial blood glucose 80–120 mg/dL and <180 mg/dL postprandial
- Adolescents with type 2 diabetes may be initially treated with oral agents, though there is less experience with their use in this population. See Table 18-3.
- Currently, there are 5 types of glucose-lowering oral agents available for treatment of type 2 diabetes. Since the pathophysiology of type 2 diabetes in children and adolescents is similar to adults, it is reasonable to assume these agents will be effective in children. However efficacy and safety data are not available and these products are not FDA approved for use in children

IN ABSENCE OF DKA:

- Initially, insulin dosing generally dictated by endocrinology. Typically, begin with 1 u/kg/day total insulin dosage with a range of 0.5–1.5 u/kg/day.
- Monitor blood glucose tid (before each meal) and at bedtime at a minimum and adjust insulin doses accordingly. Increased testing, e.g., middle of the night, may be necessary to maximize control
- Once comfortable with management, some children and families may choose insulin delivery via a pump See Table 18-4.

IN THE PRESENCE OF DKA:

- Hospitalization (preferably in a pediatric intensive care unit) is required
- Assess hydration status, and administer IV fluids slowly
- Administer insulin drip (once serum glucose is known) at a rate of 0.1 u/kg/hr, checking serum glucose q 1–2 hrs. (in addition to electrolytes, calcium, phosphorus, pH, and serum and urine ketones) and adjusting insulin drip and IV fluids accordingly until acidosis has resolved and serum glucose has stabilized.

IN ACUTE HYPOGLYCEMIA:

- Glucagon should be used if patient is unable to swallow or does not respond to oral therapy. Give 0.5 mL < if weight <20 kg; 1.0 mL if weight >20 kg IM or SQ. Repeat 1–2 times if no response in 15 minutes. Keep child on the side in case of vomiting

When to Consult, Refer, Hospitalize

- All newly diagnosed patients with Type 1 diabetes mellitus that have ketosis should be hospitalized; some new cases of DM in the absence of DKA may also require hospitalization
- Refer all new cases to an endocrinologist
- Enroll all newly diagnosed patients and their families in a diabetes education program
- Refer to an ophthalmologist for a baseline exam in the first year

Follow-up

- Continue ongoing follow-up with an endocrinologist and diabetic educator
- Annual eye exams with a pediatric ophthalmologist to evaluate for retinopathy
- Annual physical exams with primary care physician
- 6 month dental checks up due to increased sugar content of saliva
- Check HgbA1C q 3 months to monitor long-term diabetes control and compliance with management plan
- Annual urinalysis to monitor for microalbuminuria and urinary creatinine
- Annual thyroid function tests, fasting lipid panel and comprehensive chemistries to monitor hepatic and renal status
- Teach proper nail and foot care and importance of prevention of foot injuries
- Consider psychological counseling if needed to address issues of altered body image and individual and family stressors related to disease and its management
 - Needle phobia
 - Acceptance of chronic illness
 - Parental burden of care
- New therapies currently under investigation include inhaled insulins, new implantable devices and pancreatic transplants

Complications

- DKA
- Delayed healing
- Poor growth in poorly controlled children
- Hypoglycemia

Table 18-3: Oral Antidiabetic Agents

Generic & Class	Brand Name	Action	Dosage Range	Comments & Major Side Effects
Biguanides—Decrease hepatic glucose production; Increases muscle glucose uptake. Should be first oral agent used in children				
Metformin	Glucophage Glucophage XL	Improves insulin sensitivity, fasting and postprandial glucose and triglycerides. Does not promote weight gain	500–2000 mg in 1–3 divided doses; maximum dose in children rarely >2000 mg/day	May cause GI distress which can be lessened by slowly titrating dose up; glucophage XL may cause less GI symptoms. May cause lactic acidosis; contraindicated in cases of impaired renal function. Requires the presence of insulin to be effective. May normalize ovulatory abnormalities in girls with PCOS and increase risk of pregnancy; pregnancy counseling important. Monitor LFTs. Low dose may be used in obese kids with pre-diabetes/increased insulin resistance with resultant appetite suppression and improved insulin sensitivity
Sulfonylureas—Increase endogenous insulin through stimulation of beta cells; no significant advantage over newer agents such as metformin, insulin sensitizers				
Glipizide 2nd generation (Works best in early diabetes)	Glucotrol Glucotrol XL	Intermediate acting; metabolized in liver Long acting	5–40 mg day/divided 5–10 mg daily; maximum 20 mg/day	Useful for control of postprandial hyperglycemia; may be used as second agent when metformin not successful. Excreted via renal system; use with caution with renal impairment
Glyburide 2nd generation	Micronase	Long acting; onset <1 hr, duration of action 24 hrs	1.25–20 mg single or divided	Not affected by food, more likely to cause hypoglycemia

Meglitinides—Increase endogenous insulin by short-term promotion of glucose-stimulated insulin secretion			
Repaglinide	Prandin	Short acting	0.5–4 mg within 30 min. of meals 2–4×/d Quick onset which may be useful in adolescents with irregular eating schedules. Use with caution with liver disease. May be used as an adjunct with metformin
Nateglinide	Starlix	Short acting	60–120 mg tid, give within 30 min. before meals Quick onset which may be useful in adolescents with irregular eating schedules; do not take if a meal is skipped Use with caution with severe renal disease. May be used as an adjunct with metformin
Thiazolidinediones—Insulin sensitizer, increase insulin action on muscle & fat glucose uptake			
Pioglitazone	Actos	Long acting, peak 1 hour, duration 24 hours	15 or 30 mg daily; maximum 45 mg/day Use with caution in children and adolescents due to potential hepatic toxicity. Not affected by food. May cause edema, weight gain. GI side effects may occur. Monitor LFTs
Rosiglitazone	Avandia	Long acting, with onset in 15–30 min; peak action 1 hr, duration of action 24 hrs.	2–4 mg/day as starting dose, usual maintenance dose is 4–6 mg qd Use with caution due to potential hepatic toxicity. Not affected by food. May cause edema, weight gain, GI distress especially at onset. May elevate LFTs
Alpha-Glucosidase Inhibitors—Delays CHO digestion & decreases postprandial glucose			
Acarbose	Precose	Acts locally in GI tract; thus low systemic bioavailability therapeutically advantageous	50–100 mg 3×/day; maximum dose 300 mg/day May cause diarrhea, flatulence. Do not use in presence of inflammatory bowel disease. Does not cause weight gain
Miglitol	Glyset		50 mg 3×/day; maximum dose 300 mg/day Not associated with weight gain. Less risk of hypoglycemia than with other agents.

Table 18-4: Commonly used insulin products

Product	Onset(hr)	Peak(hr)	Duration(hr)
Rapid Acting			
Humalog	0.25	1	3.5–4.5
Humulin R	0.5	2–4	6–8
Novolog	0.25	45 min.	3–5
Novolin R	0.5	2–5	8
Intermediate Acting			
Humulin N	1–2	6–12	18–24
Novolin N	1.5	4–12	24
Humulin L (used less frequently)	1–3	6–12	18–24
Novolin L (used less frequently)	2.5	7–15	12
Long Acting			
Lantus	1.1	None	24
Mixtures			
Humulin 50/50	0.5	3.5	24
Humulin 70/30	0.5–1	2–12	24
Novolin 70/30	0.5	2–12	24

Complications (continued)

- Nephropathy
- Neuropathy
- Retinopathy
- Vascular Disease
- Periodontal disease
- Increased risk of birth defects in infants of diabetic mothers
- Increased incidence of the above complications with persistent lack of control of serum glucose or noncompliance with management of the disease

GROWTH DISORDERS

See Table 18-5 on following page.

SHORT STATURE

Familial Short Stature And Constitutional Delay In Growth

Description

- Familial short stature: height below the 3rd to 5th percentile; appropriate growth in relation to parents' height with no underlying cause
- Constitutional delayed growth: also a normal variant of short stature. Well child who is short, takes longer to get to his/her eventual height (which is usually average height), with a biologically slower maturation and delay in puberty
- Both are normal variants; no underlying disorders

Etiology

- Genetics
 - Familial short stature: both parents typically short with height <10%
 - Constitutional delayed growth: often a family history of “late bloomers”; parents are usually average height

Table 18-5: Tests Used to Assess Growth Disorders and Delayed/Precocious Puberty

Growth factors (IGF-BP3 and IGF-1): indirect test to screen for growth hormone deficiency. Growth hormone levels fluctuate because they are released in a pulsatile manner. Levels of growth factors are constant, released by the liver in response to circulating growth hormone. Low levels are seen in growth hormone deficiency and malnutrition.

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH): gonadotropin releasing hormone (GnRH) from the hypothalamus stimulates the release of LH and FSH from the pituitary which then stimulates the ovaries to produce estrogen and the testes to produce testosterone. Low levels seen with normal prepubertal state or hypothalamic pituitary deficiencies. High levels may be secondary to gonadal dysgenesis or agenesis

Estradiol (estrogen)—reflective of estrogen levels produced by ovaries, which induce secondary sex characteristics. Low levels seen in prepuberty conditions, ovarian or pituitary gonadotropin failures.

Testosterone—hormone released by testes that induce secondary sex characteristics in the male. Levels reflect the same conditions as in the female (equivalent to estradiol).

Prolactin—hormone produced by the pituitary involved in breast development and lactation. May be elevated with CNS lesions (e.g., tumors) that cause precocious or delayed puberty.

Human chorionic gonadotropin (HCG)—hormone produced during pregnancy but also by certain tumors of the ovaries, uterus, testes, and liver. Useful in the evaluation of precocious puberty

Thyroid function tests (TFT)—usually consist of free T₄, T₃, TSH, and antithyroid antibodies. Thyroid alterations may affect growth and pubertal changes.

Bone age (BA)—X-ray of left hand and wrist, evaluates age of skeletal maturation. Delayed BA is seen with constitutional delay in growth or growth hormone deficiency, normal with genetic short stature and advanced in some causes of precocious puberty.

CT scan or MRI head—able to identify lesions and/or structural abnormalities in the hypothalamic pituitary area.

Ultrasound—may be obtained of the pelvis (ovarian, uterine growths), abdomen (liver tumors), testicles (testicular tumors) and/or adrenal glands (adrenal tumor).

- Suggested other causes for constitutional delay have included abnormal growth hormone structure or growth hormone receptor defect

Incidence and Demographics

- Familial short stature occurs in 3–5% of children
- Constitutional delay in growth is less common; higher incidence in males

Risk Factors

- Family history

Prevention and Screening

- Routine growth measurements and accurate plotting at well exams with evaluation of growth velocity

Assessment

History

- Birth history—both with normal birth weight and height
- Both variants characteristically experience a period of deceleration of height velocity reaching the 3rd to 5th percentile by age 2–3 years and will follow the growth curve until adolescence; then familial short stature will continue along the 3rd to 5th percentile; those with constitutional delay will not experience pubertal changes until later. They will begin to fall off the growth curve in adolescence; after a lag period, they will then experience pubertal changes including growth spurt completing their growth in late teens with final height typically in average range.

- Past medical history (starting at birth) and a complete review of systems is negative for both normal variants. The differential diagnosis for “growth failure” is extensive. Key conditions to assess for include:
 - Celiac disease—may or may not have accompanying diarrhea
 - Renal disease—such as renal tubular acidosis
 - Hypothyroidism (see section on hypothyroidism)
 - Growth hormone deficiency (GHD)—may have midline facial defects or a history of central nervous system insults (trauma, including birth, infection, irradiation)
 - Chromosomal abnormalities
- Family history:
 - Familial short stature—one or both parents (or genetic “pool”—aunts, grandparents) are short
 - Parents may be short for possibly undiagnosed inherited medical conditions such as celiac disease, growth hormone deficiency or hypochondroplasia
 - Constitutional delay—often a history of late developers

Physical (see Table 18-6)

- For both conditions, physical exam will be normal except delayed puberty in constitutional delay
- Complete physical exam with emphasis on neurological exam including fundoscopic, visual fields, cranial nerve I (lack of smell secondary to pituitary tumor) body proportions and dysmorphic features (chromosomal abnormalities such as Turner syndrome)
- Weight should correlate with height in both conditions. Weight well below 3rd percentile is not consistent with normal variants and may be due to malnutrition, malabsorption, renal or cardiac disease
- Short stature coupled with normal or increased weight may indicate an endocrinological condition
- Delayed puberty in constitutional delay

Table 18-6: Comparison of Normal Variants

	Familial Short Stature	Constitutional Delay
Parents	Short (or family history)	Average height
Birth History & Early Years	Normal; often born at 25–75 percentile, followed by a deceleration period until age 2, at which point they are in 3–5 percentile	Same growth shift as genetic short stature
Growth Velocity	Steady after age 2 to adulthood; parallels growth curve	Steady until puberty and because pubertal growth spurt is delayed—begins to fall away further from growth chart
Puberty Changes	Normal age	Males: failure to achieve Tanner genital 2 by age 13.8 years, or Tanner pubic 2 by 15.6 years. Females: failure to achieve Tanner breast 2 by age 13.3 years
Bone age	Normal	Delayed (usually 2–4 years)
Ultimate Height	Short	Average (can be tall) Males >163 cm (64 inches) Females >150 cm (59 inches)
Diagnostic Studies	All normal	All normal except delayed bone age. A more extensive work up likely will be done because of the delayed puberty. (See Table 18-7 for laboratory evaluations)
Treatment	Reassurance	None

Diagnostic Studies

- If obtained, all tests will be normal
- Laboratory tests that may be obtained for children with possible delay in growth are listed in Table 18-7. Most common screening panel includes CBC, ESR, chemistry panel, free T₄ and TSH, tissue transglutaminase, antiendomysial antibody, urinalysis and bone age

Differential Diagnosis

- Intrauterine growth retardation
- Malnutrition/failure to thrive
- Renal disorders
- Celiac disease
- Turners syndrome
- Noonan syndrome
- Prader-Willi Syndrome
- Russell-Silver Syndrome
- Down Syndrome
- Inflammatory bowel disease (Crohn disease, ulcerative colitis)
- Skeletal dysplasia
- Pulmonary—Cystic Fibrosis, poorly controlled asthma
- Cardiac disease
- Type 1 Diabetes Mellitus
- Anemia
- Hypothyroidism
- GH deficiency
- Psychosocial deprivation
- CNS tumors
- Malignancy

Management

Nonpharmacologic Treatment

- Monitor height, weight, growth velocity and sexual development with accurate plotting of growth parameters
- Education and reassurance regarding growth pattern

Table 18-7: Common Laboratory Tests for Evaluation of Short Stature

Test	Interpretation
Complete blood cell count (CBC)	Anemia; nutritional, chronic disease, malignancy
Erythrocyte sedimentation rate (ESR)	Leukocytosis: inflammation, infection
Chemistry panel (electrolytes, liver enzymes, BUN, creatinine, calcium and phosphorus)	Inflammatory diseases particularly Crohn's and ulcerative colitis, malignancy
Urinalysis	Occult renal and hepatic disorders, renal tubular acidosis, metabolic bone disease
Thyroid stimulating hormone (T ₄ and TSH), Free T ₄	Renal dysfunction
Antiendomysial antibody α -Gliadin antibody or Tissue Transglutaminase antibodies	Thyroid dysfunction.
Insulin-like growth factor—I (IGF-I) and Insulin-like growth factor binding protein 3 (IGFBP-3)	In children under 3 years, primary concern is preservation of brain growth, children through end of puberty, primary concern is optimal growth.
Bone Age	Celiac disease; α -Gliadin antibodies found in 80–90% of children with untreated celiac disease
Karyotype	Reflects growth hormone status
Cranial imaging (MRI, CT)	Results will vary depending on condition; also indicates eventual height potential
	Turners or other suspected chromosomal syndromes
	Hypothalamic—pituitary tumors; evaluation of pituitary size

Adapted from: Kliegman, Robert et al. (1996) *Practical Strategies in Pediatric Diagnosis and Therapy*, Philadelphia, PA: W.B. Saunders.

Pharmacologic Treatment

- In unusual cases, human growth hormone has been used during middle childhood years though this is very controversial
- In constitutional delay in cases of boys with significant psychological stress secondary to pubertal delay, testosterone should be considered

When to Consult, Refer, Hospitalize

- Children and families who are unwilling to accept short stature as the diagnosis may require endocrinology evaluation and counseling re. use of human growth hormone
- Psychological counseling, endocrine referral may be indicated for children with either condition

Follow-up

- Routine

Short Stature—Turner Syndrome

Description

- Chromosomal abnormality in girls characterized by short stature, gonadal dysgenesis, and dysmorphic features and associated problems
- Short stature occurs in all girls; average final adult height 4'8" (125–150 cm)
- There is a mosaic Turner syndrome with varying features
- Gonadal dysgenesis (90%) usually complete but maybe partial—no pubertal changes, amenorrhea and infertility
- Associated problems/features—multiple, but not consistently present; some present at birth and others not until later
- Normal intelligence though may have learning difficulties particularly with spatial relationships and math

Etiology

- Absence or defect of an X chromosome, usually 45,X (monosomy) (approx. 60%) or 46,XX (mosaicism) (approx. 15%); female has one normal and one abnormal or absent X chromosome
- The reason for the chromosome loss is unknown; risk not increased with maternal age and no family history

Incidence and Demographics

- Occurs in girls only; Incidence is 1 in 60 in girls whose height falls below the 3rd percentile
- About 1 in 2,000 live female births (98% of pregnancies with TS abort spontaneously)
- About 50,000 females (infants, children, and adult women) affected in the United States

Risk Factors

- No known risk factors

Prevention and Screening

- No known prevention

Assessment

History

- Most consistent feature is short stature; usually present from birth and progressively worsens; occasionally may be the only symptom
- Associated features are variably present (see Table 18-8)

Physical

- Short stature
- Dysmorphic features (see Table 18-8)
- Complete physical exam but emphasis on:
 - Vision and hearing screening routinely
 - Femoral pulses and blood pressures on arms and legs (because of possible coarctation of the aorta)

Table 18-8: Common features of Turner syndrome

External features	Internal features
<ul style="list-style-type: none"> • Growth and development Significant short stature (100%) No adolescent growth spurt No secondary sex characteristics (90–95%) with absent breast development by 13 years of age • Characteristic facial features (50–75%) Small jaw, high arched palate, prominent ears • Neck: Short Webbed posterior Low hair line • Skin/Nails Multiple pigmented nevi Increase incidence of psoriasis, alopecia areata Nail dysplasia in 75% of patients • Skeletal features: Abnormal chest—shield shaped, mild pectus excavation, widely-spaced nipples Flat feet Increase incidence of scoliosis Short metacarpals • Lymphedema “puffy hands and feet”; common in newborns and persists into childhood. May be initial presenting sign 	<ul style="list-style-type: none"> • Amenorrhea and infertility • Normal intelligence but learning disabilities (>75%; particularly math and nonverbal problem solving). • Delays in motor skills; clumsiness • Psychosocial issues • Otitis media (frequent/chronic) (75%) • Hearing loss (50%; 27% use hearing aid in adulthood)—usually gradual progressive sensorineural and impacts learning, socialization and language development • Strabismus (25–50%) • Hypothyroidism (25%) (Hashimoto thyroiditis) • Cardiac defects (≈25–50%) Coarctation of the aorta Bicuspid aortic valve Aortic aneurysm (later) Aortic Atresia • Renal anomalies • Horseshoe or absent kidney Structural abnormalities • Glucose intolerance (40%) • Increase in Type 1 DM in adulthood

- Palpation of the thyroid
- Assessment for scoliosis
- Dental exam—high arched palate, small jaw may contribute to malocclusion and crowding of teeth
- Skin evaluation for dysplastic nevi, psoriasis

Diagnostic Studies

- Diagnosis made with chromosomal karyotype
 - Full karyotype rather than buccal smear recommended to detect all variants
 - Usually 45,X but other variants (e.g., 45,X/46,XX or 45,X/46,XY)
- Additional tests to determine associated problems:
 - Check levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH); often obtained in infancy and adolescence, increased if younger than 4 years of age or older than 10
 - Echocardiogram recommended at diagnosis for evaluation of aortic root/valve.
 - Renal ultrasound at time of diagnosis to rule out structural abnormalities; if normal usually does not need to be repeated. Obtain routine urinalysis

- Obtain yearly thyroid function studies (free T₄, TSH, thyroid antibodies)
- Routine testing for glucosuria and blood glucose levels
- Pelvic ultrasound—may be obtained in teen years to determine size of ovaries (if any) and presence of adnexal mass (dysgenetic gonads may become neoplastic—gonadoblastoma; particularly if karyotype with Y chromosome material)

Differential Diagnosis

- Intrauterine growth retardation
- Malnutrition/failure to thrive
- Renal disorders
- Celiac disease
- Inflammatory bowel disease (Crohn disease, ulcerative colitis)
- Skeletal dysplasia
- Cardiac disease
- Noonan syndrome
- IDDM
- Anemia
- Hypothyroidism
- GH deficiency

Management

Nonpharmacologic Treatment

- Education regarding TS and supports for associated problems (see referrals)
- Elastic stockings may be helpful for lymphedema
- Orthotics for flat feet
- Preventative gonadectomies in adolescence if karyotype contains Y material

Pharmacologic Treatment

- Treatments may vary depending on the provider
- For increased growth:
 - Growth hormone 0.05 mg/kg/day may be initiated when TS girls <5th percentile
 - May combine with anabolic steroids (oxandrolone) begun at bone age of 9–10 yrs
- To induce pubertal change, estrogen and progestin preparations usually started at age 14–15 years

When to Consult, Refer, Hospitalize

- Possibly genetic referral if uncertain of diagnosis
- Endocrinologist for evaluation and management of medications
- Referral to specialists as indicated—cardiology, nephrology, orthopedics, dermatology, dentist, psychologist and/or plastic surgery
- Family and patient support groups such as the Turner Syndrome Society

Follow-up

- Routine follow-up with endocrinologist
- Monitor LFTs in girls treated with anabolic steroids
- Yearly visual acuity, hearing evaluations, urinalysis, thyroid function tests, scoliosis check, blood pressure and femoral pulses
- Echocardiogram as indicated by clinical status
- Tendency to become obese. Monitor for signs of Type 2 diabetes

TALL STATURE AND EXCESSIVE GROWTH SYNDROMES

Genetic Tall Stature, Growth Hormone Excess

Description

- Height more than 2–3 SD above the norm for age and sex (>95% on standardized growth chart)
- Nonpathologic—no underlying etiology or associated problems

Etiology

- Usually related to having tall parents or family members

Incidence and Demographics

- Unknown

Risk Factors

- Tall parents or other family members

Prevention and Screening

- No known prevention
- Accurately assess height, weight, and head circumference at each well child visit

Assessment*History*

- Family history of tall stature
- Normal birth size

Physical

- Noted tall stature within the first 18 months of life
- Height >2–3 SD above the norm for age and sex
- Growth follows a normal curve above the 95th percentile on the growth chart
- Puberty timing follows family characteristics

Diagnostic Studies

- Normal bone age
- Normal GH parameters or may have elevated growth hormone and IGF-1 levels
- GH excess associated with functioning pituitary adenomas; check GH and prolactin levels

Differential Diagnosis

- | | |
|---|-------------------------------|
| • Constitutional acceleration of growth and development | • Congenital lipodystrophy |
| • Marfan syndrome | • Soto syndrome |
| • Pituitary gigantism | • Beckwith-Wiedemann syndrome |
| • Precocious puberty | • Weaver syndrome |
| • Thyrotoxicosis | • Klinefelter's syndrome |
| • Homocystinuria | • Nutritional obesity |

Management*Nonpharmacologic Treatment*

- Counsel parents in regard to the potential risks of pharmacologic therapy
- Girls especially may need supportive therapy; consider referral for counseling

Pharmacologic Treatment

- Girls:
 - Very rarely, high dose estrogen replacement (about 4 times adult replacement doses) until patient reaches a bone age of 15–16 years (at which time the epiphyses have hopefully fused)
- Boys:
 - Treatment only rarely done in the United States, although can be treated with high dose testosterone injections every 2–3 wks (starting prior to puberty) in order to potentially reduce adult height by about 2 in.

When to Consult, Refer, Hospitalize

- Refer to a pediatric endocrinologist if parents and child are requesting treatment

Follow-up

- Continue follow-up with a pediatric endocrinologist if patient is receiving pharmacologic treatment
- Follow growth accurately at annual physical exams

Table 18-9: Normal Tanner Stages of Development

Tanner Stage	Male Genitals	Male & Female Pubic Hair	Female Breasts
I	Preadolescent	Preadolescent	Preadolescent
II	Testes: increased volume with some enlargement; scrotum with some reddening and enlargement	Sparse, straight, or slightly curled along the labia or at the base of the penis	Breast bud with slight enlargement of the areolar diameter
III	Growth of penis with some increase in width; continued enlargement of testes and scrotum	Spreading sparsely over the junction of the pubis; darker, coarser, curlier	Breast and areolar enlargement with no separation in their contours
IV	Increased length and width of penis with darkening of the scrotal skin	Hair thickened in quantity but not yet spread to inner aspect of thighs	Areola and papilla projecting, forming a secondary mound above the level of the breast
V	Adult sized and shaped genitalia	Spread of hair to medial thighs; adult in type and quantity	Recession of the areola to the breast resulting in projection of the papilla only

Adapted from Finberg L (1998) *Saunders Manual of Pediatric Practice*. Philadelphia, PA: W.B. Saunders Company.

Pubertal Disorders

Normal Onset of Puberty

- Girls: 8–13 years
- Boys: 9–14 years
- Pubertal changes usually follow familial pattern in both onset and progression. See Table 18-9.

Precocious Puberty

Description

- Early onset of pubertal changes:
 - Girls: <6–8 years of age
 - Boys: <9 years of age
- Normal variants of early onset puberty:
 - Premature thelarche—benign breast development (typically Tanner II) usually in toddlers (see next section)
 - Premature adrenarche—small amounts of pubic hair prior to age 8 in girls and 9 in boys (possibly axillary hair and body odor). No growth spurt, breast development, testicular enlargement (needs to be differentiated from true and pseudo precocious puberty).

Etiology

- True precocious puberty or central precocious puberty (CPP) results from premature activation of the hypothalamic-pituitary-gonadal axis; referred to as gonadotropin-releasing hormone dependent. Hypothalamic-pituitary (CNS) stimulation of gonads produces estrogen and testosterone which induces the pubertal changes. May be the result of:
 - Idiopathic—no identifiable cause (system turns on spontaneously at an earlier than expected age); 75% of precocious puberty in females is idiopathic; approximately 33% in males
 - Neurogenic—damage to areas of the CNS that affect the hypothalamic pituitary axis and may include: CNS tumors, infections, trauma, radiation, cerebral malformations, hydrocephalus, seizure disorders, neurofibromatosis and tuberous sclerosis

- Pseudo (or peripheral) precocious puberty:
 - Cause is from a source outside the central hypothalamic-pituitary system such as the ovaries or adrenals; the hypothalamic-pituitary system is not activated and does not mature
 - Results in the same secretion of pubertal amounts of estrogen and testosterone
 - Can occur from ovarian or testicular tumors, liver tumors (hepatomas), congenital adrenal hyperplasia, exposure to exogenous sex steroids from food (e.g., soybeans), drugs (e.g., oral contraceptives or estrogen containing creams), or familial trait (e.g., familial testotoxicosis)

Incidence and Demographics

- More common in girls than in boys
- Usually idiopathic in girls
- In boys, approximately 50% related to a tumor, congenital adrenal hyperplasia, or familial testotoxicosis

Risk Factors

- CNS insult
- Family history

Prevention and Screening

- No known prevention

Assessment

History

- Pubertal changes—age of onset, progression and specific symptoms (e.g., breast budding, hair, menses)
- Symptoms of possible underlying etiology such as headaches, weight loss, fatigue and constipation (hypothyroid)
- History of CNS insult (meningitis, radiation)
- Exogenous sources of hormones
- Family history of early onset puberty

Physical

- Assess all pubertal changes—such as breast development, testicular size, pubic hair staging, presence of adult body odor, acne, any growth spurt (plot on growth chart)
- Obtain blood pressure—increased blood pressure may be consistent with increased intracranial pressure or congenital adrenal hyperplasia
- Thorough neurological exam including fundoscopic exam (papilledema), visual acuity, and visual fields
- Palpate scrotum/testicles for any masses; the abdomen for possible hepatomegaly or enlarged ovary or uterus
- Assess skin for café-au-lait spots, myxedema
- Palpate the thyroid

Diagnostic Studies

- Results of tests will vary depending on the etiology
- Levels of FSH and LH are usually in the prepubertal ranges with true precocious puberty; therefore in order to document the premature activation of the hypothalamic-pituitary axis a gonadotropin-stimulating test must be obtained. If premature activation has occurred, an increase in LH in response to a GnRH stimulation (e.g., serum concentration >10 IU/L 30–40 minutes after administering GnRH SQ) will occur. A positive response indicates the presence of true precocious puberty (not the cause but the presence).
- In both true and pseudo precocious puberty levels of testosterone or estradiol will be elevated. Levels are normal for normal variants such as premature adrenarche
- Adrenal androgens particularly dehydroepiandrosterone sulfate (DHEAS) are obtained to rule out congenital adrenal hyperplasia (CAD). Levels would be elevated

- Thyroid function studies (free T₄ and TSH) if hypothyroidism suspected
- Bone age should be obtained on all patients to assist with determine etiology (e.g., advanced with true precocious puberty, normal with normal variants), height potential and if treatment is warranted. May need to be repeated in the follow-up of patients
- Pelvic and testicular ultrasounds may be obtained to rule out tumors
- Cranial CT scan or MRI of the hypothalamic/pituitary regions can determine tumors or structural abnormalities
- CT scan of the adrenals if adrenal tumor suspected

Differential Diagnosis

- Premature thelarche
- Premature adrenarche
- Ovarian tumors
- Ovarian cysts
- Adrenal tumors
- McCune-Albright syndrome
- Exogenous sex steroids
- Congenital adrenal hyperplasia
- Familial testotoxicosis (Leydig cell tumors)
- Cerebral lesions

Management

Nonpharmacologic Treatment

- Treatment of underlying causes (e.g., surgical removal of tumor, remove estrogen source, thyroid replacement in hypothyroidism or correction of CAD)

Pharmacologic Treatment

- If no underlying cause (idiopathic) decision is made whether to initiate medications to stop or slow the progression of the precocious puberty:
 - Decision should be made by pediatric endocrinologist
 - May not treat if progression is very slow
 - If treated, analogues of hypothalamic GnRH (e.g., leuprolide) are used, which decrease secretion of FSH and LH and consequently estrogen to prepubertal levels
 - Lupron given as a depot every 28 days 0.2–0.3 mg/kg IM

How Long to Treat

- With GnRH analogs, patient is usually treated until adequate growth

When to Consult, Refer, Hospitalize

- All forms of precocious puberty (CPP or peripheral) need a referral—depends on cause
- Refer to a pediatric endocrinologist if no underlying pathology for management
- Refer to a pediatric neurosurgeon for organic brain lesions or oncologist
- Hospitalization for more intensive treatments (e.g., surgery, chemotherapy)

Follow-up

- Continue to follow-up with a pediatric endocrinologist for management
- After treatment with GnRH analogs, puberty usually starts within 6 months–2 years

Complications

- The most significant complication of precocious puberty is stature below expectation as a result of early closure of epiphyseal plates

Delayed Puberty

Description

- Lack of initial pubertal changes.
 - Girls: no pubertal changes by 13 years, no menses by age 16 or >5 years since the onset of pubertal changes without progression to menarche
 - Boys: no onset of pubertal changes by age 14 years or >5 years without completion of genital growth

Etiology

- Causes are factors affecting the hypothalamic-pituitary axis and those affecting the gonads. The

etiologies are categorized as either causing elevated gonadotropin levels (disorder at the level of the gonads) and those that result in normal or low gonadotropin levels (etiology affecting the hypothalamic—pituitary axis)

- In general, the most common causes are constitutional delay in growth (up to 90%), Turner syndrome or previously diagnosed chronic disease
- Elevated gonadotropin levels:
 - Gonadal damage or absence such as testicular atrophy following testicular torsion or mumps, trauma, infection, gonadal agenesis, polycystic ovaries
 - Congenital adrenal hyperplasia (involves a different steroid than with precocious puberty)
 - Chromosomal abnormality: Turner or Klinefelter syndrome
- Normal or low gonadotropin levels:
 - Constitutional delay in growth
 - Chronic disease—chronic kidney, pulmonary, bowel (celiac or inflammatory bowel disease), neoplasms, hemoglobinopathies, collagen vascular disease
 - Malnutrition (anorexia nervosa)
 - Excessive exercise
 - CNS insults or tumors (e.g., craniopharyngioma)
 - Severe emotional stress

Incidence and Demographics

- Occurs in 2.5% of all adolescents
- Constitutional delay accounts for about 90–95% of pubertal delay

Risk Factors

- Positive family history in 60% of patients with constitutional delay
- CNS insult
- Chronic disease
- Poor nutrition
- Prior malignancy

Prevention and Screening

- No known prevention

Assessment

History

- Past medical history—any chronic disease, past history of meningitis, encephalitis, head trauma, malignancies, mumps, prior surgeries that might suggest a disorder
- Any symptoms suggestive of an underlying cause—headaches, visual disturbances, diarrhea, fatigue, joint pain, depression
- Dietary history—any dieting, bingeing, food aversions, special diets
- Excessive exercise
- Psychosocial history—major stressors present
- Family history of “late bloomers”

Physical

- Growth patterns—if child has always been in 3rd percentile, consider possible Turners or constitutional delay; in child with gradual decrease in growth in the past few years, consider endocrine disease
- Presence of any features (e.g., facies, stature, skeletal findings) suggestive of a chromosomal abnormality or syndrome
- Thorough neurological including cranial nerves, visual acuity, visual fields and fundoscopic
- Evidence of malnutrition—lack of adipose tissue

Diagnostic Studies

- Results will vary depending on etiology (see Table 18-10)

Table 18-10: Comparison of Causes of Delayed Puberty

	Constitutional Delay of Growth and Puberty	Hypothalamic Pituitary Failure	Gonadal Failure
History and Physical	<3–5 th percentile in height since birth, delayed dentition; usually family history of delayed puberty. Normal history and physical	Onset at any age. History of CNS insult. Usually normal growth	Onset at any age. Possibly due to tumors of the sex organs or liver.
Bone Age	Delayed	Delayed	Delayed
Labs			
LH, FSH	Normal for BA	Low for age	Elevated
Testosterone	Normal for BA	Low for age	Low
Estradiol	Normal for BA	Low for age	Low
IGF-1	Normal	Normal—low	Normal
IGF-BP3	Normal	Normal—low	Normal

LH Leuteinizing hormone, FSH—follicle stimulating hormone IGF-BP3 and IGF-1 Insulin-like growth factors (see Table 13-3) Adapted from Fox J (1997) *Primary Health Care of Children* St. Louis, MO: Mosby, pg. 750.

- Bone age—usually delayed
- LH and FSH, testosterone, and estradiol
- Growth factors (IGF-BP3 and IGF-1)
- Chemistry panel, CBC, sedimentation rate, and urinalysis to evaluate for undetected chronic disease (liver, gastrointestinal and kidney disorders)
- Thyroid studies
- Karyotype—if indicated because of facies or characteristic physical features
- MRI, CT, and skull X-Rays—indicated by history and/or physical (headaches, behavior changes, visual alterations)

Differential Diagnosis

- Infection
- Pituitary adenomas
- Tumors
- Trauma
- Turner syndrome
- Noonan syndrome
- Prader-Willi syndrome
- Systemic lupus erythematosus
- Anorexia nervosa
- Malnutrition
- Chemotherapy
- Prostradiation therapy

Management

Nonpharmacologic Treatment

- Education if normal variant such as constitutional delay and emotional support

Pharmacologic Treatment

- Treat any underlying cause
- Hormone replacement
- Boys:
 - Testosterone—may be administered either by intramuscular injections or as a scrotal patch
 - Typical regime—testosterone enanthate IM in a dose of 50 mg/month with gradual increase to 300 mg/3 weeks
- Girls
 - Cyclic therapy with either estrogen alone or estrogen and progesterone replacement therapy. May consider patch or oral therapy
 - Typical regime is estrogen at 0.3 mg/day with gradual increase in dose to achieve desired

- breast development. After 1–2 years on estrogen therapy or if vaginal spotting has occurred, begin with estrogen/progesterone cycle (estrogen for 24 days with progesterone the last 10–14 days of the cycle).
- For fertility—human chorionic gonadotropin (HcG) and pulsatile GnRH has been used in both males and females

How Long to Treat

- Treat as above
- If patient has permanent hypogonadism, hormone replacement may be long term

When to Consult, Refer, Hospitalize

- Refer to a pediatric endocrinologist
- Hospitalization is not required, unless underlying cause is severe (e.g., anorexia nervosa with malnutrition, tumor management)

Special Considerations

- Testosterone should not be administered on a long-term basis because of the possibility of hepatotoxicity

Follow-up

- Follow up with endocrinologist

BREAST ALTERATIONS
Newborn Breast Engorgement

Description

- Enlargement of the breasts in the newborn

Etiology

- Occurs as a result of transplacentally obtained maternal hormones in late gestation
- Physiologic

Incidence and Demographics

- Very common—60–90% of all newborns
- Occurs in both boys and girls

Risk Factors

- No known risk factors except persistent manipulation of the breasts may worsen the condition and lead to mastitis

Prevention and Screening

- None

Assessment

History

- Newborn less than 4–6 wks. of age

Physical

- Enlarged breasts, usually bilateral, non-erythematous, non-tender
- Occasional nipple discharge, referred to as “witches’ milk”

Diagnostic Studies

- None

Differential Diagnosis

- Mastitis

Management

- No treatment is usually required

Follow-up

- No follow up is required. Reassure parents that this is a normal physiologic finding, which will

usually resolve within 4–6 weeks.

Premature Thelarche

Description

- Breast development in girls <8 years of age without any other signs of puberty

Etiology

- Increased estrogen activity
- May occur secondary to exogenous ingestion or application of estrogen (e.g., application of estrogen containing creams, birth control pills, or ingestion of meats contaminated with excess amounts of estrogen such as liver or chicken)
- Low levels of estrogen secreted by an ovarian follicular cyst

Incidence and Demographics

- Incidence is unknown; not uncommon
- Usually, occurs prior to age 2 years, regresses, and peaks again at 6–8 years of age

Risk Factors

- Exposure to exogenous estrogen
- Often physiologic

Prevention and Screening

- Avoid exogenous sources of estrogen

Assessment

History

- Family history of early puberty
- Gradual onset of breast tissue development over several months

Physical

- Breast enlargement; less than Tanner 3
- Unilateral or if bilateral, one breast > than other
- Non-erythematous
- Transient tenderness
- No galactorrhea
- No other signs of puberty
- Regresses over time
- Normal stature
- Normal skeletal maturation

Diagnostic Studies

- Bone age; if normal, no further evaluation is needed

Differential Diagnosis

- Exposure to exogenous estrogen (e.g., creams, foods, oral contraceptives)
- Benign lipomas
- Precocious puberty
- Hematoma
- Mastitis
- Hemangioma
- Metastatic tumor (rare)
- Breast cancer (very rare)
- Cyst
- Adipose tissue if overweight

Management

Nonpharmacologic Treatment

- Reassure patient and parents that this condition is benign

When to Consult, Refer, Hospitalize

- No referral is necessary if symptoms do not progress
- Surgical removal of breast bud will result in failure of the breast to develop

Follow-up

- No known effects on future growth
- Monitor for other signs of early puberty
- Regression of breast tissue may take up to 6 years
- If breast development occurred after the age of 2 years, increased incidence of precocious puberty

Gynecomastia

Description

- Presence of palpable mammary tissue in males

Etiology

- Pubertal (normal variant); approximately 25% due to high estrogen to androgen ratio
 - Approximately 40–70% of boys develop some degree of gynecomastia (measuring >0.5 cm) usually between 13–15 years of age
 - May be unilateral or bilateral (20%); usually slightly tender
 - Resolves usually in 1–2 years
 - Onset in late adolescence (>15 years of age) usually a pathological cause
- Obesity—adipose tissue
- Drugs/medications (approximately 10–20%) include marijuana, cimetidine, isoniazid, anabolic steroids, hydroxyzine, meprobamate, estrogen containing compounds, phenothiazine, reserpine, spironolactone, minoxidil, ergotamine, theophylline, metoclopramide, captopril, digitalis, diazepam and tricyclic antidepressants
- Drugs of abuse—especially marijuana, but also heroin, alcohol, amphetamines
- Liver cancer or cirrhosis (approximately 8%)
- Tumors—testicular (approximately 3%), adrenal, pituitary, bronchogenic
- Breast—lipomas, neurofibromas, cancer, abscess, hematoma (trauma)
- Malnutrition—usually in recovery phase
- Hyperthyroidism (approximately 1.5%), rarely hypothyroidism
- Chronic disease, particularly liver and kidney
- Idiopathic (approximately 25%)—usually a diagnosis of exclusion, may be familial, usually regresses in one year
- Klinefelter syndrome—about one-third develop gynecomastia. Also have about a 16 times greater risk of developing breast cancer.
- Gonadal dysfunction (approximately 2%) (such as from cryptorchidism, varicocele)

Incidence and Demographics

- May occur in up to 60–80% of pubertal males
- Peaks usually between Tanner stage II and III and lasts for about 2 years (peak age: 13–15 years)
- Often bilateral

Risk Factors

- Family history of gynecomastia (uncommon)
- History of cryptorchidism (even if corrected)
- Chronic disease (e.g., renal, hepatic, malnutrition)

Prevention and Screening

- Avoidance of exogenous estrogen (e.g., from hormone treated foods)
- Avoidance of drugs of abuse
- Treat underlying causes

Assessment

History

- Onset in relation to puberty, particularly between Tanner stages II and III

- Assess rate of progression
- Possible drug exposure or use of drugs of abuse—particularly marijuana
- Symptoms that may suggest an underlying etiology such as fevers, weight loss, pain (tumors), nausea, vomiting and abdominal pain (liver disease), signs of hyperthyroidism
- Complaints of decreased libido, erectile dysfunction suggest hypogonadism.
- Chest wall trauma
- History of chronic disease
- History of cryptorchidism—possible gonadal dysfunction, increased incidence of testicular cancer.
- Learning disabilities (e.g., in Klinefelter syndrome)
- Positive family history

Physical

- Assess growth (indicator of health) and pubertal changes
- Testicular exam for growths, size of testicles (>2 cm indicates puberty has started and small testicles seen in Klinefelter syndrome), presence of a hydrocele (possible underlying tumor)
- Breast exam: unilateral or bilateral (may be both with pubertal gynecomastia but acute onset of unilateral gynecomastia is concerning), progression (rapidly progressive more indicative of pathological process; pubertal tends to be slower growth), redness (indicative of infection), discharge is abnormal (may see with pituitary tumor), size >4 cm usually pathological. Mild tenderness common with pubertal gynecomastic; painful is not consistent.
- Abdominal exam to assess for masses, hepatomegaly
- Palpate thyroid
- Neurological exam including cranial nerve I (pituitary tumor), fundoscopic
- Signs of chronic illness/malnutrition: minimal adipose tissue, pale, ill-appearing, tachycardia

Diagnostic Studies

- None usually required if signs and symptoms reveal only pubertal gynecomastia
- Consider further testing if any of the following are present:
 - Onset before puberty or after puberty is completed
 - Testicular size is prepubertal size (<2 cm)
 - Duration of gynecomastia greater than 2 years
 - Macrogynecomastia (>5 cm breast tissue)
 - Other abnormalities on physical exam such as papilledema, hepatomegaly
- Chemistry panel, CBC, sedimentation rate to assess for chronic disease, liver and kidney function
- Thyroid function tests—for hyperthyroidism
- Sex hormone levels (LH, FSH, estradiol, testosterone, HcG)
- Prolactin level increased—pituitary tumor
- Karyotype if small testicles (rule out Klinefelter's)
- 24-hour urine for 17 keto-steroids (adrenal hyperplasia)
- CT of abdomen to detect masses (possibly also lung)
- Head MRI or CT to assess for a pituitary tumor
- MRI or ultrasound of testicles in the presence of a testicular mass or hydrocele

Differential Diagnosis

- Breast abscess
- Liver tumors
- Testicular cancer
- Trauma
- Breast cancer (rare)
- Klinefelter syndrome

Management

Nonpharmacologic Treatment

- Reassurance and emotional support with pubertal gynecomastia

- If breast tissue is extremely excessive, may consider surgery for cosmetic reasons
- Stop or change medications contributing to problem

Pharmacologic Treatment

- Eliminate or decrease any medication that may have a side effect of gynecomastia
- Treat specific hormonal disorders
- May consider hormonal agents, e.g., antiestrogens (clomiphene, tamoxifen, danazol), testosterone, and androgens

When to Consult, Refer, Hospitalize

- Refer to an endocrinologist or other specialist if any of the following conditions exist:
 - Physical abnormalities in addition to gynecomastia
 - Gynecomastia in puberty without genital changes
 - Gynecomastia lasting >2 years or >2–4 cm
 - Males >18 years of age
- Hospitalization is not required unless a condition exists which requires surgery or chemotherapy

Follow-up

- In pubertal gynecomastia, reevaluate q 3–6 months
- Usually resolves within 6 months to 2 years
- Watch for any signs of abnormal progression of puberty, chronic illness, or emotional/psychological disorders.
- Increased risk of breast cancer in patients with Klinefelter's syndrome
- Usually, good prognosis

CASE STUDIES

Case 1: A 10-year-old female presents with complaints of increased urination over the past few weeks with increased thirst. Her mother states that her daughter also appears to be losing weight.

PMH: No prior health problems

Medications: None

1. What other significant history is needed?
2. What physical findings may also be present?
3. What diagnostic studies would you perform first?
4. How would you manage this patient, and would you refer her to a subspecialist?
5. How would you advise the patient and parents about the prognosis?

Case 2: A 7-year-old female presents to you with breast budding and a sparse amount of pubic hair. She has had no recent illness, and denies any other complaints.

PMH: Noncontributory

Medications: None

1. What other history needs to be obtained?
2. What other physical findings may also be present?
3. What diagnostic studies would you perform? What concerns may there be in reference to growth and development?
4. How would you manage this patient?
5. Would you refer her to a subspecialist?
6. What is her prognosis?

REFERENCES

- American Academy of Pediatrics (1999). *Policy Reference Guide of the American Academy of Pediatrics*. Elk Grove Village, IL: AAP.
- Berman S (2003). *Pediatric Decision Making* (4th ed.). St. Louis: Elsevier-Mosby.
- Behrman R et al. (Ed.) (2004). *Nelson's Textbook of Pediatrics* (17th ed.). Philadelphia, PA: Elsevier-Saunders.
- Burns C, Brady M, Dunn A, Starr N. (2004). *Pediatric Primary Care: A Handbook for Nurse Practitioners* (3rd ed.). Philadelphia: Elsevier-Saunders.
- Chase HP (2002). *Understanding Diabetes* (10th ed.). Denver, CO: Children's Diabetes Foundation.
- Dershewitz R (Ed) (1999). *Ambulatory Pediatric Care* (3rd ed.). Philadelphia: Lippincott Williams & Wilkins.
- Edmunds MW, Mayhew MS (2004). *Pharmacology for the Primary Care Provider* (2nd ed.). Philadelphia: Elsevier-Mosby.
- Finberg L (2002). *Saunders Manual of Pediatric Practice* (2nd ed.). Philadelphia: Elsevier-Saunders.
- Gilbert-Barness E and Barness LA (2003). *Clinical Use of Pediatric Diagnostic Tests*. Philadelphia: Lippincott Williams & Wilkins.
- Graham M, Uphold C (2003). *Clinical Guidelines in Child Health* (3rd ed.). Barmarrae Books, Inc: Gainesville FL.
- Guyton A, Hall J (2000). *Textbook of Medical Physiology* (10th ed.). Philadelphia: Elsevier-Saunders.
- Halac I, Zimmerman D (2004). Coordinating Care for Children with Turner Syndrome. *Pediatric Annals*.33(3) 189–196.
- Halac I, Zimmerman D (2004). Evaluating Short Stature in Children. *Pediatric Annals*. 33(3), 170–6.
- Hay W et al. (2002). *Current Pediatric Diagnosis and Treatment* (16th ed.). New York: Lange Medical Books/McGraw Hill.
- Kemper AR, Foster CM (2003). Congenital Hypothyroidism: A Guide for the General Pediatrician. *Contemporary Pediatrics*. 20(6), 32–48.
- Miller BS, Zimmerman D (2004). Idiopathic Short Stature in Children . *Pediatric Annals*. 33(3), 177–181.