# Endocrinologic Findings That Necessitate Referral

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## EDUCATION GAP

In the last decade, pediatric endocrinology referrals have consistently increased.[1] Additionally, more pediatric primary care is provided by advanced practice registered nurses and physician assistants who may have had less pediatric-specific training. Prompt intervention is vital in optimizing outcomes and responses to treatment for many endocrine conditions.

## OBJECTIVES *After completing this article, readers should be able to:*

1. Describe the initial assessment of endocrine disorders in the primary care setting.
2. Facilitate timely, appropriate, and equitable referrals to pediatric endocrinologists.

## ABSTRACT

This paper aims to support primary care providers to recognize pediatric endocrine conditions, assisting with initial evaluation and timely identification of children and adolescents who may need endocrinology referral.

## INTRODUCTION

Many children face barriers to subspecialty care access (geographic, socioeconomic, and structural), and endocrinology fellowship positions remain unfilled despite an increasing need for pediatric endocrinologists.[1] The current care model is not projected to provide appropriate pediatric subspecialty care for all children, even if the size of the pediatric subspecialty workforce increases. Endocrinology subspecialty care is a particularly limited resource because the number of endocrinology fellows entering training is not increasing to meet the increased needs of the current pediatric population. The limited numbers of endocrinologists place a significant burden on many families that need to travel to academic centers, often requiring time off work and costly transportation. Collaborative assessment and management of common endocrine conditions can help reduce patient barriers to subspecialty care and ensure timely care is available for those patients with conditions requiring urgent endocrinology evaluation. Early identification of children with rare but potentially life-threatening endocrine conditions in the primary care office can also help children receive appropriate care more quickly and improve disease outcomes.

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**ABBREVIATIONS**

| | |
|---|---|
| ACTH | adrenocorticotropic hormone |
| BMP | basic metabolic panel |
| CAH | congenital adrenal hyperplasia |
| CBC | complete blood count |
| CMP | comprehensive metabolic panel |
| CPP | central precocious puberty |
| DHEA-S | dehydroepiandrosterone sulfate |
| ED | emergency department |
| ESR | erythrocyte sedimentation rate |
| FSH | follicle-stimulating hormone |
| LH | luteinizing hormone |
| mFG | modified Ferriman-Gallwey score |
| PTH | parathyroid hormone |
| SGA | small for gestational age |
| SMR | sexual maturity rating |
| T3 | triiodothyronine |
| T4 | thyroxine |
| TSH | thyroid-stimulating hormone. |



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This article outlines some of the most common endocrine conditions and laboratory abnormalities encountered in primary care settings and recommends initial assessment and guidance on when to refer.

While laboratory evaluation is the diagnostic backbone for endocrinologists, many of the components of well-child and primary care are vital in identifying patients who need further evaluation. Evaluating growth and puberty is critical in determining the appropriate timing for endocrinology evaluation and timely intervention. Growth charts and pubertal examinations with standardized sexual maturity rating (SMR) documentation are excellent tools available to all pediatric providers that effectively communicate concerns to the endocrinologist. Bone age can provide additional information in a child with problematic linear growth or precocious or delayed puberty. This article aims to help pediatric providers to use growth charts and pubertal examinations, along with targeted laboratory assessment, to identify endocrine disorders commonly encountered in general practice. Another aim is to ensure timely identification and intervention, which may or may not require referral to endocrinology evaluation, to optimize health outcomes.

## HYPERGLYCEMIA

Consider hyperglycemia if the patient has polyuria, polydipsia, fatigue, weight loss, and nocturnal enuresis. For classification of hyperglycemia see Table 1.

Consider insulin resistance if the patient has obesity with acanthosis nigricans and dyslipidemia.

Children with a clinical picture concerning type 1 diabetes, a newly identified hemoglobin $A_{1c}$ ($HbA_{1c}$) measurement consistent with diabetes, or evidence of a hyperglycemic crisis should be evaluated promptly either in an emergency department (ED) or by a pediatric endocrinologist.[2]

Children with signs or symptoms of insulin resistance with an increase in $HbA_{1c}$ despite efforts with lifestyle modification may benefit from outpatient endocrinology evaluation. Random insulin or C-peptide measurements are generally not helpful in assessing dysglycemia or risk of progression to overt diabetes mellitus. Endocrinology clinics can often provide additional services such as dietitian counseling and connection with dedicated obesity management services.

In patients with pancreatic insufficiency secondary to cystic fibrosis, early insulin initiation has been shown to improve pulmonary function and outcomes.[3] Children with a history of pancreatitis or exocrine pancreatic insufficiency are at a higher risk for developing overt beta cell failure. Mild elevations in $HbA_{1c}$ (5.7%–6.4%) may indicate early beta cell failure. Insulin treatment in these patients can help preserve the remaining beta cell function. Abnormal glucose tolerance is more sensitive in diagnosing early dysglycemia in this patient population.

- When to refer for endocrinology evaluation:
  - $HbA_{1c}$ measurement results of at least 6.5% or at least 5.7% with concern for type 1 diabetes (normal body mass index, no features of metabolic syndrome)
  - Fasting glucose concentration greater than 126 mg/dL or abnormal oral glucose tolerance testing results
- Information to include with referral:
  - Growth charts
  - $HbA_{1c}$ measurement results
  - Complete blood count (CBC)
  - Basic metabolic panel (BMP)
  - Urinalysis, including ketones and glucose
  - Type 1 diabetes antibodies: glutamic acid decarboxylase, islet cell antigen 512, islet cell antibody, and zinc transporter 8 antibody

## OBESITY

Treatment of obesity without associated comorbidities is complex and varies considerably by region and institution. A discussion of the treatment of obesity in the absence of endocrine comorbidity or genetic syndrome is beyond the

**TABLE 1.** Classification and Diagnosis of Hyperglycemia

| Definition | Laboratory Results | Recommendations |
|---|---|---|
| Prediabetes, insulin resistance | $HbA_{1c}$ 5.7%–6.4% | Lifestyle modification and consider pediatric endocrinologist evaluation |
| Diabetes mellitus | One of the following: $HbA_{1c}$ >6.5%, fasting glucose >126 mg/dL, or random glucose >200 mg/dL | Pediatric endocrinologist evaluation |
| Hyperglycemic crisis | Hyperglycemia with acidosis or hyperosmolarity | Emergency management and urgent insulin initiation |

Abbreviation: $HbA_{1c}$, hemoglobin $A_{1c}$.



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scope of this article. The 2023 American Academy of Pediatrics (AAP) clinical practice guidelines offer a comprehensive guide for screening for comorbidities and treatment of obesity.[4] It is important for the primary care pediatrician to assess comorbidities to connect families with all needed specialists. Consideration of pharmacologic therapy by the pediatric practitioner may be appropriate for many children regardless of a need for subspecialty evaluation.[4] Careful measurement of blood pressure and assessment for obstructive sleep apnea are important in the initial evaluation of obesity in addition to laboratory screening.

- When to refer for endocrinology evaluation:
  - Younger than 6 years
  - Rapid weight gain not explained by nutritional assessment
  - Rapid weight gain with poor linear growth in a growing child
- Information to include with referral:
  - $HbA_{1c}$ measurement results
  - Comprehensive metabolic panel (CMP)
  - Lipid profile
  - Growth charts

## HYPOGLYCEMIA

Consider hypoglycemia if an infant has irritability, lethargy, poor feeding, cyanosis, tremor, jitteriness, or seizure.

Consider hypoglycemia in an older child if there is sweating, tremors, palpitations, tachycardia, hunger, lethargy, confusion, loss of consciousness, or seizure.

Serum glucose concentration less than 50 mg/dL with clinical symptoms requires immediate treatment of hypoglycemia and ED management if identified in the outpatient setting. For children not taking insulin, the following laboratory evaluation, if available, should be obtained at the time of hypoglycemia to assess for an underlying cause: insulin, C-peptide, cortisol, growth hormone, serum beta-hydroxybutyrate (alternatively can obtain urine ketones with next void), ammonia, free fatty acids, lactate, pyruvate, and acylcarnitine profile.

Concern for hypoglycemia despite not having laboratory evidence for hypoglycemia due to symptoms that improve with treatment is a common scenario encountered by endocrinologists and general pediatricians. Some patients may benefit from dietary intervention to minimize processed simple carbohydrates. Screening with $HbA_{1c}$ is reasonable in these patients because they may have insulin resistance and features of metabolic syndrome.

Symptoms of hypoglycemia are nonspecific, and the focus should be a broad workup until the hypoglycemia is confirmed.[5,6]

- When to refer for endocrinology evaluation:
  - Measured serum glucose concentration less than 50 mg/dL
- Information to include with referral:
  - Any laboratories obtained at the time of hypoglycemia
  - $HbA_{1c}$ measurement results
  - Growth charts

## SHORT STATURE

The definition of short stature in children that warrants further evaluation is height less than the third percentile, a decline of more than 1 height percentile line after age 3 years, height greater than 2 SD below genetic potential, or a history of being small for gestational age (SGA) without evidence of catch-up growth by age 2 years. To look at normal growth and puberty please see Table 2.

The most common causes of short stature beyond the second year of life are familial short stature and constitutional delay of growth and puberty, which are normal nonpathologic growth variants. Short stature may also manifest as a chronic systemic disease affecting a child's growth. Prolonged steroid treatment can also affect a child's growth. Children with poor weight gain relative to linear growth velocity or who are crossing weight percentiles before a decline in linear growth should have a thorough evaluation for nutrition and malabsorption.[7]

Diagnosis and treatment before puberty improve final height prognosis.

- When to refer for endocrinology evaluation:
  - Chronic disease is excluded and patient has 1 of the following:
    - Low growth velocity for age measured over at least a 6-month interval
    - Height less than 2 SD of calculated mid-parental height (genetic potential)
    - Height curve has deviated downward
    - History of being SGA without catch-up growth at the age of 2 years
- Information to include with referral:
  - Growth charts
  - Bone age
  - Physical examination with SMR
  - CBC
  - CMP
  - Thyrotropin (TSH) and free thyroxine ($T_4$) concentrations
  - Erythrocyte sedimentation rate (ESR)
  - Celiac screen—tissue transglutaminase antibody and immunoglobulin A antibody
  - Urinalysis
  - Karyotype (female only to rule out Turner syndrome)



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**TABLE 2.** Normal Growth and Puberty

| | | |
|---|---|---|
| Normal growth velocity | 2–4 y: 5.5–9 cm/y (2.2–3.5 in/y)<br>4–6 y: 5–8.5 cm/y (2–3.3 in/y)<br>6 y to puberty: 4–6 cm/y (1.6–2.4 in/y)<br>Puberty: 8–14 cm/y (3.1–5.5 in/y) | |
| Mid-parental height calculation | Female:<br>Subtract 13 cm (5.12 in) from the father's height and average the result with the mother's height. | Male:<br>Add 13 cm (5.12 in) to the mother's height and average the result with the father's height. |
| Pubertal onset | Female:<br>Between ages 8 and 13 y | Male:<br>Between ages 9 and 14 y |

## TALL STATURE

The definition of tall stature is length or height in at least the 97th percentile, growth velocity greater than the 90th percentile, or height greater than 2 SD above the mid-parental height.[7,8]

Tall stature is socially acceptable, and families often do not seek medical attention. However, it is essential to identify children with accelerated growth rates to identify underlying disorders such as precocious puberty, Marfan syndrome, homocystinuria, Klinefelter syndrome, and Sotos syndrome. Serial measurements of height are important to calculate height velocity.

Familial tall stature has normal height velocity for age and normal bone age. With precocious puberty, bone age would be advanced for chronological age. Growth pattern, SMR breast development, and testicular size (measured with an orchidometer) are important to rule out precocious puberty.

Obesity is accompanied by modest linear growth, especially in girls with advanced bone age and precocious puberty.

- When to refer for endocrinology evaluation:
  - High growth velocity for age (Table 2)
  - Height above calculated mid-parental height
  - Height curve deviating upward above 97.7%
  - Growth acceleration in the absence of puberty
  - Bone age greater than 2 SD
- Information to include with referral:
  - Growth charts
  - Bone age
  - SMR
  - TSH and free $T_4$ concentrations

## THYROID ABNORMALITIES

Consider hyperthyroid and hypothyroid disease if the patient has the symptoms listed in Table 3.

Adequate thyroid hormone is critical for neural development and growth. Early identification and treatment are crucial.[9]

Congenital hypothyroidism is part of routine newborn screening in the United States. Infants with abnormal thyroid newborn screening results need prompt serum laboratory testing and endocrinology evaluation to ensure levothyroxine replacement begins within the first 2 weeks of life. Levothyroxine replacement is crucial to optimize neurodevelopmental outcomes.[9]

The prevalence of autoimmune hypothyroidism in childhood is estimated at 1%–2%, with a 4:1 female predominance. Approximately 50% of children with autoimmune hypothyroidism have a family history of autoimmune thyroid disease. Thyroid peroxidase antibodies help confirm an autoimmune etiology for hypothyroidism but should not be used as a stand-alone tool in the absence of abnormal thyroid function for diagnosis of hypothyroidism. Routine

**TABLE 3.** Thyroid Abnormality Symptoms

| | Hyperthyroid | Hypothyroid |
|---|---|---|
| General | Heat intolerance | Cold intolerance |
| | Fatigue or hyperactivity | Fatigue |
| Growth | Acceleration of growth | Declining growth velocity |
| Mood | Anxiety, mood swings, panic attacks | Depression |
| School performance | Inability to concentrate | Altered school performance, decline in or better ability to concentrate |
| Physical examination | Palpitations, new tremors | Bradycardia, delayed reflexes |
| Stool | Diarrhea | Constipation |
| Weight | Weight loss | Mild weight gain |
| Menstrual | Irregular menses, oligomenorrhea | Heavy, irregular menses |
| Skin | Warm and smooth skin | Dry, pale skin |



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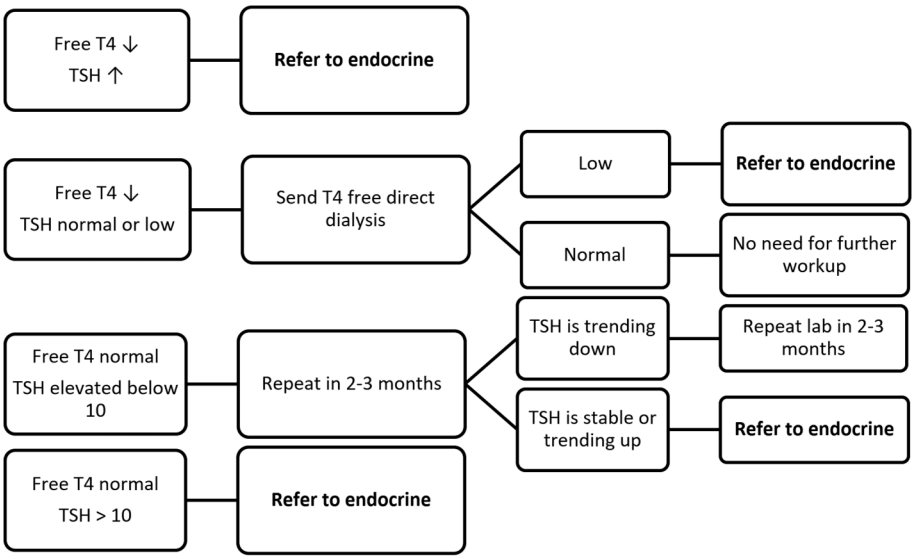


**FIGURE 1.** Hypothyroid evaluation algorithm.
Abbreviations: $T_4$, thyroxine; TSH, thyroid-stimulating hormone.

thyroid screening in an asymptomatic child or a child with obesity is not recommended. Children with hypothyroidism typically have deceleration in linear growth with inconsistent effects on weight.

Several syndromes and autoimmune disorders are associated with an increased risk of developing autoimmune hypothyroidism, including Down syndrome, Turner syndrome, type 1 diabetes, alopecia, vitiligo, and celiac disease.

The first step in the diagnosis of thyroid abnormality is evaluating TSH and free $T_4$ concentrations. A low free $T_4$ and an elevated TSH concentration or a TSH concentration of 10 mU/L or greater should prompt a referral for pediatric endocrinology evaluation. If the TSH concentration is mildly elevated or the free $T_4$ concentration is mildly low without an elevated TSH concentration, additional evaluation is indicated (Figure 1).

About 15% of pediatric patients with thyroid disease can be classified as having hyperthyroidism; most of these cases are due to Graves disease. Transient hyperthyroidism can occur early in the disease process for patients with Hashimoto hypothyroidism due to the release of preformed thyroid hormone as the gland is destroyed.

Thyrotoxicosis, or thyroid storm, is a rare but life-threatening diagnosis in pediatrics that presents with tachycardia, hyperreflexia, fever, and mental status changes and warrants ED evaluation and stabilization.

- When to refer for endocrinology evaluation:
  - Hyperthyroidism, elevated free $T_4$ and triiodothyronine ($T_3$) concentrations
    - Should always be referred
    - When thyroid storm suspected, send to the ED for urgent evaluation
  - Acquired hypothyroidism; see Figure 1 for thyroid laboratory abnormalities algorithm
- Information to include with the referral:
  - Growth chart
  - Current medication list
  - TSH and free $T_4$ concentrations
  - Total $T_3$ concentration (only if hyperthyroidism is suspected)

## EXCESSIVE CORTISOL PRODUCTION

Consider excessive cortisol production if the patient has rapid weight gain, particularly with poor linear growth, ecchymosis, round face, menstrual changes, hirsutism, hypertension, violaceous striae more than 1 cm wide, proximal myopathy, lethargy, depression, and hyperglycemia.

Children with normal to accelerated linear growth with rapid weight gain are unlikely to have cortisol excess, as linear growth is typically suppressed by supraphysiologic cortisol, whether cortisol originates from ectopic or autonomous secretion or from an iatrogenic source in the form of chronic glucocorticoid treatment.

A low-dose overnight dexamethasone suppression test with 1 mg dexamethasone has excellent negative predictive value with a sensitivity of approximately 95%, if the morning cortisol concentration is less than 1.8 μg/dL.[10] In patients with altered hormone-binding globulins, most commonly



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caused by the use of estrogen, such as seen with a combined oral contraceptive, a 24-hour urine collection for measuring free cortisol is a better first evaluation.

- When to refer for endocrinology evaluation:
  - Obesity and rapid weight gain with declining growth velocity
- Information to include with referral:
  - Growth charts
  - Low-dose overnight dexamethasone suppression test if completed before referral

## ADRENAL INSUFFICIENCY

Consider adrenal insufficiency if the patient has weakness, weight loss, nausea, vomiting, low blood pressure, and dizziness. Adrenal insufficiency should be ruled out in every case of hyponatremia with or without hyperkalemia.

Acute management should focus on administering dextrose- and sodium-containing intravenous fluids and stress-dose hydrocortisone even if the etiology of adrenal insufficiency is unclear.

In the acute setting, separate mineralocorticoid replacement is unnecessary because hydrocortisone given at high doses has sufficient mineralocorticoid activity. The addition of fludrocortisone will be required once the child has stabilized and is ready for the transition to physiologic steroid replacement.

Physical examinations are essential to assess for hyperpigmentation, signs of virilization, and penile or clitoral enlargement. Careful measurements of blood pressure in the referring documentation are helpful. If laboratory measurements are obtained, baseline adrenal steroids and electrolytes help risk stratify those patients who are more likely to have an underlying pathology.

- When to refer for endocrinology evaluation:
  - Concern for cortisol deficiency
- Information to include with referral:
  - Growth charts
  - Blood pressure measurement
  - SMR
  - Laboratory test results noted in Table 4

## PREMATURE PUBARCHE

The definition of premature pubarche is girls younger than 7 years and boys younger than 9 years who present with true pubic hair, which is coarse and pigmented, in contrast to downy hairs, without evidence of breast or testicular enlargement or growth acceleration.

The most common cause of the physical examination finding of pubarche is isolated premature adrenarche, which is due to early activation of the hypothalamic-pituitary-adrenal axis. Additional signs and symptoms of adrenarche can include body odor and acne. Although isolated premature adrenarche is the most common cause of this presentation, nonclassical congenital adrenal hyperplasia (CAH) and, very rarely, adrenal tumors can be the cause.

- When to refer for endocrinology evaluation:
  - Pubic or axillary hair in girls younger than 7 years or boys younger than 9 years
  - Penile or clitoral enlargement warrants a more urgent referral

**TABLE 4.** Age Group, Differential Diagnosis, and Recommended Workup for Adrenal Insufficiency

| Age | Common Causes of Adrenal Insufficiency | Initial Workup |
|---|---|---|
| Infants | CAH, central pituitary deficiency | BMP<br>Adrenal steroids: 17-OH progesterone, testosterone, androstenedione, progesterone, 11-deoxycortisol, 11-deoxycorticosterone<br>ACTH<br>Cortisol (measurement in the morning is less important because infants lack diurnal variation) |
| Toddlers to school age | Genetic syndromes, iatrogenic (topical or inhaled steroids), autoimmune (Addison disease) | BMP<br>ACTH (morning)<br>Cortisol (morning)<br>Renin, aldosterone |
| Puberty through adulthood | Autoimmune (Addison disease), adrenal hemorrhage or infarct, iatrogenic | BMP<br>ACTH (morning)<br>Cortisol (morning)<br>Renin, aldosterone<br>21-hydroxylase antibodies |

Abbreviations: ACTH, adrenocorticotropic hormone; BMP, basic metabolic panel; CAH, congenital adrenal hyperplasia.



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**TABLE 5.** Precocious Puberty Definition[11]

| Female | Male |
|---|---|
| Before age 8 y | Before age 9 y |
| Breast development, vaginal discharge, or bleeding | Testicular volume ≥4 mL, softening of the testicles and thinning of the scrotum |
| Growth acceleration, advanced bone age | Growth acceleration, advanced bone age |

- Information to include with referral:
  - Growth charts
  - Physical examination with SMR and blood pressure
  - BMP
  - Bone age

## PRECOCIOUS PUBERTY

The definition of precocious puberty is as shown in Table 5.

Puberty timing is influenced by many factors, including genetics, nutrition, and environment.

Central precocious puberty (CPP) can result in reduced adult height in both boys and girls and has adverse psychosocial effects with increased risk of mental health issues.[12]

Early activation of the hypothalamic-pituitary-axis leading to CPP is the most common presentation. Primary gonadal disorders can also cause peripheral, gonadotropin-independent production of estrogen or testosterone and lead to precocious pubertal development. Obesity appears to be contributing to the trend toward earlier pubertal onset in girls. Breast tissue development should be evaluated with palpation, as adipose tissue can be visually mistaken for glandular tissue. Breast ultrasound is not recommended for diagnosis of CPP.[11] In overweight boys, earlier pubertal timing is observed, whereas boys who are obese might have a later onset of puberty.[13]

History should include past exposure to estrogens, androgens, or mimetic compounds; topical estrogens or androgens; and over-the-counter products such as lavender, soy, and tea tree oils.

Referral to a pediatric endocrinologist gives the patient the best chance to benefit from therapeutic intervention for the best height outcome. Girls receive the most height benefit if treatment is initiated before 6 years of age.[13] It is not clear whether final height benefits occur if treatment is started after the age of 6 years. Early menarche has been linked to depression.[12]

- When to refer for endocrinology evaluation:
  - CNS abnormalities such as headaches, seizures, or visual changes—send to ED for evaluation in addition to referral for endocrinology evaluation
  - 17-OH progesterone concentration greater than 200 ng/dL
  - Rapidly progressing puberty
  - Initial presentation is vaginal bleeding
  - Bone age at least 2 SD from chronologic age
  - Signs of rapid virilization or voice deepening
- Information to include with referral:
  - Growth chart
  - Physical examination with SMR
  - Bone age
  - Serum 17-OH progesterone concentration
  - Luteinizing hormone (LH) concentration
  - Follicle-stimulating hormone (FSH) concentration
  - Estradiol or testosterone concentration
  - TSH and free $T_4$ concentrations

## DELAYED PUBERTY

The definition of delayed puberty is as shown in Table 6.

The most common cause for delayed puberty is constitutional delay of puberty and growth. Other causes can be functional hypogonadotropic hypogonadism due to undernutrition, chronic disease, or permanent or primary gonadal failure.[14]

Reproductive hormone, LH, FSH, testosterone, and estradiol measurements should be obtained in the morning, if possible, but are not essential before referral.

- When to refer for endocrinology evaluation:
  - Criteria for delayed puberty

**TABLE 6.** Delayed Puberty Definition

| Female | Male |
|---|---|
| No breast development by age 13 y | Testicuxlar volume <4 mL by age 14 y |
| Lack of menarche by age 16 y<br>Lack of menarche >3 y after breasts start to develop | >5 y between testicular enlargement and completion of puberty |
| May or may not have delayed adrenarche: points to presence of pubic hair, axillary hair, body odor, acne | |



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**TABLE 7.** Physiological Gynecomastia Definition

| Age | Midpuberty 12–14 y |
|---|---|
| Sex maturity rating | Stage 3–4 pubic hair |
| Testes volume | 8–10 mL |
| Side | Bilateral, may be nonsymmetrical |
| Size | Up to 4 cm in diameter |
| Tenderness | Tender for approximately 6 months after the onset |

- Information to include with referral:
  - Growth charts
  - Bone age
  - TSH and free $T_4$ concentrations
  - ESR
  - Prolactin concentration
  - Karyotype

## GYNECOMASTIA

The definition of gynecomastia is palpable subareolar breast tissue in a male.

Up to 60% of boys have clinically detectable physiological gynecomastia by age 14 years. In more than 90% of cases, physiological gynecomastia resolves within 3 years of onset.[15]

Breast budding in infancy is a common condition in both boys and girls and usually resolves spontaneously, typically within the first year of life.

Boys with physiological gynecomastia (Table 7) typically have a decreased ratio of androgen to estrogen. Pathologic gynecomastia can occur at any age and is due to an increase in the circulating or local breast tissue ratio of androgen to estrogen, which can be due to a tumor, hyperthyroidism, primary hypogonadism, drugs, or genetic mutations or can be idiopathic.[16]

- When to refer for endocrinology evaluation:
  - Prepubertal (excluding breast budding of infancy)
  - Rapid progression
  - 4-cm diameter or larger
  - Persistence for more than 2 years or after the age of 17 years

**TABLE 8.** Amenorrhea Definition

| | |
|---|---|
| Primary amenorrhea | No menarche by age 15 y or No menarche 3 y after breast development |
| Secondary amenorrhea | 3 mo without menses with history of previously regular menses or 6 mo without menses with history of previously irregular menses |

- Information to include with referral:
  - Growth charts
  - Physical examination with SMR

## AMENORRHEA

The definition of amenorrhea is as shown in Table 8.

Amenorrhea can be caused by obstruction in the outflow tract with normal sex steroid levels and gonadotropins, primary ovarian insufficiency, and gonadotropin insufficiency due to hypothalamic or pituitary disease.[17]

Changes in weight, diet, exercise habits, or illness might result in hypothalamic amenorrhea. The presence of acne or hirsutism may suggest hyperandrogenism. Diagnosis and treatment are essential to achieve fertility and bone health.

Reproductive hormone, LH, FSH, testosterone, and estradiol measurements should be obtained in the morning. The results can be challenging to interpret and are not generally necessary before referral.

- When to refer for endocrinology evaluation:
  - Amenorrhea (primary or secondary)
- Information to include with the referral:
  - Growth charts
  - Pregnancy test results
  - TSH and free $T_4$ concentrations
  - Prolactin concentration
  - Karyotype—should be considered in those with short stature (to rule out Turner syndrome)
  - Pelvic ultrasound
  - Consider LH, FSH, testosterone, and estradiol concentrations (obtain in the morning)
  - Physical examination including SMR

## HYPERPROLACTINEMIA

Consider hyperprolactinemia if the patient has the signs and symptoms described in Table 9.

Hyperprolactinemia accounts for approximately 10% to 20% of cases of amenorrhea.[19]

Prolactinomas account for approximately 40% of all pituitary tumors. It is important to exclude drug-induced hyperprolactinemia and ask about family history to consider genetic syndromes associated with neoplasia.

A single measurement of serum prolactin above the upper limit of normal confirms the diagnosis of hyperprolactinemia.

- When to refer for endocrinology evaluation:
  - Elevated prolactin concentration in the absence of a drug with a known side of hyperprolactinemia



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**TABLE 9.** Hyperprolactinemia Signs and Symptoms by Sex

| | |
|---|---|
| Female[18] | Oligomenorrhea or amenorrhea, galactorrhea, breast discharge, hot flashes, and vaginal dryness |
| Male | Galactorrhea, or breast discharge (less often seen than in girls)<br>Signs of decreased testosterone secretion: decreased energy, libido, muscle mass, and body hair; erectile dysfunction |

- Information to include with the referral:
  - Prolactin concentration (measured at any time of day)
  - TSH and free T4 concentrations
  - BMP
  - If the prolactin level is elevated, a pituitary MRI is recommended.

## HIRSUTISM

The definition of hirsutism is "Excessive growth of terminal hair on the face and body of a female in a typical male pattern distribution."[20] Hirsutism affects 5% to 10% of women of reproductive age. Hirsutism is one of the most prevalent health problems in women of reproductive age that causes negative impacts on their quality of life.

The modified Ferriman-Gallwey score (mFG)[21] is the gold standard for evaluating hirsutism. This method uses numerical scoring to assess the severity of hirsutism in women. A visual depiction of the scoring system can be found online: https://myendoconsult.com/learn/ferriman-gallwey-score.

An mFG score of 8 or more is indicative of hirsutism.

Testosterone, 17-OH progesterone, and dehydroepiandrosterone sulfate (DHEA-S) measurements can help with excluding tumor or nonclassical CAH as a cause for hyperandrogenism.

- When to refer for endocrinology evaluation:
  - Urgent:
    - Total testosterone concentration greater than 200 ng/dl
    - DHEA-S concentration greater than 700 µg/dl
    - Clitoral enlargement or voice deepening
- Nonurgent
  - mFG score of at least 8
  - Elevated 17-OH progesterone concentration
- Information to include with referral:
  - Total and free testosterone concentrations, DHEA-S concentration (obtain in the morning)
  - 17-OH progesterone concentration
  - Growth charts

## ELECTROLYTES AND MINERALS

Abnormal sodium and calcium levels can be seen in many different medical conditions. This section will discuss the endocrine aspect of electrolyte and mineral abnormalities.

### Hypernatremia

Consider hypernatremia if the patient has irritability, restlessness, weakness, vomiting, polyuria, polydipsia, muscular twitching, fever, or altered mental status (Table 10).

Infants can present, in addition, with a high-pitched cry or tachypnea.

Hypernatremia warrants urgent evaluation. If a rapid rise is suspected, then ED evaluation and management are appropriate, given the risk of neurologic compromise or severe dehydration.[22] Children presenting with hypernatremia, polyuria, or polydipsia should be evaluated for central arginine vasopressin deficiency (previously known as central diabetes insipidus), as treatment will require vasopressin replacement. Intensive care unit treatment is often appropriate for precise fluid management and close monitoring of response to administration of desmopressin acetate. Brain imaging, if not previously obtained, is indicated for new diagnoses of arginine vasopressin deficiency to look for mass lesions compromising the posterior pituitary.[22]

### Hyponatremia

Consider hyponatremia if the patient has nausea, malaise, headache, lethargy, or seizures.

**TABLE 10.** Sodium Abnormality and Differential Diagnosis

| | Hypernatremia | Hyponatremia |
|---|---|---|
| Endocrine causes | Central arginine vasopressin deficiency | Cortisol deficiency<br>Hypothyroidism<br>Syndrome of inappropriate antidiuretic hormone |
| Common non-endocrine causes | Dehydration<br>Renal resistance to arginine vasopressin | Dehydration Medications |



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Acute hyponatremia or moderate to severe hyponatremia warrants emergent evaluation given the risk of neurologic compromise, including seizures, and the need for very close monitoring as sodium is corrected.[23] Most children with hyponatremia have excess volume losses rather than underlying endocrine disorders. For children without a clinical picture to support hypovolemia, inappropriate antidiuretic hormone secretion, hypothyroidism, and cortisol deficiency should be considered because treatment for these conditions differs from that of hypovolemic hyponatremia.[23,24] Serum osmolality is important in the evaluation of hyponatremia because normal serum osmolality in the setting of hyponatremia indicates pseudohyponatremia, most commonly due to the presence of hyperglycemia or hypertriglyceridemia, and requires management of the underlying process.

Adrenal insufficiency should be ruled out in the case of hyponatremia.

## Hypercalcemia

Consider hypercalcemia if the patient has constipation, fatigue, depression, polyuria, polydipsia, anorexia, or muscle weakness.

With initial evaluation, careful consideration of volume status, possibility of malignancy, and immobility is needed. In settings where the albumin level is low, it is essential to correct the serum calcium level for hypoalbuminemia, as total serum calcium level is directly related to albumin level. Alternatively, ionized calcium is independent of albumin, although it may be altered by significant acidosis or alkalosis. See Figure 2 for differential diagnosis of hypercalcemia.

Fluid resuscitation should be the primary intervention while additional workup is pending.

- When to refer for endocrinology evaluation:
  - Serumx calcium concentration of at least 12.0 mg/dL or less than 12.0 mg/dL with symptoms of hypercalcemia warrants urgent ED evaluation
  - Elevated serum calcium concentration less than 12.0 mg/dL
- Information to include with referral:
  - Parathyroid hormone (PTH) concentration
  - 25-hydroxyvitamin D concentration
  - 1,25-dihydroxyvitamin D concentration
  - CMP
  - Phosphorus concentration

## Hypocalcemia

Consider hypocalcemia if the patient has tetany, irritability, hypotension, anxiety, or seizures.

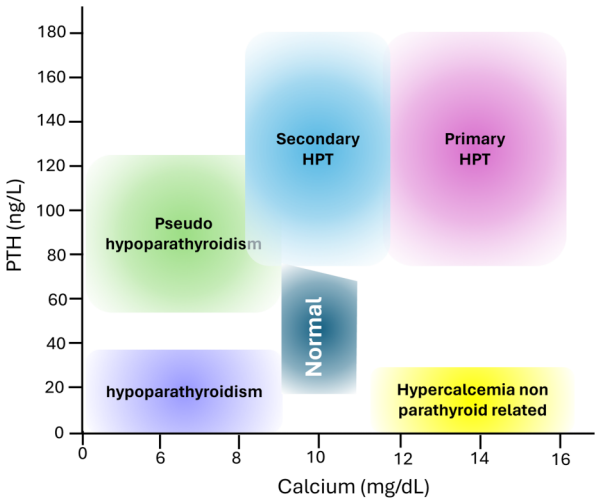


**FIGURE 2.** Calcium and PTH levels differential diagnosis.
Abbreviations: HPT, hyperparathyroidism; PTH, parathyroid hormone.

Hypocalcemia in infants and children can result in cardiac arrhythmias or seizures and should be corrected promptly with close monitoring. Intravenous calcium replacement should be given to all children with symptoms of neurologic irritability.[25] Determining the underlying etiology can help guide treatment (Figure 2). The addition of calcitriol, cholecalciferol/ergocalciferol, and magnesium may be needed to maintain calcium in the normal range. Pseudohypocalcemia can be due to hypoalbuminemia, and serum calcium level should be corrected to albumin level, or ionized calcium should be obtained in the presence of hypoalbuminemia.

- When to refer for endocrinology evaluation:
  - Symptomatic hypocalcemia warrants urgent ED evaluation
  - Asymptomatic hypocalcemia confirmed with 2 measurements
- Information to include with referral:
  - PTH concentration
  - 25-hydroxyvitamin D concentration
  - CMP
  - Magnesium concentration
  - Phosphorus concentration

## Rickets, Osteopenia, and Vitamin D Deficiency

Consider rickets and osteopenia if the patient has bone pain, skeletal deformities, dental problems, poor growth, delayed gross motor milestones, and fragile bones. Children with lower calcium levels can present with muscle cramps, twitching, and seizures (Table 11).



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**TABLE 11.** Rickets Subtype

| Type | Deficiency | Cause |
|---|---|---|
| Calcipenic rickets | Calcium deficiency | Low vitamin D intake<br>Failure to metabolize vitamin D<br>Low calcium intake |
| Phosphopenic rickets | Phosphorus deficiency | Renal wasting—common<br>Low nutritional intake—rare |

Vitamin D deficiency is more common in people with dark skin pigmentation, people who avoid sun exposure, children who live at higher latitudes, exclusively breastfed infants, infants born to mothers with vitamin D deficiency, and former premature infants.[26]

Rickets is best visualized at the growth plates of rapidly growing bones (metaphysis), where mineral demand is most significant. Initially, distal forearm, knee, and costochondral junctions are affected.

Calcipenic rickets can affect the musculoskeletal system with decreased muscle tone.

Before starting treatment, it is crucial to refer because treatment can mask and affect further evaluation.

- When to refer for endocrinology evaluation:
  - Signs of osteopenia and rickets
- Information to include with referral:
  - X-ray: wrists and knees
  - CMP
  - Phosphorus concentration
  - Magnesium concentration
  - PTH concentration
  - 25-hydroxyvitamin D concentration
  - Calcium to creatinine urine ratio
  - Growth charts

## Summary

- Hypothyroidism is rarely the etiology of weight gain in children and adolescents (based on some research evidence as well as consensus).[9]
- Girls with CPP receive the most benefit in terms of adult height if treatment occurs before age 6 years, making prompt identification of girls with precocious puberty important in optimizing outcomes (based on strong research evidence).[11]
- Children with rapid weight gain and poor linear growth should have an evaluation for an underlying endocrinopathy (thyroid hormone deficiency, growth hormone deficiency, cortisol excess); by contrast, those with rapid weight gain and accelerated linear growth are unlikely to have an underlying endocrine disorder (based on consensus opinion).

## QI PROJECT IDEA

- "Streamlining Endocrinology Referrals": Measure the number of referrals for endocrinology evaluation for which additional information is requested before scheduling before and after using the initial workup and guidelines outlined in this article.

*Take the quiz! Scan this QR code to take the quiz, access the references, and view and save images and tables (available February 1, 2025).*



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# PIR QUIZ

1. A mother brings her 5-year-old son to a clinic because she is concerned that he is "too small." He is otherwise healthy and developmentally appropriate for his age. There are no dietary or nutritional concerns/restrictions. Of the following, what growth chart data/observations would best support a referral to an endocrinology specialist for further evaluation?

   A. Expected height based on mid-parental height calculation
   B. Low growth velocity for more than 6 months
   C. No change in head circumference curve percentiles
   D. No change in height curve percentiles
   E. Similar decline in weight and height percentiles over time

2. You are completing the initial evaluation of an internationally adopted 4-month-old girl with delayed milestones, poor linear growth, and constipation. There is no past medical or family history available. Which of the following is the most appropriate first diagnostic study to obtain to explain this patient's presentation?

   A. Bone age
   B. Karyotype
   C. Morning serum cortisol level
   D. Serum thyroid peroxidase antibodies (TPO) titers
   E. Serum thyroid-stimulating hormone (TSH) and free thyroxine ($T_4$) levels

3. A 5-year-old girl is seen in a clinic for recent breast development (>3 cm) and the presence of coarse, dark pubic hair. There is no history of any unusual dietary or environmental exposures. Of the following diagnostic results, which one would be most consistent with these physical examination findings?

   A. Decreased morning cortisol level
   B. Delayed bone age
   C. Elevated prolactin level
   D. Elevated 17-OH progesterone level
   E. Elevated total testosterone level

4. An 18-month-old boy is brought to the emergency department by his parents with recent onset of irritability, vomiting, and constipation. He appears mildly dehydrated on initial examination. There are no other sick contacts at home. This child is known to have fine and gross motor delays with hypotonia and a long history of feeding difficulties and is followed by cardiology for his heart murmur. He does not look like anyone in his family. This patient's clinical presentation is most likely to be associated with which of the following laboratory findings?

   A. Elevated parathyroid hormone (PTH) level
   B. Elevated 25-OH vitamin D level
   C. Hypercalcemia
   D. Hypoglycemia
   E. Hypernatremia

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5. While supervising medical students in a well-child clinic, you review the importance of discussing nutritional risk in specific patient populations as part of the anticipatory guidance. Which of the following factors would potentially increase an infant's need for vitamin D supplementation?

   A. Being born at term
   B. Being exclusively breastfed
   C. Experiencing frequent sun exposure
   D. Having light skin pigmentation
   E. Living in the southern United States



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