35 Endocrinology

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CHAPTER OUTLINE

Key Points

- The hypothalamic–pituitary axis (HPA) orchestrates the hormonal secretions of the other endocrine glands.
- The pituitary is composed of the adenohypophysis, or anterior lobe, and the neurohypophysis, or posterior lobe.
- The hormonal secretions of the anterior pituitary are regulated by a number of hypothalamic-releasing hormones and inhibitory molecules.
- The posterior lobe of the pituitary is where nerve endings, originating in the paraventricular and supraoptic nuclei, project as the supraopticohypophyseal tract.

Hypothalamic–Pituitary Axis

The hypothalamus affects several nonendocrine functions, including appetite, sleep, body temperature, and activity of the autonomic nervous system. In addition, the hypothalamus modulates the pituitary hormone secretions. The other half of the HPA, the pituitary gland, is often referred to as the "master gland" in recognition of its role in orchestrating the hormonal secretions of the other endocrine glands (Mooradian and Korenman, 2007; Mooradian and Morley, 1988).

The pituitary gland is located in the anterior fossa, in the sella turcica, in close proximity to the optic chiasm. The pituitary is composed of the adenohypophysis, or anterior lobe, and the neurohypophysis, or posterior lobe, and is connected to the hypothalamus by the pituitary stalk.

See Table 35-1 for a listing of hormones from each lobe of the pituitary.

Control of pituitary hormones is a complex process involving the hypothalamus, both lobes of the pituitary, and hormones endogenously produced by the various organs of the endocrine system.

Hormones secreted from the anterior pituitary lobe are regulated by a number of hypothalamic-releasing hormones and inhibitory molecules. These factors reach the pituitary through the portal circulation and, upon interaction with specific receptors, either stimulate or inhibit the secretion of the anterior pituitary hormones. The main releasing hormones produced in the hypothalamus include thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH), corticotropin-releasing hormone (CRH), and growth hormone–releasing hormone (GHRH). There are two major inhibitory factors: dopamine, which principally inhibits prolactin release, and somatostatin, a potent inhibitor of growth hormone (GH) and, to a lesser extent, thyrotropin or thyroid-stimulating hormone (TSH).

A number of other factors have been identified and shown to have important regulatory effects on anterior pituitary function. The kisspeptin hormones are a family of peptides encoded by the *KiSS-1* gene and are thought to play a critical role in reproduction. Kisspeptin receptors stimulate GnRH release and activation of the mammalian reproductive axis. Mutations in kisspeptin receptor GPR-54 cause idiopathic hypogonadotropic hypogonadism (HH) characterized by delayed or absent puberty (Jayasena and Dhillo, 2009).

There is a short-loop regulatory system within the HPA, which, via the portal circulation, allows pituitary hormones to flow in a retrograde direction back to the hypothalamus to feedback on their own releasing hormones. In addition, there is a long-loop negative feedback on the pituitary, mediated by hormones secreted by endocrine glands in the periphery (Mooradian and Korenman, 2007; Mooradian and Morley, 1988). It is the interplay between the effects of the hypothalamic-releasing hormones, the short-loop regulatory system and the long-loop negative feedback that controls pituitary hormonal secretions. For example, a rise in plasma thyroid hormone level feeds back and suppresses pituitary TSH and hypothalamic TRH secretion.

As we achieve better understanding of the intricacies of these processes and feedback controls, new therapeutic modalities are postulated. Secretion of GH is regulated by two hypothalamic hormones, GHRH and somatostatin. New data suggest that γ-aminobutyric acid (GABA) may also play a role in GH secretion. Although research in this area is relatively new, it does suggest a possible alternative approach to growth retardation caused by insufficient GH secretion or gigantism caused by GH excess (Powers, 2012).

The posterior pituitary lobe is essentially an extension of the hypothalamus, where the nerve endings, originating in the paraventricular and supraoptic nuclei, project as the supraopticohypophyseal tract. The posterior pituitary

Table 35-1 Pituitary Hormones

Hormones of the adenohypophysis or anterior pituitary lobe	Thyroid-stimulating hormone (TSH or thyrotropin) Follicle-stimulating hormone (FSH) Luteinizing hormone (LH) Prolactin (PRL) Growth hormone (GH or somatotropin) Adrenocorticotropic hormone (ACTH) α-Melanocyte-stimulating hormone (α-MSH)
Hormones of the neurohypophysis (pars nervosa) or posterior pituitary lobe	Antidiuretic hormone (ADH or vasopressin) Oxytocin

hormones are directly controlled by neural impulses and are released into the inferior hypophyseal veins and then into the systemic circulation (Mooradian and Morley, 1988).

Approach to Pituitary Disease

Key Points

- Pituitary disease may manifest with pituitary hormone excess or deficiency or symptoms of mass expansion, including headaches and visual disturbances.
- Pituitary adenoma is the most common cause of pituitary dysfunction in adults.
- HPA function should be assessed whenever a mass is discovered in the sella turcica.
- Evaluation of pituitary function (deficiency or excess) involves imaging and serum measurements of prolactin, GH, insulin-like growth factor type 1 (IGF-1), free thyroxine (FT_4), TSH, adrenocorticotropic hormone (ACTH), cortisol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (in men), and estradiol (in women). Twenty-four-hour urinary free cortisol and dexamethasone suppression tests (DSTs) are used for evaluating cortisol excess.

The most common cause of pituitary disease is the development of benign tumors (adenomas). These tumors can cause symptoms because of excessive production of hormones such as prolactin, GH, or ACTH or can cause pituitary hormone insufficiency secondary to tissue destruction. The pituitary hormones that can be lost early from gradual destruction of pituitary tissue include GH and GnRH followed by TSH and ACTH (Mooradian and Korenman, 2007; Mooradian and Morley, 1988). However, occasionally, the autoimmune destruction of the pituitary can be cell specific and cause selective pituitary hormone deficiency.

Pituitary tumors can expand into surrounding tissue such as the optic chiasm and hypothalamus and cause visual field defects and symptoms of hypothalamic disease, respectively. Early manifestations of optic chiasm impingement can be subtle and include seeing images that float apart or seeing half of a face higher than the other half (the Picasso effect or hemifield slide phenomenon). These symptoms emerge when the patient is tired or anxious and are the result of failure to fuse the images from both eyes because of the lack of nasal fields (Mooradian and Morley, 1988). Expansion of tumors into the hypothalamus can cause disturbances in sleep, appetite, temperature regulation, sweating, water balance, and memory (Mooradian and Morley, 1988).

In children, pituitary adenomas are less common, and hypothalamic pituitary dysfunction is usually the result of hypothalamic tumors, notably craniopharyngiomas.

When microadenoma (<10 mm) is discovered incidentally, the initial evaluation should seek hormone hypersecretion by measuring levels of serum prolactin, IGF-1, TSH, and FT_4, as well as 24-hour urine free-cortisol or a 1-mg overnight DST (Mooradian and Korenman, 2007; Mooradian and Morley, 1988). More extensive workup is required for pituitary masses larger than 10 mm (macroadenoma) regardless of symptoms.

The overall workup and management of pituitary disease should include identifying and treating hormonal deficiency or excess as well as diagnosing and managing mass effects of the tumors.

HYPOPITUITARISM

Key Points

- Hypopituitarism refers to total or partial deficiency of one or more pituitary hormones.
- Hypopituitarism could be the result of a genetic cause; a deficiency in hypothalamic releasing factor; or, more commonly, the result of pituitary tissue destruction secondary to mass expansion, infiltrative process, autoimmune or infectious disease, vascular accidents, radiation injury, or trauma.
- Pituitary apoplexy may result in life-threatening hypocortisolism.
- Lymphocytic hypophysitis is a rare autoimmune disease of the pituitary occurring in women during late pregnancy or in the postpartum period. This disease may mimic pituitary tumor but does not require resection.
- Kallmann syndrome is characterized by an isolated defect in GnRH secretion.
- Approximately 10% of patients with empty sella syndrome have clinically apparent hypopituitarism, and some may have pituitary adenomas.
- Systemic disease, including end-stage liver disease or chronic renal failure, is associated with variable degrees of hypopituitarism without significant histopathologic changes in the pituitary.

Hypopituitarism refers to total or partial deficiency of one or more pituitary hormones resulting in end-organ changes or reduced hormonal secretion of target endocrine glands (Toogood and Stewart, 2008). The deficiencies could be the result of primary disease of the pituitary or secondary to failure of hypothalamic hormone synthesis or transport. There are no good estimates of the incidence of hypopituitarism because the disease is often subclinical.

Causes

Hypopituitarism could be the result of a genetic cause; a deficiency in hypothalamic releasing factor; or, more commonly, the result of pituitary tissue destruction secondary to mass expansion, infiltrative process, autoimmune or infectious disease, vascular accidents, radiation injury, or trauma (Toogood and Stewart, 2008). Sometimes the etiology of hypopituitarism cannot be identified and is considered idiopathic. Most of these cases are sporadic, although there are well described familial causes of hypopituitarism.

The most common cause of hypopituitarism in the adult population is *intrasellar pituitary tumors*. Occasionally, hypopituitarism is resolved with surgical or medical treatment of the pituitary mass. Parasellar masses that cause hypopituitarism include craniopharyngiomas, meningiomas, optic nerve gliomas, teratomas, germinomas, chordomas, metastatic cancer, and lymphomas.

The second most common cause of hypopituitarism in adults is *postpartum pituitary necrosis* (Sheehan syndrome). The portal system of the anterior pituitary vascular supply, increased oxygen demand of an enlarged pituitary gland during pregnancy, excessive blood loss, and possibly increased intravascular coagulation converge to cause ischemic injury of the pituitary. Other ischemic causes of pituitary necrosis can occur in systemic vascular diseases such as diabetes mellitus, temporal arteritis, and sickle cell disease. These diseases can also result in hemorrhagic infarction *(apoplexy)* of the pituitary with acute onset of severe headache, visual impairment, altered mental status, and hypopituitarism. The sudden decline in ACTH, and thus hypocortisolism, may be the most life-threatening consequence of hypopituitarism, requiring emergency treatment with corticosteroids. Although pituitary adenomas are the most common cause of pituitary apoplexy, often it may be related to complications of diabetes, radiotherapy, or open heart surgery (Toogood and Stewart, 2008).

Rarely, infectious diseases can lead to hypopituitarism. Examples include meningitis, intracranial abscess, septic shock, fungal infections of the central nervous system (CNS), tuberculosis (TB), malaria, and syphilis.

Infiltrative diseases of the pituitary, and more commonly of the hypothalamus, can cause hypopituitarism. Sarcoidosis can present with hypopituitarism along with polydipsia and polyuria. Histiocytosis X may present as a suprasellar tumor. Lipid storage diseases and hemochromatosis can cause hypopituitarism often with hypogonadotropin deficiency.

Lymphocytic hypophysitis is a rare autoimmune disease of the pituitary occurring in women during late pregnancy or in the postpartum period. Lymphocytes and plasma cells infiltrate the pituitary gland, which results in the destruction of anterior pituitary cells (Toogood and Stewart, 2008). Lymphocytic hypophysitis cannot be distinguished from tumor except by biopsy. The diagnosis is suspected in women who develop hypopituitarism during or immediately after pregnancy in the absence of a history of hemorrhage during delivery or previous history of infertility or menstrual disorders.

Mutations in the *PROP-1* gene are the most common causes of congenital hypopituitarism and present as deficiencies of GH, prolactin, TSH, LH, and FSH. Older adults with *PROP-1* gene mutations may manifest with ACTH deficiency (Wu et al., 1998). Mutations of genes that code for specific anterior pituitary hormones have also been described, the most common of which is isolated genetic deficiencies of GH, which manifests with short stature and begins in infancy or childhood. *Kallmann syndrome* is characterized by an isolated defect in GnRH secretion. Young men develop a eunuchoid appearance and testosterone deficiency, and women manifest with amenorrhea or oligomenorrhea. The syndrome may also be associated with hyposmia or anosmia (Oliveira et al., 2001). Iatrogenic causes of hypopituitarism include surgical ablation and radiotherapy. Hypothalamic and pituitary deficiency may occur after several years, with GH and gonadotropin deficiencies the most common. Prolactin level may be mildly elevated.

Approximately 10% of patients with *empty sella syndrome* have clinically apparent hypopituitarism and some may have pituitary adenomas (Mooradian and Morley, 1988). The empty sella syndrome occurs when a defect in the sellar diaphragm allows the subarachnoid space to herniate into the pituitary fossa. It is a relatively common disorder found in 5% to 8% of autopsies. Systemic disease, including end-stage liver disease or chronic renal failure, is associated with variable degrees of hypopituitarism without significant histopathologic changes in the pituitary (Mooradian, 2001; Nowak and Mooradian, 2007).

Clinical Manifestations

Key Points

- Progressive loss of hormones occurs in pituitary injury with loss of GH and gonadotropin followed by TSH and ACTH deficiency.
- ACTH deficiency results in cortisol deficiency, leading to hypotension, shock, and cardiovascular collapse.
- TSH deficiency results in signs and symptoms of hypothyroidism.
- Gonadotropin deficiency results in signs and symptoms of hypogonadism.
- GH deficiency causes short stature in children and may be asymptomatic in adults.

The clinical manifestations of hypopituitarism are highly variable and depend on the age and sex of the patient as well as on the etiology of the pituitary disease (Toogood and Stewart, 2008). Patients can be completely asymptomatic for many years or present with dramatic symptoms of nausea, vomiting, headache, and vascular collapse. The latter is more common in pituitary apoplexy when the sudden withdrawal of ACTH and ensuing adrenal insufficiency cause hemodynamic instability. It is believed that at least 75% of the glandular tissue must be destroyed before an individual becomes clinically symptomatic. If the etiology is a space-occupying lesion, such as an expanding adenoma or carotid aneurysm, the clinical manifestations will include headache and visual field defects, which are classically bitemporal hemianopsia (loss of peripheral vision). Other subtle changes in vision include changes in color perception, patchy scotomas, and difficulty in passing a thread through the eye of a needle (Mooradian and Morley, 1988).

Failure to lactate may be the first clinical sign of Sheehan syndrome. Lethargy, anorexia, weight loss, failure to resume normal menstrual periods, and loss of pubic hair may also be present later in the postpartum period. On the other hand, symptoms and signs of pituitary infarction may be subtle and not recognized for years.

Patients with *panhypopituitarism* (Simmonds syndrome) are usually pale and lethargic; have dry skin and low blood pressure (BP); and, rarely, may look cachectic (Mooradian and Morley, 1988; Toogood and Stewart, 2008). These patients have lost all the anterior pituitary hormones, and the clinical manifestations are the result of a mixture of hypogonadism, hypothyroidism, adrenal insufficiency, and GH deficiency. The clinical manifestations depend on whether the deficiency is partial or complete. Individual signs and symptoms are reflections of the biologic actions of various hormones secreted by the pituitary.

Growth hormone deficiency manifests as growth retardation in children. The body proportion and primary teeth are normal, but secondary tooth eruption is delayed. In up to 10% of children with GH deficiency, symptomatic hypoglycemia may occur. In adults, GH deficiency may be asymptomatic. Subtle changes may occur in insulin sensitivity, manifested by reduced insulin requirements in patients with diabetes, decreased muscle and bone mass with increased adiposity, delayed wound healing, and fasting hypoglycemia, and may contribute to anemia of hypopituitarism. Additional adverse effects associated with GH deficiency in adults include an increase in low-density lipoprotein (LDL) and a decrease in high-density lipoprotein (HDL) cholesterol, decreased cardiovascular function, increased risk of cardiovascular events, and a diminished sense of well-being. Life expectancy is reduced in these patients compared with age-matched control participants (Svensson et al., 2004).

Gonadotropin deficiency results in HH or secondary hypogonadism (Toogood and Stewart, 2008). In prepubertal children, HH manifests as failure to achieve pubertal changes along with a lack of a pubertal growth spurt. Girls have primary amenorrhea and lack breast development and widening of the pelvis. In boys, the testicular size remains small; the scrotal skin does not thicken; and penile growth, muscle development, and hoarseness of voice do not appear. In adults, HH presents as infertility, loss of libido, decreased facial hair, and muscle mass in men and amenorrhea, decreased breast size, and atrophic vaginal mucosa in women. If left untreated, men and women with hypogonadism develop osteoporosis. A deficiency in TSH causes secondary hypothyroidism unless the patient has concomitant Graves disease or an autonomously functioning thyroid nodule. The classical clinical manifestations of hypothyroidism include lethargy, easy fatigability, dry skin, cold intolerance, constipation, fine silky hair, slow mentation, and slow relaxation phase of deep tendon reflexes. Other features include anemia and hyponatremia secondary to increased antidiuretic hormone (ADH) secretion. In general, these symptoms are less severe in patients with TSH deficiency compared with patients with primary thyroid failure, and other findings, such as hypercholesterolemia, hypercarotenemia, myxedema, and effusions in body cavities, may occur less frequently (Toogood and Stewart, 2008).

A deficiency in ACTH results in deficiency of cortisol secretion and is referred to as *secondary adrenal insufficiency*. The clinical features resemble primary adrenal disease such as Addison disease. In both entities, anorexia, lethargy, nausea, vomiting, abdominal pain, postural hypotension, and vascular collapse may occur. Whereas hyponatremia is more common in ACTH deficiency, hyperkalemia is seen only in primary adrenal insufficiency and loss of aldosterone secretion, primarily regulated by the renin–angiotensin system (RAS) and serum potassium and sodium concentrations. Hyperpigmentation of the skin and vitiligo are features of primary adrenal insufficiency, and patients with ACTH deficiency have difficulty tanning upon exposure to sunlight. Mild ACTH deficiency may be asymptomatic and go undiagnosed for a long time.

Diagnosis

Key Points

- If one pituitary hormone insufficiency is documented, the other pituitary hormones should be tested.
- An 8 AM plasma cortisol level below 3 µg/dL strongly suggests hypocortisolism. A level 18 µg/dL or greater excludes ACTH deficiency.
- Serum FT_4 must be used with serum TSH concentration in assessing thyroid function.
- A normal or subnormal LH level in menopausal or amenorrheic women, in the presence of a low estradiol level, indicates secondary hypogonadism (in men, a low testosterone level).
- The diagnosis of GH deficiency requires provocative testing.

Because the presenting complaints of hypopituitarism can be subtle, clinicians need a high index of suspicion to arrive at the correct diagnosis (Toogood and Stewart, 2008). If the clinical manifestations fit hypogonadism, hypothyroidism, or adrenal insufficiency, those hormonal tests should be ordered to confirm the diagnosis. After one pituitary hormone insufficiency is documented, every attempt should be made to test the status of the other pituitary hormones as well. The underlying etiology of the disease should be determined by computed tomography (CT) or magnetic resonance imagining (MRI) of the hypothalamic–pituitary area. Occasionally, angiography is needed when carotid artery aneurysm is suspected or to define the blood supply of the tumor. Formal ophthalmologic examination, with visual field evaluation, should be ordered if the patient is symptomatic or harbors a pituitary mass lesion.

Pituitary hormone secretion is episodic, and in general, dynamic testing is more valuable than single baseline hormone measurements. For practical reasons, however, screening can be done with pituitary hormone and target hormone measurements simultaneously. For evaluating suspected hypopituitarism, tests include thyroid function, LH, serum testosterone in men and estradiol in women, IGF-1 (because GH has a short half-life in blood), prolactin, and morning cortisol. Provocative testing for GH and ACTH reserves may be required as well. Patients with known pituitary disease and deficiencies of ACTH, TSH, or

gonadotropins have a 95% chance of subnormal provocative stimulus for GH. Also, patients with known pituitary disease and a serum IGF-1 concentration lower than normal can be presumed to have GH deficiency (Gharib et al., 2003). Provocative tests for GH are either physiologic (sleep or exercise) or pharmacologic, such as insulin-induced hypoglycemia, GHRH with arginine test, and levodopa with arginine test (Biller et al., 2002; Gharib et al., 2003). GH deficiency is diagnosed when GH does not rise above 5 ng/mL in response to two or more stimuli.

A plasma cortisol level below 3 µg/dL at 8 AM on two occasions in a patient with a disorder known to cause hypopituitarism strongly suggests hypocortisolism, and in the presence of normal or low serum ACTH concentration, it establishes the diagnosis of secondary adrenal insufficiency. Conversely, a cortisol level of 18 µg/dL or greater virtually excludes the diagnosis of ACTH deficiency.

To evaluate ACTH reserve, an insulin hypoglycemia test (0.1-0.15 U/kg IV) should be done. A normal cortisol response to adequate hypoglycemic stimulus (blood glucose <50 mg/dL) is either an incremental level of 6 to 10 µg/dL or an absolute level greater than 20 µg/dL. The test allows for concomitant evaluation of GH reserve; however, it is contraindicated in elderly adults and those with coronary artery disease (CAD) or epilepsy (Nowak and Mooradian, 2007).

An alternative is the metyrapone test, 750 mg orally every 4 hours for 6 doses, which assesses the sensitivity of the pituitary to negative inhibition of cortisol. Metyrapone blocks 11β-hydroxylase, an enzyme that catalyzes the final step in cortisol biosynthesis, which inhibits cortisol production. The decrease in cortisol secretion after metyrapone is given should result in a compensatory increase in the ACTH level. The level of the precursor steroid 11-deoxycortisol should also increase. A normal response is an increase in serum 11-deoxycortisol level greater than 10 µg/dL, when serum cortisol level is reduced to less than 8 µg/dL, indicating adequate suppression of glucocorticoid synthesis. In the more convenient overnight test, metyrapone 30 mg/kg orally, is administered at midnight. An increase in the 8 AM serum 11-deoxycortisol level to greater than 7 µg/dL is found in healthy persons. If symptomatic postural hypotension occurs after metyrapone administration, hydrocortisone should be administered exogenously.

Cosyntropin (synthetic ACTH), 250 µg administered intramuscularly or intravenously should result in an increase in the serum cortisol level to 18 µg/dL or greater at 60 minutes in normal subjects. The test may not reliably determine the ACTH reserve, especially in those with recent ACTH deficiency and in patients whose adrenal glands may not be atrophied enough. There is some controversy whether the 1-µg cosyntropin stimulation test (intravenous [IV] only) may be more sensitive for the diagnosis of subtle secondary adrenal insufficiency.

Thyrotropin (TSH) deficiency is diagnosed when low baseline FT_4 and low or normal TSH is documented on more than one measurement. Gonadotropin deficiency in men is tested with measurements of baseline LH, FSH, and total testosterone. Serum samples are drawn between 8 AM and 10 AM, and low concentrations should be confirmed with a second serum sample. The 8 AM to 10 AM serum testosterone concentration generally should be 300 to 1000 ng/dL. A low testosterone value (< 200 ng/dL) with low or normal LH is indicative of HH (Mooradian and Korenman, 2006). For serum total testosterone levels between 200 and 400 ng/dL, free testosterone level should also be ordered (Mooradian and Korenman, 2006).

The presence of amenorrhea in premenopausal women, along with a low estrogen level (<30 pg/mL), establishes the diagnosis of HH. In menopausal women, the absence of elevated FSH and LH is sufficient for the diagnosis.

Elevated serum prolactin levels in a hypogonadal individual suggest a pituitary adenoma. Prolactin deficiency often indicates severe intrinsic pituitary disease and is uncommon without concomitant deficiencies of other anterior pituitary hormones.

Conditions known to mimic hypopituitarism should be excluded when evaluating patients, including anorexia nervosa, protein-calorie malnutrition, systemic illness, chronic renal failure, and liver cirrhosis.

Treatment

Key Points

- Hydrocortisone is given to ACTH-deficient adults at 20 to 30 mg/day and increased twofold to threefold during times of illness and other stresses.
- Serum IGF-1 concentration and growth rate in children are used for monitoring the effectiveness of GH replacement.

The treatment of hypopituitarism depends on the etiology and the particular hormonal deficiency (Mooradian and Morley, 1988; Toogood and Stewart, 2008). Surgical and medical interventions may be necessary for treatment of pituitary masses, infiltrative diseases, and carotid aneurysms.

Growth hormone deficiency is treated with recombinant human GH (somatotropin) preparations (Gharib et al., 2003). The recommended GH dose in children with GH deficiency is 0.04 mg/kg/day. In adults, recombinant human GH is administered subcutaneously at 0.001 to 0.008 mg/kg/day. The usual starting dose is 0.1 to 0.3 mg/day for a 70-kg man with a typical maintenance dose of 0.3 to 0.6 mg/day (Gharib et al., 2003). In general, women require higher doses than men because estrogen increases GH resistance. Serum IGF-1 concentration should be monitored to maintain it at the midnormal range. Side effects that should be monitored include edema, carpal tunnel syndrome, arrhythmias, paresthesias, and glucose intolerance.

Growth hormone can also be used in other causes of growth retardations such as chronic renal disease, Turner syndrome, and Prader Willi syndrome . Mortality caused by hypopituitarism is a significant issue; however, this may not translate when GH is used alone. For a pediatric patient who has one of these other nonpituitary causes of growth retardation, this might be a clinically appropriate option to consider. Early referral to a pediatric endocrinologist bears consideration (Sherlock and Stewart, 2013).

Treatment of secondary hypogonadism depends on the gender of the individual and whether fertility is desired.

Estradiol and progesterone replacement is the treatment of choice for secondary hypogonadism in premenopausal women who have intact uteri and do not desire fertility. These hormones can be given cyclically or daily in fixed-dose combinations. In individuals who have undergone hysterectomy, estrogen replacement alone is sufficient to maintain vulvar and vaginal lubrication, relieve symptoms of vasomotor instability, and reduce bone loss.

HYPERFUNCTIONING PITUITARY ADENOMAS

Key Points

- Pituitary adenomas may present with visual impairment, headache, or hormonal abnormalities.
- Prolactinomas are the most common type of functioning pituitary adenoma. These adenomas manifest with galactorrhea and hypogonadism.
- Nonpathologic causes of hyperprolactinemia are sought, and primary hypothyroidism is excluded.
- MRI is the imaging modality of choice for the anatomic evaluation of the hypothalamus and pituitary gland.
- Prolactin level greater than 150 ng/mL and pituitary adenoma not identified on imaging studies suggest macroprolactinemia.
- A dopamine agonist (bromocriptine or cabergoline) is the first-line treatment of prolactinomas.

Pituitary adenomas can arise from any cell type and can be either functioning or nonfunctioning. The precise pathogenesis of these adenomas is not known, but mutations found in several genes can play a role in the development of many adenomas.

With prolactinomas the most common type, other functioning pituitary adenomas include gonadotropic, thyrotropic, somatotropic, and corticotropic adenomas.

Hyperprolactinemia and Prolactinomas

Diagnosis. Prolactin is a polypeptide secreted from the lactotrophs of the anterior pituitary (Leung and Pacaud, 2004; Mancini et al., 2008). Its main function is the development of breast tissue in preparation for milk production and the maintenance of lactation during the postpartum period. Unlike the other pituitary hormones, the regulation of prolactin release is predominantly under inhibitory control. Whereas dopamine is the principal inhibitor, prolactin stimulators, such as TRH and estrogen, have minor roles.

Hypersecretion of prolactin may be physiologic or pathologic in origin (Leung and Pacaud, 2004; Mancini et al., 2008). Physiologic stimulators include exercise, pain, breast stimulation, sexual intercourse, general anesthesia, and pregnancy. Pathologic causes of hyperprolactinemia include prolactinomas, decreased dopaminergic inhibition of prolactin secretion through pharmacologic agents, and decreased clearance of prolactin.

Early manifestation of prolactin hypersecretion is galactorrhea and menstrual irregularities, notably amenorrhea in women and erectile dysfunction or loss of libido in men. Rarely, galactorrhea with gynecomastia can occur in men. These patients are at risk of developing osteoporosis secondary to hypogonadism as well as a result of the direct inhibitory effect of prolactin on bone formation. Galactorrhea is rarely found in postmenopausal women with hyperprolactinemia and mass effect of prolactinomas, such as headache or visual disturbance, cause the principal presenting symptoms (Mancini et al., 2008). Similarly, the diagnosis of prolactinomas in men is often delayed because the clinical signs and symptoms of hyperprolactinemia are less obvious.

Clinical evaluation of patients suspected to have prolactinomas should include a thorough evaluation of medication history and the presence of comorbidities. Many drugs are known to cause hyperprolactinemia, including phenothiazines, haloperidol, metoclopramide, H2 antagonists, imipramines, selective serotonin reuptake inhibitors (SSRIs), calcium channel blockers, and hormones (Leung and Pacaud, 2004; Mancini et al., 2008). The physical examination may reveal galactorrhea and visual field defects. Women may have mild hirsutism, and men may have decreased facial hair growth.

Laboratory tests include serum prolactin and thyroid function. Primary hypothyroidism is associated with hyperprolactinemia secondary to elevated levels of TRH that induces prolactin secretion. Laboratory testing should also seek systemic illnesses, such as liver or renal failure. MRI is the imaging modality of choice for the anatomic evaluation of the hypothalamus and pituitary gland. Complete pituitary hormone evaluation should be performed when an adenomatous mass is noted in the region of the pituitary.

Features to distinguish hyperprolactinemia associated with pituitary tumors include (1) prolactin levels greater than 150 ng/mL, (2) loss of normal sleep-associated increases in prolactin levels, and (3) failure of prolactin levels to rise in response to exogenous TRH. None of these tests are absolute, and the diagnosis of prolactinoma depends on radiologic studies.

Clinicians should be aware of two prolactin assay-related conditions that may cause diagnostic confusion. In *macroprolactinemia,* large-molecular-weight prolactin aggregates with globulins, which are then recorded in the assay as elevated levels of prolactin in the absence of any physiologic or pathologic cause of hyperprolactinemia (Mancini et al., 2008). This condition is suspected when the patient is found to have very high prolactin level without galactorrhea or any tumor demonstrated on pituitary MRI. The second area of confusion occurs when very high concentrations of serum prolactin overwhelm the assay reagents such that the measurements underestimate the true concentration of prolactin. This is referred to as the "hook" effect.

The gold standard for differentiating hyperprolactinemia from macroprolactinemia is via gel filtration chromatography (GFC). But if available, a simple, inexpensive, and suitable alternative to GFC that should be considered is polyethylene glycol (PEG) precipitation. Because macroprolactinemia is a benign condition, early laboratory testing, such as PEG, which can definitively determine the presence of macroprolactin molecules, eliminating the need for further hormonal or imaging investigation or surgery (Kasum et al., 2012).

Treatment. The treatment of hyperprolactinemia depends on the etiology, presence or absence of mass effects, (e.g.,

visual changes), presence of bothersome galactorrhea or associated pituitary hormone deficiencies, and whether fertility is desired (Leung and Pacaud, 2004; Mancini et al., 2008). If possible, drugs known to cause prolactin elevation should be discontinued, and the serum prolactin concentration should be measured again. Persistent hyperprolactinemia requires imaging of the pituitary and hypothalamus.

Treatment of prolactinomas includes dopamine agonists as first-line therapy. In select subgroups, surgical excision is recommended, usually through the transsphenoidal approach. In rare cases, with large residual tumor mass postsurgery, nonresponsive to medical therapy, radiation therapy may be offered. Associated hormone deficiency should also be targeted. Often, as the prolactin levels are normalized, symptoms of hypogonadism can be reversed.

Bromocriptine and cabergoline are U.S. Food and Drug Administration (FDA)–approved dopamine agonists for treatment of hyperprolactinemia. Cabergoline has greater tolerability than bromocriptine and is more effective in achieving normalization of prolactin levels in 90% of individuals with prolactinomas. Because of long-standing experience, however, bromocriptine is the preferred agent in women who wish to become pregnant. Bromocriptine should be discontinued after pregnancy has been confirmed even though the risk of teratogenicity is small. Pregnant women with prolactinomas should be warned to report any visual disturbances or headaches because up to 10% of microprolactinomas and 30% of macroprolactinomas increase in size sufficient to cause symptoms. During pregnancy, prolactin levels should be monitored periodically, but interpretation of the results may be difficult. Pregnant women with macroadenomas should receive similar advice and have serial visual field testing. Pergolide is an alternative to bromocriptine and cabergoline, but it is not FDA-approved for this use. Caution should be exercised with all of these ergot derivatives because of rare case reports of valvular heart damage in patients taking the drug at very high doses for prolonged periods.

The dosage of dopamine agonist may be reduced when prolactin levels have been normalized for 1 year and tumor size has been significantly reduced. Medication withdrawal may be considered after 2 years in those with normal prolactin levels and an MRI scan showing no tumor or tumor reduction more than 50% and more than 5 mm from the optic chiasm with no invasion of the cavernous sinus. Withdrawal of therapeutic drug may lead to recurrent prolactin hypersecretion and adenoma growth, although in some patients, microadenomas have resolved after a few years of treatment. MRI of the pituitary and serum prolactin levels should be monitored closely thereafter.

Indications for transsphenoidal surgery in patients with prolactinomas include medical treatment failure or medication intolerance, very large tumors threatening visual pathways, or hemorrhagic infarcts (apoplexy). Approximately 30% of macroadenomas can be successfully removed surgically.

ACROMEGALY AND GIGANTISM

See eAppendix 35-1 online.

CUSHING DISEASE

Key Points

- Cushing syndrome is categorized into ACTH-dependent and ACTH-independent cases. Pituitary ACTH-dependent Cushing syndrome is Cushing disease.
- The diagnosis is established when the clinical findings of Cushing syndrome are associated with laboratory documentation of excess cortisol production.
- Measurement of 24-hour urinary free cortisol excretion is a good screening tool.
- Comparison of serum ACTH concentration with serum cortisol level can help determine the cause of hypercortisolism.
- Treatment of Cushing syndrome is directed at the cause of hypercortisolism. The treatment of choice for Cushing disease is selective transsphenoidal resection.

Hypercortisolemia, (also hypercortisolism, hyperadrenocorticism) caused by either exogenous administration of cortisol or other synthetic glucocorticoids or endogenous overproduction of cortisol leads to a constellation of clinical and biochemical findings referred to as Cushing syndrome (Arnaldi et al., 2003; Biller et al., 2008; Findling and Raff, 2005). The multiple causes include pituitary adenomas, excess production of CRH leading to hyperplasia of corticotropes in the pituitary, ectopic production of ACTH and CRH, and adrenal cortical adenomas and carcinomas. The term *Cushing disease* specifically refers to pituitary-dependent cortisol hypersecretion (Biller et al., 2008).

Whereas pituitary, ACTH-dependent Cushing disease accounts for at least 70% of endogenous cases, the most common cause of ACTH-independent Cushing syndrome is prolonged glucocorticoid therapy.

Patients who have undergone bilateral adrenalectomy for hypothalamic pituitary–dependent Cushing syndrome may develop pituitary tumors associated with marked skin pigmentation. This condition is referred to as *Nelson syndrome*. The skin hyperpigmentation occurs because of excess production of melanocyte-stimulating hormone (MSH), which is a product of the gene that also encodes ACTH and β-endorphin.

Diagnosis

A high index of suspicion is required to make the diagnosis of Cushing syndrome as manifestations of the disease are insidious and develop over months (Arnaldi et al., 2003; Findling and Raff, 2005). The clinical features include weight gain with centralized obesity distributed in the face, neck, trunk, and abdomen with facial rounding and plethora. The thinning of the skin and loss of subcutaneous tissue results in easy bruising and emergence of violaceous abdominal striae (Arnaldi et al., 2003; Findling and Raff, 2005).

In cases of ectopic ACTH-dependent Cushing syndrome, extreme elevations of ACTH levels cause rapid hyperpigmentation and are more likely to demonstrate features of mineralocorticoid excess, such as hypokalemia and metabolic alkalosis (Findling and Raff, 2005).

EAPPENDIX

35-1 Acromegaly and Gigantism

Key Points

- Excess growth hormone (GH) secretion in children before the fusion of epiphyses results in gigantism. In adults, bones grow wider and thicker along with overgrowth of soft tissues, resulting in acromegaly.
- The vast majority of patients with acromegaly have a pituitary tumor.
- Elevated serum concentration levels of age and gender-matched serum insulin-like growth factor type 1 (IGF-1) provides the best single test to screen for acromegaly. The diagnosis of acromegaly is confirmed when GH is not suppressed 1 to 2 hours after ingestion of 75 g of glucose.
- Transsphenoidal surgery to remove the pituitary adenoma is usually the treatment of choice in individuals with acromegaly.
- Octreotide (Sandostatin) is a somatostatin analogue that is often effective in normalizing growth hormone and IGF-1 levels. Pegvisomant is a GH receptor antagonist also approved for the treatment of acromegaly.

Acromegaly is a rare disease with approximately 400 new cases per year in the United States. Excess GH secretion in children before the fusion of epiphyses results in gigantism. In adults, bones grow wider and thicker along with overgrowth of soft tissues, resulting in acromegaly (Ben-Shlomo and Melmed, 2008; Clemmons et al., 2003; Melmed et al., 2009).

The vast majority of patients with acromegaly have a pituitary tumor. In rare cases, acromegaly can be the result of ectopic production of GH or GH-like peptides or growth hormone–releasing hormone by nonpituitary tumors such as carcinoid or islet cell tumors.

The clinical manifestations of the disease result from local expansion of the pituitary mass, associated pituitary hormone deficiency, and the effects of excess GH.

Acromegaly has an insidious course, and a burn-out phase may emerge after years of ailment when changes in physical appearance may become static or slow down. In these patients, GH levels remain elevated, and the metabolic complications persist. Rarely, the tumor may undergo autoinfarction with the resolution of GH oversecretion.

Patients with acromegaly have a twofold increase in risk of dying, mostly because of cardiovascular events. Cardiovascular complications include hypertension and cardiomyopathy, with diastolic dysfunction and arrhythmias. It is also associated with an increased incidence of colon polyps and possibly an increased risk of colon cancer. Visceromegaly occurs in acromegaly with involvement of the thyroid, heart, liver, and prostate. Uterine leiomyomata are also more common in women with the syndrome of acromegaly (Ben-Shlomo and Melmed, 2008).

Diagnosis

When acromegaly is suspected, based on finding of the classic clinical characteristics, the diagnostic approach includes (1) documentation of GH excess, (2) evidence of activity, (3) tumor localization, (4) evidence of other pituitary hormonal excess or deficiencies, and (5) exclusion of multiple endocrine neoplasia (MEN) type 1 (Ben-Shlomo and Melmed, 2008; Melmed et al., 2009). GH excess is documented when elevated serum levels of IGF-1 and GH are not suppressed 1 to 2 hours after ingestion of 75 g of glucose. This glucose load in healthy individuals should result in the suppression of the GH level to 1 ng/mL or lower within 1 to 2 hours of administration. In contrast, a paradoxical rise in GH level is often found in patients with acromegaly. Administration of thyrotropin-releasing hormone or L-DOPA (levodopa) also paradoxically raises serum GH levels (Ben-Shlomo and Melmed, 2008; Clemmons et al., 2003; Katznelson et al., 2011; Melmed et al., 2009;).

Evidence of GH activity is demonstrated with elevated IGF-1; an impaired glucose tolerance test result; and increased phosphate, alkaline phosphatase, and urinary hydroxyproline levels. Postprandial plasma glucose levels may reveal impaired glucose tolerance in as many as 50% of those with acromegaly. Prolactin levels should be measured because hyperprolactinemia is associated with acromegaly in 25% to 30% of cases. Prolactin levels may be higher than 200 ng/mL when a somatomammotropic adenoma is present. Thyroid function tests should be obtained to work up hypopituitarism. Workup for other hormonal dysfunction can be postponed until after therapy because these may change. Patients should be routinely given stress doses of steroids during surgery and all other invasive procedures.

Tumor localization should start with magnetic resonance imaging (MRI) of the pituitary. If pituitary imaging results are normal, an extrapituitary ectopic source should be considered and MRI of the chest, abdomen, and pelvis obtained.

Finally, to exclude MEN type 1, serum calcium should be measured and other hormonal parameters tested if appropriate.

Treatment

The objectives of treatment are to arrest the deleterious effects of growth hormone excess on bone and soft tissue growth and on metabolic parameters as well as prevent or reverse the pressure effects of the tumor. Transsphenoidal surgery to remove the pituitary adenoma is the initial treatment of choice (Ben-Shlomo and Melmed, 2008; Clemmons et al., 2003; Melmed et al., 2009). The success rate of

surgery is variable and depends on the size of the adenoma and the surgical skills of the surgeon. Many adenomas originally thought to be cured with surgery have very high relapse rates. Pharmacologic treatment recently was proposed as first-line therapy of choice for select individuals such as those who decline after surgery and in those who have an unacceptable surgical risk (Clemmons et al., 2003; Melmed et al., 2009).

In general, pharmacologic treatment is used as an adjuvant when surgery has not reduced GH and IGF-1 levels to normal. Octreotide (Sandostatin) is a somatostatin analogue often effective in normalizing GH and IGF-1 levels (Freda, 2002). It can also reduce tumor size in some patients. Clinical manifestations of acromegaly may improve more significantly than normalization of GH and IGF-1 levels (Freda, 2002). Side effects include gastrointestinal symptoms and an increased incidence of gallstones. The depot forms of octreotide can be given intramuscularly once monthly.

Pegvisomant is a GH receptor antagonist approved for the treatment of acromegaly (Clemmons et al., 2003). It is given as a daily subcutaneous injection. Less effective therapies include dopamine agonists. These tend to be more effective when there is concomitant hyperprolactinemia, suggesting a somatolactotropin origin of tumor.

Radiotherapy may be required for patients in whom surgery and medical therapy fail to control GH excess and its clinical manifestations.

Gonadal dysfunction is associated with decreased testosterone levels in men; in women, it is associated with decreased serum estradiol levels and menstrual disorders, notably amenorrhea. Virilization and androgen excess are more common in cases of Cushing syndrome caused by adrenal carcinomas. Glucocorticoid excess also interferes with calcium and bone metabolism and leads to osteoporosis. Catabolic effects of excess glucocorticoid on muscles cause proximal muscle weakness. Glucose intolerance is found in 30% to 60% of those with hypercortisolism.

Other complications of hypercortisolism include risk of opportunistic infections, including *Pneumocystis jiroveci* (formerly *carinii*) pneumonia, and hypercoagulable state with thromboembolic events secondary to increased plasma concentration of several clotting factors and neuropsychiatric changes (Arnaldi et al., 2003; Findling and Raff, 2005).

Establishing the Cause

The diagnosis is established when the clinical findings of Cushing disease are associated with laboratory documentation of excess cortisol production, loss of diurnal variation of plasma cortisol level, and more than 50% suppression of plasma and urine cortisol after the administration of 2 mg of dexamethasone every 6 hours (high-dose DST). Measurement of 24-hour urinary free cortisol excretion is a good screening tool (Arnaldi et al., 2003; Findling and Raff, 2005). Late night salivary cortisol is another good screening tool (Nieman et al., 2008). Alternatively, impaired suppression of cortisol, after an overnight 1-mg DST, can be used as a screening tool in nonobese individuals. A plasma ACTH concentration less than 5 pg/mL and a serum cortisol concentration greater than 15 μg/dL suggest an ACTH-independent cause. Plasma ACTH concentration greater than 15 pg/mL in a patient with hypercortisolism suggests ACTH-dependent hypercortisolism (Arnaldi et al., 2003; Findling and Raff, 2005).

Suppression of urinary cortisol excretion after administration of high-dose dexamethasone is consistent with the diagnosis of Cushing disease, but urinary cortisol excretion in cases of ectopic ACTH syndrome is usually not suppressible. When the high-dose DST fails to differentiate an ectopic source from a pituitary source of ACTH and radiographic imaging is not conclusive, further CRH testing and petrosal sinus sampling of ACTH are indicated to localize the tumor to the pituitary.

The vast majority of patients with ACTH-dependent Cushing syndrome have a pituitary adenoma as the cause. The few who have an ectopic source of ACTH must be identified with high-resolution CT scanning of the chest, abdomen, and pelvis.

Treatment

The treatment of choice for Cushing disease is selective transsphenoidal resection of the pituitary adenoma. The cure rate for this procedure, at experienced centers, is 70% to 80% for microadenomas. In some patients, total hypophysectomy is considered when the disease recurs after transsphenoidal resection. Many postsurgical patients require low-dose cortisol replacement for up to 12 months until their endogenous adrenal function recovers.

Bilateral adrenalectomy with or without pituitary irradiation is offered to patients who have recurrence of hypercortisolemia or have severe disease. For those who are poor surgical candidates, adjunctive medical therapy is offered and includes metyrapone (a blocker of 11-β-hydroxylase), mitotane, and cyproheptadine. These treatment options have variable efficacy (Biller et al., 2008; Nieman et al., 2008).

CRANIOPHARYNGIOMAS, THYROTROPIN-SECRETING PITUITARY ADENOMAS, GONADOTROPIC ADENOMAS, AND OTHER ADENOMAS

See eAppendix 35-2 online.

POSTERIOR PITUITARY DISORDERS

Arginine vasopressin (AVP) and oxytocin are the principal hormones secreted from the posterior pituitary (Mooradian and Korenman, 2007; Mooradian and Morley, 1988). The two major stimuli of oxytocin secretion are suckling during lactation and dilation of the cervix during labor. Oxytocin is not essential for initiation of labor but can be used pharmacologically to initiate labor or to control postpartum hemorrhage and uterine atony. Rarely, it has been used to induce milk ejection. The physiologic role of this hormone in males is not known (Mooradian and Morley, 1988).

Arginine vasopressin differs from oxytocin by only one amino acid. AVP is found in all mammals except pigs and related species in which lysine vasopressin replaces AVP. In humans and many mammals, AVP and oxytocin are associated with two neurophysins (Mooradian and Morley, 1988). The exact roles of the latter are not known except that they are carrier proteins involved in storage and transport of posterior pituitary hormones.

Antidiuretic hormone is synthesized in the hypothalamus and migrates down into the posterior lobe of the pituitary to be stored and later secreted. Some ADH is secreted directly into the cerebrospinal fluid (CSF) rather than the posterior pituitary. Thus, pathologic lesions affecting the hypothalamus below the median eminence may preserve some functional ADH that migrates from the CSF into the systemic circulation.

The half-life of AVP in circulation is only 20 minutes because of its susceptibility to peptidases. Loss of the terminal amino group in position 1 makes this peptide resistant to degradation; substitution of the *levo* analogue of arginine for dextro-arginine in position 8 reduces presser effect without altering its antidiuretic properties (Mooradian and Morley, 1988). The resultant peptide deamino-8-D-arginine vasopressin (DDAVP; desmopressin) is currently the treatment of choice for central diabetes insipidus (DI).

The biologic effects of AVP are initiated at two receptors referred to as V1 and V2. The V1 receptors are located in the vascular system, and their stimulation results in vasoconstriction. V2 receptors are located in the kidneys, and stimulation of these receptors results in free water reabsorption (Korbonits and Carlsen, 2009).

Plasma osmolality, blood volume, and BP are the most important physiologic stimuli of AVP secretion. Other

EAPPENDIX

35-2 Craniopharyngiomas, Thyrotropin-Secreting Pituitary Adenomas, Gonadotropic Adenomas, and Other Adenomas

Craniopharyngiomas

Key Points

- Also known as Rathke pouch tumors, craniopharyngiomas are histologically benign but act similar to low-grade malignancies.
- Individuals with craniopharyngioma may present with hypopituitarism, headache, and visual disturbance.
- Central diabetes insipidus is the most common endocrine dysfunction associated with craniopharyngiomas.

Craniopharyngiomas, also known as Rathke pouch tumors, are rare and generally benign tumors (Karavitaki and Wass, 2008). Although craniopharyngiomas are histologically benign, they act similar to low-grade malignancies. The 20-year survival rate for children with craniopharyngioma is 60%; in those with tumor recurrence, this rate decreases to 25% (Biller et al., 2008). They are usually diagnosed in infants and children and in adults between the ages of 55 and 65 years (Bunin et al., 1998). The clinical presentation includes headache; visual disturbances; and features of hypopituitarism, notably growth failure in children and hypogonadism in adults. Hypothyroidism is found in 40% and adrenal insufficiency in 25% of patients (Biller et al., 2008).

Central diabetes insipidus is the most common endocrine dysfunction associated with craniopharyngiomas. A variation of this tumor is a "Rathke" cleft cyst. As with craniopharyngioma, it is benign, but because of its location in the posterior portion of the anterior pituitary gland, it has a similar symptom complex (i.e., visual disturbance, pituitary dysfunction, and headaches). Most are asymptomatic, although not uncommon, occurring in 2% to 26% of autopsies, with a female-to-male ratio of 2 : 1. Symptomatic Rathke cleft cysts are extremely rare with only approximately 150 reported cases (Naik and Thakore, 2013).

DIAGNOSIS

These tumors are identified with magnetic resonance imaging (MRI) or computed tomography of the head. Key radiologic features that differentiate a craniopharyngioma from other tumors include calcification noted in the suprasellar region and the presence of at least one cyst in the tumor. The diagnostic workup should include visual field testing and evaluation of pituitary hormone function (Karavitaki and Wass, 2008).

TREATMENT

Treatment may consist of surgery, radiation, or a combination of both. Surgical resection may be technically difficult, and the operative mortality rate can be as high as 20%; recurrence rates of 25% to 50% have been reported. Radiotherapy is used as an adjuvant. Pituitary hormone deficiencies should be identified and corrected.

Thyrotropin-Secreting Pituitary Adenomas

Key Points

- Thyroid-stimulating hormone (TSH)–secreting adenomas should be considered in hyperthyroid patients with diffuse thyroid enlargement and normal to high serum TSH levels.
- The differential diagnosis includes syndrome of thyroid hormone resistance.
- Transsphenoidal resection of the TSH-secreting pituitary adenoma is the treatment of choice.

Pituitary TSH-secreting tumors are very rare. The mean age at presentation is 41 years, with a slightly higher percentage of cases occurring in women. A number of these tumors have been identified in patients with long-standing untreated hypothyroidism. However, in most cases, the etiology is unknown and may cause hyperthyroidism due to excess production of TSH and thyroid hormones.

Thyroid-stimulating hormone adenomas may be responsible for concomitant secretion of other pituitary hormones, such as growth hormone; prolactin; and, rarely, gonadotropin.

DIAGNOSIS

Most patients present with classical symptoms of hyperthyroidism. Because of variable biologic activity of TSH secreted by the adenoma, some patients may have mild or no symptoms of hyperthyroidism (Beck-Peccoz et al., 1996; Losa et al., 2008). Other clinical features include a diffuse goiter, visual field disturbance, other pituitary hormone excess or deficiencies commonly presenting with menstrual dysfunction, and galactorrhea (Beck-Peccoz et al., 1996).

Laboratory tests reveal normal to high serum TSH and high serum free thyroxine (FT_4) and free triiodothyronine (FT_3) levels. The nocturnal surge in TSH levels seen in normal subjects is not seen in those with TSH-secreting adenomas. Other biochemical abnormalities include elevations of the α-subunit of glycoprotein hormones. In a handful of patients, TSH hypersecretion occurs in the absence of a pituitary tumor, and the cause is attributed to a disturbance in the TSH secretory set point or thyroid hormone resistance. The disproportionate elevation of serum α-subunit relative to TSH distinguishes patients with TSH-secreting tumors from those who do not have tumors.

Hyperthyroid patients with normal or elevated serum TSH values should have MRI scanning to evaluate the contents of the sella turcica (Beck-Peccoz et al., 1996; Losa et al., 2008).

TREATMENT

Transsphenoidal resection of a TSH-secreting pituitary adenoma is the treatment of choice (Beck-Peccoz et al., 1996; Losa et al., 2008). β-Blockers may be useful in ameliorating symptoms of hyperthyroidism. Adjuvant medical therapy, in those with concomitant hyperprolactinemia, includes bromocriptine and cabergoline. The use of the somatostatin analogue octreotide may result in normalization of serum TSH and T_4 and T_3 concentrations in a significant percentage of patients. Tumor size may also be reduced with the use of octreotide and is currently used postoperatively in unsuccessful surgical cases and before surgery for 6 to 12 months in those with large macroadenomas (Beck-Peccoz et al., 1996; Losa et al., 2008).

Medications that inhibit thyroid hormone synthesis are not indicated because they may result in pituitary tumor growth.

Gonadotropic and Other Adenomas

Key Points

- Many adenomas, previously misdiagnosed as nonsecretory, are found to secrete gonadotropins or their subunit fragments.
- Because hormonal secretions from a gonadotropic adenoma do not usually result in a clinical syndrome, the diagnosis is often delayed, and patients present with manifestations related to tumor expansion.
- Gonadotropic adenomas are suspected when the follicle-stimulating hormone (FSH) level is supranormal in the presence of a subnormal luteinizing hormone (LH) concentration or serum free α-subunit concentration is elevated while concentrations of intact FSH and LH are normal.

Many adenomas, previously misdiagnosed as nonsecretory, are found to secrete gonadotropins or their subunit fragments. Currently, gonadotropic adenomas are considered to be the most common pituitary adenoma (Korbonits and Carlsen, 2009).

DIAGNOSIS

Hormonal secretions from a gonadotropic adenoma do not usually result in a clinical syndrome. Therefore, the diagnosis of these adenomas is often delayed and presents with manifestations related to tumor expansion such as visual impairment or headaches. Some adenomas are discovered incidentally when head imaging is performed for nonrelated symptoms.

In occasional patients, ovarian hyperstimulation and an elevated serum testosterone level may cause clinically appreciable changes in women, including menstrual irregularities. In prepubertal girls and boys, premature puberty may occur. Occasionally, large adenomas may interfere with the normal gonadotropin secretions and result in hypogonadism (Korbonits and Carlsen, 2009).

Magnetic resonance imaging of the brain will detect a microadenoma and should prompt pituitary hormone evaluation. A gonadotropic adenoma is suspected when (1) the serum prolactin concentration is less than 100 ng/m, (2) insulin-like growth factor type 1 levels are not elevated, (3) the patient does not have high TSH-driven hyperthyroidism, and (4) the patient is not acromegalic and does not have Cushing syndrome. A supranormal FSH level and free α-subunit of glycoprotein hormones in a male patient often indicates a gonadotropic adenoma. Using gonadotropin assays to differentiate a gonadotropic adenoma from natural menopause is not possible. A supranormal FSH level in the presence of subnormal LH concentration is unusual in menopause. A supranormal serum free α-subunit concentration and normal concentrations of intact FSH and LH also suggest a gonadotropic adenoma. In some cases, a thyrotropin-releasing hormone (TRH) stimulation test may be helpful. Although exogenous TRH given to a patient with a gonadotropic adenoma will raise the serum levels of FSH, LH, and α-subunit, it does not stimulate gonadotrophs in primary hypogonadism.

TREATMENT

Adenomas that are not causing neurologic or hormonal dysfunction may be conservatively managed with observation and monitoring. For large or symptomatic cases, transsphenoidal surgery is the treatment of choice to reduce tumor size, reduce hormonal hypersecretion, and relieve pressure-related symptoms and signs. Comparing pre- and postoperative measurements of FSH or free α-subunit levels may assist with the determination of residual tumor.

Radiation therapy may be used as an adjuvant when residual tumor is present. Drug therapy has not been found to be consistently effective in people with these adenomas.

factors that modulate AVP secretion include pain, stress, nausea, hypoglycemia, hypercapnia, angiotensin II, atrial natriuretic hormone, and a host of drugs. Many stimuli of AVP release also promote thirst. Thirst is less sensitive for AVP release than these other stimuli and therefore thirst is a second-line defense against dehydration.

Central Diabetes Insipidus

Key Points

- DI is characterized by excessive dilute urine with thirst and polydipsia and results from decreased ADH secretion.
- The differential diagnosis of hypotonic polyuria includes neurogenic DI (vasopressin sensitive), nephrogenic DI (vasopressin resistant), and primary polydipsia.
- The water restriction test assists in the diagnosis.
- DDAVP is the primary treatment for central DI.

Clinical Features. The disease is characterized by the production of excessive dilute urine with secondary thirst and polydipsia. *Polyuria* is defined as 3 L/day or greater in adults and 2 L/day or greater in children. Central DI can be familial or sporadic and can be caused by head trauma, neurosurgery, neoplasms, granulomas, infections, inflammation, chemical toxins, vascular disorders, congenital malformations, and genetic causes. Other causes include hypoxic encephalopathy; infiltrative disorders, notably *histiocytosis X* (Hand-Schuller-Christian disease); anorexia nervosa; acute fatty liver of pregnancy; and Wolfram syndrome (central DI, diabetes mellitus, optic atrophy, and deafness) (Reddy and Mooradian, 2009). An autoimmune process is probably the cause of idiopathic DI and accounts for 30% to 50% of cases of central DI (De Bellis et al., 1999).

Thickening or enlargement of the posterior pituitary seen on MRI may represent lymphocytic infiltration and inflammation. Classically, DI after head trauma or neurosurgical procedures goes through three phases. Polyuria appears in the first 1 to 2 days after surgery followed by a period of oliguria for 3 to 4 days, which culminates in a polyuric phase. These phases are a reflection of the early paralysis of vasopressin-producing cells followed by neuronal degeneration and massive release of vasopressin with subsequent permanent loss of vasopressin production.

Vasopressin-resistant DI is usually a familial disorder, although sporadic causes are recognized in chronic medullary kidney disease associated with sickle cell disease, multiple myeloma, amyloidosis, Sjögren syndrome, and renal medullary cystic disease. In addition, prolonged primary polydipsia can wash out the normal medullary concentration gradient and may mimic vasopressin-resistant nephrogenic DI.

Diagnosis. Although a variety of diseases may present as polyuria and polydipsia, thorough history and routine laboratory evaluation can narrow the differential diagnosis of hypotonic polyuria to three possibilities: neurogenic DI (vasopressin sensitive), nephrogenic DI (vasopressin resistant), or primary polydipsia (Mooradian and Morley, 1988).

Serum sodium concentrations less than 137 mEq/L and polyuria are usually manifestations of primary polydipsia. For patients with serum sodium concentrations less than 143 mEq/L, a water deprivation test should be carried out after an overnight fast, with hourly measurement of body weight, urine volume, and osmolality. In severe cases, the dehydration test can be started at 6 AM. When the urine osmolality remains constant during three consecutive measurements or if the patient loses more than 5% total body weight, then plasma osmolality, vasopressin, and sodium concentrations should be determined, and aqueous vasopressin (0.1 unit/kg subcutaneously) or 10 µg of nasal desmopressin should be administered and the response evaluated. An increase in urine osmolality of 150 mOsm/kg above baseline will exclude nephrogenic DI.

In central DI, administration of 10 µg of nasal desmopressin will result in increases in urine osmolality of as much as 800%. The response to desmopressin in partial central DI may result in urine osmolality increases of 15% to 50%.

Patients with nephrogenic DI continue to have urine osmolality levels that remain below isosmotic. Patients with primary polydipsia respond to the water deprivation test with urine concentrating to 500 mOsmol/kg, or higher. In comparison, urine osmolality in normal subjects undergoing the water deprivation test will increase to 800 mOsmol/kg or higher. Administration of exogenous vasopressin produces no further concentration in cases of primary polydipsia.

When the water suppression test yields equivocal results, the serum AVP concentration at baseline and following the water restriction test should be measured. However, the results of these tests may still be misleading because primary polydipsia results in submaximal secretion of AVP, mimicking the pattern of AVP secretion in partial central DI.

Treatment. The treatment of choice for central DI is DDAVP. DDAVP can be administered intravenously, subcutaneously, nasally, or orally. An initial nasal inhalation of 5 µg at bedtime is given. The dose is increased by 5-µg increments until nocturia has been resolved. After nocturia is successfully treated, a morning dose is given. The total daily dosage of nasally administered desmopressin is 5 to 20 µg /day (Loh and Verbalis, 2008). Desmopressin given by mouth should be given on an empty stomach. Absorption can be reduced by up to 50% when desmopressin is taken with food. A 0.1-mg tablet is equivalent to 2.5 to 5.0 µg of nasal inhalation spray (Loh and Verbalis, 2008).

Patients with partial DI will benefit from oral agents that potentiate AVP action or stimulate the release of AVP. These agents include chlorpropamide, carbamazepine, or clofibrate. In such cases, desmopressin requirements may be lower than available preparations can provide. Patients with nephrogenic DI benefit from thiazide diuretics or indomethacin.

Patients with DI should wear a medical ID bracelet. When the ability to drink fluids is impaired, IV hydration will be required to avoid dehydration and hypernatremia.

Syndrome of Inappropriate Antidiuretic Hormone Secretion

Key Points

- Laboratory evaluation of plasma osmolality, urine osmolality, and urine sodium concentration assist in determining the cause of hyponatremia.
- Water restriction and salt replacement are the most important treatment modalities in hyponatremia. The underlying cause should be identified and treated when possible.
- Vasopressin antagonists are currently indicated for the treatment of euvolemic and hypervolemic hyponatremia.

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is associated with plasma ADH concentrations that are inappropriately high for the plasma osmolality. Laboratory and clinical features of SIADH include (1) euvolemic hyponatremia; (2) decreased measured plasma osmolality (< 275 mOsm/kg); (3) urine osmolality greater than 100 mOsm/kg; (4) urine sodium usually greater than 40 mEq/L; (5) normal acid–base and potassium balance; (6) blood urea nitrogen (BUN) less than 10 mg/dL; (7) hypouricemia less than 4 mg/dL; (8) normal thyroid and adrenal function; and (9) absence of advanced cardiac, renal, or liver disease (Reddy and Mooradian, 2009).

Conditions or factors associated with SIADH include CNS trauma and infections, tumors, drugs, major surgery, pulmonary disease (e.g., TB), hormone administration, human immunodeficiency virus (HIV) infection, hereditary SIADH, idiopathic causes, and cerebral salt wasting. In some cases, it is difficult to differentiate SIADH from mild to moderate depletional hyponatremia (Reddy and Mooradian, 2009) (Table 35-2).

The response of urinary and plasma sodium concentration to an infusion of 1 to 2 L of 0.9% (isotonic) saline may help in the differential diagnosis. In a patient with SIADH who is at equilibrium, the administered saline will be excreted; therefore, there will be an increase in urinary sodium while plasma sodium concentration will either not change or decrease slightly. If the patient has depletional hyponatremia from renal losses, sodium from the administered saline is retained, and the excess water is excreted. Urinary sodium decreases, and plasma sodium concentration increases (Reddy and Mooradian, 2009).

A *reset osmostat* may be suspected when mild hyponatremia persists despite changes in fluid and salt intake. A reset osmostat may be confirmed by having the patient receive a fluid bolus of 10 to 15 mL/kg. Normal patients, or those with a reset osmostat, should excrete 80% of this bolus in 4 hours, which does not occur with SIADH (Reddy and Mooradian, 2009).

Cerebral salt wasting induces SIADH-like symptoms. Salt wasting followed by volume depletion occurs in some cases of cerebral disease. This leads to a secondary rise in ADH levels. The mechanism underlying cerebral salt wasting is unclear (Reddy and Mooradian, 2009).

Treatment. Management of SIADH should begin with water restriction and treatment or elimination of the underlying etiology. In all patients with hyponatremia, free water intake from all sources should be restricted to less than 1 to 1.5 L/d. In patients with mild symptoms, the rate of urinary solute excretion, which is the main determinant of urine output, can be increased by a high-salt, high-protein diet or supplementation with urea (30-60 g/day) or salt tablets (200 mEq/day) (Reddy and Mooradian, 2009). However, salt therapy is generally contraindicated in patients with hypertension and edema because it leads to exacerbation of both conditions. In addition, water restriction is contraindicated in patients with subarachnoid hemorrhage with hypovolemia, in whom water restriction may result in hypotension, creating a risk for cerebral infarction. This risk is more pronounced if the patient has cerebral salt wasting, which must be treated first with isotonic or hypertonic saline solution until adequate volume status has been demonstrated.

In general, plasma sodium concentration should be corrected at a rate of 1 mEq/L/hr until the reversal of neurologic symptoms (Reddy and Mooradian, 2009). Then the correction rate is reduced to 0.5 mEq/L/hr until the plasma sodium has reached a level of 120 to 125 mEq/L. This approach effectively prevents the devastating neurologic consequences of acute hyponatremia and is associated with reduced risk of osmotic demyelination of pontine and extrapontine neurons.

The most specific treatment for SIADH is to block the V2 receptors in the kidney that mediate the diuretic effect of ADH. Vasopressin antagonists are currently indicated for the treatment of euvolemic and hypervolemic hyponatremia (Loh and Verbalis, 2008; Reddy and Mooradian, 2009).

For hospitalized patients, conivaptan is given as an IV loading dose of 20 mg delivered over 30 minutes and then as 20 mg continuously over 24 hours. Subsequent infusions may be administered every 1 to 3 days at 20 to 40 mg/day by continuous infusion (Reddy and Mooradian, 2009). More recently, an orally active vasopressin receptor antagonist, tolvaptan, became available. Rapid correction of hyponatremia has been reported in patients receiving these agents; therefore, frequent checks of plasma sodium are needed.

Chronic SIADH can occur in patients with ectopic ADH-producing tumors and in patients in whom antipsychotic drugs cannot be discontinued. If water restriction and salt tablet therapy are ineffective, the following drug therapy could be attempted: (1) administration of loop diuretic along with salt tablets, (2) demeclocycline, (3) lithium carbonate, and (4) orally active vasopressin antagonists such as tolvaptan. (Cost and increased liver enzymes limit tolvaptan's utility. In addition, tolvaptan should not be used for longer than 30 days and should not be used in patients with liver disease.) Demeclocycline is nephrotoxic in patients with cirrhosis and is contraindicated in children because of interference with bone development and teeth discoloration. (It also has a cost consideration.) Lithium carbonate may induce interstitial nephritis and renal failure; therefore, lithium should be considered for use only in patients in whom demeclocycline is contraindicated (Reddy and Mooradian, 2009).

Table 35-2 Select Causes of Syndrome of Inappropriate Antidiuretic Hormone Secretion

Nonosmotic stimuli	Nausea, pain, stress Human immunodeficiency virus (HIV) Acute psychosis Surgery Pregnancy (physiologic) Hypokalemia Congestive heart failure exacerbation
CNS lesions	Tumors (neuroblastoma) Cerebrovascular accident (stroke) Meningitis, encephalitis Abscess Guillain-Barré syndrome Hydrocephalus Pituitary stalk lesion Delirium tremens Demyelinating disease Acute porphyria
Malignancies	Lymphoma, leukemia, Hodgkin disease Carcinoma of the uterus Ureteral, prostate, and bladder carcinoma Carcinoma of the duodenum and pancreas Ectopic production of vasopressin by tumors (small cell lung carcinoma, carcinoids) Cancers of the head and neck and nasopharynx Renal cell carcinoma Osteosarcoma
Increased intrathoracic pressure	Mediastinal tumors (thymoma, sarcoma) Positive-pressure ventilation Infections (pneumonia, TB, aspergillosis, lung abscess) Bronchogenic carcinoma, mesothelioma Bronchiectasis, empyema COPD Pneumothorax
DRUG INDUCED	
Antipsychotics	Phenothiazines Haloperidol
Antidepressants	SSRIs, TCAs, MAOIs Bupropion
Anticonvulsants	Carbamazepine, oxcarbazepine Sodium valproate
Analgesics and recreational drugs	Morphine (high doses) Tramadol MDMA ("ecstasy")
Nonsteroidal antiinflammatory drugs	Colchicine, venlafaxine Duloxetine (Cymbalta)
Cardiac drugs	Thiazides, clonidine ACE inhibitors, aldosterone antagonists Amiloride, loop diuretics Methyldopa, amlodipine Amiodarone, lorcainide Propafenone, theophylline, terlipressin Unfractionated heparin (aldosterone antagonist)
Antidiabetic drugs	Chlorpropamide Tolbutamide, glipizide
Lipid-lowering agent	Clofibrate
Antineoplastic agents	Cyclophosphamide Vincristine, vinblastine Cisplatin, hydroxyurea Melphalan
Immunosuppressives	Tacrolimus, methotrexate Interferon-α and -γ, levamisole Monoclonal antibodies
Antibiotics	Azithromycin, ciprofloxacin Trimethoprim–sulfamethoxazole Cefoperazone–sulbactam, rifabutin

ACE, Angiotensin-converting enzyme; *CNS,* central nervous system; *COPD,* chronic obstructive pulmonary disease; ; *MAOI,* monoamine oxidase inhibitor; *MDMA,* 3,4-methylenedioxymethamphetamine; *SSRI,* selective serotonin reuptake inhibitor; *TB,* tuberculosis; *TCA,* tricyclic antidepressant.

Modified from Reddy P, Mooradian AD. Diagnosis and management of hyponatremia in hospitalized patients. *Int J Clin Pract.* 2009;63:1494-1508.

KEY TREATMENT

- Hydrocortisone is given to ACTH-deficient adults at 20 to 30 mg/day, increased twofold to threefold during times of illness and other stresses (Toogood and Stewart, 2008) (SOR: A).
- The goal of thyroid replacement should be to achieve a normal serum free thyroxin concentration and clinical euthyroidism (Oiknine and Mooradian, 2006) (SOR: A)
- A dopamine agonist is first-line treatment of prolactinomas (Mancini et al., 2008) (SOR: A).
- Transsphenoidal surgery to remove the pituitary adenoma is usually the treatment of choice in individuals with acromegaly (Melmed et al., 2009) (SOR: A).
- Octreotide (Sandostatin) is often effective in normalizing GH and IGF-1 levels. Pegvisomant is a GH receptor antagonist also approved for the treatment of acromegaly (Melmed et al., 2009) (SOR: A).
- Treatment of Cushing syndrome should be directed at the cause of hypercortisolism. The treatment of choice for Cushing disease is selective transsphenoidal resection (Biller et al., 2008) (SOR: A).
- Desmopressin is the primary treatment for central DI (Loh and Verbalis, 2008; Reddy and Mooradian, 2009) (SOR: A).
- Water restriction and salt replacement are the most important treatment modalities in hyponatremia. The underlying cause should be identified and treated when possible (Reddy and Mooradian, 2009) (SOR: A).
- Vasopressin antagonists are currently indicated for the treatment of euvolemic and hypervolemic hyponatremia (Loh and Verbalis, 2008; Reddy and Mooradian, 2009) (SOR: A).

Pineal Gland

The pineal gland, in general, is rarely thought of and especially not as part of the endocrine system, which is not surprising because there are rare (if any) diseases directly attributed to the pineal gland. The one area where there does seem to be consensus is the role the pineal gland appears to play in our orientation to day and night. It is also widely accepted that this is probably a teleologic holdover from more primitive parts of the human brain. There appears to be an interrelationship between some of our neurohormones, sleep, and what is generally referred to as the circadian rhythm (or sleep cycle). Sleep appears to have a significant effect on some hormones (GH) but little effect on others (MSH). One area where this occurs, of which most physicians are aware, is the normal cortisol surge that occurs in early morning and that seems to be absent or dulled when sleep deprived.

The deleterious effect of sleep deprivation is well known, anecdotally, in long-haul truckers and airline transport pilots. Over the past 15+ years, there have been significant changes in work hours for medical and surgical residents in an effort to eliminate, or at least ameliorate, sleep deprivation–induced iatrogenic errors. The negative physiologic effects of sleep deprivation have long been documented. Animal studies have definitively shown that when sleep deprived long enough (total sleep deprivation), the animal dies (Rechtschaffen et al., 1989). New data suggests that during sleep, the brain clears "toxins," specifically β-amyloid, which is associated with Alzheimer disease (Spira et al., 2013; Xie et al., 2013).

Thyroid Disorders

Key Points

- Primary thyroid disorder is caused by abnormal function of the thyroid gland.
- Secondary thyroid disorder is the result of abnormalities at the level of the pituitary.
- Tertiary thyroid disorder is caused by malfunction at the level of the hypothalamus.

Thyroid disorders can be categorized into processes that affect function (physiology) as well as structure (anatomy). The etiology of some of these are extraglandular, including metastatic neoplasia, pituitary disorders, dietary issues, autoimmune diseases, infections, and genetic or familial diseases (multiple endocrine neoplasia [MEN] IIA and familial medullary thyroid carcinoma [FMTC]). Other causes are intrinsic to the thyroid and include cysts, nodules, goiter, and primary neoplasia.

Irrespective of the disease process, all thyroid diseases exist in one of three functional states: euthyroid, hyperthyroid, or hypothyroid, each defined by the level of total bound and free circulating thyroid hormone. The presence of any one of these states in an individual can be transient, static, or progressing. Laboratory abnormalities of circulating thyroid hormone, at any point in time, do not prove disease and do not depend on the etiology of thyroid dysfunction. All three states may exist at different times during the course of an illness, and each state can exist with or without disease or clinical findings. In addition, the various thyroid structures can reflect disease independent of endocrinologic function.

Accurate assessment of thyroid function, with determination of presence or absence of disease, requires data in addition to levels of circulating thyroid hormones. These data include serum free thyroid hormone levels; thyrotropin (TSH) levels; and in some cases, antithyroid antibody titers. This battery of tests provides diagnosis in the majority of common thyroid disorders. When imaging studies and fine-needle aspiration are added, 90% to 95% of patients with thyroid disease who present in the primary care setting can be diagnosed and appropriately managed (Figure 35-1).

Thyroid disorders affect 60 to 80/1000 adults worldwide and up to 8.9% of the adult U.S. population (Bagchi et al., 1990; Vanderpump et al., 1995). Because most thyroid disorders have an insidious onset or closely mimic other, more common disorders, they are easily missed and, although rarely fatal, can cause significant morbidity. Early recognition is critical to minimizing that morbidity. With the exception of conditions such as simple goiter or visible nodule, patients who ultimately are diagnosed with thyroid disease rarely present to family physicians with complaints suggesting thyroid disorder.

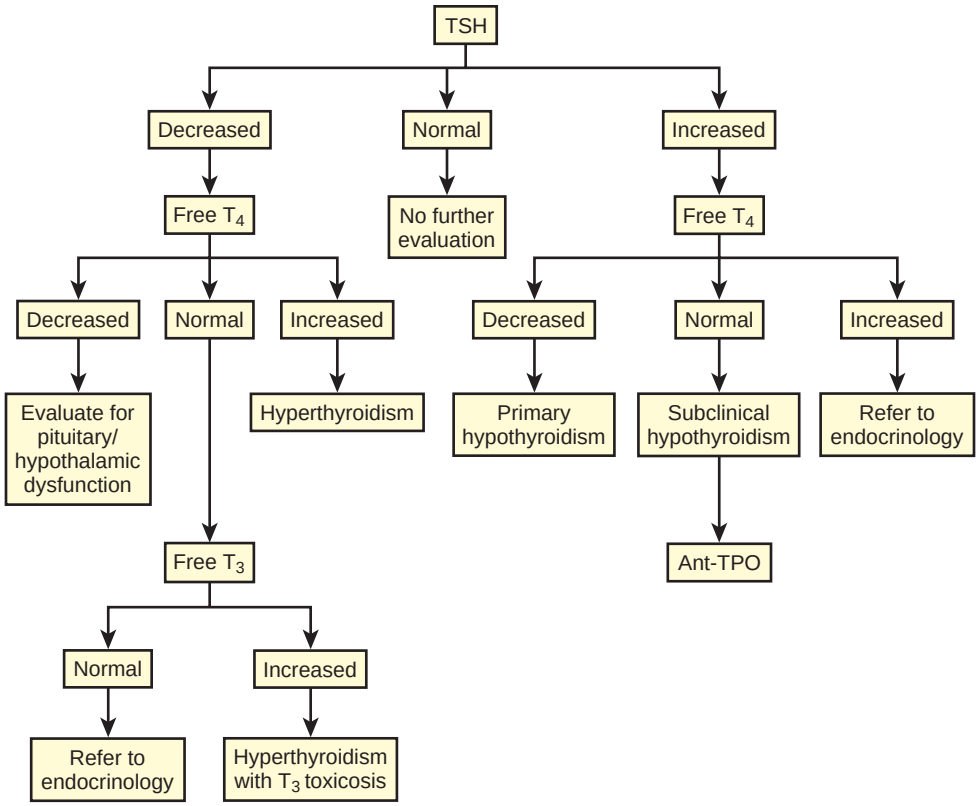


Figure 35-1 Algorithm for the diagnosis of thyroid dysfunction, beginning with an abnormal serum thyrotropin level. *anti-TPO,* Anti-thyroid antibodies; *T_3,* triiodothyronine; *T_4,* thyroxine; *TSH,* thyroid-stimulating hormone.

ANATOMY AND PHYSIOLOGY

Key Points

- Thyroxine (T_4) is the major product of the thyroid gland.
- Triiodothyronine (T_3) is the active hormone at the cellular level.
- The majority of circulating T_3 is formed in the peripheral circulation by deiodination of T_4.
- T_4 serves as a reservoir (prohormone) for T_3.
- Serum thyrotropin (sTSH) is required in all evaluations of dementia and depression.

Histologically, the thyroid gland consists of five primary elements: follicular cells, colloid, interstitial tissue, "C" cells, and lymphoid cells. The most prominent element is the follicular cell, which produces colloid. The thyroid follicle is the functional unit of the gland and the site where colloid is stored. It is within the follicle where thyroid hormone (thyroxine or T_4) synthesis occurs. The remaining cellular elements are "C" cells, which are few in number, and lymphoid cells. The few "C" cells are located in the intrafollicular space and produce calcitonin. Lymphoid cells are found scattered throughout the gland stroma in small, isolated clusters.

Circulating Thyroid Hormones

Biosynthesis of thyroid hormone is unique among endocrine glands because final assembly occurs extracellularly in the follicular lumen. The source of thyroid hormones (T_4 and triiodothyronine [T_3]) is *thyroglobulin* (Tg), an iodoprotein, produced by the follicular cells. Thyroglobulin is the major portion of intraluminal colloid and is the most important protein of the thyroid gland (Kopp, 2005). Thyroglobulin provides a matrix for the synthesis of thyroid hormones and a vehicle for subsequent storage. Stored thyroglobulin is oxidized by thyroid peroxidase (TPO), adding an iodine molecule to tyrosine to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). MIT and DIT are then assembled into the final products, tetraiodothyronine (T_4) and triiodothyronine (T_3), which are stored in the follicular colloid for future use. When stimulated by serum thyrotropin (sTSH), thyroglobulin within the colloidal space is internalized by thyroid cells and enzymatically degraded to release T_4 and T_3 into the peripheral circulation. Approximately one third to half of T_4 released into the peripheral circulation is deiodinated to form T_3.

In the peripheral circulation, T_4 and T_3 are bound to thyroid-binding globulin (TBG). Thyroxine is bound to TBG in concentrations 10 to 20 times greater than T_3, and neither bound T_4 nor bound T_3 is directly available to tissues. Only unbound or "free" portions of T_4 and T_3 are metabolically available at the cellular level. The free portion of T_4 represents 0.02% to 0.05% of total serum T_4, and the free portion of T_3 represents 0.1% to 0.3% of total serum T_3 (Benvenga, 2005; Meier and Burger, 2005; Toft and Beckett, 2005). Most T_3 (>99.5%) is bound to TBG, but T_3 is not as tightly bound as T_4, allowing easier release into the free-state.

Table 35-3 Laboratory Tests for Evaluation of Thyroid Function

	Screening	Hyper	Hypo	Graves	CAT	Nodule	Thyroiditis	Other
TSH	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
T_4	No	No	No	No	No	No	No	No
T_3	No	Yes	No	Yes	No	No	No	No
FT_4	No	Yes	Yes	Yes	No	Yes	Yes	No
FT_3	No	No	No	No	No	No	No	No
Thyroglobulin	No	No	No	No	No	No	No	Yes
TSH-RS Abs	No	Yes	No	Yes	No	No	No	No
TPO Abs	No	No	No	No	Yes	No	No	No
Tg Abs	No	No	No	No	±	No	No	No
Thyroid microsomal Abs	No	No	No	No	No	No	Yes	±

CAT, Chronic autoimmune thyroiditis; *FT_3,* free triiodothyronine; *FT_4,* free thyroxine; *T_3,* triiodothyronine; *T_4,* thyroxine; *Tg Abs,* thyroglobulin antibodies; *TPO Abs,* thyroid antiperoxidase antibodies; *TSH,* thyroid-stimulating hormone (thyrotropin); *TSH-RS Abs,* TSH receptor-stimulator antibodies.

Thyroid hormones exert their effect by binding to thyroid receptors (TRs) within cells. At the cellular level, T_3 is roughly twice as biologically active as T_4. This is, in part, because T_3 binds more strongly to TR than T_4 does, thus, it easily displaces T_4 from binding sites (Yen, 2005). T_3 is the biologically active form of thyroid hormone. Thyroxine's role in this process appears to be that of a prohormone, providing a readily accessible reservoir for conversion to T_3. What other purpose(s) or role(s) T_4 plays is unknown (Bianco and Larsen, 2005).

Thyroid hormones (T_4 and T_3) regulate growth, development, and metabolism by affecting oxygen consumption and protein, carbohydrate, and vitamin metabolism. Around puberty, the effect on growth and development begin to wane, and in adults, thyroid hormones essentially affect only metabolism (Yen, 2005).

Normal thyroid function, in terms of circulating levels of T_4, T_3, FT_4, and free T_3 (FT_3) and the thyrotropin feedback system, appears to remain stable throughout life. Without intrinsic disease of the hypothalamic–pituitary–thyroid axis, age does not appear to have an adverse effect on the function of the thyroid gland or its component parts in terms of serum concentration of T_4 and T_3 (Hassani and Hershman, 2006; Oiknine and Mooradian, 2006). Although changes in measurable levels of total serum T_4 and T_3 do occur as a result of changes in transport protein concentrations, FT_4 and FT_3 levels remain mostly constant (Hassani and Hershman, 2006).

LABORATORY TESTING

Tests for thyroid disorders include laboratory studies, imaging, and biopsy. Before imaging or biopsy is undertaken, it is important to determine the functional state of the thyroid gland even when the initial presentation is a thyroid mass or thyromegaly. This is accomplished via laboratory testing of a peripheral blood sample. These simple and readily available tests provide direction for further workup. Initial laboratory tests, regardless of presenting complaint or finding, include sTSH and FT_4. The results of these initial studies help determine the functional state of the gland (hyperthyroid, euthyroid, or hypothyroid) and thus suggest which additional tests are required (Garber et al., 2012) (Table 35-3).

Second-tier laboratory tests include thyroid antibodies and FT_3 if T_3 toxicosis is suspected. As noted previously, aging and comorbidities that affect circulating levels of thyroid transport protein can result in T_4 levels that appear to be abnormally low, suggesting a hypothyroid state. However, FT_4 and FT_3 will be normal, as will sTSH. Thyroid antibodies are useful in evaluating several disease states, primarily Graves disease and chronic autoimmune thyroiditis (CAT or Hashimoto thyroiditis). In Graves disease, the primary antibody culprit is TSH receptor-stimulator antibody (TSH-RS Abs). In CAT, the primary antibodies are thyroid anti-peroxidase antibodies (TPO Abs) and thyroglobulin antibodies (Tg Abs). Patients with hypothyroidism occasionally exhibit TSH receptor-blocker antibodies (TSH-RB Abs), but the role this plays in the disease course is unclear. Thyroid microsomal antibodies (TPO Abs, Tg Abs) are occasionally seen in the self-limited processes of postpartum thyroiditis and silent thyroiditis. Figure 35-1 provides an algorithm for diagnosing thyroid dysfunction.

Imaging

Thyroid ultrasonography is the first-line study a primary care physician should obtain for a palpable thyroid mass. The goal is to determine whether the mass is cystic, solid, or mixed. It is also used as a presumptive screen for malignancy in the hands of an experienced radiologist because malignant thyroid nodules have unique ultrasonographic characteristics. If the patient is hyperthyroid, with suppressed sTSH, ultrasonography is done in conjunction with radioisotope scan.

Nuclear imaging uses iodine 123 (^{123}I) to evaluate gland activity. Patients with normal gland function show homogeneity throughout the gland, with the exception of areas where cysts or nonfunctioning nodules are located. Patients with autonomously functioning nodules or multinodular goiter show uptake of ^{123}I in nodular areas, with the remainder of the gland, under the control of sTSH, being hypoactive or inactive.

CT and MRI are not useful in diagnosis and treatment of nonmalignant diseases of the thyroid and thus are not

recommended as initial studies. For biopsy-proven malignancy, CT and MRI can be useful preoperatively to define the area of involvement and for postoperative follow-up. CT and MRI should be reserved for the surgeon and oncologist.

Biopsy

Ultrasound-guided fine-needle aspiration (FNA) biopsy is a well-defined procedure for evaluating thyroid masses. It is safe and virtually painless in the hands of an experienced interventional radiologist, endocrinologist, or pathologist. When a definitive diagnosis cannot be made and there is concern for possible malignancy, surgical referral is required. This usually results in a lobectomy or subtotal thyroidectomy.

HYPERTHYROIDISM

Key Points

- Hyperthyroidism is diagnosed with a suppressed sTSH and increased FT_4.
- Graves disease is caused by an abnormal response to circulating antithyroid antibodies.
- Serum TSH in Graves disease is usually less than 0.01 mIU/L and may be unmeasurable. TSH-RS Abs are often present.
- Diagnosis of Graves disease in a patient without goiter and ophthalmic abnormality should be suspect.

Hyperthyroidism is a biochemical process represented by an increase in thyroid hormone biosynthesis and secretion (Bahn et al., 2011; Toft, 2001). The diagnosis of hyperthyroidism is based on sTSH level less than 0.1 mIU/L and elevated FT_4 and FT_3 and is often associated with symptoms consistent with a hypermetabolic state (Table 35-4). Determining the exact etiology requires further testing, including laboratory studies and imaging (Table 35-5).

Table 35-4 Symptoms Consistent with a Hypermetabolic State

Tachycardia, wide pulse pressure
Systolic hypertension
Fever, tremor
Warm moist skin
Anxiety, hyperactivity
Diarrhea, weight loss

Modified from Braverman LE, Utiger RD. Introduction to thyrotoxicosis. In Braverman LE, Utiger RD, eds. *The thyroid: a fundamental and clinical text.* 9th ed. Philadelphia: Lippincott, Williams & Wilkins; 2005.

Table 35-5 Common Causes of Hyperthyroidism

Autonomous functioning (toxic) nodule
Toxic multinodular goiter (TMNG, Plummer disease)
Factitious disorder (Munchausen disease)
Iatrogenic disease
TSH receptor-stimulator antibody production (Graves disease)
Acute thyroiditis
TSH-producing pituitary tumor (adenoma)

TMNG, Toxic multinodular goiter; *TSH,* thyroid-stimulating hormone (thyrotropin).

Graves Disease

Graves disease is the most common cause of hyperthyroidism and results from the development of TSH-RS Abs. These antibodies attach to TSH receptors in the thyroid gland and "mimic" the action of TSH, stimulating production and release of T_4. Because of excess circulating T_4, the pituitary feedback loop for TSH production is suppressed, resulting in sTSH levels significantly below 0.01 mIU/L. Serum TSH levels greater than 0.05 mIU/L, although not impossible with Graves disease, should make the diagnosis suspect.

Graves disease can present at the family physician's office as thyrotoxicosis or thyroid storm but more often presents with hypermetabolic symptoms or goiter. How it is treated initially is determined by the patient's age, comorbidities, and acuity of symptoms. The primary symptomatic treatment is directed toward the cardiovascular responses of tachycardia, systolic hypertension, and volume depletion. Concurrent with this is the administration of antithyroid medication (propylthiouracil [PTU] or methimazole [MMI]). After the patient's symptoms have been controlled and there is evidence the hyperthyroid state is resolving, planning for long-term treatment can ensue.

Three courses of action can be followed for long-term treatment of patients with Graves disease. The goal is to maintain a euthyroid state. This can be accomplished with continued use of antithyroid medication, adjusting the dose to maintain sTSH in a normal range. A second option is ablation of the thyroid gland using ^{131}I or total thyroidectomy (Bahn et al., 2011). Either is appropriate, and in either case, the patient must take some medication on a permanent basis. As a third option, an occasional patient will undergo spontaneous remission, so a trial of antithyroid medication for 6 months to 1 year may be worthwhile. When this approach is tried, it requires close follow-up in case the patient rebounds. The majority of patients with Graves disease elect radioactive ablation and long-term treatment with thyroxine replacement.

Intervention to treat the symptoms of hyperthyroidism begins with a β-adrenergic receptor blocker as a temporizing agent to control sympathetically mediated symptoms. Specific therapy is deferred pending confirmation of the cause. For Graves disease, autonomously functioning nodule, or toxic multinodular goiter (TMNG), specific intervention includes PTU or MMI to control thyroxine synthesis and, with PTU, to reduce conversion of T_4 to T_3 in the peripheral circulation. Cases of serious liver injury have been associated with PTU use; thus, some experts suggest that MMI be used in every patient who chooses antithyroid medications as treatment for Graves disease with the exception of the women in the first trimester of pregnancy, in whom PTU is preferred (Bahn et al., 2011). After the patient is converted to a euthyroid state, specific treatment, based on cause, can be instituted.

With treatment of Graves disease, the goiter, which is found in more than 90% of these patients, may shrink. However, large goiters often require surgery for a satisfactory cosmetic appearance.

Thyroxine-Producing Nodules

Autonomously functioning thyroid nodules are found occasionally during workup for a hypermetabolic state

or palpation of a thyroid mass. Autonomous nodules have a much higher incidence of occurring in iodine deficient areas, accounting for approximately 60% of cases of thyrotoxicosis.

Autonomous functioning nodules and TMNG (Plummer disease) produce values for sTSH and FT_4 similar to those found in Graves disease, although sTSH is generally not less than 0.05 mIU/L. In both cases, one would expect the TSH-RS Abs to be negative or, at most, at an extremely low titer. Evaluation includes radioisotope scan with ^{123}I, which will demonstrate the nodule(s). These tumors are rarely malignant, and treatment is surgical after appropriate thyroid suppression. Long-term results are excellent, with no expectation of recurrence.

For patients with TMNG, and those with autonomous nodules who cannot tolerate surgery, ^{131}I ablation can be used. The ^{131}I is picked up by the most active portion(s) of the gland, so residual normally functioning thyroid gland often remains. However, iatrogenic hypothyroidism is always possible. After ^{131}I treatment of an autonomous nodule or TMNG, sTSH levels are required to determine if the gland can provide sufficient T_4 to meet physiologic requirements.

Other Causes of a Hyperthyroid State

Two often overlooked causes of a hyperthyroid state are fictitious and iatrogenic hyperthyroidism caused by excess exogenous T_4. In each case, patients have suppressed sTSH but generally only in the low normal range. From a laboratory perspective, these entities mimic painless, sporadic thyroiditis, with elevated T_4, low sTSH, and negative thyroid antibodies. If one measures FT_4 and FT_3, the relative ratio ($FT_4 : FT_3$) will be altered from what is normal. To identify fictitious thyrotoxicosis, it may be necessary to obtain an ^{123}I uptake study, which will demonstrate a minimally active thyroid gland. With Graves disease, autonomous functioning nodule, or TMNG, there is marked glandular activity. Elevated sTSH and elevated FT_4 levels are consistent with central hyperthyroidism or thyroid hormone resistance syndrome, and an evaluation of the pituitary for a TSH-producing tumor is required.

Thyrotoxicosis

Thyrotoxicosis is a physiologic process manifesting as hypermetabolism and hyperactivity that is caused by high serum concentrations of T_4, T_3, or both (Braverman and Utiger, 2005). It is not necessarily caused by excess hormone production and therefore may not represent a true hyperthyroid state. Although in the majority of patients the cause of thyrotoxicosis is excess T_4, in 2% to 4% of patients, it is due to elevated T_3 levels, with concomitant upper limit of normal T_4 levels (Meier and Burger, 2005).

Thyrotoxicosis is more common in female patients and in persons of northern European extraction and is rare in blacks. Spontaneous thyrotoxicosis is most often caused by Graves disease, accounting for 60% to 90% of all cases, followed by silent, or postpartum, thyroiditis caused by the sudden spike of circulating T_4, although it is transient and usually not clinically significant. Other less common, but not rare, causes of thyrotoxicosis include TMNG, autonomous functioning adenoma, and ingestion of exogenous thyroid hormone. Acute onset of thyrotoxicosis is almost always caused by thyroiditis. Thyrotoxicosis associated with Graves disease has a more insidious course, evolving over a more protracted period. If a patient is thyrotoxic and the thyroid gland is not palpable, consider painless thyroiditis, unsuspected Graves disease, or exogenous thyroxine. A thyrotoxic patient with a goiter or ophthalmopathy has Graves disease until proven otherwise. Treatment of hypermetabolic symptoms should not be delayed pending further testing or referral.

Symptoms of hyperthyroidism in younger individuals are usually the result of sympathoadrenal activity, but elderly patients have an age-related desensitization of β-adrenergic receptors, which probably accounts for a blunting of some symptoms usually associated with hyperthyroidism (Hassani and Hershman, 2006; Oiknine and Mooradian, 2006; Trivalle et al., 1996).

In older individuals with altered sympathetic and parasympathetic function, symptoms of thyrotoxicosis tend to include cardiovascular dysfunction, dyspnea, weight loss, and proximal muscle weakness. Cardiovascular symptoms in elderly adults usually consist of resting tachycardia, wide pulse pressure, exercise intolerance, and dyspnea on exertion. Atrial fibrillation is uncommon but occurs more often in older individuals (5%-15%) (Franklyn and Gammage, 2005).

Other cardiovascular effects that affect both young and old individuals are decreased peripheral resistance, decreased cardiac filling times, increased blood volume, and fluid retention. Individuals with preexisting CAD may have ischemic congestive heart failure (CHF) as a result of their hypermetabolic state, but this generally improves with appropriate antithyroid therapy. Atrial flutter, paroxysmal supraventricular tachycardia, premature ventricular beats, and ventricular fibrillation are rare complications of thyrotoxicosis and may represent unsuspected CAD.

Signs and symptoms of CHF are common in both young and old individuals with thyrotoxicosis (Trivalle et al., 1996). Because of decreased effective circulating arterial volume, aldosterone secretion increases, with a concomitant increase in sodium retention that results in dependent edema. After the thyrotoxicosis is effectively treated, all CHF symptoms quickly resolve. When periorbital edema is present, a diagnosis of Graves disease should be considered, and TSH-RS Abs titers should be checked.

Apathetic thyrotoxicosis is an uncommon presentation but represents the most common mental disorder associated with excess thyroid hormone production and release. Symptoms include apathy, lethargy, pseudodementia, weight loss, and depressed mood. It usually occurs in older patients without symptoms of tachycardia, hyperphagia, sweating, warm skin, or goiter (Wagle et al., 1998). This syndrome is easily confused with depression or dementia and, unless specifically sought, is easy to miss. A screening sTSH should be included in every depression or dementia workup.

The treatment of thyrotoxicosis is straightforward with three objectives; ameliorate acute symptoms, suppress synthesis and secretion of thyroid hormones, and treat the primary cause to prevent recurrence (Bahn et al., 2011). Acute symptoms respond readily to β-adrenergic receptor blocking agents, which should be continued until FT_4 levels have returned to the normal range. Calcium channel

blockers can be used in patients who cannot tolerate β-blockers. Inhibition of synthesis of thyroid hormones is achieved with PTU or MMI. Adjunct therapies include fluid resuscitation with D5 or D10 normal saline and administration of steroids. Fever generally responds satisfactorily to acetaminophen. The high fevers associated with thyroid storm may require cooling blankets. Nonsteroidal drugs and salicylates should be avoided in the acute phase because of competition for thyroid hormone binding sites on transport proteins. This can cause release of bound thyroid hormone into the peripheral circulation. With aggressive therapy, acute symptoms of thyrotoxicosis should improve within 12 to 24 hours. After acute symptoms are controlled, treatment of the primary cause can be considered. This could include watchful waiting in the case of thyroiditis, surgery for an autonomously functioning adenoma, or ^{131}I in Graves disease.

Thyroid Storm

Key Points

- Unrecognized thyroid storm has a mortality rate as high as 75%.
- Thyroid storm is usually the result of another disorder that unmasks a preexisting, but unidentified, hyperthyroid state.
- Thyroid storm is a clinical diagnosis, not defined by levels of TSH, T_4, or T_3.
- Suspicion of thyroid storm is a medical emergency with close monitoring in the intensive care unit and appropriate consultation by an endocrinologist.

Thyroid storm is a severe variant of thyrotoxicosis in which the metabolic state is sufficiently increased such that organ system failure can occur. It represents a rare complication of thyrotoxicosis and has a mortality rate as high as 75%, depending on how quickly it is recognized and treated (Tiegens and Leinung, 1995; Trzepacz et al., 1989; Wartofsky, 2005).

The diagnosis of thyroid storm is based on clinical findings, not measured levels of circulating T_4 or sTSH. Thyroid storm is often precipitated by infection, with associated symptoms that mask a thyrotoxic state. Clinical findings in thyroid storm include hyperpyrexia (>102° F), tachycardia out of proportion to temperature, gastrointestinal (GI) dysfunction (nausea, vomiting, diarrhea, jaundice), and CNS dysfunction (marked hyperirritability, anxiety, confusion, apathy, coma) (Wartofsky, 2005). There is usually pronounced decompensation of one or more organ systems. Any patient presenting with goiter, fever, and marked tachycardia should be considered to be in thyroid storm and treated accordingly. Admission to the medical intensive care unit and consultation with an endocrinologist are appropriate.

Treatment of thyroid storm includes β-blockers, antithyroid drugs, corticosteroid therapy, antipyretics, aggressive fluid replacement, and identification and treatment of any precipitating process. For patients with severe symptoms, Lugol solution or supersaturated potassium iodide will help inhibit release of T_4 into the peripheral circulation.

Table 35-6 Causes of Hypothyroidism

Insufficient intake of dietary iodine (uncommon in the United States)
Autoimmune disease (primarily Hashimoto thyroiditis)
Surgery (thyroid surgery)
Radiation exposure (head and neck)
Viral infection
Central disease (primary pituitary failure)

If either is used, it should only be given after loading doses of antithyroid drugs, to block iodine-induced synthesis of T_4. Lithium also has an antithyroid effect and can be used in severe cases of thyroid storm. Severe thyrotoxic symptoms, unresponsive to all of these regimens, may respond to sodium ipodate at 500 mg/day.

HYPOTHYROIDISM

Hypothyroidism is a hypometabolic state resulting from levels of circulating thyroid hormone insufficient to meet body requirements. Serum TSH will be greater than 10 mIU/L and can be significantly increased (>25 mIU/L) in protracted cases. Primary causes are listed in Table 35-6.

Chronic Autoimmune Thyroiditis (Hashimoto Thyroiditis)

Key Points

- Hashimoto thyroiditis is an autoimmune disorder that results in fibrosis of the thyroid gland.
- Hashimoto thyroiditis is the most common cause of hypothyroidism in the United States.
- Diagnosis of Hashimoto thyroiditis is based on an elevated sTSH, low normal to low FT_4, and TPO Abs.

The most common cause of hypothyroidism worldwide is inadequate dietary intake of iodine. Because of the addition of iodine to table salt, however, this is a rare cause in the United States. In the United States and the rest of the developed world, the most common cause of hypothyroidism is CAT (Hashimoto disease). CAT is caused by the development of antithyroid antibodies that attack the thyroidal struma, causing progressive fibrosis. TPO Abs and Tg abs appear to be responsible, with TPO Abs considered the primary cause (Dayan and Daniels, 1996). Diagnosis is based on elevated sTSH, a low normal or low FT_4, and the presence of TPO Abs (Garber et al., 2012).

Hashimoto thyroiditis occurs most often in women, with a female-to-male ratio of 10-14:1. CAT is usually diagnosed in the fifth decade of life and is progressive (Vanderpump, 2005). As it progresses, more functioning thyroid gland becomes fibrotic, and less indigenous T_4 is produced. After diagnosis, replacement doses of T_4 should be used. In adults, the average replacement dose of L-thyroxine is 1.6 μg/kg/day. Serum TSH is followed annually to ensure adequate control.

Other Forms of Hypothyroidism

Central hypothyroidism is caused by pituitary failure and is rare. The diagnosis is suggested with low to nonexistent

sTSH levels in a patient without symptoms of hypermetabolism (thyrotoxicosis) and with low circulating FT_4. Generally, when presented with these data, further evaluation to determine the etiology of the hypothyroidism is not necessary. However, the patient should be evaluated for pituitary failure if this has not already been done (see Approach to Pituitary Diseases).

Depending on the degree of injury, thyroiditis (postpartum, sporadic, or subacute) can result in a transient hypothyroid state, with eventual recovery. Subacute thyroiditis is more likely to undergo this process with insufficient T_4 production for 3 to 6 months. Treatment is usually unnecessary, but low-dose thyroxine replacement can be used on a temporary basis for patients who become symptomatic.

Other causes of hypothyroidism include dietary iodine deficiency, surgery, ^{131}I radiation therapy, and nonthyroid head and neck cancer treatment.

Hypothyroidism is typically treated with L-thyroxine replacement alone. However, some believe that patients occasionally have T_4-resistant disease and recommend mixed T_4–T_3 replacement. Although true T_4 resistance is controversial, if a patient receiving replacement T_4 has sTSH in the therapeutic range but continues to complain of hypothyroid symptoms, combination T_4–T_3 can be tried to alleviate symptoms. But it is prudent to ensure that the sTSH is maintained above 1.0 mIU/L to guard against unintended consequences of iatrogenic hyperthyroidism (Gencer et al., 2013; Taylor et al., 2013).

Initial dose of L-thyroxine will depend on the patient's age, duration of hypothyroid state, and comorbidities. In a young healthy adult, treatment with L-thyroxine may start with full replacement dosing. For someone older than 50 to 60 years without evidence of CAD, an L-thyroxine dose of 0.05 mg (50 µg) daily is recommended, with increases weekly of 0.025 mg to 0.05 mg, depending on clinical response (Garber et al., 2012). If the patient becomes tachycardic, is tremulous, or sweats, the time interval should be extended between increases in dosage to every 2 to 3 weeks. After the patient is stabilized on 0.1 to 0.125 mg of L-thyroxine daily, further increases are made based on sTSH response. Serum TSH only needs to be checked every 4 to 6 weeks. More frequent testing does not allow a sufficient interval for developing homeostasis and can result in overdosing. When the patient is on a steady dose, further treatment is adjusted so that sTSH remains at 0.5 to 4.5 mIU/L (mean, 2.5 mIU/L). Doses of L-thyroxine resulting in sTSH less than 0.1 mIU/L indicate iatrogenic hyperthyroidism and should be avoided (Gencer et al., 2013).

Thyroiditis

Forms of thyroiditis include tender thyroiditis such as subacute granulomatous thyroiditis (probable viral etiology), infectious thyroiditis (probable bacteria etiology), radiation thyroiditis, and palpation- or trauma-induced thyroiditis. Nontender thyroiditis includes silent thyroiditis, postpartum thyroiditis, drug-induced thyroiditis, fibrous thyroiditis, and CAT (Hashimoto thyroiditis) (Bahn et al., 2011; Farwell, 2005; Lazarus, 2005).

The mechanism of injury to the thyroid gland is disruption of thyroid architecture caused by lymphocytic infiltration, resulting in leakage of colloid-stored thyroxine into the peripheral circulation. This nonphysiologically triggered leakage of stored T_4 causes a spike in peripheral circulating T_4 and transient hypermetabolic symptoms. Early testing in the disease can demonstrate an elevated FT_4 level, although not necessarily outside the normal range. Depending on the duration of the destructive process and degree of injury, sTSH may be normal, low normal, or low. If the cause of this variability is not appreciated, it could lead to the erroneous initial diagnosis of Graves disease (increased FT_4 and low sTSH). With protracted acute thyroiditis, however, sTSH is not as low as in Graves disease, and TSH-RS Abs titers are low to absent. In addition, patients with acute thyroiditis lack Graves disease optic findings and goiter.

As a general rule, acute thyroiditis is a short-lived process, with T_4 stores being rapidly depleted. This represents a case of thyrotoxicosis (increased circulating T_4) but not hyperthyroidism (increased production of T_4). Follow-up testing over the next few weeks demonstrates progressively lower T_4 levels, which eventually return to normal. As T_4 levels return to normal, the acute hypermetabolic symptoms begin to decline. The duration of T_4 elevation determines how low the sTSH will go and how quickly it will return to normal.

Treatment of Hypothyroid Disease

Synthetic levothyroxine (L-thyroxine) is the drug of choice for the treatment of TSH-deficient hypothyroidism (Oiknine and Mooradian, 2006). A typical replacement dose in adults is approximately 1.6 µg/kg/day. The daily requirements should be individually determined based on clinical and biochemical evaluations. The FT_4 level should be in the middle to upper third of normal range. Attention to other, coexistent diseases is required when replacing thyroid hormone (Garber et al., 2012). Thyroid replacement increases the clearance of cortisol and will uncover a subclinical adrenal insufficiency. This must be considered when replacing thyroxine in a patient with secondary hypothyroidism. The ACTH status should be assessed and, if deficient or the status is uncertain, glucocorticoid replacement is indicated before thyroid hormone is replaced.

Subclinical Thyroid Disease

Key Points

- Subclinical thyroid disease is based on a TSH level that is above the normal reference range in an asymptomatic patient with normal FT_4.
- The American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) recommend that screening for hypothyroidism should be considered in all adults over the age of 60 years.
- The decision to treat subclinical hypothyroidism when serum TSH is less than 10 mIU/L should be individualized
- The ATA and AACE suggest treatment of subclinical hypothyroidism (sTSH <10 mIU/L in patients positive for TPO Abs or a history of atherosclerotic vascular disease or symptoms consistent with hypothyroidism).

Discussion about subclinical thyroid disease has focused on whether it is a real clinical entity. Subclinical thyroid diseases are defined as (1) subclinical hyperthyroidism (or subclinical thyrotoxicosis) with sTSH less than 0.1mIU/L and normal circulating FT_4 and FT_3 or (2) subclinical hypothyroidism with sTSH greater than 4.5 mIU/L but less than 10.0 mIU/L with normal circulating FT_4. Both entities assume a patient who is asymptomatic or has minimal signs and symptoms.

The primary questions concerning subclinical thyroid disease are whether early intervention is beneficial and whether patients should be screened. The only disease state that has been directly related to subclinical thyroid disease is overt hypothyroidism. Individuals with subclinical hypothyroidism have a higher incidence of progression to overt hypothyroidism than the general population. Annually, 3% to 5% of patients identified with subclinical hypothyroidism progress to overt hypothyroidism with sTSH levels greater than 10.0 mIU/L (Toft and Beckett, 2005). The majority of these represent early CAT. For patients with subclinical hypothyroidism, a TPO Ab measurement should be considered.

Currently, no consensus exists among national organizations as to whether these individuals should start therapy during this phase of their disease. Treating those with symptoms seems appropriate, but there is no evidence to support the premise that early treatment alters the disease course or associated comorbidities (hyperlipidemia, hypertension, CAD).

Studies have demonstrated a two to three times higher incidence of atrial fibrillation in patients with subclinical hyperthyroidism compared with individuals with normal sTSH levels (Ross, 2005a, 2005b). The Framingham data suggest that some individuals with subclinical hyperthyroidism are at increased risk for paroxysmal atrial fibrillation (Oiknine and Mooradian, 2006). In addition, good evidence indicates that osteoporosis is associated with overt hyperthyroidism. New evidence suggests that osteoporosis is also associated with subclinical hyperthyroidism (Gencer et al., 2013).

Although data supporting adverse consequences of subclinical hyperthyroidism continue to accumulate, there still are no outcomes data to show a decrease in mortality or morbidity from early intervention. The AACE, however, does recommend treatment of subclinical hyperthyroidism caused by nodular thyroid disease (AACE, 2002).

New guidelines from the ATA and AACE, published in 2012, have moved from their previous position of not recommending treatment of subclinical hypothyroidism to suggesting that treatment be considered for individuals with a sTSH between 4.5 and 10 mIU/L who are positive for TPO Abs or have a history of atherosclerotic vascular disease and anyone with symptoms suggestive of hypothyroidism (Garber et al., 2012).

A review of the literature on how variation of thyroid function tests affect cardiovascular, bone, metabolic, pregnancy, neurologic, and psychologic outcomes, suggests there may be a correlation between these and thyroid test variability (i.e., "normal" range) (Taylor et al., 2013). Evidence synthesis shows that higher sTSH and lower T_4 levels are associated with more cardiovascular risk factors and cardiovascular events and worse metabolic parameters and pregnancy outcomes. Furthermore, it shows that lower sTSH and higher T_4 levels are associated with reduced bone mineral density (BMD) and increased fracture risk. High-quality data are lacking for neurologic and psychological outcomes. The conclusion suggests that even with thyroid function data within currently accepted normal range (0.1-4.5 mIU/L), there is an association with adverse health outcomes (Taylor et al., 2013). Data from the Thyroid Studies Collaboration support these findings. Specifically, subclinical hypothyroidism is associated with an increased risk of coronary heart disease (CHD) events, increased CHD mortality, and heart failure (HF). Subclinical hyperthyroidism is associated with an overall risk of total mortality, CHD mortality, HF, and atrial fibrillation. Atrial fibrillation is particularly increased in individuals whose sTSH is suppressed below 0.1 mIU/L (Gencer et al., 2013; Rodondi et al., 2005).

By extrapolation from the results of these data, it is reasonable to assume that treatment of subclinical thyroid disease could be beneficial, but definitive outcomes data are lacking. However, it is clear that careful control and follow-up of treatment of overt thyroid disease is essential.

ANATOMIC DISEASES

Anatomic diseases of the thyroid gland include a number of primary and secondary disorders (Table 35-7). The list includes goiter, nodules, primary neoplasia, metastatic neoplasia (rare), and familial disorders.

Goiter

Goiter is the most common anatomic disease, and the major cause of goiter worldwide is iodine deficiency. When simple goiter occurs in areas of adequate iodine intake, there appears to be a strong genetic component to the disease. In the United States, goiter found independent of Graves disease is usually associated with CAT as the disease progresses to a hypothyroid state. Goiter is the result of both hypertrophy and hyperplasia of the thyroid gland. In the case of iodine deficiency, this is caused by excess thyrotropin production, leading to glandular growth and colloid production.

In Graves disease, stimulation of the thyroid by TSH-RS Abs causes excess production of T_4 and T_3, in turn resulting in uncontrolled production of colloid to store the excess production of thyroid hormone. In fact, goiter is the most common clinical finding in Graves disease after thyrotoxicosis, occurring in nearly 100% of patients (Chiovato et al., 2001).

Goiter is one of the five hallmarks of Graves disease. Goiter associated with hypothyroidism often improves after euthyroid doses of thyroxine have been achieved, although

Table 35-7 Anatomic Diseases of Thyroid

Goiter	Simple, toxic, iodine deficiency
Nodule	Adenoma, incidental, toxic
Cyst	Simple, complex
Malignancy	Primary: papillary or follicular, medullary, lymphoma Metastatic: lymphoma, breast, pulmonary, other Familial: multiple endocrine neoplasia type IIA

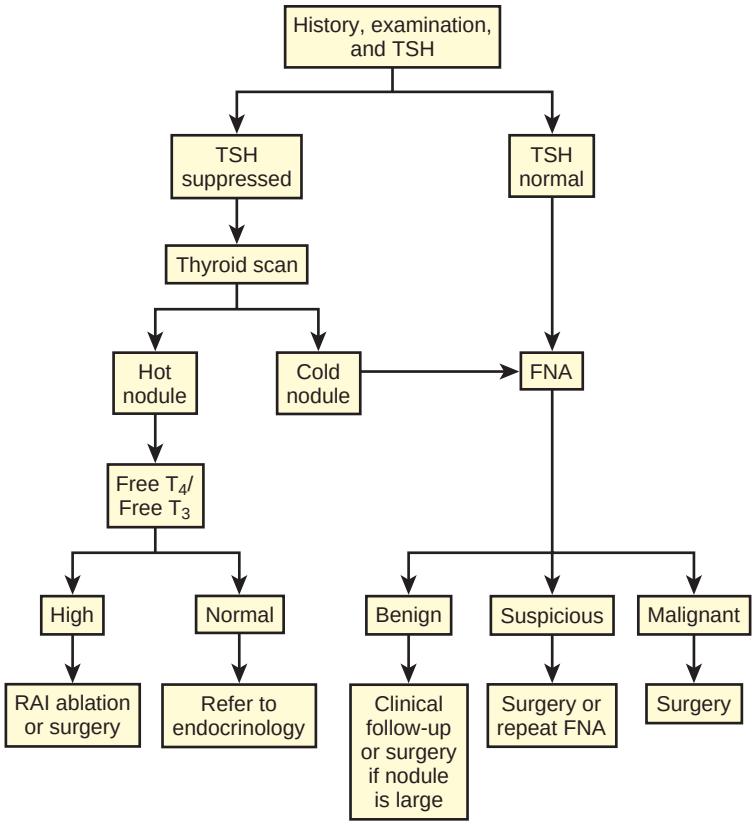


Figure 35-2 Algorithm for the clinical evaluation of thyroid nodule. *FNA,* Fine-needle aspiration; *RAI,* radioactive iodine; T_3, triiodothyronine; T_4, thyroxine; *TSH,* thyroid-stimulating hormone.

it may take 6 months to 1 year. If the goiter does not involute with thyroxine replacement, excision may be required. Besides goiter, the other four hallmarks of Graves disease are thyrotoxicosis, ophthalmopathy, local myxedema, and acropachy (clubbing of fingers and toes).

Nodules and Cysts

Thyroid nodules come in a variety of sizes and types. The incidence of malignancy in nodules smaller than 1.0 cm in size, which typically are found incidental to some non–thyroid-related diagnostic procedure (e.g., head and neck ultrasonography), is less than 0.5%. Current recommendations for evaluation of these "incidentalomas" include TSH and FT_4 levels and careful palpation of the thyroid gland (Ross, 2005a) and adjacent cervical nodes (Cooper et al., 2009) (Figure 35-2).

If results of tests and palpation are normal or negative, annual follow-up with palpation by the physician is recommended. As long as growth remains minimal and there were no ultrasonographic hallmarks of malignancy on the initial scan, these nodules can be monitored clinically.

The exception to annual follow-up in nodules smaller than 1.0 cm is when a solitary nodule occurs before 14 years of age because these have a greater than 50% incidence of malignancy. Other reasons to obtain FNA of a nodule smaller than 1.0 cm include high-risk history (nodules >5 mm) or presence of cervical adenopathy (all nodules regardless of size) (Cooper et al., 2009).

A nodule that is palpable on examination or 1.0 cm or larger on ultrasonography requires further evaluation. If the sTSH is within normal range and a local endocrinologist experienced in FNA is available, referral without imaging is appropriate. However, if ultrasonography is performed and it shows a purely cystic lesion, FNA is not necessary. As long as the cyst remains small or is asymptomatic, no intervention is required. However, if the cyst increases in size or becomes symptomatic, it can be drained via FNA.

If the patient with a palpable nodule has a suppressed sTSH, this would suggest a nodule that is functioning autonomously. Before any intervention (surgical or FNA), a radioisotope ^{123}I scan is indicated. If the lesion is "hot," suppression is the course of action before FNA or surgery is performed. If "cold," it could represent a cystic, mixed, or solid mass, thus requiring further evaluation by FNA (first choice) or surgical exploration.

Benign nodules do not require therapeutic intervention unless the nodule's size is causing symptoms (tracheal compression or pain). These generally do not respond to suppression; thus, surgical excision is the treatment of choice.

Malignancy

Malignancy of the thyroid, both primary and secondary, is rare, accounting for fewer than 2% of all cancers, and generally, tumors are not aggressive. *Papillary carcinoma* is the most common, accounting for approximately 80% of primary thyroid malignancies. Follicular carcinoma, which arises from the same cell type as papillary carcinoma, accounts for about 5% of thyroid neoplasia. Undifferentiated and anaplastic carcinoma makes up fewer than 10% of all thyroid malignancies, and medullary carcinoma of the

thyroid about 5% of thyroid malignancies (Baloch and Livolsi, 2005).

The most common cancers that metastasize to the thyroid are breast, lung, and kidney. Primary lymphoid cancer occurs in the thyroid, but its incidence is unknown because it cannot be distinguished from lymphoma that originates elsewhere in the body. Treatment of thyroid cancers is generally surgical with ^{131}I therapy with subtotal thyroidectomy. As with cancers elsewhere in the body, primary treatment will depend on tissue diagnosis and clinical evaluation. New imaging techniques are being used to evaluate patients who are thyroglobulin positive but whole-body iodine scan negative for differentiated thyroid cancer. This imaging technique uses ^{18}fluorine-labeled fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F FDG PET/CT), and ATA guidelines from 2009 recommend this screening in select patients with any one of five main indicators. Presently, this level of nuclear scan may only be available in larger metropolitan areas and academic medical centers (Cooper et al., 2009; Palaniswamy and Subramanyam, 2013).

Two familial thyroid malignancies include MEN IIA and FMTC. MEN IIA is an autosomal dominant disorder that can cause "C"-cell hyperplasia and hyperparathyroidism. The diagnosis is often serendipitously found during evaluation for hypercalcemia or renal calculi.

LONG-TERM FOLLOW-UP OF THYROID DISORDERS

For patients receiving long-term thyroid therapy for hypothyroidism, monitoring is done via sTSH unless there is hypothalamic-pituitary disease. It takes 4 weeks after initiating treatment (or changing dose) before clinically significant change occurs in sTSH level. In most patients, checking sTSH once every 4 weeks is sufficient until steady state is reached. After the patient is stabilized, sTSH can be checked at 6 months and then annually unless the patient develops new symptoms (Garber et al., 2012).

Patients determined to have benign nodules after adequate evaluation are followed annually with careful palpation of the thyroid gland. Unless there is a size change or new symptoms, no additional testing is required. Ultrasound imaging of the thyroid is not recommended for follow-up of nodules smaller than 1.0 cm. Repeat ultrasonography is required in patients with an enlarging nodule, evidence of a new thyroid mass, or who complain of pain or pressure. Unless the patient is experiencing symptoms of hyper- or hypothyroid, repeat testing of sTSH or FT_4 is not indicated (Cooper et al., 2009).

SICK EUTHYROID SYNDROME (THYROID HORMONE ADAPTATION SYNDROME)

Thyroid function can appear suppressed during severe illness and may not represent abnormal thyroid function. Serious illness has been shown to affect laboratory tests of thyroid function (sTSH, T_4, thyroglobulin), but there is no clear evidence that this reflects a disease state (Chopra, 1997). Because these changes appear to have no direct adverse effect on the patient's overall clinical state, this condition is labeled "sick euthyroid syndrome." In broad terms, sick euthyroid syndrome is more of academic interest than clinical. Administration of T_4 to a seriously ill individual does not improve the outcome for most patients, but evidence suggests that high doses of T_3 after cardiac surgery may be beneficial (Wiersinga, 2005).

The physician should remember the rare patient whose thyroid disease is uncovered by serious illness. If a seriously ill patient is not responding as expected, (e.g., difficulty in weaning from ventilator support), checking thyroid function may be appropriate, although any interpretation of results should be reviewed by a clinician experienced in interpreting thyroid tests in seriously ill patients before intervention (Garber et al., 2012).

DRUGS AFFECTING THYROID FUNCTION AND TESTING

Key Points

- Therapeutic drugs have a variety of effects on thyroid function, including delayed or suppressed synthesis.
- Therapeutic drugs may block the effect of thyroid hormone at the cellular level.
- Phenothiazines, dopamine, phenytoin, and glucocorticoids block release of TSH from the pituitary.
- Amiodarone can cause both hyperthyroidism and hypothyroidism. Approximately 20% of patients can develop hypothyroidism from fibrosis of the gland.

Many common drugs can affect thyroid function, bioavailability of thyroid hormone, and laboratory testing. Drugs that affect thyroid function fall into several categories: some inhibit synthesis of T_4, some block secretion of T_4, some block TSH release, some affect extrathyroidal conversion of T_4 to T_3, and some influence thyroxine at the tissue or cellular level (Table 35-8). PTU and MMI inhibit thyroid hormone synthesis by interfering with thyroid peroxidase. PTU has the added advantage of inhibiting extrathyroidal conversion of T_4 to T_3. Neither PTU nor MMI inhibits T_4 release (secretion) from the thyroid gland. Amiodarone, lithium, and cytokines can affect synthesis and secretion. In the absence of iodine, amiodarone can precipitate both hyperthyroid and hypothyroid events. In the United States, where dietary iodine is plentiful, patients taking amiodarone tend to develop hypothyroidism from fibrosis of the

Table 35-8 Drugs That Affect Thyroid Function at the Glandular Level

Drug	Inhibits T_4 Synthesis	Blocks T_4 Secretion	Blocks TSH Release
Iodine	Yes	—	—
Propylthiouracil	Yes	—	—
Methimazole	Yes	—	—
Antipsychotic	—	—	Yes
Amiodarone	Yes	Yes	—
Lithium	Yes	Yes	—
Phenytoin	—	—	Yes
Dopamine	—	—	Yes
Glucocorticoid	—	—	Yes
Cytokines	Yes	Yes	—

T_4, Thyroxine; *TSH*, thyroid-stimulating hormone (thyrotropin).

Table 35-9 Drugs and Oral Agents That Affect Thyroid Function at the Peripheral Level

Drug	Compete for Protein Binding	Inhibit Deiodination of T_4 to T_3	Inhibit Action at Tissue Level	Inhibit Uptake of T_3 at Tissue Level	Affect Thyroid Hormone Clearance Time	Inhibit GI Absorption	Adverse Effect on Lab Tests
Phenytoin	—	—	—	—	Yes	—	—
Phenobarbital	—	—	—	—	Yes	—	—
Carbamazepine	—	—	—	—	Yes	—	—
Rifampin	—	—	—	—	Yes	—	—
Salicylates	Yes	—	—	—	—	—	Yes
NSAID	Yes	—	—	—	—	—	Yes
Furosemide	Yes	—	—	—	—	—	Yes
Heparin	Yes	—	—	—	—	—	Yes
Enoxaparin	Yes	—	—	—	—	—	Yes
Sucralfate	—	—	—	—	—	Yes	—
Ca carbonate	—	—	—	—	—	Yes	—
Al hydroxide	—	—	—	—	—	Yes	—
Soy	—	—	—	—	—	Yes	—
Ferrous sulfate	—	—	—	—	—	Yes	—
PTU	—	—	Yes	—	—	—	Yes
Dexamethasone	—	Yes	—	—	—	—	Yes
β-Blocker	—	Yes	Yes	—	—	—	Yes
Benzodiazepine	—	—	—	Yes	—	—	—
CCB	—	—	—	Yes	—	—	—
Amiodarone	—	Yes	—	—	—	—	—
Contrast agent	—	Yes	—	—	—	—	—

Al, aluminum; *Ca,* calcium; *CCB,* Calcium channel blocker; *GI,* gastrointestinal; *NSAID,* nonsteroidal antiinflammatory drug; *PTU,* propylthiouracil; T_3, triiodothyronine; T_4, thyroxine.

thyroid gland. The incidence is approximately 20% (Harjai and Licata, 1997; Roti and Vagenakis, 2005). Patients taking these drugs, especially amiodarone, should be screened regularly with sTSH for developing thyroid dysfunction. Dopamine, glucocorticoids, and phenytoin have been shown to inhibit release of TSH from the anterior pituitary. Salicylates and other NSAIDs, furosemide, heparin, and enoxaparin compete for binding sites on thyroid hormone transport proteins. Use of these drugs in acute thyroid disease can potentially exacerbate thyrotoxic symptoms by releasing thyroid hormone into the peripheral circulation. Serum TSH and FT_4 should be monitored in regular users of these medications (Table 35-9).

Phenytoin, phenobarbital, carbamazepine, and rifampin stimulate hepatic enzymatic activity, thus shortening thyroid hormone clearance times and increasing conversion of T_4 to T_3. Serum TSH levels should be monitored routinely, until stable, when these medications are added or deleted from a patient's regimen. Sucralfate, cholestyramine, calcium carbonate, aluminum hydroxide, soluble fiber, soy products, and ferrous sulfate inhibit absorption of exogenous L-thyroxine from the gut. Oral L-thyroxine should be taken on an empty stomach.

β-Blockers exert their effect on thyroid hormones at the cellular level, and benzodiazepines block uptake of T_3 at the cellular level (Hedley et al., 1989; Tiegens and Leinung, 1995; Wartofsky, 2005). Calcium channel blocking agents inhibit uptake of thyroid hormone by hepatic and muscle cells (Table 35-9).

THYROID DISEASE IN PREGNANCY

Pregnancy can exacerbate an already existing thyroid disorder, thus requiring extra vigilance on the part of the family physician. Careful monitoring and proactive clinical intervention are key. The majority of women with hypothyroidism, who are euthyroid on stable doses of thyroid replacement, require increased doses of thyroxine replacement during their pregnancy. In pregnancy, the normal range for sTSH is trimester specific. If trimester-specific sTSH ranges are not available at the local laboratory, the recommended upper levels for normal are 2.5 mIU/L for the first trimester, 3.0 mIU/L for the second trimester, and 3.5 mIU/L for the third (Garber et al., 2012). Being aware of this need and being prepared to make dosage adjustments in a timely manner are important. Consulting an endocrinologist to help with the care of these patients is advised (Shankar et al., 2001).

Silent or postpartum thyroiditis during pregnancy is essentially a benign, short-term disease and requires only symptomatic treatment. Occasional checks of sTSH and FT_4 levels are justified to monitor recovery. For the rare pregnant patient who requires suppression of T_4 synthesis, judicious use of antithyroid drugs (PTU and MMI) is generally considered to be safe. There is some concern that MMI may cross the placental barrier more readily than PTU, but this has not proven to be of concern in a clinical setting. It is important, however, to remember that prolonged suppression of the thyroid or suppression late in pregnancy can

result in a transient depression of neonatal thyroid function and may induce goiters in the neonate. PTU and MMI can be found in breast milk. This has not proven to be of concern as long as the dose is kept low. PTU (maximum, 150 mg/day) and MMI (maximum, 20 mg/day) caused no problems with a nursing child (Glinoer, 2005). Both PTU and MMI are category D pregnancy risk, and the American Academy of Pediatrics reports no sign or symptom in infants or adverse effects on lactation and supports use of these drugs during breastfeeding. In the United States, PTU has generally been the antithyroid drug of choice in pregnant and nursing women; however, recent reports concerning hepatotoxicity from PTU have limited use of PTU to the preferred agent during the first trimester of pregnancy, and MMI is first-line therapy during the second and third trimesters of pregnancy and nursing.

SCREENING FOR THYROID DISEASE

Screening for asymptomatic thyroid disease is controversial, but screening in specific populations may be beneficial (American Academy of Family Physicians [AAFP], 2009; Bahn et al., 2011; Garber et al., 2012; Helfand, 2004; Ladenson et al., 2000). Women older than the age of 50 years have the highest incidence of spontaneous hypothyroidism compared with all males and mixed younger populations, approaching 5% per year. Thus, screening has a good chance of finding disease early. However, the evidence supporting benefit from early intervention is not strong and probably does not justify the cost. However, the ATA and AACE changed their guidelines in 2012 to say that screening for hypothyroidism should be considered in adults older than 60 years old (Garber et al., 2012). Patients who present with paroxysmal atrial fibrillation should be routinely screened for hyperthyroidism, although the incidence of positive findings is low.

One area where screening is advantageous is patients with newly diagnosed dementia. This is especially true if the clinical course is atypical or accelerated. Both hypothyroidism (myxedema) and hyperthyroidism (apathetic thyrotoxicosis) can present with dementia-like symptoms and, in these patients, timely intervention can completely reverse the signs and symptoms of dementia or depression caused by thyroid dysfunction.

If screening is undertaken, the test of choice is a sTSH. When coupled with FT_4, the vast majority of clinically significant hyperthyroidism and hypothyroidism can be diagnosed. If symptoms are present or there are overt signs of disease, the initial testing should include sTSH, FT_4, and FT_3. Thyroid panels providing T_4, T_3, T_7, FT_4 index, and T_3 uptake are no longer advocated.

KEY TREATMENT

- Thyrotoxicosis is treated initially with β-blockers and antithyroid medication to control symptoms and stop synthesis and release of thyroid hormone into the peripheral circulation (Bahn et al., 2011; Oiknine et al., 2006; Trivalle et al., 1996) (SOR: A).
- Hypothyroid (TSH >10 mIU/L) replacement T_4 dose is approximately 1.6 µg/kg/day (Oiknine et al., 2006) (SOR: A).
- With the exception of thyroid antibody–positive subclinical hypothyroidism with TSH less than 10 mIU/L, prophylactic treatment has not been shown to have a positive effect on lipids or CAD risk (Bahn et al., 2011; Garber et al., 2012; Helfand, 2004; Ladenson et al., 2000) (SOR: A).
- Treatment of subclinical hyperthyroidism should be considered when TSH is less than 0.1 mU/L in all patients older than 65 years and in patients younger than 65 years with any of the following comorbidities: heart disease, osteoporosis, menopause, or hyperthyroid symptoms (ATA and AACE, 2011) (SOR: B).

Adrenal Glands

PHYSIOLOGY

The adrenal glands are located at the superomedial aspects of the kidneys. The glands consist of two endocrine tissues of different embryologic origins: the primarily steroid-producing adrenocortical tissue in the cortex and the catecholamine-producing chromaffin cells in the medulla. The adrenal cortex consists of three zones that vary in both their morphologic features and the hormones they produce. The outer, *zona glomerulosa*, is the unique source of the mineralocorticoid aldosterone. The intermediate, *zona fasciculate,* and the inner, *zona reticularis,* produce the glucocorticoids cortisol and corticosterone and the androgens dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEA-S). The chromaffin cells in the adrenal medulla mainly secrete the catecholamines epinephrine and norepinephrine (Table 35-10) (Williams and Dluhy, 2008).

Mineralocorticoids are major regulators of extracellular fluid volume and potassium metabolism. Volume is regulated through a direct effect on the collecting duct of the kidney, where aldosterone causes an increase in sodium retention and in potassium excretion. The release of aldosterone is regulated by the RAS, plasma potassium levels, and ACTH. The RAS maintains the circulating blood volume by regulating aldosterone secretion. Aldosterone-induced sodium retention occurs in volume deficiency states, but aldosterone-dependent sodium retention is reduced when volume is ample. An increase in plasma potassium or a decrease in plasma sodium stimulates aldosterone release. ACTH stimulates mineralocorticoid output, but this effect on aldosterone secretion is transient.

Table 35-10 Adrenal Gland Anatomy and Steroids

Cortex	Zona glomerulosa Aldosterone Zona fasciculata Zona reticularis Glucocorticoids Cortisol Corticosterone Dehydroepiandrosterone (DHEA) DHEA sulfate (DHEA-S)
Medulla	Epinephrine Norepinephrine Dopamine

The release of *cortisol*, the main glucocorticoid in humans, is pulsatile and directly stimulated by ACTH or its precursors, such as pro-opiomelanocortin. The release of ACTH from the anterior pituitary is regulated by corticotrophin-releasing hormone (CRH), which is produced by the hypothalamus. High cortisol levels inhibit the biosynthesis and secretion of CRH and ACTH through a negative feedback mechanism. Cortisol release follows a circadian rhythm with its highest level in the morning and is sensitive to light, sleep, stress, and disease. The glucocorticoid effects are multisystemic. They stimulate proteolysis and gluconeogenesis, inhibit muscle protein synthesis, and increase fatty acid mobilization. Gluconeogenesis results in an increase in blood glucose concentrations. At high levels, glucocorticoids are catabolic and result in loss of lean body mass. Glucocorticoids modulate the immune response through their antiinflammatory effects and modulate perception and emotion in the CNS.

The production of the adrenal androgens is controlled by ACTH, not by gonadotropins. Among the adrenal androgens, DHEA is the most abundant circulating hormone in the body and is readily conjugated to its sulfate ester DHEA-S. The adrenal androgens are converted into androstenedione and subsequently into potent androgens (testosterone) or estrogens (estradiol) in the peripheral tissues. Adrenal secretion of DHEA and DHEA-S increases in children around 6 to 8 years of age and peaks between the ages of 20 to 30 years. However, the production of DHEA-S by the adrenal glands is reduced by 70% to 95% during the aging process; by age 70 years, serum DHEA-S levels are approximately 20% of their peak values and continue to decrease with age. Adrenal androgens have minimal effects in men, whose sexual characteristics are predominantly determined by gonadal steroids (testosterone). In women, adrenal-derived testosterone is important in maintaining pubic and axillary hair. Adrenal androgen hypersecretion in men causes no clinical signs but in women manifests with signs of hirsutism and masculinization.

The adrenal medulla secretes epinephrine, norepinephrine, and dopamine. Most catecholamine output in the adrenal vein is epinephrine; norepinephrine also enters the circulation from noradrenergic nerve endings. In emergency situations, the secretion of adrenal catecholamines is increased to prepare the individual for stress ("fight or flight" response). Hypoglycemia and certain drugs are also potent stimuli to catecholamine secretion.

DISORDERS OF CORTICAL HYPOFUNCTION

Primary Adrenal Insufficiency

Key Points

- Primary adrenal insufficiency is defined as the failure of the adrenal cortex to produce glucocorticoids and mineralocorticoids.
- The most frequent cause of primary adrenal insufficiency is autoimmune. In the developing world, however, TB remains the most common cause.
- Symptoms are usually insidious and include fatigue, orthostatic hypotension, weight loss, and hyperpigmentation.
- Acute adrenal insufficiency should be considered in critically ill patients with unexplained hypotension.
- A baseline cortisol and ACTH level followed by an ACTH stimulation test can establish diagnosis.
- Detection of adrenal cortex antibodies or 21-hydroxylase autoantibodies supports the diagnosis of autoimmune adrenalitis. Abdominal CT may be helpful if other causes are suspected.

Primary adrenal insufficiency (AI) is defined as the failure of the adrenal cortex to produce adequate amounts of glucocorticoids and mineralocorticoids (Arlt and Allolio, 2003; Salvatori, 2005). Primary AI can result from processes that damage the adrenal glands or from drugs (e.g., ketoconazole, etomidate) that block the synthesis of cortisol. All causes of primary AI involve the adrenal cortex as a whole and result in a deficiency of cortisol and aldosterone (plus adrenal androgen), although the severity of the deficiencies may vary. An exception is the *syndrome of isolated glucocorticoid deficiency*. The reported prevalence of primary AI (Addison disease) in developed countries is 39 to 60 persons per 1 million population. In adult patients, the mean age at diagnosis is 40 years (range, 17-72 years).

The most frequent cause of primary AI in developed countries is *autoimmune adrenalitis*. However, in the developing world, TB remains the most common cause of adrenal failure. Autoimmune adrenalitis is sometimes accompanied by other autoimmune endocrine deficiencies (autoimmune polyglandular syndromes [APS]). The adult form (type II, Schmidt syndrome) of polyglandular syndrome consists mainly of AI, autoimmune thyroid disease, and insulin-dependent (type 1) diabetes mellitus. Several infectious processes associated with acquired immunodeficiency syndrome (AIDS) such as cytomegalovirus (CMV), *Mycobacterium tuberculosis*, *Cryptococcus neoformans*, *Mycobacterium avium intracellulare*, *Histoplasma capsulatum*, and Kaposi sarcoma may damage the adrenal gland and lead to insufficiency. In young males, adrenoleukodystrophy (or the less severe adrenomyeloneuropathy), an X-linked recessive disorder of metabolism of long-chain fatty acids, can cause spastic paralysis and adrenal insufficiency. AI can precede neurologic symptoms and should prompt the clinician to perform a careful neurologic examination in young males with primary AI. Other causes are listed in Table 35-11.

Chronic (Primary) Adrenal Insufficiency. Most of the symptoms are nonspecific and occur insidiously. Chronic AI manifestations include weakness, chronic fatigue, anorexia, unintentional weight loss, listlessness, joint pain, and orthostatic hypotension. Some patients may initially present with GI symptoms (abdominal pain, nausea, vomiting, diarrhea), but others may present with symptoms that can be attributed to depression or anorexia nervosa. In contrast to secondary AI, primary AI is often associated with lack of aldosterone as well as cortisol. Thus, signs of mineralocorticoid deficiency (salt craving, postural hypotension, electrolyte abnormalities) are usually indicative of primary AI. The most specific sign of primary AI is hyperpigmentation of the skin and mucosal surfaces, which results from the melanocyte-stimulating activity of β-lipotropin that derives from the same precursor as ACTH.

Table 35-11 Causes of Primary Adrenal Insufficiency

Autoimmune	Isolated adrenal insufficiency (Addison disease) Polyglandular autoimmune syndrome types I and II
Infectious	Tuberculosis Fungal Histoplasmosis Paracoccidioidomycosis HIV/AIDS Cytomegalovirus Syphilis African trypanosomiasis
Vascular	Bilateral adrenal hemorrhage Sepsis (Waterhouse-Friderichsen syndrome) Coagulopathy Thrombosis, embolism Infarction
Infiltrative	Metastatic carcinoma (most often lung, breast, stomach, or colon) Lymphoma Sarcoidosis Amyloidosis Hemochromatosis
Congenital	Congenital adrenal hyperplasia 21α-Hydroxylase deficiency 11β-Hydroxylase deficiency 3β-ol-Dehydrogenase deficiency 20,22-Desmolase deficiency Familial adrenocorticotropic hormone resistance syndromes Familial glucocorticoid deficiency Adrenoleukodystrophy Adrenomyeloneuropathy Adrenal hypoplasia
Iatrogenic	Bilateral adrenalectomy Anticoagulation therapy Drugs Adrenolytic: mitotane, aminoglutethimide, metyrapone, trilostane Other: ketoconazole, rifampin, etomidate, phenytoin, barbiturates, megestrol acetate

Patients with autoimmune adrenalitis present with vitiligo, Hashimoto thyroiditis (70% in APS II), type I diabetes, and pernicious anemia. Thinning or loss of pubic and axillary hair may occur in women as a result of lack of androgen production by the adrenal cortex. Both systolic and diastolic BP are usually reduced (systolic BP <110 mm Hg).

Acute (Primary) Adrenal Insufficiency. In critically ill patients, it is crucial to consider the possibility of adrenal insufficiency. AI should be suspected in the presence of unexplained catecholamine-resistant hypotension, especially if the patient has pallor, hyperpigmentation, vitiligo, scanty axillary and pubic hair, hyponatremia, or hyperkalemia. Furthermore, AI caused by adrenal hemorrhage and adrenal vein thrombosis should be considered in a severely ill patient with abdominal pain or rigidity, vomiting, confusion, and arterial hypotension. In acutely ill patients, a plasma cortisol level greater than 25 μg/dL rules out adrenal insufficiency, but a level in the normal range does not. Further testing may be required.

Laboratory Evaluation. Patients with adrenal insufficiency present with hyponatremia (frequent), hyperkalemia, acidosis, mild elevation of plasma creatinine concentrations, hypoglycemia, hypercalcemia (rare), mild normocytic anemia, lymphocytosis, and mild eosinophilia. In addition, hormone levels are useful in diagnosis. A random measurement of serum cortisol level is usually inadequate to assess adrenal function caused by the pulsatile and diurnal variation of cortisol secretion. However, a morning cortisol level (measured between 8 and 9 AM) of 3μg/dL or less indicates primary AI and obviates the need for further tests. A level of 19 μg/dL or greater rules AI out. Patients with levels between 3 and 19 μg/dL need further testing. If primary AI is suspected, basal ACTH and cortisol levels should be measured followed by a short ACTH stimulation test. For testing, synthetic ACTH (cosyntropin) is given intravenously or intramuscularly at 250 μg, and the serum cortisol level is measured 60 minutes after injection. A normal response to this test (cortisol ≥20 μg/dL) excludes primary AI. In patients with severe secondary AI, plasma cortisol increases little or not at all after the administration of cosyntropin because of adrenocortical atrophy.

Detection of adrenal cortex antibodies or 21-hydroxylase autoantibodies supports the diagnosis of autoimmune adrenalitis. Antibodies against other endocrine glands are common in patients with autoimmune AI, and evaluation might be warranted. However, the incidence of antiadrenal antibodies in serum from patients with normal adrenal function who have other autoimmune endocrine diseases is low (2%), with the exception of those with hypoparathyroidism (16%). Abdominal CT scan may be helpful if infection, hemorrhage, infiltration, or neoplastic disease is suspected.

Treatment. In chronic AI, any underlying cause, such as infection or malignancy, should be treated. Glucocorticoid replacement is usually required for symptomatic patients and is given in two or three daily doses with half to two thirds of the daily dose given in the morning to mimic the physiologic daily pattern of cortisol secretion. Hydrocortisone (15-25 mg) or cortisone acetate (25-37.5 mg) is preferred because of its mineralocorticoid action and shorter biological half-life, which prevents unfavorably high nighttime glucocorticoid activity. The goal is to use the smallest dose that relieves the patient's symptoms to prevent side effects from steroid use, such as weight gain and osteoporosis. Because a reliable marker of glucocorticoid action is lacking, clinical judgment and careful assessment of clinical signs and symptoms guide treatment.

In patients with primary AI, mineralocorticoid replacement is necessary and is attained by fludrocortisone, in a single daily dose of 0.05 to 0.2 mg, as a substitute for aldosterone. The dose can be adjusted based on measurements of BP, serum sodium and potassium, and renin activity (aiming at concentrations within the middle or upper normal range). All patients should carry a card or wear a bracelet or necklace with information on current treatment and recommendations in emergency situations. Patients should be advised to double or triple the dose of hydrocortisone temporarily when they have a febrile illness or injury. In addition, they should be given ampoules of glucocorticoid for self-injection or glucocorticoid suppositories to be used in case of vomiting.

Patients with ACTH deficiency should be treated with glucocorticoids, preferably hydrocortisone (i.e., the

glucocorticoid that the adrenals produce). Hydrocortisone replacement, usually 10 to 12 mg/m^2, should be given orally as 20 to 30 mg/day divided into two doses with two thirds of the daily dose given in the morning and one third given in the early afternoon or evening (Coursin and Wood, 2002; Toogood and Stewart, 2008). Alternatively, prednisone is given at a total daily dosage of 5 to 7.5 mg/day in one to two doses. Clinical evaluation is the primary modality to assess the adequacy of cortisol replacement. It is important to increase the dose of hydrocortisone two- to threefold in time of illness and other stresses. All patients should carry medical alert tags or cards to identify the need for high-dose glucocorticoids in an emergency. Those with secondary adrenal insufficiency usually do not require mineralocorticoid replacement because ACTH is not essential for aldosterone secretion.

Secondary and Tertiary Adrenal Insufficiency

Key Points

- Secondary adrenal insufficiency results from ACTH deficiency and is often seen in panhypopituitarism or after chronic glucocorticoid excess.
- Lack of production of CRH from the hypothalamus results in tertiary adrenal insufficiency.
- In secondary adrenal insufficiency, mineralocorticoid production is maintained by the RAS. Thus, hyperkalemia is absent, but hyponatremia may occur as a result of loss of glucocorticoid effect on free-water clearance.
- Low ACTH and cortisol levels suggest secondary or tertiary adrenal insufficiency.

Secondary adrenal insufficiency is defined as a deficiency of ACTH. Isolated ACTH deficiency is rare and may be congenital or caused by lymphocytic hypophysitis. Secondary AI more commonly occurs in the setting of panhypopituitarism from underlying causes such as pituitary or metastatic tumors, craniopharyngioma, infections (TB, histoplasmosis), infiltrative disease (sarcoidosis), head trauma, or postpartum pituitary necrosis (Sheehan syndrome). Chronic glucocorticoid excess, either exogenous (glucocorticoid treatment for >4 weeks) or endogenous (Cushing syndrome), causes secondary AI by prolonged suppression of the production of CRH. Tertiary adrenal insufficiency results from the lack of CRH production from the hypothalamus.

Clinical Presentation. Signs and symptoms are similar with those of primary AI, but electrolyte and fluid abnormalities or hypotensive symptoms are absent because the mineralocorticoid production is still maintained by the RAS. Hyperpigmentation is not seen. Menstrual dysfunction, headache and visual symptoms, hypothyroidism, and DI may be present as a result of panhypopituitarism (see Approach to Pituitary Diseases).

Laboratory Evaluation. Plasma cortisol and ACTH levels should be checked initially. Low ACTH (<5 pg/mL) and cortisol levels suggest secondary or tertiary adrenal insufficiency, and pituitary CT or MRI is indicated. The cosyntropin stimulation test may be helpful in identifying adrenal insufficiency. With an abnormal result, ACTH level may determine primary (high ACTH) versus secondary (normal or low ACTH) disease. However, in secondary AI, the ACTH stimulation test might not be abnormal because sufficient ACTH might be present to prevent adrenal gland atrophy. In these patients, CRH stimulation test can assess ACTH response. Secondary AI shows little or no increase in the ACTH or cortisol level throughout the test but in tertiary AI, the ACTH increases in an exaggerated fashion and remains elevated longer. The insulin tolerance test and the metyrapone test are also available but less commonly used to assess the integrity of the HPA axis by its response to hypoglycemia or inhibited cortisol synthesis, respectively.

Treatment. As described in primary AI, treatment of underlying disorders and glucocorticoid replacement are necessary in secondary and tertiary AI; however, mineralocorticoid replacement is not.

Isolated Aldosterone Deficiency

See eAppendix 35-3 online.

DISORDERS OF CORTICAL HYPERFUNCTION: HYPERCORTISOLISM

Cushing Syndrome

Key Points

- Cushing syndrome results from chronic exposure to excessive levels of glucocorticoids.
- Cushing syndrome may be ACTH dependent (pituitary or ectopic tumors) or ACTH independent (adrenal or exogenous glucocorticoids).
- Reddish purple striae, plethora, proximal muscle weakness, easy bruising, and unexplained osteoporosis are discriminatory symptoms.
- CT or MRI of the adrenal glands may differentiate among the various types of ACTH-independent Cushing syndrome.

Cushing syndrome is a group of signs and symptoms that result from prolonged and inappropriately high exposure of tissue to glucocorticoids (Nieman et al., 2008). Excess cortisol production is the hallmark of endogenous Cushing syndrome and may result from excess ACTH secretion from the pituitary (Cushing disease) or from ectopic tumors secreting ACTH or CRH. ACTH-independent adrenal production of cortisol is caused by adrenocortical tumors or hyperplasias. However, the most common cause of Cushing syndrome is *iatrogenic* from exogenous glucocorticoid administration. Certain psychiatric disorders (anxiety, depression), poorly controlled diabetes, and alcoholism can be associated with mild hypercortisolism and may produce results suggestive of Cushing syndrome.

Clinical Presentation. Although Cushing syndrome might be easy to diagnose when full blown, the diagnosis can be challenging in mild cases. The spectrum of clinical presentation is broad. Some discriminatory symptoms

EAPPENDIX

35-3 Isolated Aldosterone Deficiency

Key Points

- Isolated aldosterone deficiency may be congenital or acquired.
- In hyporeninemic hypoaldosteronism, chronic asymptomatic hyperkalemia, normal or low sodium level, and mild to moderate renal insufficiency are usually present.
- Aldosterone secretion does not increase appropriately in response to salt restriction in all forms of hypoaldosteronism.

Background

Aldosterone deficiency disorders may be congenital or acquired. The congenital disorders may be caused by ineffective aldosterone synthesis or pseudohypoaldosteronism (ineffective aldosterone action). However, aldosterone deficiency is most commonly a secondary cause or due to impaired renin release from the kidney (hyporeninemic hypoaldosteronism).

Clinical Presentation

The typical patient with acquired aldosterone deficiency is 50 to 70 years old and usually presents with chronic asymptomatic hyperkalemia with a normal or low sodium level and mild to moderate renal insufficiency. Half of patients present with hyperchloremic metabolic acidosis caused by renal tubular acidosis type IV, and more than half have diabetes.

Diagnostic Studies

In most cases of isolated hypoaldosteronism, a deficiency in renin production is noted in adults with diabetes mellitus and mild renal failure and in whom hyperkalemia and metabolic acidosis are out of proportion to the degree of renal impairment. The feature common to all forms of hypoaldosteronism is the inability to increase aldosterone secretion appropriately in response to salt restriction. Most patients have unexplained hyperkalemia, which is often exacerbated by restriction of dietary sodium intake. Plasma renin levels fail to increase normally after sodium restriction and postural changes.

Treatment

The treatment is to replace the mineralocorticoid deficiency. Administration of fludrocortisone (0.05-0.15 mg/day orally) should restore the electrolyte imbalance if the salt intake is adequate (e.g., 150-200 mmol/day). Higher doses of mineralocorticoid may be required in patients with hyporeninemic hypoaldosteronism to correct hyperkalemia, which might be problematic in patients with hypertension or congestive heart failure. An alternative approach is to reduce salt intake and administer furosemide, which can ameliorate acidosis and hyperkalemia.

include reddish purple striae, plethora, proximal muscle weakness, bruising without any obvious trauma, and unexplained osteoporosis. More often, patients present with features caused by cortisol excess such as obesity, depression, diabetes, hypertension, or menstrual irregularity. A dorsocervical fat pad (buffalo hump), facial and supraclavicular fullness, thin skin, peripheral edema, hirsutism or female balding, and poor skin healing are typically seen in Cushing syndrome. Children usually have slow growth, abnormal genital virilization, short stature, and pseudoprecocious or delayed puberty.

Laboratory Evaluation. Before the diagnosis of Cushing syndrome is considered, exogenous intake of glucocorticoids should be excluded. According to the 2008 Endocrine Society Clinical Practice Guidelines (Nieman et al., 2008), tests to be considered for diagnosis include urine free cortisol (UFC); a late-night salivary cortisol, 1-mg overnight DST; or the longer, low-dose DST (2mg/d for 48 h). UFC and salivary cortisol should be obtained at least twice. The diagnosis of Cushing syndrome is made if two test results are unequivocally abnormal. The diagnostic accuracy of other tests previously used, such as random cortisol levels, is too low to recommend them for testing (Figure 35-3).

The UFC provides an integrated assessment of cortisol secretion over 24 hours and measures the cortisol not bound to cortisol-binding globulin (CBG). Unlike serum cortisol, which measures both free and CBG-bound cortisol, UFC is not affected by conditions and medications that alter CBG. A 24-hour urine cortisol secretion or an overnight urine sample (10 PM to 8 AM) can be ordered in conjunction with urine creatinine to assure accuracy of the results. UFC reflects renal filtration, and values are significantly lower in patients with moderate to severe renal impairment. A patient can be assumed to have Cushing syndrome if basal urinary cortisol secretion is more than three times the upper limit of normal and one other test is abnormal. However, UFC may be normal in mild cases of Cushing syndrome, in which case salivary cortisol may be more useful.

Late-night salivary cortisol is usually measured at bedtime or between 11 PM and midnight because the loss of circadian rhythm, with absence of a late-night cortisol nadir, is a consistent biochemical abnormality in those with Cushing syndrome. The active free cortisol in the blood is in equilibrium with cortisol in the saliva, and the concentration of salivary cortisol does not appear to be affected by the rate of saliva production. Overall, in adults, the accuracy of the test is similar to that of UFC.

Various protocols have been used for the DST, but most commonly 1 mg of dexamethasone is given between 11 PM and midnight, and cortisol is measured between 8 AM and 9 AM the following morning. In patients with endogenous Cushing syndrome, a low dose of dexamethasone fails to suppress ACTH and cortisol secretion. A normal response is a serum cortisol of 5 µg/dL or less. To enhance DST sensitivity, experts have advocated requiring a lower cutoff for suppression of the serum cortisol to 1.8 µg/dL or less to achieve sensitivity rates greater than 95%.

Some endocrinologists prefer to use the 48-hour 2-mg/day, low-dose DST (LDDST) as an initial test because of its improved specificity compared with the 1-mg test. The LDDST may be helpful in conditions with overactivation of the HPA axis but without true Cushing syndrome, such as in certain psychiatric disorders, obesity, and alcoholism. Dexamethasone is given in doses of 0.5 mg every 6 hours for 48 hours, beginning at 9 AM on day 1. Serum cortisol is measured at 9 AM on the second day 6 hours after the last dose of dexamethasone (Funder et al., 2008).

New studies have shown a link between baseline levels of ACTH and major depressive disorder. One study published in the *Journal of Affective Disorders* in 2013 using a combined dexamethasone suppression–CRH stimulation test

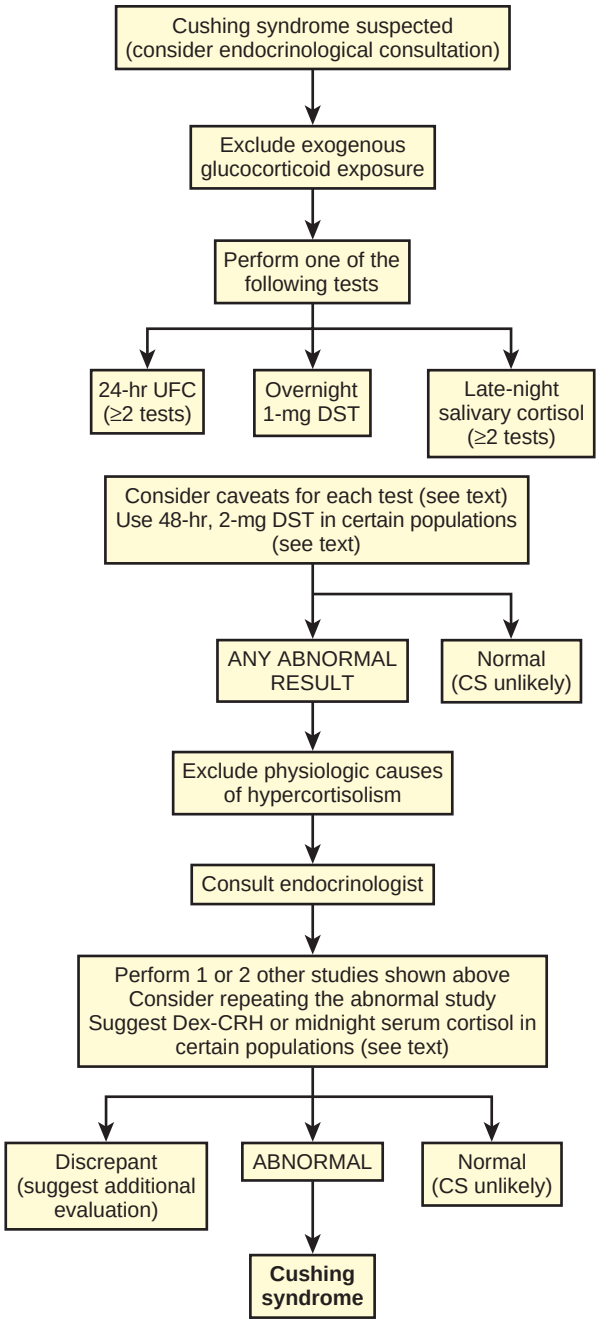


Figure 35-3 Clinical approach to a patient with suspected Cushing syndrome. *CS,* Cushing syndrome; *Dex-CRH,* dexamethasone/corticotropin-releasing hormone test; *DST,* dexamethasone suppression test; *UFC,* urine free cortisol. (Courtesy The Endocrine Society.)

found higher baseline levels of ACTH in patients with major depressive disorder compared with control participants (Sher et al., 2013). These results implied decreased feedback control of ACTH by circulating cortisol levels. The correlation between these finding is not known but may represent a new area for diagnosing and treating major depression. Additional testing is recommended for patients with initial abnormal or discordant results, such as the dexamethasone–CRH stimulation test or the midnight serum cortisol test. The dexamethasone–CRH stimulation test has been developed to improve the sensitivity of the LDDST. The administration of dexamethasone at a dose of 2 mg/day over 48 hours is followed by administration of CRH (1 µg/kg IV) 2 hours after the last dose of dexamethasone. Cortisol is measured 15 minutes later. ACTH and cortisol should increase after administration of CRH in patients with Cushing disease.

After hypersecretion of cortisol is confirmed, the next step is to determine whether the Cushing syndrome is ACTH dependent or independent. This is accomplished through measurement of the late-afternoon ACTH level when it is normally low. Cushing syndrome is ACTH *dependent* if plasma ACTH is greater than 10 pg/mL and ACTH *independent* if ACTH level is less than 5 pg/mL. For an intermediate ACTH level, further testing with the CRH stimulation test is performed. A rise in cortisol by 20% or in ACTH of at least 50% over baseline after administration of CRH is considered evidence for an ACTH-dependent lesion. In these patients, high-dose dexamethasone suppression test (HDDST), combined with cranial MRI studies, may help in localizing the site of ACTH overproduction. HDDST (2 mg of dexamethasone every 6 hours for 2 days) provides close to 100% specificity if the criterion used is suppression of urinary free cortisol by more than 90% and can differentiate Cushing disease from ectopic ACTH production. If the workup results are still equivocal or suggestive of ectopic ACTH production, inferior petrosal sampling is performed, obtaining ACTH samples from the periphery and petrosal sinuses simultaneously. A ratio of petrosal sinus to peripheral ACTH of 2 to 1 is diagnostic of a pituitary source and can be further used to localize the side of ACTH production from the pituitary gland. For patients with ACTH-independent lesions, abdominal CT or MRI may localize the site of the lesion.

Treatment. The treatment of Cushing syndrome depends on the cause. For endogenous disease, surgical resection of the causative tumor is indicated. The treatment of choice for Cushing disease is transsphenoidal hypophysectomy. Other treatment modalities include various forms of radiation therapy and pharmacologic inhibition of ACTH secretion.

Patients with adrenal adenomas are treated with unilateral adrenalectomy and have an excellent prognosis. These patients require glucocorticoid therapy both during and after surgery until the residual adrenal gland recovers. For patients with biopsy-proven adrenal carcinoma that is not amenable to surgery, mitotane is the treatment of choice. For ectopic ACTH syndrome, ideal treatment is the excision of identified benign tumors. However, for ectopic tumors that are unidentified or unresectable, medications that block steroidogenesis, such as ketoconazole, metyrapone, or aminoglutethimide, may be useful.

Aldosteronism

Key Points

- In primary aldosteronism (PA), secretion of aldosterone is inappropriately high and, when it is the result of an adrenal adenoma, it is relatively autonomous from renin–angiotensin secretion.
- Secondary aldosteronism is generally related to hypertension, and the aldosterone secretion is driven by high plasma renin.
- Patients present with hypokalemia and hypertension that may be resistant to treatment (Conn syndrome).
- The ratio of plasma aldosterone to renin is the most reliable test for screening for PA.
- A ratio of plasma aldosterone to renin of 20 or greater and a plasma aldosterone higher than 15 ng/dL support the diagnosis of primary hyperaldosteronism.

Background. Primary aldosteronism was first described by Jerome Conn in 1955 as a syndrome (Conn syndrome) characterized by hypertension and hypokalemia caused by an adrenal aldosterone-producing adenoma (APA). The secretion of aldosterone from the adrenal *zona glomerulosa* is regulated mainly by the RAS and by potassium anions. PA is now recognized to be the most common form of secondary hypertension. In PA, the secretion of aldosterone is inappropriately high, relatively autonomous from the RAS, and nonsuppressible by volume expansion or sodium loading. In secondary aldosteronism associated with hypertension, the aldosterone secretion is driven by high plasma renin and is suppressed by volume expansion.

Primary aldosteronism is commonly caused by an APA (35% of cases); unilateral or bilateral idiopathic adrenal hyperplasia (IHA) (2% and 60% of cases, respectively); an adrenal carcinoma (rare); or in rare cases, familial hyperaldosteronism (FH), either type I (glucocorticoid-remediable aldosteronism [GRA]) or type II (familial occurrence of APA, IHA, or both). There are two types of aldosteronomas: a corticotrophin-responsive (and renin-unresponsive) type and a renin-responsive type. PA had been previously described in fewer than 1% of patients with hypertension. However, recent studies estimate the prevalence of PA is 5% to 13% among hypertensive patients.

Clinical Presentation. Few symptoms are specific to the syndrome. Patients present with moderate to severe hypertension that may be resistant to usual pharmacologic treatments. Hypokalemia is usually present, and the serum sodium concentration tends to be high-normal or slightly above the upper limit of normal. Patients with marked hypokalemia may have muscle weakness and cramping, headaches, palpitations, polydipsia, polyuria, or nocturia (Funder et al., 2008). However, hypokalemia might be absent; thus, any patient with hypertension could be a candidate for this disorder. Patients with PA may be at higher risk than other patients with hypertension for target organ damage of the heart and kidney. A significantly higher rate of cardiovascular events (i.e., stroke, atrial fibrillation, and myocardial infarction [MI]) has been noted in patients with APA or IHA compared with patients matched for age, gender, and hypertension. Patients with APA have more severe hypertension, more frequent hypokalemia, and

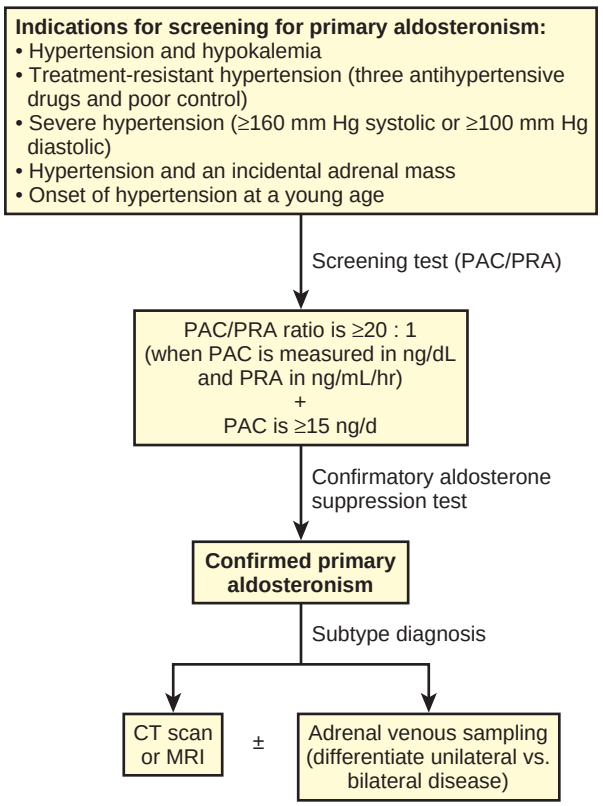


Figure 35-4 Indications for screening for primary aldosteronism and flow chart for clinical assessment. *CT,* computed tomography; *MRI,* magnetic resonance imaging; *PAC,* plasma aldosterone concentration; *PRA,* plasma renin activity.

higher plasma and urinary levels of aldosterone and are younger (<50 years) than those with IHA.

Hypokalemia, when present, strongly suggests associated mineralocorticoid excess. However, most patients with PA have baseline blood levels of potassium in the normal range. Therefore, hypokalemia should not be the criterion used to make the diagnosis of PA. Screening for PA should be considered in patients with hypertension and hypokalemia, treatment-resistant hypertension (three antihypertensive drugs and poor control), severe hypertension (≥160 mm Hg systolic or ≥100 mm Hg diastolic), hypertension and an incidental adrenal mass, and onset of hypertension at a young age (Figure 35-4). When an evaluation for secondary hypertension is performed, the diagnosis of PA should also be considered. In patients with suspected PA, the screening can be accomplished by measuring a morning ambulatory paired random plasma aldosterone concentration (PAC) and plasma renin activity or concentration (PRA or PRC). This test can be performed while the patient is taking antihypertensive medications (except for spironolactone, eplerenone, and high-dose amiloride) and without posture stimulation. The aldosterone-to-renin ratio (ARR) is currently the most reliable available means of screening for PA. A test result is considered positive when the PAC/PRA ratio is 20:1 or greater (when PAC is measured in nanograms per deciliter and PRA in nanograms per deciliter per hour) and the PAC is higher than 15 ng/dL. All positive results should be followed by a confirmatory aldosterone suppression test to verify autonomous aldosterone production before treatment is initiated.

If the diagnosis of PA is confirmed, lateralization of the source of the excessive aldosterone secretion is critical to guide further management. All patients with PA should undergo an adrenal CT scan as the initial study in subtype testing and to exclude large masses that may represent adrenocortical carcinoma. MRI has no advantage over CT in subtype evaluation of PA. In patients with PA, adrenal venous sampling is the reference standard test to differentiate unilateral from bilateral disease. This is important because unilateral adrenalectomy in patients with APA or primary adrenal hyperplasia results in normalization of hypokalemia and improvement of hypertension in all patients and cure of hypertension in 30% to 60%. Glucocorticoid-remediable aldosteronism is an autosomal dominant disease and may be diagnosed by genetic testing.

Treatment. The treatment approach depends on the cause of PA. Unilateral laparoscopic adrenalectomy is an excellent treatment option for patients with APA or unilateral hyperplasia. BP control improves in almost 100% of these patients postoperatively, and the average long-term cure rates of hypertension after unilateral adrenalectomy for APA range from 30% to 72%. A potassium supplement or a mineralocorticoid receptor antagonist (or both) should be given preoperatively to correct the hypokalemia but should be discontinued postoperatively.

Medical management is recommended for patients with APA who do not undergo surgery and for those with IHA or GRA. Spironolactone has been the drug of choice for PA and is titrated to achieve BP control and normokalemia without the aid of oral potassium supplement. Eplerenone is a competitive and selective aldosterone receptor antagonist and may be used as an alternative agent. Compared with spironolactone, eplerenone has less antiandrogenic and progestational actions but is more expensive. In patients who are intolerant to aldosterone receptor antagonists, amiloride may be an alternative treatment that can reduce BP and normalize potassium levels, but it does not protect against the negative effects of aldosterone excess. Patients with IHA may be resistant to drug therapy caused by hypervolemia and may require a second antihypertensive agent such as a thiazide diuretic in combination with the aldosterone receptor antagonist.

DISORDERS OF HYPERFUNCTION: ADRENAL MEDULLA

Pheochromocytoma

Key Points

- Pheochromocytomas are catecholamine-secreting neuroendocrine tumors that originate in the adrenal medulla (80% to 85% of cases) or in any sympathetic ganglion (paragangliomas).
- Hypertension, tachycardia, pallor, palpitations, diaphoresis, and anxiety are common.
- Paroxysmal hypertension often occurs, even in normotensive persons, and may be severe and result in hypertensive emergencies.
- Plasma and urine catecholamines and metanephrines are measured to diagnose pheochromocytoma.
- CT, MRI, and iodine-123-meta-iodo-benzyl-guanidine (^{123}I-MIBG) may be helpful for tumor localization.

Pheochromocytomas are catecholamine-secreting neuroendocrine tumors arising from chromaffin cells of neural crest origin (Lenders et al., 2005). About 80% to 85% of pheochromocytomas originate in the adrenal medulla, and 15% to 20% are extraadrenal (paragangliomas). Pheochromocytomas are rare tumors with an incidence of one to two per 100,000 adults per year. Sporadic forms of pheochromocytoma are usually diagnosed in individuals age 40 to 50 years, but hereditary forms are diagnosed earlier, most often before age 40 years. The traditional "rule of 10" for pheochromocytomas (10% bilateral, 10% extraadrenal, 10% familial, 10% malignant) is now challenged by advances in diagnosis and genetics. Hereditary pheochromocytomas occur in MEN II, von Hippel-Lindau syndrome, neurofibromatosis type 1, and familial paragangliomas. Pheochromocytoma is rare in children but, when found, is often extraadrenal, multifocal, and associated with hereditary syndromes.

Clinical Presentation. Paroxysmal signs and symptoms due to the episodic secretion of catecholamines provide clues to the diagnosis of pheochromocytoma. The presentation can vary greatly, and therefore the pheochromocytoma is often referred to as the "great mimic." Anesthesia and tumor manipulation are the most well-known stimuli to elicit a catecholaminergic crisis. Hypertension, tachycardia, pallor, palpitations, diaphoresis, headache, and feelings of panic or anxiety are common. The hypertension is often paroxysmal and may occur in patients with hypertension or in normotensive persons. The hypertensive episodes can be severe, resulting in hypertensive emergencies. Persons with paragangliomas may have normal BP or hypotension. Orthostatic hypotension (a result of hypovolemia), fever, nausea, flushing, leukocytosis, and polycythemia are less common findings. Metabolic abnormalities may be present and include hyperglycemia, lactic acidosis, and weight loss.

Laboratory Evaluation. All patients with suspected pheochromocytoma should undergo biochemical testing. Traditional tests include measurements of urinary and plasma catecholamines, urinary metanephrines (normetanephrine and metanephrine), and urinary vanillylmandelic acid. Measurement of plasma-fractionated metanephrines (normetanephrine and metanephrine) is a newer test. Plasma and urine metanephrine measurements are the most sensitive tests for diagnosis but do not always indicate a pheochromocytoma. Many physiological stimuli (i.e., stress), drugs (e.g., phenoxybenzamine, tricyclic antidepressants), and clinical conditions (i.e., hyperthyroidism, heart failure, stroke) may cause an increase in circulating catecholamines and metabolites and lead to false-positive test results. The use of clonidine or glucagon to suppress catecholamine release from the sympathoadrenal system provides a dynamic pharmacologic test to distinguish increased catecholamine release caused by sympathetic activation from increased release caused by a pheochromocytoma.

If there is biochemical evidence for pheochromocytoma, tumor localization by CT scan of the entire abdomen (and pelvis), with and without contrast, should be performed. MRI with gadolinium has similar diagnostic sensitivity (90%-100%) and specificity (70%-80%) and is usually the preferred modality, especially for extraadrenal lesions. ^{123}I-MIBG isotope scanning has increased specificity (95%-100%) over CT and MRI and is more appropriate for patients with extraadrenal, metastatic, multifocal, or recurrent disease.

Treatment. Preoperatively, phenoxybenzamine, prazosin, doxazosin, or urapidil can be used for the blockade of the a-adrenoceptors. Phenoxybenzamine is often preferred because it blocks α-adrenoceptors noncompetitively. Alternative drugs for preoperative management are labetalol or calcium channel blockers, either alone or in combination with α-adrenergic receptor blockers. Treatment must be initiated 10 to 14 days before surgery and is titrated until mild orthostasis (systolic BP should not fall below 90 mm Hg in standing position) is present. Blockade of β-adrenoceptors should never be initiated before blockade of α-adrenoceptors. Laparoscopic removal of intra- and extraadrenal pheochromocytomas is the preferred surgical approach. All patients should be followed up every year for at least 10 years after surgery. BP and catecholamines should be monitored indefinitely in patients with extraadrenal or familial pheochromocytoma to detect possible recurrence. For malignant disease, radical surgical removal is recommended, but the 5-year survival rate remains poor (~50%). Treatment with ^{131}I-MIBG, cytotoxic chemotherapy, and molecularly targeted therapies have shown disappointing results.

MIXED DISORDER: CONGENITAL ADRENAL HYPERPLASIA

See eAppendix 35-4 online.

KEY TREATMENT

- In primary adrenal insufficiency, long-term glucocorticoid and mineralocorticoid replacement is necessary. The baseline steroid dose should be increased two- to threefold during periods of febrile illness or injury (Arlt and Allolio, 2003; Salvatori, 2005) (SOR: A).
- Therapeutic intervention for secondary and tertiary adrenal insufficiency requires treatment of underlying disorders. Glucocorticoid replacement is necessary (Arlt and Allolio, 2003) (SOR: A).
- Oral fludrocortisone (0.05-0.15 mg/day) is the treatment of choice for aldosterone deficiency. In hyporeninemic hypoaldosteronism, furosemide with reduced salt intake can ameliorate acidosis and hyperkalemia (Arlt and Allolio, 2003) (SOR: A).
- Surgical resection is usually the treatment of choice for Cushing disease and ACTH-independent Cushing syndrome (Nieman et al., 2008) (SOR: A).
- Treatment of aldosteronism is directed at the underlying cause. Aldosterone antagonists such as spironolactone are effective therapy (Funder et al., 2008) (SOR: A).
- Laparoscopic removal of intra- and extraadrenal pheochromocytomas after α-adrenoceptor blockade is the preferred treatment (Lenders et al., 2005 (SOR: A).
- Treatment of congenital adrenal hyperplasia with glucocorticoids may result in amelioration of symptoms (New, 2004, 2010) (SOR: A).

EAPPENDIX

35-4 Mixed Disorder: Congenital Adrenal Hyperplasia

Key Points

- Congenital adrenal hyperplasia is a family of inherited disorders of adrenal steroidogenesis.
- Whereas female patients may present with symptoms of androgen excess, male patients may be asymptomatic or present with diminished fertility or oligozoospermia.
- Patients can be identified early with hormonal and molecular genetic testing.

Congenital adrenal hyperplasia (CAH) is a family of inherited disorders of adrenal steroidogenesis. These defects result in the absence of or the decreased synthesis of cortisol, which causes oversecretion of adrenocorticotropic hormone via feedback regulation that leads to overstimulation and hyperplasia of the adrenals. The clinical symptoms vary from mild to severe and depend on the particular hormones that are deficient or produced in excess. In the classical form of CAH, there is a severe enzymatic defect owing to mutations in the CYP21 gene. The affected female may present with genital ambiguity at birth because of virilization of the genitalia prenatally (New, 2004). The late-onset form of CAH does not present with prenatal virilization and is less severe. The milder enzyme deficiency, called nonclassical 21-hydroxylase deficiency (NC21OHD), is most frequent in Ashkenazi Jews and is the most common autosomal recessive disorder in humans. Similar to classical CAH, NC21OHD may cause premature development of pubic hair, advanced bone age, accelerated linear growth velocity, and diminished final height in both men and women. Women may present with symptoms of androgen excess, including hirsutism, temporal baldness, and infertility. In women, secondary amenorrhea is a frequent occurrence, and menarche may be normal or delayed. Male patients may be asymptomatic or present with diminished fertility or oligozoospermia, early beard growth, acne, and growth spurt. Patients can be identified early with hormonal and molecular genetic testing and be treated with glucocorticoids, which results in reversal of symptoms within 3 months (New, 2010).

Ovarian and Testicular Disorders

Sexual development in both males and females is driven by the HPA. The normal process is the result of pulsatile release of GnRH from the hypothalamus, which stimulates the pituitary to release FSH and LH (GHRH and GH also play a role). Release of FSH and LH activates the ovaries and testes to produce estrogen and testosterone and is responsible for stimulation of gametogenesis. This process is assisted by conversion of adrenal androgens from the adrenal cortex into androstenedione and subsequently into potent androgens (testosterone) or estrogens (estradiol) in the peripheral tissues (see Adrenal Glands section). Errors can occur along this complex pathway, resulting in early sexual development (precocity), delayed sexual development (delayed menarche), errors of translation (male feminization syndrome), early loss of reproductive function (premature menopause), and inappropriate response to stimuli (polycystic ovary syndrome [PCOS])

NORMAL SEXUAL DEVELOPMENT

Sexual differentiation in humans is controlled by genetics (presence of Y chromosome determines development of testis and absence determines the development of ovary with additional X chromosome), environment (e.g., nutrition), and hormones (MacLaughlin and Donahoe, 2004). Congenital conditions associated with aberrations of chromosomal, gonadal, or anatomic sex development are called "disorders of sex development" (Houk et al., 2006).

In the postgonadal phase, hormones control external genitalia differentiation and secondary sexual development. Puberty refers to a physiological transition phase (>4 years long) between childhood and adulthood during which there is pubertal growth spurt and development of secondary sexual characteristics. Puberty is preceded by adrenarche (6-7 years in girls and 7-8 years in boys), marked by increasing amounts of adrenal androgens (DHEA, DHEA-S, and androstenedione). The growth spurt (a striking increase in growth velocity during puberty) is a complex hormonal phenomenon in which GH, thyroid hormones, and sex steroids play major roles. Gonadarche (the secretion of gonadal sex steroids) follows adrenarche and is initiated by activation of the GnRH pulse generator in the hypothalamus. These GnRH pulses result in increased gonadotropin secretion and subsequent production of sex hormones by the gonads.

Sexual maturation in females starts with breast development (thelarche) at a mean age of 11 years followed by pubic hair development and menses (menarche). In males, it starts with scrotal corrugation and testicular enlargement at a mean age of 11.5 years followed by growth of the penis and pubic hair.

In males, release of LH stimulates testicular Leydig cells to produce testosterone. FSH, in conjunction with testosterone, stimulates spermatogenesis. In females, FSH stimulates development of primary ovarian follicles and increases production of estrogen from ovarian granulosa cells. LH in females stimulates ovarian theca cells to produce androgens and the corpus luteum to synthesize progesterone. LH induces ovulation through the midcycle surge.

Estradiol production in males increases the bone age, BMD, and the rate of epiphyseal fusion. In females, it stimulates the development of the breasts, labia, vagina, and uterus and proliferation of endometrium. In addition, estradiol enhances development of and increase in the ducts of the breast and body fat. Whereas estrogen in low levels enhances linear growth, high levels increase the rate of fusion of epiphyses. Testosterone is responsible for the increase in muscle mass, sebaceous glands, and voice changes seen in pubertal males, and it is a linear growth accelerator. In females, testosterone accelerates linear growth and stimulates pubic and axillary hair development. Progesterone in females is responsible for development of a secretory endometrium and plays a role in breast development. Lineal growth and pubic hair development in both males and females is caused by androgens from the adrenal gland.

Figures 35-5 and 35-6 show normal pubertal developmental stages of Marshall and Tanner.

ABNORMAL PUBERTY

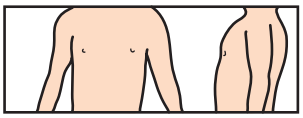
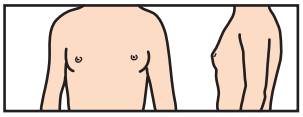
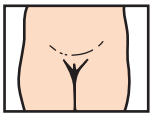
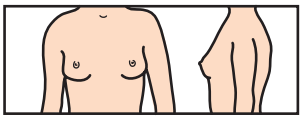
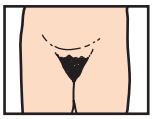
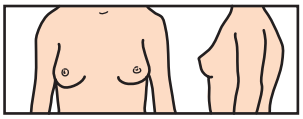
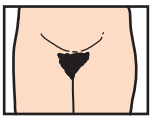
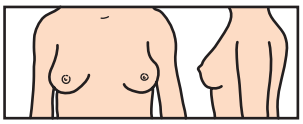
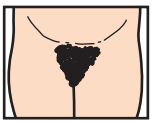
Key Points

- Evaluation should begin if signs of puberty develop in girls younger than 8 years or in boys younger than 9 years.
- Diagnoses of true puberty and pseudopuberty should be differentiated.
- Evaluation includes a comprehensive history and physical examination, growth chart, and wrist radiograph.
- If true puberty is suspected, consider cranial CT or MRI to rule out CNS lesions.

Evaluation of suspected abnormal puberty begins with obtaining a detailed history, including growth and development (timing of physical and developmental milestones), medical conditions, dietary history, social history, ethnicity, and family history. Physical examination should be thorough, including current weight, and a complete examination, with focused examination for development of secondary sexual characteristics and genitalia. A detailed growth chart from birth to the present day should be obtained. A radiograph of the left wrist is needed to estimate bone age (Blondell et al., 1999).

Precocious Puberty

Precocious puberty (premature onset of puberty) may be defined as the appearance of secondary sexual maturation at an early age. The age of onset of puberty before the age of 8 years in girls and before the age of 9 years in boys is considered precocious puberty. The Lawson Wilkins Pediatric Endocrine Society guidelines recommend that breast development or pubic hair in white girls before age 7 years and in black girls before age 6 years should be evaluated for precocious puberty. Boys of all races should be evaluated for precocious puberty with signs of secondary sexual development at 9 years of age or younger (Kaplowitz and Oberfield, 1999). These guidelines are under some debate as setting perhaps too early an age for defining

Tanner stage	Breasts*	Standard	Pubic hair*	Standard	Growth	Other
1	Prepubertal, elevation of papilla only		Prepubertal, villus hair only	—	Basal; about 5.0 to 6.0 cm (2.0 to 2.4 in) per year	Adrenarche Ovarian growth
2	Breast buds appear under enlarged areaolae (11.2 years)		Sparse growth of slightly pigmented hair along the labia (11.9 years)		Accelerated: about 7.0 to 8.0 cm (2.8 to 3.2 in) per year	Clitoral enlargement Labia pigmentation Uterus enlargement
3	Breast tissue beyond areola without contour separation (12.4 years)		Hair is coarser, curled, and pigmented; spreads across the pubes (12.7 years)		Peak velocity: about 8.0 cm (3.2 in) per year (12.5 years)	Axillary hair (13.1 years) Acne (13.2 years)
4	Projection of areola and papilla forms a secondary mound (13.1 years)		Adult-type hair but no spread to medial thigh (13.4 years)		Deceleration: <7.0 cm (2.8 in) per year	Menarch (13.3 years) Regular menses (13.9 years)
5	Adult breast contour with projection of papilla only (14.5 years)		Adult-type hair with spread to medial thigh but not up linea alba (14.6 years)		Cessation at about 16 years	Adult genitalia

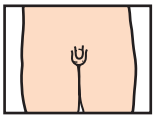
*The Tanner stages of puberty in girls are based on breast size and shape and pubic hair distribution. Mean age of milestone attainment is shown in parentheses for the reference population of Marshall and Tanner. Actual age at milestone attainment may vary among individuals and among different study populations.

Figure 35-5 Pubertal milestones for girls. (From Blondell RD, Foster MB, Dave KC. Disorders of puberty. *Am Fam Physician.* 1999;60:209, 223.)

precocity. Some child endocrinologists believe that defining precocity as only children with sexual development younger than 7 years will lead to missing some conditions that may respond to early intervention; they prefer the formerly used age of younger than 8 years old in girls to trigger investigation (Carel and Léger, 2008; Midyett et al., 2003; Traggiai and Stanhope, 2003). Children with developmental disabilities have a higher incidence of precocity (Siddiqui et al., 1999). However, the majority of children (>75%) investigated for precocious puberty have benign diagnoses that are considered to be normal variations and do not require any treatment (Kaplowitz, 2004).

Precocious puberty is classified as *central* (GnRH dependent) or *peripheral* (non-GnRH dependent). The peripheral group includes autonomous gonadal activation, gonadal tumors with production of sex steroids, adrenal disorders, and exposure to exogenous agents with properties of sex steroids. Precocious puberty may be differentiated into *progressive* (one stage to next in 3-6 months) or *nonprogressive* (no progression of pubertal signs over time). Other terminology is based on the pubertal signs in relation to the individual's gender. *Isosexual* refers to precocity in the same gender (e.g., feminization of a female). *Heterosexual* (or contrasexual) would be precocious puberty resulting in virilization of a female.

Benign variants of precocious pubertal development (incomplete precocious puberty or variations in pubertal development) include nonprogressive precocious puberty, isolated precocious thelarche, isolated precocious pubarche, isolated menarche, and adolescent (male) gynecomastia. *Isolated thelarche* (unilateral or bilateral breast development) without progression of other signs of puberty generally resolves spontaneously, especially in girls younger than 2 years and requires no treatment. *Isolated precocious pubarche* (pubic hair development) as a result of early adrenarche is usually self-limited. Evaluation beyond a complete history, physical examination, and bone age determination would include an ACTH stimulation test to rule out late-onset congenital adrenal hyperplasia. *Gynecomastia* in adolescent males is common and presents more of a social than a

Tanner stage	Standard	Genitalia*	Pubic hair*	Growth	Other
1		Prepubertal testes: <2.5 cm (1.0 in)	Prepubertal, villus hair only	Basal: about 5.0 to 6.0 cm (2.0 to 2.4 in) per year	Adrenarche
2		Thinning and reddening of scrotum (11.9 years) Testes: 2.5 to 3.2 cm (1.0 to 1.28 in)	Sparse growth of slightly pigmented hair at base of penis (12.3 years)	Basal: about 5.0 to 6.0 cm (2.0 to 2.4 in) per year	Decrease in total body fat
3		Growth of penis, especially length (13.2 years) Testes: 3.3 to 4.0 cm (1.32 to 1.6 in)	Thicker, curlier hair spreads to the mons pubis (13.9 years)	Accelerated: about 7.0 to 8.0 cm (2.8 to 3.2 in) per year	Gynecomastia (13.2 years) Voice breaks (13.5 years) Muscle mass increases
4		Growth of penis and glands, darkening of scrotum (14.3 years) Testes: 4.1 to 4.5 cm (1.64 to 1.8 in)	Adult-type hair but no spread to medial thigh (14.7 years)	Peak velocity: about 10.0 cm (4.0 in) per year (13.8 years)	Axillary hair (14.0 years) Voice change (14.1 years) Acne (14.3 years)
5		Adult genitalia (15.1 years) Testes: >4.5 cm (1.8 in)	Adult-type hair with spread to medial thigh but not up linea alba (15.3 years)	Deceleration and cessation (about 17 years)	Facial hair (14.9 years) Muscle mass continues to increase after stage 5

*The Tanner stages of puberty in boys are based on the development of the genitalia and pubic hair distribution. Mean age of milestone attainment is shown in parentheses for the reference population of Marshall and Tanner. Actual age at milestone attainment may vary among individuals and among different study populations.

Figure 35-6 Pubertal milestones for boys. (From Blondell RD, Foster MB, Dave KC. Disorders of puberty. *Am Fam Physician.* 1999;60:209, 223.)

physical problem. Careful explanation and reassurance for the child and parent that this is a self-limited condition is the best approach.

Accidental precocity occasionally results from unusual dietary habits or inappropriate use of medications (estrogen creams). A careful review for these, early in the evaluation, is helpful.

Central (GnRH-Dependent) Precocious Puberty. Central (or true) precocious puberty is caused by early activation of hypothalamic GnRH secretion. Most patients have no identifiable cause, and the precocity is labeled as "idiopathic." Initial evaluation begins with history, examination, growth chart, and wrist radiographs. Morning testosterone levels are useful in boys, and GnRH-agonist stimulation tests are helpful in females to identify a central etiology. A wide variety of CNS lesions are known to cause central isosexual precocity, so cranial CT or MRI is indicated to rule out these pathologies. An underlying CNS disorder is not unusual in boys presenting with precocious puberty. Treatment is focused on managing the underlying cause. GnRH analogues that reversibly inhibit gonadotropin secretion can be used to prevent secondary sexual development and early epiphyseal fusion that occurs in children who are very young at the onset of puberty, especially when it progresses rapidly (Carel et al., 2004). The optimal age to discontinue therapy is 11 years. When therapy is discontinued, puberty commences normally. There is a slowly progressive form of central isosexual precocity in which no height is lost. These patients may be considered for a nontherapeutic approach with careful observation (Palmert et al., 1999) (Table 35-12).

In many studies, the most common causes of precocity are benign and need no treatment. Detailed evaluation with hormonal studies and imaging may be reserved for patients with severe symptoms and signs (Kaplowitz, 2004, 2005; de Vries and Phillip, 2005).

KEY TREATMENT

- Common causes of precocity are benign and require no treatment. Careful nontherapeutic observation may be considered (Carel et al., 2004) (SOR: A).
- Treatment of precocity with GnRH analogues, which reversibly inhibit gonadotropin secretion, can be used to prevent secondary sexual development and early epiphyseal fusion (Carel et al., 2004) (SOR: A).

Table 35-12 Precocious Puberty: Types, Causes, and Treatment

Etiology	Symptoms	Tests and Treatment
CENTRAL PRECOCITY*		
Idiopathic	Development of secondary sexual characteristics	GnRH analogues Discontinue at 11 years
CNS lesions (including congenital defects): hamartomas, tumors, infection, trauma, radiation, after androgen exposure, craniopharyngioma, others	History of trauma Medical history Headache, visual changes possible	FSH, LH, prolactin, sex steroids, TSH MRI of brain Treatment per pathology
Primary hypothyroidism	Signs of hypothyroidism without increase in growth velocity	Thyroid profile Treatment with thyroxine
INCOMPLETE ISOSEXUAL PRECOCITY		
Females: Isolated precocious thelarche	Breast enlargement without other secondary sexual changes	Most cases are benign
Females: Isolated precocious adrenarche	Pubic hair development, adult odor, acne	DHEA may be increased Adrenal steroid hormones and sex hormones: normal ACTH stimulation test to exclude CAH Usually benign; no treatment needed
Females: Isolated precocious menarche	Menarche precedes breast development or appearance of pubic hair	Normal bone age Ultrasonography: normal pelvis with prepubertal uterus Usually benign; check for abuse and ovarian and genital pathology
Females: Estrogen-secreting tumors of ovary or adrenal glands Ovarian cysts	Abdominal symptoms Signs of precocious puberty	CT or MRI in addition to hormonal tests Treat as per pathology
Females and males: McCune-Albright syndrome	Autonomous hyperfunction of gonads; rapid development of precocity Café au lait spots, fibrous dysplasia	Ultrasonography or CT of abdomen: large ovarian masses LFTs, DHEA sulfate, TSH, phosphate, cortisol
Males: Gonadotropin-secreting tumors; excessive androgen production Testicular or adrenal tumors Virilizing CAH Premature Leydig and germinal cell maturation	Excessive virilization Enlargement of testis (unilateral)	CT or MRI of abdomen Ultrasonography Hormonal tests Treat per pathology Surgery may be indicated
Males and females: Iatrogenic	History of using sex steroids and related products	Stop causative agent
CONTRASEXUAL PRECOCITY (ISOLATED VIRILIZATION)		
Isolated Precocious Adrenarche		
Females: Virilizing CAH, androgen-secreting ovarian or adrenal neoplasm, Cushing syndrome, glucocorticoid resistance, arrhenoblastoma	Prepubertal masculinization	Tests for CAH Cortisol Testosterone MRI of abdomen and pelvis Treat per pathology
Males: Estrogen-secreting tumor, chorionepithelioma; increased extraglandular aromatization of adrenal steroids causing increased extraglandular estrogen production and unusual CAH variations	Prepubertal feminization in boys is rare	Tests for CAH Cortisol and estrogen levels Testosterone MRI of abdomen and pelvis Treat per pathology
Iatrogenic	History of using sex steroids and related products	Stop causative agent
Nonprogressive precocious puberty	Stabilization of precocity Normal bone age	Normal bone age Ultrasonography: normal pelvis with prepubertal uterus

*True precocious puberty: gonadotropin dependent.
ACTH, Adrenocorticotropic hormone; *CAH,* congenital adrenal hyperplasia; *CNS,* central nervous system; *CT,* computed tomography; *DHEA,* dehydroepiandrosterone; *FSH,* follicle-stimulating hormone; *GnRH,* gonadotropin-releasing hormone; *LFT,* liver function test; *LH,* luteinizing hormone; *MRI,* magnetic resonance imaging; *TSH,* thyroid-stimulating hormone.
Modified from Carel JC, Léger J. Precocious puberty. *N Engl J Med.* 2008;358(22):2366-2377.

DELAYED PUBERTY

Key Points

- Lack of thelarche (breast development) by the age of 12 years in girls or lack of testicular enlargement by the age of 14 years in boys indicates delayed puberty.
- Whereas constitutional delay is characterized by delayed but spontaneous onset of puberty, organic delay is caused by gonadal, pituitary, or central dysfunction.

Delayed puberty in girls is defined as lack of thelarche by age 12 years or duration between thelarche and menarche

longer than 5 years (age 17 years). In boys, delayed puberty is defined as no testicular enlargement by age 14 years with more than 5 years between initial and complete development of the genitalia (age 19 years). Delayed puberty in both males and females is classified as *constitutional* (idiopathic) or *organic* (gonadal, pituitary, or central cause). A retrospective study of 232 male and female patients with delayed puberty revealed that the majority (53%) had constitutional delay of growth and maturation, with much higher incidence in males (63%) compared with females (30%). The remaining 47% of the total 232 patients had mixed etiologies; 19% had functional HH, 12% had permanent HH, 13% had permanent hypergonadotropic hypogonadism, and there was no clear etiology for the remaining 3% (Sedlmeyer and Palmert, 2002).

Constitutional delay is characterized by physiologic delay but subsequent spontaneous onset of puberty, and it is a diagnosis of exclusion. The cause is a delay in GnRH pulse generation, with low levels of gonadotropins. Height and weight in these children tend to be below the fifth percentile, but most catch up during adolescence, reaching normal adult height and weight. Family history may reveal similar delays of puberty in one or both parents, which can be reassuring for the child and parent. Values for FSH, LH, DHEA-S, prolactin, testosterone, and estradiol levels will be consistent with prepubertal values until onset of puberty and normal sexual maturation.

The two common causes of delayed puberty from organic etiologies are pituitary dysfunction and HH. Panhypopituitarism in children may present as delayed puberty, but it would occur in conjunction with growth failure, secondary hypothyroidism, and adrenal insufficiency. Differentiation of organic forms of delay from constitutional delay may be difficult to establish in certain patients, requiring a series of observations and testing (no single study or imaging technique will differentiate these). HH presents with low levels of FSH and LH as a result of defective GnRH pulsation. Causes include anorexia nervosa, excessive weight loss, extreme exercise (cross country runners), tumors, head trauma, infiltrative processes, infection, and radiation. *Hypergonadotropic* hypogonadism is usually caused by gonadal failure and presents with high levels of gonadotropins and low levels of sex steroids (Table 35-13).

Evaluation of delayed puberty, as with all evaluations for abnormal sexual development, begins with a detailed history focusing on growth patterns, presence of any secondary sexual development, diet, exercise habits, congenital abnormalities, neurologic symptoms, and family history. Physical examination includes a thorough search for early signs of sexual maturation using Tanner staging. Measurement of arm span in relation to height is helpful in growth assessment. Arm span that exceeds height more than 5 cm is consistent with adult configuration. When this is present in children, it may mean delayed epiphyseal closure caused by hypogonadism. Wrist radiography is useful to determine bone age. Initial laboratory screening should include complete blood cell count, erythrocyte sedimentation rate, and liver function tests. Serum FSH, LH, estradiol, and testosterone levels can distinguish between primary and secondary hypogonadism. In primary hypogonadism (ovarian and testicular failure), serum gonadotropin levels are elevated. In patients with constitutional delay of puberty and congenital GnRH deficiency, serum gonadotropin levels are low. Prolactin, TSH, adrenal androgens, and karyotype (to rule out Turner, Klinefelter, and Noonan syndromes) should be evaluated if the clinical presentation warrants.

Therapy for delayed puberty is targeted at the underlying disorder, if identified. If the cause is unknown, observation with reassurance and psychosocial support and reevaluation after 4 to 6 months is an option. Hormonal therapy with estrogen (girls older than 12 years) or testosterone (boys older than 14 years) is an option. Short-term use of exogenous hormones does not appear to have long-term sequelae, except for the potential effect on skeletal maturation, which might result in failure to achieve potential adult height. In females taking estrogen replacement therapy, progestins should be added to the regimen after breakthrough bleeding occurs or after 1 year of therapy.

Table 35-13 Causes of Hypogonadotropic Hypogonadism

CONGENITAL	
Isolated gonadotropin deficiency	Idiopathic HH Kallmann syndrome Non–X-linked Partial HH (fertile eunuch syndrome)
Associated with CNS disorders	Prader-Willi syndrome Laurence-Moon-Biedl syndrome Möbius syndrome Lowe syndrome Noonan syndrome LEOPARD syndrome X-linked ichthyosis
Genetic defects	GnRH receptor gene mutations *FGFR1* *GPR54*
	Adrenal hypoplasia, congenital Multiple pituitary hormone deficiency
ACQUIRED	
Organic lesions	Tumors Craniopharyngiomas Pituitary adenomas (e.g., prolactinoma, nonfunctioning tumor) Meningioma Pituitary apoplexy Infiltrative disorders Sarcoidosis, hemochromatosis Histiocytosis X Head trauma Leydig cell tumors, choriocarcinoma CNS radiation therapy
Systemic disorders affecting HPT axis	Critical illness, including burns Extreme exercise Malnutrition (anorexia nervosa) Morbid obesity Anabolic steroid abuse Glucocorticoid excess (endogenous: Cushing syndrome; exogenous) Narcotics

CNS, Central nervous system; *GnRH,* gonadotropin-releasing hormone; *HH,* hypogonadotropic hypogonadism; *HPT,* hypothalamic–pituitary–testicular; *LEOPARD,* lentigines, electrocardiographic defects, optic hypertelorism, pulmonary stenosis, abnormalities of genitalia, retarded growth, deafness.

From Allan CA, McLachlan RI. Androgen deficiency disorders. In DeGroot LJ, Jameson, JL, eds. *Endocrinology*. 5th ed, vol 3. Philadelphia: Saunders; 2006.

PROBLEMS OF THE TESTICLE AND OTHER MALE ENDOCRINE ISSUES

Male Hypogonadism

Male hypogonadism is defined as "inadequate gonadal function" manifested by deficiency in gametogenesis or secretion of gonadal hormones. Primary hypogonadism is caused by dysfunction in the testes from either chromosomal or acquired disorders (Table 35-13). Secondary hypogonadism is caused by an abnormality of the HPA. Males may present with infertility, decreased testicular size, changes in libido, impotency, gynecomastia, delayed puberty, or a combination of these (Swerdloff and Wang, 2004).

Diagnosis. The clinical diagnosis begins with history, including information about sexual developmental milestones, current symptoms, ambiguous genitalia at birth, cryptorchidism, behavioral abnormalities, anosmia, surgeries, sexually transmitted diseases (STDs), and medications. The history should include the presence of acute and chronic medical conditions and neurologic symptoms. The physical examination is directed toward sexual characteristics, body habitus, gynecomastia, and signs of hypogonadism. The testes should be measured for length and width with an orchidometer. Consistency of the testes should be noted and a scrotal examination done for the presence of varicocele. A nonpalpable prostate may imply testosterone deficiency. A low morning (8-10 AM) serum testosterone level is suggestive of hypogonadism. Serum LH and FSH levels are elevated in primary hypogonadism and normal to low in secondary hypogonadism. Semen analysis assesses the capability of spermatogenesis. An increase in sex hormone–binding globulin (SHBG) may imply hyperthyroidism, severe androgen deficiency, liver disease, or estrogen excess. A low level of SHBG may indicate hypothyroidism, PCOS, obesity, or acromegaly. The prolactin level should be measured to identify a prolactinoma followed by CT or MRI if the level is elevated. Other studies, such as BMD; pituitary imaging; genetic studies; and, in some cases, testicular biopsy may be indicated.

Two congenital conditions causing hypogonadism are Klinefelter syndrome and Kallmann syndrome. Klinefelter syndrome is the most common genetic cause of male infertility caused by hypogonadism. It is caused by a chromosomal aberration, most often 47,XXY. Phenotypic males can present with small, firm testicles; infertility; tall height; long legs; gynecomastia; and varying symptoms of androgen deficiency and undervirilization. Kallmann syndrome is an inherited disorder (see Approach to Pituitary Diseases [Hypopituitarism]). The most common form is isolated gonadotropin deficiency caused by defective GnRH secretion from the hypothalamus. Patients with Kallmann syndrome usually come to medical attention because of delayed puberty or incomplete sexual development. Anosmia or hyposmia is present in 80% of patients and establishes the diagnosis of Kallmann syndrome in those with isolated gonadotropin deficiency.

Requests to measure serum testosterone have become common in primary care. The increased interest in this disorder has been brought about by a number of things. First, and perhaps most important, is access to information. For example, if one enters "male hypogonadism" in Google, there are more than 300,000 results. It is common now for a patient to present with a list of symptoms and Internet data supporting his belief that he has a problem. In addition, there are now a wide variety of pharmacologic options available, including testosterone injections, topical gels, and oral medications. Added to this is the plethora of over-the-counter preparations on the market which are touted to increase testosterone. In addition, there are growing numbers of articles in the scientific literature (albeit perhaps not totally objective) supporting hypogonadism as a disorder causing significant morbidity that requires therapeutic intervention (Dandona and Rosenberg, 2010).

Laboratory Evaluation. To start the discussion of laboratory evaluation, it is important to understand that a low serum testosterone level does not, by itself, provide a diagnosis of hypogonadism. Whether or not a low level represents a pathologic condition or is merely a laboratory phenomenon is not clear cut. An article published in the *American Family Physician* (2006) provides a very good review of this topic, and one of its main points is that in the absence of specific symptoms or physical findings, there is no clearly agreed upon normal testosterone level for defining hypogonadism (Margo and Winn, 2006). Generally accepted normal values for total serum testosterone are 300 to 1000 ng/dL, but when hypogonadism becomes a real physiologic condition is unclear. The level most often used for defining hypogonadism is 200 ng/dL, which is the level set by the AACE in its 2002 guidelines (update). But data clearly defining this level as a pathologic state are lacking (AACE, 2002).

When a low serum total testosterone level is obtained, it is necessary to verify that this does represent a pathologic condition before any consideration of therapeutic intervention can be entertained. Specific testing to evaluate a low testosterone level includes a repeat total serum testosterone and FSH. Some experts recommend that the serum testosterone be checked in the early morning (8-10 AM). Although this does improve reproducibility, it must be remembered that pituitary gonadotrophs are released in surges so limiting collection of serum testosterone to a specific time of day is not a guarantee that the results represent actual 24-hour circulating levels.

If the second testosterone level is low and the FSH level is normal or elevated, a free testosterone level is obtained (reference range, 9-30 ng/dL). If the free serum testosterone level is low, then there is good evidence to support a diagnosis of primary hypogonadism. To further document this assumption, LH and prolactin levels are obtained (see Approach to Pituitary Diseases [Clinical Manifestations]). These tests are sufficient to determine if the testosterone level is truly low and whether it is due to testicular failure (primary) or failure somewhere along the HPA (secondary). Further workup, if any, is determined by these results.

Screening. There are clear instances in which hypogonadism is a defined entity (i.e., secondary to pituitary failure, congenital hypogonadism, premature aging of the testes, testicular cancer, intraabdominal cryptorchidism). In these patients, screening of testosterone is warranted. But in the primary care setting, the large majority of patients interested in testing their serum testosterone level

are concerned about decreased libido, strength, and stamina; loss of muscle mass (sarcopenia); increasing truncal obesity; frailty; and overall lethargy in the absence of specific common diseases and etiologies.

Data in support of screening for hypogonadism are lacking. At the present time, there are insufficient data to determine if male hypogonadism is increasing in the population or is only a phenomenon of more access to laboratory testing. So, when is it appropriate to screen for hypogonadism? One is male infertility. Screening testosterone is part of an infertility workup given appropriate history or physical findings. The American Urologic Association's (AUA's) position on endocrine testing in evaluating male infertility is discussed in its publication *The Optimal Evaluation of the Infertile Male: AUA Best Practice Statement* (Jarow et al., 2010). The AUA recommends endocrine testing when there is an abnormal semen analysis, with impaired sexual function, or with other clinical findings suggestive of endocrinopathy.

Other reasons to screen for low testosterone include clearly identified physical signs of decreased testosterone such as lack of facial hair, sparse or lacking pubic hair, atrophic testes, or clinical evidence of pituitary dysfunction. After these, however, screening for hypogonadism is not recommended. As occurs with other conditions in which screening provides a very low yield ("n" to diagnose), screening for low testosterone is not justified.

Testosterone Replacement Therapy (Risk versus Benefit)

When presented with a below published normal total serum testosterone, especially when definitive physical findings are absent, it is essential to try and provide a precise cause before therapeutic intervention is initiated. Once a diagnosis of hypogonadism is confirmed and categorized as either primary or secondary, then consideration for hormone replacement can begin. But, before moving on to treatment, it is necessary to discuss risk versus benefit. This is especially true when the patient is elderly and/or has other disease processes that could be aggravated by testosterone therapy.

Recent data published in the *Journal of the American Medical Association* (November 2013) report on the incidence of mortality, MI, and stroke in men with low total serum testosterone levels (<300 ng/dL) who receive replacement therapy ($n = 1223$). When those treated with testosterone replacement were compared with those who did not receive exogenous testosterone ($n = 7486$), there was a statistically significant difference in outcomes for the two groups. The group receiving replacement therapy had a 25.7% higher event (death, MI, stroke) level compared with an event level of 19.9% in the untreated group (an absolute risk difference of 5.8%) (Vigen et al., 2013).

A meta-analysis by a group from University of Hong Kong had results similar to those above, although their analysis of risk was reported as odds ratio (OR) instead of relative or absolute risk. In their review of 27 trials, testosterone therapy increased risk of cardiovascular events to an OR of 1.54 (with OR of 0.0 being no difference). There was, however, an unexpected finding in their analysis. The OR for each individual study varied depending on funding source for the study. Whereas studies funded by pharmaceutical industry had an OR of 0.89, studies funded by other entities (nonpharmaceutical) had an OR of 2.06. The conclusion was that "Appropriately prescribed testosterone is undoubtedly beneficial. However, caution needs to be exercised to ensure that the associated health benefits of testosterone therapy outweigh the potential increased risk of cardiovascular-related events, particularly in older men when cardiovascular disease is common" (Xu et al., 2013).

Treatment. Once a definitive diagnosis of hypogonadism is made, referral to an endocrinologist for management is certainly appropriate. However, if the cause is definitely primary hypogonadism, and the risk to benefit analysis has been completed, initiation of treatment and ongoing management can be done by the primary care physician.

In some cases, such as Klinefelter and Kallmann syndromes, hormone replacement is aimed at specific end points. In Klinefelter syndrome, treatment is directed to preventing the sequelae of androgen deficiency. For Kallmann syndrome, treatment is directed at virilization by the administration of testosterone. In both of these, the primary care physician may want to refer to an endocrinologist, at least for initiation of therapy. This may also be the best choice for secondary hypogonadism when restoration of fertility is the goal. In these cases, gonadotropin replacement or human chorionic gonadotropin therapy is required. If the defect is in the hypothalamus, GnRH is the treatment of choice.

In primary hypogonadism, testosterone replacement is the treatment of choice. Many preparations are now available for testosterone replacement (Mooradian and Korenman, 2006). The currently used injectable testosterone esters, such as testosterone enanthate or testosterone cypionate, act similarly. The usual replacement dose is 200 mg intramuscularly every 2 weeks. In older men, it may be prudent to start at 50 to 75 mg weekly. Testosterone undecanoate is available as an oral preparation that does not have hepatotoxicity; however, because of its short half-life, it must be taken three times daily. Transdermal preparations can be given as patches or gels. Some androgen skin patches are associated with a high incidence of skin reactions. The commercially available transdermal gel preparations (Androgel 1% or 1.62%, Testim 1%, Fortesta 2%, and Axiron 2%) are applied over the trunk of the body daily (Mooradian and Korenman, 2006). Subcutaneous pellets, sublingual preparations, and buccal preparations of testosterone are also available for replacement therapy (Mooradian and Korenman, 2006).

Side effects of testosterone replacement should be monitored carefully. Digital rectal examinations, hematocrit (Hct), and prostate-specific antigen (PSA) should be measured at 3, 6, and 12 months of follow-up and then annually or semiannually (preferable). Bone density measurements should be obtained at baseline and, if low, at 2-year intervals to monitor improvement. In addition to monitoring clinical response, serum testosterone levels should be measured with the goal of achieving a midnormal range midway between injections of testosterone enanthate or cypionate, at 3 to 10 hours after application of a testosterone patch, or at any time after application of a testosterone gel.

Absolute contraindications to testosterone therapy currently are history of prostate or breast cancer, Hct of 55%

or greater, elevated PSA level that has not been completely investigated by a qualified urologist, or sensitivity to ingredients of the testosterone preparation (Mooradian and Korenman, 2006). There are currently no data to suggest testosterone replacement aggravates subclinical prostatic cancer.

Relative contraindications include obstructive sleep apnea, CHF, obstructive symptoms of prostatic hyperplasia, and Hct of 52% or greater. Patients with hyperlipidemia, atherosclerotic vascular disease, diabetes, and morbid obesity should be treated with caution and careful follow-up.

Cryptorchidism

See eAppendix 35-5 online.

Male Infertility

Infertility is defined as failure to achieve pregnancy after 1 year of unprotected intercourse. A specific cause can be identified in approximately 80% of couples, one third of which are female factors alone, one third male factors alone, and one third a combination of both. Unexplained infertility, in which no specific cause can be identified, occurs in approximately 20% of infertile couples. The initial step in evaluation of the male is a thorough medical history, focusing on general health, erectile function, STD history, medications, surgical history, previous successful pregnancy, contraception use, drug or alcohol use, and family history of genetic diseases. The first, and often only, test needed in evaluating male factors is semen analysis. If two consecutive analyses indicate oligospermia or azoospermia, ordering blood tests for testosterone, LH, FSH, and prolactin levels is warranted. *Varicocele* is the most common cause of male infertility (Griffin and Wilson, 2003) (Table 35-14).

Management consists of treating the underlying infection with appropriate antibiotics, varicocelectomy, appropriate counseling about environmental factors, and referral to an infertility specialist for more extensive therapy (Frey and Patel, 2004).

Table 35-14 Common Diagnoses in Men Evaluated for Infertility

Diagnostic Category	Incidence (%)
Idiopathic infertility	50-60
Primary testicular failure (chromosomal disorders, including Klinefelter syndrome, Y chromosome microdeletions, undescended testis, irradiation, orchitis, drugs)	10-20
Genital tract obstruction (congenital absence of vas, vasectomy, epididymal obstruction)	5
Coital disorders	<1
Hypogonadotropic hypogonadism (pituitary adenomas, panhypopituitarism, idiopathic hypogonadotropic hypogonadism, hyperprolactinemia)	3-4
Varicocele	15-35
Other (sperm autoimmunity, drugs, toxins, systemic illness)	5

From Griffin JE, Wilson JD. Disorders of the testes and the male reproductive tract. In Larsen PR, Kronenberg HM, Melmed S, Polonsky KS, eds. *Williams' textbook of endocrinology*. 10th ed. Philadelphia: Saunders; 2003.

Gynecomastia

Key Point

- Although breast cancer is an uncommon cause of breast enlargement in men, this diagnosis must be ruled out because the prognosis is worse for men diagnosed with breast cancer than for women.

Gynecomastia refers to a benign enlargement of the male breast resulting from proliferation of breast glandular tissue. When the male breast is enlarged from adipose tissue, it is called *lipomastia* or *pseudogynecomastia* and is not caused by proliferation of breast tissue. Gynecomastia can be unilateral, bilateral, or asymmetric. Any palpable breast tissue in men is abnormal except for three physiologic situations: transient gynecomastia of the newborn (caused by maternal or placental estrogens), pubertal gynecomastia (observed in 40%-70% of adolescent boys, resolving by 18 years of age), and gynecomastia that occasionally occurs in older adult men (resulting from changes in estrogen and androgen metabolism). Gynecomastia can also be iatrogenic, caused by use of some medications. Gynecomastia is occasionally seen in male adolescents from marijuana use (Mayo Clinic Health Information, 2014).

Gynecomastia occurs as concentric, palpable glandular tissue beneath the areola that is not fixed to underlying structures. The prevalence is highest in men 50 to 80 years old and generally presents as bilateral. The cause of pathologic gynecomastia is a relative or absolute increase in circulating estrogen compared with androgen. Careful history (including drugs, legal and illegal) and physical examination can usually rule out Klinefelter syndrome, androgen insensitivity syndrome, and testicular tumors (Griffin and Wilson, 2003) (Table 35-15).

Breast cancer is rare in men, but it does occur, and generally the prognosis is much worse for men than for women diagnosed with breast cancer. Typically, breast cancer presents as a painless, central breast lump that may advance to pain, bloody discharge, and skin ulceration. Although there may be some benefit to obtaining breast ultrasonography or mammography, definitive diagnosis must be confirmed by biopsy (Wise et al., 2005).

Treatment of nonphysiologic gynecomastia involves removal of the offending drug or correction of the underlying condition, either of which usually results in regression of the glandular breast tissue. If the gynecomastia persists, a trial of antiestrogen therapy may be considered. Gynecomastia present for more than 1 year will undergo fibrosis and usually not respond to medications. Surgical correction is required for alleviation of symptoms.

PROBLEMS OF THE OVARY AND OTHER FEMALE ENDOCRINE ISSUES

Menopause and Hormone Replacement Therapy

Normal menopause is defined as the cessation of menstruation for 12 months after the age of 40 years without other known (physiological or pathological) causes of amenorrhea (Table 35-16). Perimenopause refers to an indefinite period before, during, and after cessation of menstruation.

EAPPENDIX

35-5 Cryptorchidism

Key Points

- Morbidity associated with cryptorchidism includes infertility, testicular torsion, and malignancy.
- Intraabdominal testes carry the highest risk for testicular cancer.
- Management options include surgery, hormonal therapy, or both and should be offered early after diagnosis.

Cryptorchidism describes a testis (testes) not in the scrotum or one that cannot be manipulated into the scrotum. The incidence is about 5% in term infants and much more common (~30%) in preterm infants. Approximately 10% of cryptorchidism is bilateral, and about 80% of these testes descend into the scrotum in the first year of life. Cryptorchidism may be associated with disorders such as Prader-Willi syndrome, Reifenstein syndrome, Kallman syndrome, cystic fibrosis, and pituitary hypoplasia. Cryptorchidism, in association with hypospadias, has a higher incidence of intersex disorders, including mixed gonadal dysgenesis.

The initial diagnosis of cryptorchidism should include a complete medical history, noting prematurity, family history of cryptorchidism, maternal use of estrogens, central nervous system abnormalities, and prior surgeries. A thorough examination with a warm hand in a warm room should document the location of the testis (upper scrotum, inguinal pouch, canal, or abdomen) and should differentiate a retractile testis from an undescended testis. By pulling the palpable testis into the scrotum and maintaining this position for 1 minute, the cremaster muscle will fatigue. When it is released, a retractile testis will stay in the scrotum, but an undescended testis will return to its original position, thus differentiating between the two conditions. In patients with cryptorchidism, generally 40% of cases can be classified as a high scrotal testis, 20% as inguinal canal testis, and 10% as intraabdominal testis.

The remaining 30% are retractile or not identified. In patients with bilateral nonpalpable testes, a human chorionic gonadotropin (hCG) stimulation test, with luteinizing hormone, follicle-stimulating hormone, and testosterone level, will aid in determining the presence of testes. Imaging studies, such as ultrasonography (high specificity, low sensitivity) or magnetic resonance imaging, are beneficial in locating the testes.

The most significant complications from cryptorchidism are infertility, subfertility, testicular torsion, and malignancy. The combined risk of testicular cancer for all cryptorchid boys is 20 to 46 times higher than for boys with normally descended testicles (Kolon et al., 2004). Because of the location, intraabdominal testes have the highest risk for testicular cancer.

Early management of the undescended testicle is warranted to preserve the fertility and lower the risk for testicular malignancy. Repeat examination at 3 months of age is beneficial to confirm the descent. By 6 months of age, an infant with undescended testicles should be referred to a pediatric urologist or other qualified subspecialist. Hormonal therapy with hCG or gonadotropin-releasing hormone (GnRH) can be used to increase the likelihood of testicular descent, but this should not be added until a thorough evaluation has been completed (Kollin et al., 2006). Inguinal orchiopexy is a well-established operation for palpable undescended testicles and is currently the standard of care for cryptorchidism in the United States. Treatment for an undescended testis is recommended as early as 6 months of age and should be completed before the age of 2 years (Henna et al., 2004).

KEY TREATMENT

- Hormonal therapy with hCG or GnRH can be used to increase the likelihood of testicular descent (Henna et al., 2004) (SOR: A).
- Inguinal orchiopexy is a well-established procedure for palpable undescended testicle and is generally considered the standard of care for cryptorchidism in the United States (Kollin, 2006) (SOR: A).

Table 35-15 Causes of Pathologic Gynecomastia

ESTRADIOL EXCESS

Estradiol Secretion

Adrenal tumors
Sporadic testicular tumors (sex cord, Sertoli, germ, Leydig cells)
Testicular tumors associated with familial syndromes (Peutz-Jeghers, Carney complex)

Exogenous Estrogens or Estrogenic Substances

Drug therapy with estrogens
Estrogen creams and lotions
Embalming fluid exposure
Delousing powder
Hair oil
Marijuana
Estrogen analogues: digitoxin

ELEVATED ESTROGEN PRECURSORS: AROMATIZABLE ANDROGENS

Human chorionic gonadotropin (hCG) excess (eutopic or ectopic)

Exogenous Hormones

Testosterone enanthate
Testosterone propionate
Anabolic steroids
hCG administration

TESTOSTERONE DEFICIENCY

Anorchia
Hypogonadotropic syndromes
Drugs or exogenous substances
Ketoconazole
Heroin
Methadone
Alcohol

ESTRADIOL/TESTOSTERONE IMBALANCE

Hypergonadotropic syndromes
Hypogonadotropic hypogonadism syndromes
Primary gonadal diseases
Drugs

REGULATORY HORMONE EXCESS

Hyperthyroidism
Acromegaly
Prolactin Excess
Hypothyroidism
Pituitary tumor

Drug therapy with:

Catecholamine antagonists or depleters
Domperidone
Haloperidol
Methyldopa
Metoclopramide
Phenothiazines
Reserpine
Sulpiride
Tricyclic antidepressants
Administration of growth hormone
Cushing syndrome

OTHER CAUSES

Local Trauma

Hip spica cast
Chest injury
Herpes zoster of chest wall
Post thoracotomy
Spinal cord injury
Primary breast tumor

Uncertain Causes

Other Chronic Illnesses

Renal failure
Pulmonary tuberculosis
HIV
Diabetes mellitus
Leprosy
Refeeding gynecomastia
Persistent pubertal macromastia
Idiopathic

Drugs Associated with Gynecomastia with Uncertain Mechanisms:

Cytotoxic Drug-Induced Hypogonadism from:

Busulfan
Nitrosourea
Vincristine
Combination chemotherapy
Steroid synthesis inhibitory drugs

Androgen Resistance

Complete testicular feminization
Partial: Reifenstein, Lubs, Rosewater, and Dreyfus syndromes

Androgen Antagonistic Drugs

Bicalutamide
Cimetidine
Cyproterone acetate
Flutamide
Spironolactone

Blockers of 5α-Reductase

Finasteride

Tumor Related

hCG-producing tumors (e.g., testis, lung, gastrointestinal tract)
Hypogonadotropic syndromes
Isolated gonadotropin deficiency, particularly fertile eunuch syndrome
Panhypopituitarism
Systemic illnesses
Renal disease
Severe liver disease
Amiodarone
Amphetamines
Auranofin
β-Blockers
Calcium channel blockers
Captopril
Cyclosporin
Diazepam
Diethylpropion
Enalapril
Ethionamide
Etretinate
Griseofulvin
Heparin
Indinavir
Isoniazid
Methotrexate
Metronidazole
Narcotic analgesics
Nitrates
Omeprazole
Penicillamine
Phenytoin
Quinidine
Sulindac
Theophylline
Thiacetazone
Vitamin E

From Santen RJ. Gynecomastia. In DeGroot LJ, Jameson, JL, eds. *Endocrinology*. 5th ed, vol 3. Philadelphia: Saunders; 2006.

Table 35-16 Menopausal Symptoms* and Treatment

Symptoms	Pre (%)	Peri (%)	Post (%)	Treatment
Vasomotor symptoms	14-51	35-50	30-80	ET/EPT (SOR: A)
Vaginal dryness and painful intercourse	4-22	7-39	17-30	ET/EPT Vaginal ET preferred (SOR: A)
Mood symptoms	8-37	11-21	8-38	ET may be beneficial (SOR: A)
Urinary symptoms	10-36	17-39	15-36	Vaginal estrogens (SOR: B)
Sleep disturbances	16-42	39-47	35-60	Sleep hygiene; other agents

*Incidence of *pre*menopausal, *peri*menopausal, and *post*menopausal symptoms.
ET, Estrogen therapy; *EPT*, cyclic combined estrogen-progestogen therapy; *SOR*, strength of recommendation.
Modified from NIH State of the Science Conference on Management of Menopausal-Related Symptoms. Bethesda, Maryland, 2005. http://consensus.nih.gov/2005/menopausestatement.htm.

The term *climacteric* refers to the period of time after the cessation of reproductive function. Premature menopause, sometimes referred to as premature ovarian failure, is the same syndrome but occurring before age 40 years and is often thought to be the result of an autoimmune process. Premature menopause can also be the result of surgical removal of the ovaries or chemotherapy. When amenorrhea is associated with a negative pregnancy test result, elevated levels of FSH (≥35 mIU/mL) and low estradiol levels (≤35 pg/mL), it is primary ovarian failure until proven otherwise. Fluctuations in the level of various hormones (FSH, LH, estrogen, progestin) are common during the perimenopausal period. A single reading of these hormones during this period may be unreliable for a definitive diagnosis of menopause. The combination of clinical presentation plus laboratory test results in these circumstances is useful.

Menstrual Patterns and Symptom Overview

Decreasing levels of estrogens and androgens are responsible for most menopausal symptoms. Typical hormonal changes include increases in FSH and LH with a significant reduction in estradiol (E2), a moderate reduction in estrone (E1) and androstenedione, a mild reduction in testosterone, and changes in cortisol levels that are insignificant. Not all women experience symptoms associated with hormone deprivation. Obese women may experience no or relatively few symptoms of hormone deficiency and are at reduced risk of osteoporosis, but they are at increased risk for cancer (e.g., uterine cancer) and cardiovascular disease (CVD).

The most common symptoms of menopause are hot flashes (vasomotor symptom complex with sudden sensations of intense heat, sweating, and flushing, typically lasting 5 to 10 minutes, and night sweats), sleep and mood disturbances, decreased libido, and vaginal dryness. Hot flashes tend to be most intense in duration, severity, and frequency in younger women and during the first year of menopause, generally tapering thereafter. A small percentage of women have hot flashes on a lifelong basis.

Treatment of Hormonally Mediated Symptoms

Key Points

- Hormone replacement therapy (HRT) may be appropriate for the relief of severe vasomotor symptoms in selected postmenopausal women.
- HRT has previously been used for broad segments of the population. Currently, individualized therapy, predominantly nonhormonal, is advised.
- HRT increases the risks of breast cancer, CVD and stroke, deep vein thrombosis (DVT), and cognitive decline (much of this is contrary to previous findings).
- If HRT is used, the lowest dose for the shortest duration should be administered.
- HRT has been shown to improve bone density and osteoporosis and decrease colon cancer risk.

Beliefs about HRT for menopausal women have shifted substantially in recent years because of randomized clinical studies, including the landmark Women's Health Initiative (WHI) study (Anderson et al., 2004). These studies showed that hormonal therapy, particularly with combined conjugated estrogen and medroxyprogesterone regimens, not only increases the risk for developing breast cancer and thromboembolic disease but also increases the risk of cardiovascular events (Anderson et al., 2004; Hulley et al., 1998; Nelson et al., 2002; Rossouw et al., 2002; Tomson et al., 2005).

Side effects of HRT are related to the age of the patient, her baseline disease risk strata, age at time of menopause, time interval since menopause, duration and dosage of estrogen administered, and emerging medical conditions during treatment. WHI also showed hormone therapy initiated less than 10 years since menopause had a lower incidence of CHD compared with that initiated 10 years after menopause. Although the absolute risk for any individual woman for severe complications was low, the cumulative risk over large populations has led to substantial changes in prescribing patterns and recommendations for postmenopausal therapy (Anderson et al., 2004).

Recent analysis has raised the question of whether unopposed estrogen may actually be safer than combined estrogen and progesterone even in women who still have their uteruses (Rossouw et al., 2002). Prescribing progesterone to prevent endometrial cancer may be incorrect in that an increased incidence of breast cancer and other risks from adding progesterone might actually outweigh the benefit of preventing uterine cancer—the incidence of breast cancer is actually substantially higher than that of uterine cancer. The WHI estrogen-only therapy arm for hysterectomized women (average follow-up, 6.8 years) revealed reduced breast cancer (0.77 [0.59-1.01]; 95% confidence interval [CI]) and hip fracture (0.61 [0.41-0.91]), but there was a small increase in total CVD (1.12 [1.01-1.24]) and an absolute increase in strokes (12 in 10,000 person-years) with six fewer fractures per 10,000 person-years. Conjugated equine estrogen is not recommended for chronic

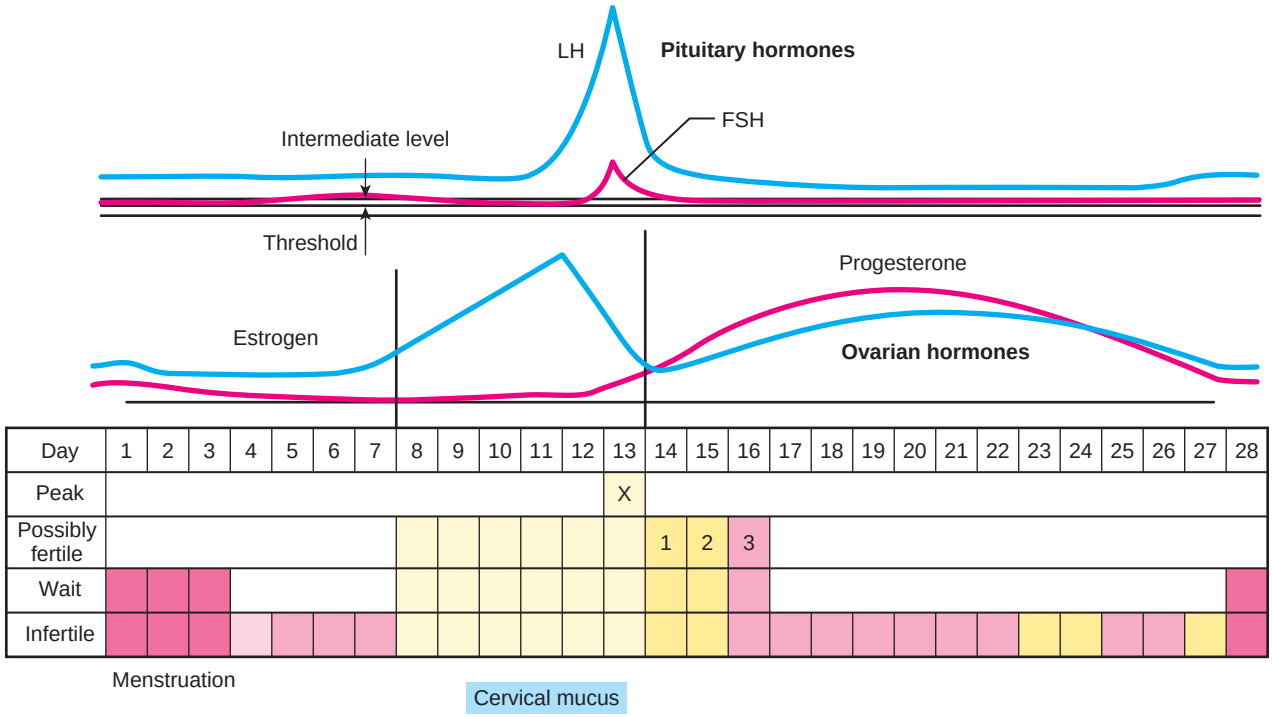


Figure 35-7 Female reproductive physiology. *FSH,* Follicle-stimulating hormone; *LH,* luteinizing hormone. From Brown, JB: Hormones of a woman's reproductive cycle [Epub, www.pearsoncustom.com].

disease prevention in post-menopausal women (Anderson et al., 2004).

Transdermal preparations of progesterone-only creams have helped relieve hot flashes (Leonetti et al., 1999). Their risks are poorly defined but may include an increased risk of breast cancer because many postmenopausal breast cancers are positive for estrogen and progesterone receptors.

Hormone therapy with estrogen-containing regimens is the most effective treatment for vasomotor symptoms. However, the U.S. Preventive Service Task Force (USPSTF) recommendations (2005) warn against the routine use of unopposed estrogen or combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women (USPSTF, 2005). The use of SSRIs, clonidine, and gabapentin is recommended. Although studies are smaller and efficacy appears to be lower, the associated risks, particularly of serious complications, are lower.

Depressed Libido in Women

See eAppendix 35-6 online.

Amenorrhea

Key Points

- Amenorrhea is categorized as primary or secondary; however, this distinction may be misleading in certain patients.
- Primary amenorrhea can be caused by obstruction of the outflow tract; androgen insensitivity; gonadal dysgenesis; hyperprolactinemia; and dysfunction of the hypothalamus, pituitary, or thyroid.
- Pregnancy is the most common cause of secondary amenorrhea.

Primary Amenorrhea. Menses is a normal, physiologic function in a sexually mature female. Amenorrhea is the absence of menses in a sexually mature woman. Amenorrhea is divided into two large categories, primary and secondary, depending on whether the female has ever had menarche, with attendant menstrual flow. *Primary* amenorrhea is defined as failure of menarche by age 16 years in a female with apparently normal sexual development or in a female age 14 years who does not demonstrate evidence of developing secondary sexual characteristics. *Secondary* amenorrhea is failure of menstruation after normal menses are established with the caveat that at least 3 months have passed with apparently normal menses or 9 months have passed in a woman with oligomenorrhea.

Menstruation is a very complex process, with many interacting and codependent processes that must occur in specific chronologic order (Figure 35-7). Dysfunction of any organ or system involved with these processes has the potential to disrupt the menstrual cycle and cause amenorrhea. The organs and systems that are involved in the menstrual cycle are the CNS (influenced by environment, stress), hypothalamus (through GnRH), anterior pituitary (FSH, LH), thyroid gland, adrenals, ovary (estrogen, progesterone), and uterus. Secondary amenorrhea is more common than primary amenorrhea, with the most common cause being pregnancy. The distinction between etiologies of primary and secondary amenorrhea may be misleading, as in the case of a woman with PCOS who presents with primary amenorrhea or a woman with partial gonadal dysgenesis who has rudimentary ovarian development and may initially ovulate, thus presenting with secondary amenorrhea (Table 35-17; see Figure 35-8).

The more common causes of primary amenorrhea fall into congenital or anatomical abnormalities. Congenital

EAPPENDIX

35-6 Depressed Libido in Women

Key Points

- Androgens may benefit some women with low libido.
- Low blood levels do not consistently identify those who would benefit.
- Monitoring blood levels to avoid exceeding physiologic levels may decrease the risk of complications.
- Risks include clitoromegaly, voice changes, and acne, as well as worsening lipid and cardiovascular (CV) risk profiles; some of these may not be reversible.

Testosterone therapy to improve libido and sexual function in women is now being prescribed. Use of these preparations remains controversial because there have been no clear and consistent studies defining specific androgen levels in women with low sexual function. Most women with low levels of androgens do not have sexual dysfunction (Davis et al., 2005). A potential side benefit from testosterone therapy is increased bone density, and it does help ameliorate hot flashes. Androgen replacement therapy may be beneficial in established cases of severe androgen deficiency, surgical menopause, or adrenal insufficiency or for patients on chronic glucocorticoid therapy, as well as for those who have impaired mood or libido (Arlt, 2006)

The cause and pathophysiology of impairment of libido or hypoactive sexual dysfunction are multifactorial, and therapy should be directed toward common correlates, including relationship distress, emotional distress, and dyspareunia, rather than relying solely on androgen replacement therapy as the only course (Schover, 2008)

Dehydroepiandrosterone (DHEA) is used by some for mood and libido enhancement in postmenopausal women, but its use is controversial. DHEA has similar risks and benefits to testosterone, but monitoring of relevant hormone blood levels may be more difficult. Tibolone has been used for menopausal symptoms and to reduce bone loss in postmenopausal women in many countries (≈90); however, it is not available in the United States. It has estrogenic, progestogenic, and androgenic properties. A recent randomized controlled trial revealed that tibolone reduced the risk of fracture and breast cancer but increased the risk of stroke (Cummings et al., 2008).

Conclusion

Treating postmenopausal women with hormone replacement therapy (HRT) has changed dramatically in recent years. It is no longer recommended to reduce risk of coronary artery disease nor as a primary management tool for osteoporosis. Although effective in treating vasomotor symptoms and osteoporosis, safer alternatives to HRT exist. Transdermal preparations and low-dose estrogen replacement therapy are being increasingly used. When estrogen is used, lower doses are recommended for the majority of patients. Present clinical practice calls for treating each patient's symptoms and risks on an individual basis.

KEY TREATMENT

- Selective serotonin reuptake inhibitors, clonidine, and gabapentin are recommended for treatment of menopausal symptoms (U.S. Preventive Service Task Force, 2005) (SOR: C).
- Tibolone is effective in controlling menopausal symptoms and reduces the risk of fracture and breast cancer but increases the risk of stroke (Cummings et al., 2008) (SOR: A).

Table 35-17 Causes of Amenorrhea*

Hyperprolactinemia	Prolactin-secreting tumor Centrally acting medications, including dopamine antagonists
Pituitary disease	Non–prolactin-secreting pituitary tumor Generalized pituitary insufficiency, including previous pituitary surgery
Hypothalamic amenorrhea	Nutrition/exercise disorders Idiopathic hypogonadotropic hypogonadism

*Resulting from disorders of the hypothalamus and pituitary.
From Illingworth P. Amenorrhea, anovulation, and dysfunctional uterine bleeding. In DeGroot LJ, Jameson, JL, eds. *Endocrinology*. 5th ed, vol 3. Philadelphia: Saunders; 2006.

Table 35-18 Causes of Primary Ovarian Failure

Iatrogenic	Surgery Chemotherapy Radiotherapy
Environmental	Smoking Viral infections
Autoimmune	Association with other autoimmune disease
Abnormal karyotypes	46,XY 45,XO
Genetic disorders with normal karyotype	Fragile X permutations Galactosemia Carbohydrate-deficient glycoprotein syndrome type 1 Inhibin α-gene mutations Follicle-stimulating hormone receptor gene mutations

From Peter Illingworth. Amenorrhea, anovulation, and dysfunctional uterine bleeding. In DeGroot LJ, Jameson, JL, eds. *Endocrinology*. 5th ed, vol 3. Philadelphia: Saunders; 2006.

absence of the uterus and vagina, known as müllerian agenesis or Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, is a significant cause of amenorrhea. Other congenital causes of primary amenorrhea include chromosomal abnormalities, prenatal adrenal hyperplasia, and female virilization syndrome. An anatomic cause of primary amenorrhea, usually discovered at time of menarche, is imperforate hymen.

To evaluate a patient with primary amenorrhea, after a thorough clinical history, the physical examination must focus on development of hormonally mediated secondary sexual characteristics (breast development, pubic or axillary hair). Although rare as a cause of primary amenorrhea, pregnancy occasionally does occur before a woman's first menstrual period, therefore, it should always be excluded before any testing or imagining is initiated.

Laboratory testing includes FSH, LH, TSH, and prolactin. If FSH is normal or reduced, this may mean the patient has chronic anovulation, functional hypothalamic amenorrhea, or PCOS. Increased FSH with breast development is likely secondary to ovarian failure. Increased FSH without secondary sexual characteristics may be caused by congenital agenesis of the ovaries. In a patient without a uterus, serum testosterone level and karyotype should be determined. In the presence of a uterus and normal secondary sexual characteristics, serum TSH levels should be evaluated (Sybert and McCauley, 2004) (Table 35-18).

Secondary Amenorrhea. Pregnancy is the most common cause of secondary amenorrhea and must always be ruled out at the initial clinical visit. Structural changes may cause amenorrhea, such as adhesions after instrumentation (Asherman syndrome) or infection in the form of TB or endometritis. Patients with PCOS present with irregular or absent menses, hirsutism, acne, subfertility secondary to a hyperandrogenic state, or a combination. Adrenal or ovarian tumors, hyperthecosis, and late-onset or mild congenital adrenal hyperplasia may also result in secondary amenorrhea and hyperandrogenism. Hypergonadotropic hypogonadism (premature ovarian failure), HH, thyroid disease, menopause, extreme exercise, anorexia nervosa, bulimia, and hyperprolactinemia are all potential causes of secondary amenorrhea.

A thorough history and physical examination will provide the diagnosis, with laboratory studies and imaging serving as collaborative evidence. Particular attention should be paid to menstrual history, diet, exercise, medications, pubertal development, hirsutism, acne, galactorrhea, and other medical conditions. Initial laboratory evaluation includes a pregnancy test and determination of TSH and prolactin levels. If these are normal and there are no signs of hyperandrogenism (e.g., hirsutism, acne, voice change), proceed with progesterone challenge by using medroxyprogesterone (Provera) 10 to 20 mg/day for 5 to 10 days. In the presence of a uterus, the progesterone withdrawal test will induce withdrawal bleeding within 10 days in a woman with adequate estrogen production. If there is no withdrawal bleed, consider repeating the test with progesterone in oil (100-200 mg intramuscular) or with norethindrone or micronized progesterone. If these test results are also negative, a 21-day course of conjugated estrogen (1.25 mg/day) or a cycle of combined oral contraceptives (OCs) should provide adequate stimulation of the endometrium to support a withdrawal bleed. If all of these fail to result in menstrual flow, additional tests may be ordered, beginning with FSH, and if there are clinical signs of hyperandrogenism, a check for DHEA-S and testosterone levels. Elevated FSH level indicates ovarian failure (including gonadal dysgenesis and secondary ovarian failure or menopause); normal or low values indicate HH or uterine abnormality (Asherman syndrome). Proceed with a workup for PCOS (discussed later), late-onset congenital adrenal hyperplasia, or Cushing syndrome if there are features consistent with these illnesses. Features of hyperandrogenemia or substantially increased serum testosterone levels should prompt appropriate studies to rule out a neoplastic source of androgen. Figure 35-8 is a diagnostic algorithm for evaluating a patient with primary or secondary amenorrhea.

Management of amenorrhea depends on establishing a diagnosis, specific treatment directed to the underlying cause, restoration of ovulatory cycles, and treating infertility if desired. Also, appropriate treatment must be provided for hypoestrogenemia and hyperandrogenemia, both medical and surgical.

Female Infertility

Infertility is defined as failure of conception after 1 year of unprotected intercourse. From 15% to 20% of all couples are infertile. In women, fertility peaks between ages 20 and 24 years. After this, there is progressive decline in fertility

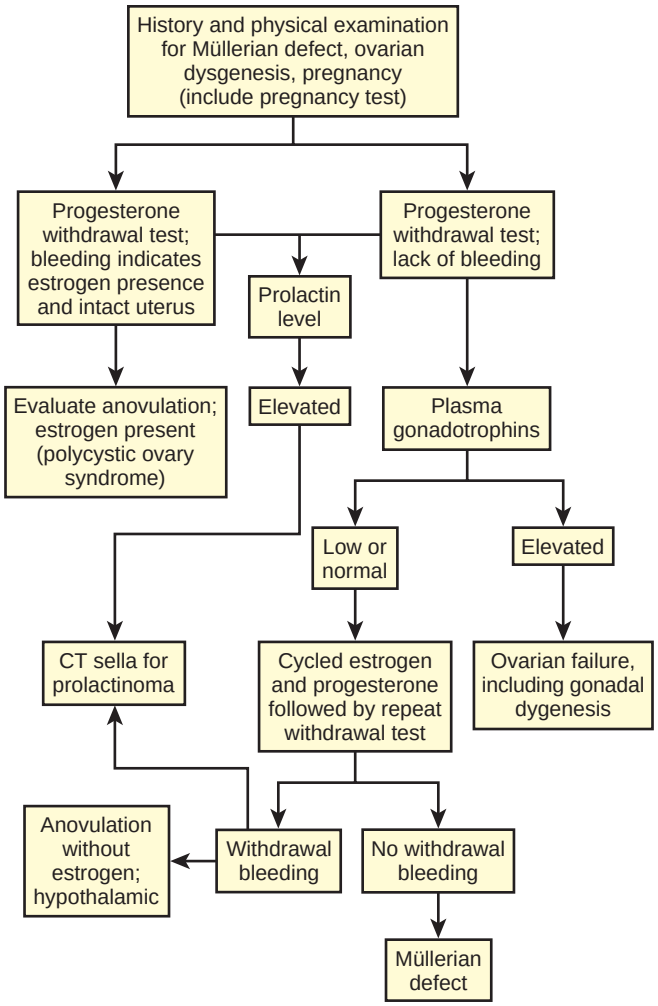


Figure 35-8 Diagnostic algorithm for evaluating a patient with primary and secondary amenorrhea. *CT,* Computed tomography. (Modified from Carr BR. Disorders of the ovaries and female reproductive tract. In Wilson JD, Foster DW, eds. *Williams' textbook of endocrinology*. 8th ed. Philadelphia: Saunders; 1992.)

until about age 32 years followed by a steep decline after 40 years. Causes of infertility in couples tend to be one third male factors, one third female factors, and one third combination. Female causes of infertility include ovarian dysfunction (40%), tubal factors (20%), cervical factors (infection, stenosis), uterine factors (infection, fibroids), and other (endometriosis, adhesions). The course of investigation for infertility should be based on a couple's wishes for fertility, their age, the duration of infertility, and unique features in the history and physical examination.

After congenital and other nonhormonal causes are excluded, ovulation should be verified by urinary ovulation prediction kits that detect the LH surge, determination of the midluteal phase serum progesterone level (7 days before anticipated menses), or both. Daily rectal temperature measurements to establish ovulation are no longer recommended. Women older than the age of 35 years should have a serum FSH level checked on day 3 of the menstrual cycle. A value higher than 12 IU/L is associated with poor ovarian response, and referral to a reproductive endocrinologist should be considered.

Table 35-19 Tests for Evaluating Female Infertility

Female Infertility	Common Tests
Ovulatory factors	Basal body temperature or urinary LH test (ovulatory predictor test); serum progesterone (during luteal phase); transvaginal ultrasound; TSH, FSH, prolactin, and androgens
Cervical factors	Cervical mucus evaluation; postcoital test (not sensitive)
Uterine factors	Ultrasonography, hysterosalpingography, hysteroscopy, sonohysterography (for submucosal myomas and endometrial polyps), MRI
Tubal factors	Hysterosalpingography; laparoscopy and chromotubation; fluoroscopic or hysteroscopic tubal cannulation
Peritoneal factors	Ultrasonography, laparoscopy

FSH, Follicle-stimulating hormone; *LH,* luteinizing hormone; *MRI,* magnetic resonance imaging; *TSH,* thyroid-stimulating hormone.
Modified from Brassard M, AinMelk Y, Baillargeon JP. Basic infertility including polycystic ovary syndrome. *Med Clin North Am.* 2008;92: 1163-1192.

Treatment should be directed toward the underlying cause. Ovulatory dysfunction is treated based on the underlying cause: bromocriptine for prolactinoma, metformin or clomiphene citrate for PCOS, human menopausal gonadotropin for HH, clomiphene citrate plus glucocorticoids for adrenal hyperplasia with elevated levels of androgens, and antibiotics for infection. The family physician should strongly consider early referral to a reproductive specialist if the patient or couple has complex medical histories or advanced reproductive age.

Women who have secondary infertility (pituitary) wishing to restore fertility should be referred to specialized centers for pharmacologic induction of ovulation with exogenous pulsatile GnRH and exogenous FSH and LH treatment. GnRH can be used to restore fertility when hypothalamic disease and tertiary hypogonadism are present. Women older than the age of 50 years with secondary hypogonadism should be treated as menopausal, taking into consideration the risk-to-benefit ratio of estrogen replacement therapy in this age group.

Assessment of fallopian tube patency is accomplished by hysterosalpingography (first choice) or laparoscopy (if history strongly suggests prior tubal damage). Postcoital tests, endometrial biopsies, and basal body temperature records are no longer recommended as routine studies in the initial evaluation (Mancini et al., 2008; Practice Committee of the American Society of Reproductive Medicine, 2004) (Table 35-19).

Galactorrhea and Hirsutism

See eAppendix 35-7 online.

Polycystic Ovary Syndrome

Polycystic ovary syndrome is the clinical condition seen most commonly with androgen excess. Women with PCOS present with complaints of abnormal menses, infertility, hirsutism, acne, and obesity, all of which are related to excess androgen. PCOS is the single most common endocrine abnormality of women of reproductive age and affects

EAPPENDIX

35-7 Galactorrhea and Hirsutism

Galactorrhea

Galactorrhea is inappropriate section of milk or milklike fluid from the breast in the absence of parturition or beyond 6 months postpartum in a non–breastfeeding woman (Leung and Pacaud, 2004).

It may occur unilaterally or bilaterally in both sexes. Galactorrhea is commonly medication induced (e.g., antipsychotics, antidepressants, opiates, calcium channel blockers, and H2 receptor antagonists); however, pathologic causes are numerous and include pituitary tumor (prolactinoma being the most common), hypothalamic and pituitary stalk lesions, thyroid disorders, chronic renal failure, neurogenic causes, transient neonatal galactorrhea, manipulation, and idiopathic causes (the largest category).

The patient history should focus on the age of onset, duration, appearance of discharge, associated symptoms (e.g., headache, vision changes, temperature intolerance, weight changes, amenorrhea, infertility), medication use, obstetric and gynecologic history, precipitating factors, and family history. Physical examination should include vital signs, height, weight, and thorough breast examination. Special attention should be accorded to identifying visual field defects and papilledema, and evidence of thyroid disorders (goiter, coarse hair, skin changes), hirsutism, and acne need to be recognized.

Laboratory evaluation is indicated when no obvious source is identified. If the patient with galactorrhea is having normal menses, thyroid-stimulating hormone (TSH) and prolactin should be measured. If the patient has abnormal menses or amenorrhea, a pregnancy test to exclude or confirm an unsuspected pregnancy should be performed (regardless of age, pregnancy must always be excluded as an initial step in evaluating menstrual abnormality). If both TSH and prolactin are normal, the patient may be monitored. If the patient has an elevated prolactin level, investigation for prolactinoma with computed tomography (CT) or magnetic resonance imagining (MRI) is indicated. A serum prolactin level above 200 ng/mL virtually confirms the presence of a prolactinoma (Leung and Pacaud, 2004).

Treatment of galactorrhea is directed at the underlying cause. Underlying disorders, such as hypothyroidism, should be treated, and follow-up after the TSH level is in therapeutic range.

Hirsutism

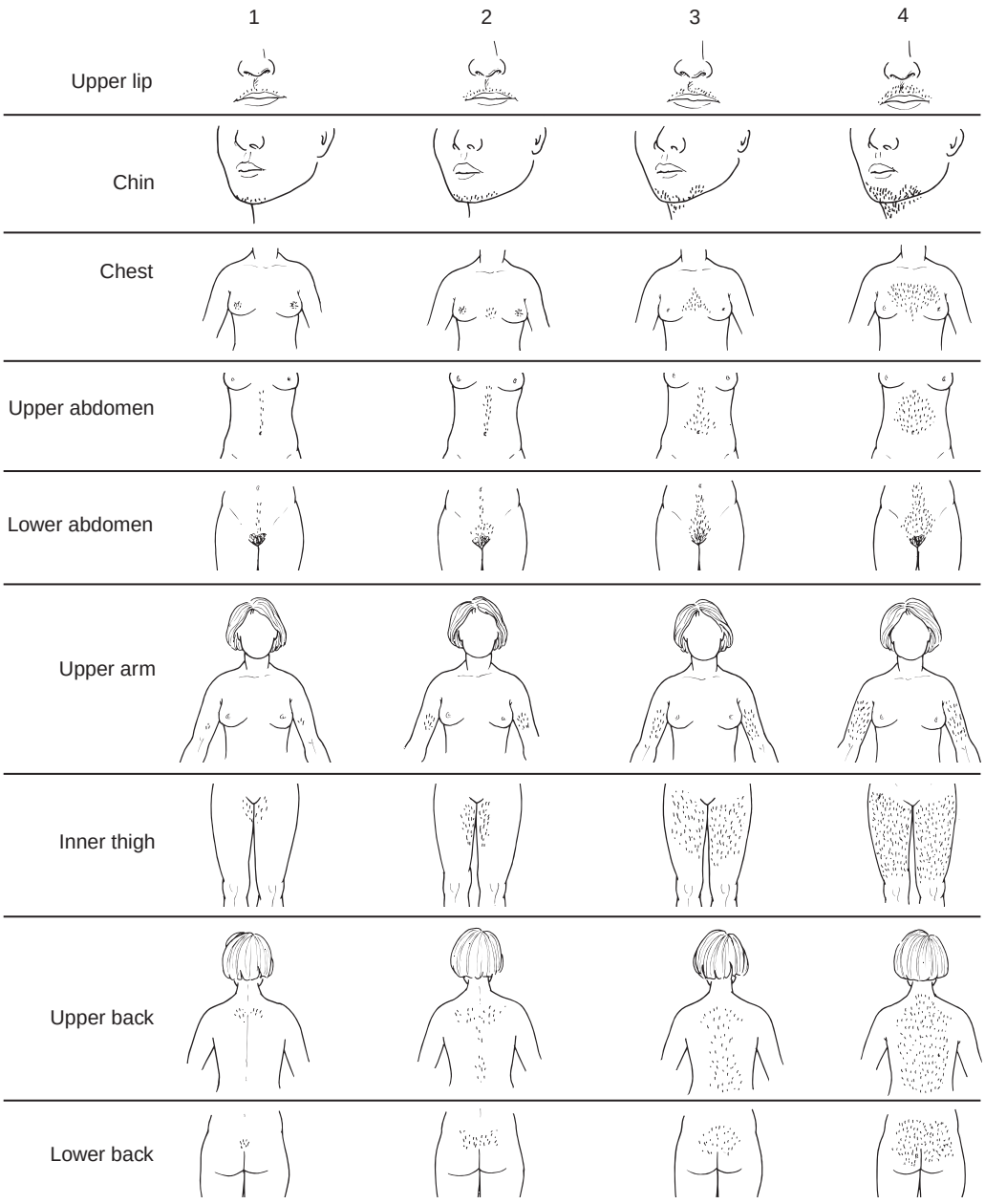
Hirsutism is the presence of excess terminal (coarse) hairs in androgen-dependent areas on a woman. It affects approximately 5% to 15% of women. This male-like pattern includes hair on the upper lip, chin, chest, lower abdomen, and extremities. Assessment of hirsutism is highly subjective, and it is recommended that a standard be applied when evaluating a patient for hirsutism. The modified Ferriman-Gallwey score is an objective scoring system used to determine hirsutism. In this system, hair from nine different body locations is scored on a scale of 1 to 4. No hair corresponds to a score of 0, and frankly virile hair corresponds to a score of 4. A score greater than 8 qualifies as hirsutism, but it is important to take into consideration normal ethnic and racial variations such as are found in women from southern European countries, who tend to have more and finer body hair (Curran and Moore, 2005). In this example, a high Ferriman-Gallwey score may not represent virilization, in which one would also expect to find deepening of the voice and clitoral hypertrophy in addition to hirsutism (eFigure 35-1).

True hirsutism is usually a sign of androgen excess in the form of testosterone, androstenedione, dehydroepiandrosterone (DHEA), DHEA sulfate (DHEA-S), or a combination. The most common causes of hirsutism are idiopathic and polycystic ovary syndrome. Other causes include congenital adrenal hyperplasia, 21-hydroxylase–deficient nonclassic adrenal hyperplasia, androgen-secreting tumors, ovarian tumors, hyperthecosis, adrenal tumors, hyperandrogenic insulin-resistant acanthosis nigricans syndrome, hyperprolactinemia, and androgenic drug intake (anabolic bodybuilding steroids) (Azziz, 2003).

Clinically, significant hirsutism (terminal, coarse hair in androgen-dependent areas) may be confused with hypertrichosis (diffuse increase in fine, vellus hair that is not androgen dependent). Hypertrichosis may be congenital or associated with other medical disorders such as hypothyroidism or anorexia nervosa or with certain medications (e.g., diazoxide, minoxidil, diphenylhydantoin).

The evaluation should begin with an appropriate history and physical examination focused on identifying possible signs and symptoms of disorders that may cause hirsutism. Patients should be asked about their ethnic background, age of onset, menstrual irregularities, hypertension, virilization, and pelvic masses. If evaluation to this point is unremarkable, proceed with testing of total and bioavailable testosterone levels, serum DHEA levels, and 24-hour urine sample for 17-ketosteroids. Ultrasonography, CT, or MRI will usually identify ovarian or adrenal masses. Treatment is unnecessary in mild cases except for strong patient preference. Cosmetic amelioration and destruction can be achieved by electrology, bleaching, laser, topical cream, or mechanical means. Hormonal suppression includes the use of oral contraceptives, long-acting gonadotropin-releasing hormone analogues, and insulin sensitizers. Peripheral androgen blockade can be achieved with spironolactone, flutamide, cyproterone acetate, or finasterid (Curran and Moore, 2005).

Low-dose steroids can be used to suppress androgen secretion in mild or late-onset congenital adrenal hyperplasia.



eFigure 35-1 Hirsutism scoring scale of Ferriman and Gallwey helps in determining whether the amount and location of body hair in a female patient are clinically significant in suspected hyperandrogenism. The nine body areas possessing androgen-sensitive pilosebaceous units (PSUs) are graded from 0 (no terminal hair) to 4 (frankly virile) and the sum totaled. Normal hirsutism score is less than 8. (Modified from Ehrmann DA, Barnes RB, Rosenfeld RL. Hyperandrogenism, hirsutism, and the polycystic ovary syndrome. In DeGroot LJ, Jameson, JL, eds. *Endocrinology*. 5th ed, vol 2. Philadelphia: Saunders; 2006.)

Table 35-20 Causes of Androgen Excess in Women

Adrenal hyperandrogenism	▪ Premature adrenarche ▪ Functional adrenal hyperandrogenism ▪ Congenital adrenal hyperplasia ▪ Cushing syndrome ▪ Hyperprolactinemia and acromegaly ▪ Abnormal cortisol action or metabolism ▪ Adrenal neoplasms
Gonadal hyperandrogenism	▪ Ovarian hyperandrogenism ▪ Functional ovarian hyperandrogenism or polycystic ovary syndrome ▪ Adrenal virilizing disorders and rest tumors ▪ Ovarian steroidogenic blocks ▪ Syndromes of extreme insulin resistance ▪ Ovarian neoplasms ▪ True hermaphroditism ▪ Pregnancy-related hyperandrogenism
Peripheral androgen overproduction	▪ Obesity ▪ Idiopathic

From Ehrmann DA, Barnes RB, Rosenfield RL. Hyperandrogenism, hirsutism, and the polycystic ovary syndrome. In DeGroot LJ, Jameson, JL, eds. *Endocrinology*. 5th ed, vol 3. Philadelphia: Saunders; 2006.

Table 35-21 Signs and Symptoms in Relation to Presence of Polycystic Ovary Syndrome (PCOS)

Symptoms and Signs	Patients with PCOS (%)
Hirsutism and unwanted hair growth	78.4
Alopecia	36.5
Hyperandrogenemia	70
Persistent acne	20-40
Normal androgen levels	20-40
Overt menstrual dysfunction	75-85
Oligomenorrhea	79.11
Polycystic ovaries	75-90
LH-to-FSH ratio	40
Insulin resistance	50-70
Type 2 diabetes	26.7
Dyslipidemia	70
Oligoanovulation	40
Obesity	50
Hyperprolactinemia	<1

FSH, Follicle-stimulating hormone; *LH,* luteinizing hormone.
Modified from Azziz R, Carmina E, Dewailly D, et al. Task Force on the phenotype of the polycystic ovary syndrome of the Androgen Excess and PCOS Society. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertil Steril*. 2009;91:456-488.

6% to 8% of women worldwide (Azziz et al., 2009). The definition of PCOS is constantly being revised. The latest Task Force on the Phenotype of the Polycystic Ovary Syndrome from the Androgen Excess and PCOS Society (AE-PCOS Society) defines PCOS by the presence of hyperandrogenism (clinical or biochemical), ovarian dysfunction (oligo-anovulation or polycystic ovaries), and the exclusion of related disorders (Azziz et al., 2009) (Table 35-20).

The typical presentation of PCOS includes hirsutism, menstrual dysfunction, obesity, insulin resistance, acanthosis nigricans, decreased fertility, and polycystic appearance to the ovaries. The onset of symptoms is usually around the time of menarche, but it may occur after puberty as a result of weight gain or other environmental factors. The differential diagnosis includes idiopathic hirsutism, ovarian hyperthecosis, ovarian tumor, adrenal tumor, nonclassic adrenal hyperplasia, Cushing syndrome, glucocorticoid resistance, and androgen-producing neoplasms.

A patient with PCOS is at higher risk for infertility, dysfunctional bleeding, obesity, endometrial hyperplasia, endometrial carcinoma, type 2 diabetes mellitus, dyslipidemia, hypertension, obstructive sleep apnea, and possibly CVD with a familial tendency (increased risk for mother and daughter) (Azziz et al., 2009; Ehrmann, 2005) (Table 35-21).

The diagnosis of PCOS is made with evidence of hyperandrogenism (clinical or biochemical), presence of ovarian dysfunction (clinical or anatomic), and excluding other conditions producing hyperandrogenism and ovarian dysfunction. Initial laboratory testing should include the determination of serum free testosterone, androstenedione, DHEA-S, and 17-hydroxyprogesterone. Other studies include prolactin, TSH, fasting glucose and insulin, and serum lipid profile. Obtaining circulating levels of LH and FSH does not contribute significantly to the diagnosis of PCOS, so these laboratory tests are not indicated with initial evaluation. Pelvic or transvaginal ultrasonography should be performed to identify the ovaries and determine their size and shape and the presence of cysts; typical PCOS ovaries have increased volume and contain 10 to 12 subcapsular follicular cysts 2 to 9 mm in diameter.

Treatment of hirsutism and acne in PCOS focuses on decreasing androgen levels, production, and effects. Metformin is used extensively to reduce insulin resistance and hyperinsulinemia related to hormonal changes and ovulation (Nestler, 2008). To decrease the risk of endometrial hyperplasia and carcinoma, cyclic progestin or a combination OC should be considered to inhibit endometrial proliferation.

In the long-term management of PCOS, steps should be taken to reduce CV complications, diabetes, obesity, and psychosocial morbidities (Figure 35-9). Screening for glucose intolerance with a 75-g 2-hour FTT and determination of serum lipid levels (total cholesterol, LDL, HDL, triglycerides) should be carried out. Lifestyle management changes include weight loss, exercise, and use of metformin and thiazolidinediones for those individuals with abnormal GTT results. In addition, clinicians should consider cardiovascular risk reduction, psychosocial issues, management of subfertility and hirsutism, and other lifetime management with insulin sensitizers and protection of the endometrium with hormonal manipulations (Figure 35-9).

KEY TREATMENT

- Patients with PCOS require cardiovascular risk reduction, psychosocial counseling, management of subfertility and hirsutism, and possible insulin sensitizers and protection of endometrium with hormonal manipulations (Azziz et al., 2009; Ehrmann, 2005; Nestler, 2008) (SOR: A).

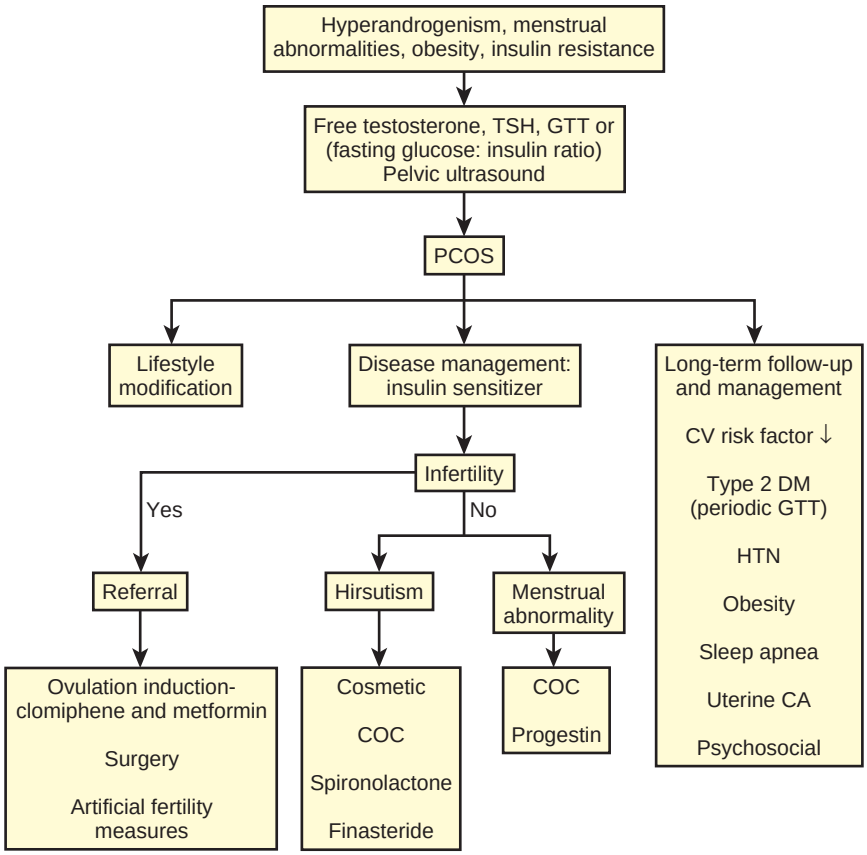


Figure 35-9 Therapeutic algorithm for management of polycystic ovary syndrome. *CA,* cancer; *COC,* combined oral contraceptives; *CV,* cardiovascular; *DM,* diabetes mellitus; *GTT,* glucose tolerance test; *HTN,* hypertension; *PCOS,* polycystic ovary syndrome; *TSH,* thyroid-stimulating hormone. (Modified from Samraj GPN, Kuritzky L. Polycystic ovary syndrome: comprehensive management in primary care. *Comp Ther*. 2002;28:208-221q.)

Disturbances in Calcium and Phosphate

Calcium homeostasis is a delicate balance among a number of organ systems and functions. These include the kidneys, thyroid, parathyroid, bone, adrenal glands, GI tract, nutrition, infectious disease, and medication. Malfunction in any of these modalities can result in hypercalcemia or hypocalcemia with the potential for serious morbidity and mortality. Total body calcium is balanced between plasma and the bony skeleton in a state of dynamic equilibrium. Approximately 1% of total calcium is in circulation, and the remaining 99% is stored in bone. In plasma, circulating calcium is approximately 40% protein (albumin) bound, 45% exists in an ionized state (Ca^{++}), and roughly 15% is found as various salts (calcium citrate, calcium lactate, calcium phosphate, and calcium sulfate). Bony calcium exists in an active state with constant deposition and resorption under the influence of parathyroid hormone (PTH, parathormone), calcitonin, osteoclastic and osteoblastic activity, and neoplastic disease.

The primary factor driving increases in circulating calcium is PTH, which increases bone resorption and converts vitamin D_3 (cholecalciferol) into 1,25-dihydroxycholecalciferol, the active form of vitamin D_3. Cholecalciferol is primarily formed in the skin from solar irradiation, and some evidence suggests that ultraviolet radiation exposure of tanning beds can raise vitamin D levels. However, the latter is not recommended as an appropriate source of vitamin D_3 (Tangpricha et al., 2004). Dietary sources of vitamin D_3 are also important and can be obtained from fortified milk, fruit juices, fish oil, and other sources. The active form of vitamin D_3 is required to facilitate calcium absorption from the gut. Calcium homeostasis is further maintained by circulating levels of ionized calcium and calcitonin's negative effect on osteoclastic bone resorption (Guyton and Hall, 2006) (Figure 35-10).

Normal levels of total circulating calcium, with normal albumin levels, range between 8.5 and 10.5 mg/dL (≈2.4 mmol/L). Ionized levels, which are not albumin dependent, will range between 1.17 and 1.33 mmol/L (≈4.7 mg/dL) (Bringhurst and Leder, 2006).

HYPERCALCEMIA

Causes of hypercalcemia are generally divided into two types: primary and secondary. Primary causes are due to excessive parathormone secretion, and secondary causes include disease processes that directly affect bone metabolism and calcium excretion. The most common cause of primary hyperparathyroidism (PHPT) is a solitary parathyroid adenoma, accounting for approximately 80% of cases. Multiple adenomas are found in 2% to 4% of cases. The second most common cause of PHPT (15%) is parathyroid hyperplasia of multiple (usually ≥4) parathyroid glands.

The etiologies for these include a mix of congenital and familial diseases such as MEN-I and MEN-IIA. Fewer than 1% of cases of PHPT are caused by primary parathyroid malignancy (Silverberg and Bilezikian, 2006) (Table 35-22).

Primary hyperparathyroidism does not present with classic symptoms. Symptoms may be as nonspecific as generalized weakness in the proximal muscles, fatigue, headache, weight loss, and constipation all the way to being as profound as renal failure, hypovolemic shock, and death (usually in patients with malignancy but sometimes previously undiagnosed). Patients rarely present with signs and symptoms immediately suggesting hypercalcemia. PHPT is usually uncovered through routine, nonspecific screening laboratory tests; during evaluation for nephrolithiasis; or, occasionally in a patient with accelerated osteoporosis and pathologic fracture (Silverberg and Bilezikian, 2006) (Table 35-23).

There is a classic "quadrad" of symptoms associated with hypercalcemia that, although seen in many disease processes, may be helpful in a patient with hypercalcemia, irrespective of etiology. The mnemonic is "bones, stones, moans, and abdominal groans," representing the four symptoms of the classic quadrad, which are bone pain, renal calculi, psychiatric disorder, and nausea and vomiting (Silverberg and Bilezikian, 2006).

The primary dysfunction in PHPT is an excess of circulating PHT. However, with bony metastases, PHT levels will be appropriately suppressed in the presence of elevated serum calcium levels because of osteolytic metastases. When the cause of hypercalcemia is malignancy, the patient usually has a history; an exception is unsuspected multiple myeloma, which may present with chronic low back pain and an elevated serum calcium level. Calcium levels in malignancy are typically higher (>14 mg/dL) than those

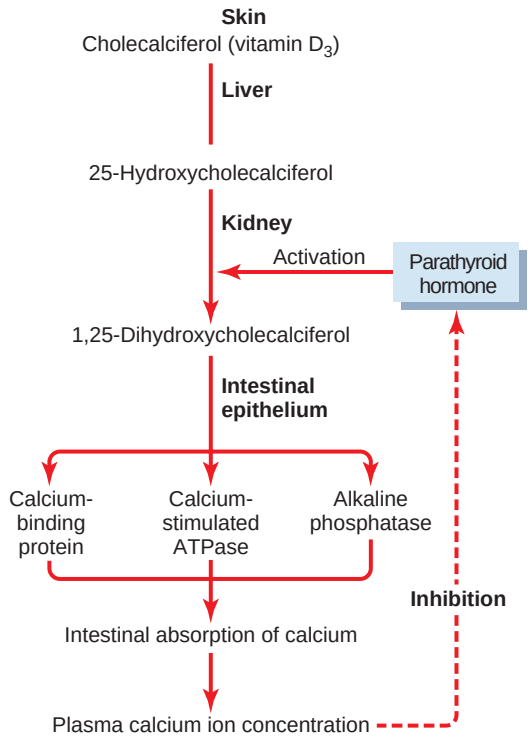


Figure 35-10 Pathway for conversion of vitamin D_3 into its active form (1,25-dihydroxycholecalciferol) and the role vitamin D plays in control of plasma calcium concentration. (From Hall JE. Parathyroid hormone, calcitonin, calcium and phosphate metabolism, vitamin D, bone, and teeth. In Guyton AC, Hall JE, eds. *Textbook of medical physiology*. 12th ed. Philadelphia: Saunders; 2011.)

Table 35-22 Differential Diagnosis of Hypercalcemia

Primary hyperparathyroidism
Parathyroid carcinoma
Hypercalcemia of malignancy
Nonparathyroid endocrine causes
Thyrotoxicosis
Pheochromocytoma
Addison disease
Islet cell tumors
Drug-related hypercalcemia
Vitamin D
Vitamin A
Thiazide diuretics
Lithium
Estrogen and antiestrogens
Familial hypocalciuric hypercalcemia
Miscellaneous
Immobilization
Milk-alkali syndrome
Parenteral nutrition

From Silverberg SJ, Bilezikian JP. Primary hyperparathyroidism. In DeGroot LJ, Jameson, JL, eds. *Endocrinology*. 5th ed, vol 2. Philadelphia: Saunders; 2006.

Table 35-23 Biochemical Profile in Primary Hyperparathyroidism

	Patients (mean ±SEM)	Reference Range
Serum calcium	10.7 ± mg/dL	8.2-10.2 mg/dL
Serum phosphorus	2.8 ± 0.1 mg/dL	2.5-4.5 mg/dL
Total alkaline phosphatase	114 ± 5 IU/L	<100 IU/L
Serum magnesium	2.0 ± 0.1 mg/dL	1.8-2.4 mg/dL
PTH (IRMA)	119 ± 7 pg/mL	10-65 pg/mL
25(OH) vitamin D	19 ± 1 ng/mL	9-52 ng/mL
$1,25(OH)_2$ vitamin D	54 ± 2 pg/mL	15-60 pg/mL
Urinary calcium	240 ± 11 mg/g creatinine	
Urine DPD	17.6 ± nmol/L/mmol/L creatinine	<14.6 nmol/L/mmol/L creatinine
Urine PYD	46.8 ± 2.7 nmol/L/mmol/L creatinine	<51.8 nmol/L/mmol/L creatinine

DPD, Deoxypyridinoline; *IRMA,* immunoradiometric assay; *PTH,* parathyroid hormone; *PYD,* pyridinoline.
From Silverberg SJ, Bilezikian JP. Primary hyperparathyroidism. In DeGroot LJ, Jameson, JL, eds. *Endocrinology*. 5th ed, vol 3. Philadelphia: Saunders; 2006.

found with parathyroid adenomas (<13 mg/dL), although this is not always the case.

Thiazide diuretics, lithium, and calcium carbonate are common medications seen in primary care that, if not properly monitored and prescribed, can result in hypercalcemia. It is also important to inquire about nonprescription medications (OTC) because excess vitamin D (intoxication) can be a cause. If a patient is taking any of these substances, the patient is asymptomatic, and the serum calcium level is less than 14 mg/dL, the approach is to discontinue the medication and repeat the calcium level in 1 week. If the serum calcium is stable or declining, continue to monitor it until it returns to normal. Occasionally, adrenal insufficiency and hyperthyroidism are uncovered in the evaluation of a patient with an elevated serum calcium level.

Patients who have symptoms consistent with hypercalcemia or serum calcium levels in excess of 13.5 mg/dL may require more aggressive treatment. These patients will almost always be volume depleted as a result of hypercalciuria with resultant polyuria. Treatment is aimed initially at aggressive rehydration. Isotonic saline, at the rate of 2 to 4 L/day until the calcium level returns to normal, is appropriate. Furosemide (loop diuretic) can be used in conjunction with fluid replacement in older patients and those with renal or cardiac disorders to prevent fluid overload. Careful fluid management must be maintained to prevent inadvertent fluid overload or depletion. Other treatments include IV bisphosphonate, calcitonin, and gallium nitrate or plicamycin (Tables 35-24 and 35-25).

Parathyroidectomy is indicated in symptomatic patients and is considered to be the first and generally the only option to cure PHPT. In addition, surgical treatment is recommended for asymptomatic patients who meet any of the following conditions: serum calcium more than 1 mg/dL or more above the upper limit of normal,

Table 35-24 Summary of the Most Generally Useful Medical Therapies for Hypercalcemia

Treatment	Onset of Action	Duration of Action	Advantages	Disadvantages
Rehydration	Hours	During treatment	Rapid action Rehydration invariably needed	None
Forced saline diuresis (with or without loop diuretics)	Hours	During treatment	Rapid action	Modest calcium-lowering effect Potential for volume overload Electrolyte disturbance Transient efficacy Inconvenient for patients
Calcitonin	Hours	1-2 days	Rapid action	Modest calcium-lowering effect Tachyphylaxis develops in a few days
BISPHOSPHONATES				
Etidronate	1-3 days	5-7 days	First-generation bisphosphonate Well tolerated	3-day infusion protocol Less effective than other bisphosphonates
Pamidronate	1-2 days	Weeks to months	Second-generation bisphosphonate Normalizes calcium levels in many patients	Fever Occasional hypocalcemia, hypophosphatemia, and hypomagnesemia
Zoledronate	1-2 days	Weeks to months	Third-generation bisphosphonate More potent than second-generation bisphosphonates Normalizes calcium levels in 90% of patients Can be given in 30 min	Fever Hypophosphatemia Hypocalcemia Renal toxicity occasional

From Finkelstein JS, Potts JT. Medical management of hypercalcemia. In DeGroot LJ, Jameson, JL, eds. *Endocrinology*. 5th ed, vol 2. Philadelphia: Saunders; 2006.

Table 35-25 Summary of Therapies for Hypercalcemia Useful in Special Circumstances

Treatment	Onset of Action	Duration of Action	Advantages	Disadvantages
Gallium nitrate	5 days	7-10 days	May normalize calcium in patients resistant to bisphosphonates	Must be infused continuously over 5 days Occasional nephrotoxicity or hypophosphatemia
Glucocorticoids	Days	Days to weeks	Oral administration	Effective in granulomatous disorders and certain types of malignancies, especially hematologic
Dialysis	Hours	During use and for 24-48 hr afterward	Rapid onset of action Useful in patients with renal failure and heart failure Useful to treat life-threatening hypercalcemia	Complex procedure Reserved for extreme or special circumstances
Oral phosphate	24 hr	During use	Minimal toxicity if serum phosphate low Oral administration	Modest calcium-lowering effect Diarrhea

From Finkelstein JS, Potts JT. Medical management of hypercalcemia. In DeGroot LJ, Jameson, JL, eds. *Endocrinology*. 5th ed, vol 2. Philadelphia: Saunders; 2006.

creatinine clearance less than 60 mL/min, osteoporosis, and age younger than 50 years (Bilezikian et al., 2009; Silverberg and Bilezikian, 2006).

For patients who have failed surgery and those who do not meet surgical criteria, medical treatment includes calcimimetics (cinacalcet), moderate calcium intake, estrogen replacement (when applicable), bisphosphonates, and selective estrogen receptor modulators (SERMs) (Bilezikian et al., 2009; Silverberg and Bilezikian, 2006).

For a patient with PHPT not caused by malignancy, determining if there is one adenoma or multiple functioning adenomas and the location(s) is important in minimizing both the duration and extent of surgery. It is possible to determine preoperatively which parathyroid gland(s) may be the source of the PTH using technetium-labeled (Tc-99m) sestamibi nuclear scan. If the latter did not provide definitive results, then ultrasonography, CT, or MRI may be used to localize the adenoma (Silverberg and Bilezikian, 2006).

HYPOCALCEMIA

Hypocalcemia has a number of primary and secondary causes. Primary causes are due to some defect in PTH availability, including (1) a lack of production (surgical removal of the parathyroid gland or hypoparathyroidism due to autoimmune disease), (2) impaired secretion (with profound hypomagnesemia), and (3) end-organ resistance. With the first two, there is a deficit in circulating PTH, but with the third, the PTH is elevated, in contrast to a low serum calcium level and hypophosphatemia. An example of end-organ resistance is Albright syndrome. Secondary causes include severe vitamin D deficiency, "hungry bone syndrome" with chondrosarcoma, and HIV/AIDS (Table 35-26).

Signs and symptoms of hypocalcemia are generally lacking in the outpatient setting. The primary clinical findings are caused by neuromuscular irritability. If hypocalcemia is suspected, two physical tests can be performed, which may help to make the diagnosis, although negative responses do not rule out hypocalcemia: the Chvostek sign (tapping the facial nerve across the cheek with contraction of the facial muscle) and Trousseau sign (carpal spasm via a BP cuff). Deep tendon reflexes may be hyperactive, and the patient may appear anxious, confused, demented, or psychotic. The signs and symptoms of hypocalcemia are related to the level of ionized calcium rather than total calcium, as well as the rapidity of decline (Levine, 2006). Alkalosis, either primary or compensatory, can cause a shift in ionized calcium to a bound state, thus exacerbating a borderline hypocalcemia situation.

Cardiac changes caused by hypocalcemia include prolongation of the QT interval, resulting in life-threatening dysrhythmia and cardiac dysfunction. Generalized seizures are also possible. The cardiac dysfunction is generally reversible with normalization of the ionized calcium levels. In acute and severe cases, IV calcium is the treatment of choice. Concurrent management of hyperphosphatemia, alkalosis, and hypomagnesemia is required. Long-term management is with oral calcium and vitamin D. Although use of thiazide diuretics is contraindicated in patients with hypercalcemia, they can be used with hypocalcemia and may, in fact, have somewhat of a beneficial effect. On the other hand, loop diuretics must be used very cautiously because they increase renal excretion of calcium and may exacerbate the problem.

Table 35-26 Causes of Functional Hypoparathyroidism

- A. Surgery
- B. Toxic agents
  - 1. High-dose radiation (rarely)
  - 2. Asparaginase
  - 3. Ethiofos
- C. Infiltrative processes
  - 1. Iron deposition
  - 2. Copper deposition
  - 3. Tumor or granuloma
- D. Defective secretion of PTH
  - 1. Magnesium deficiency
  - 2. Magnesium excess
  - 3. Activating mutation of calcium-sensing receptor gene (MIM 145980)
  - 4. Antibodies that activate the calcium-sensing receptor
  - 5. Burn injury and upregulation of calcium-sensing receptor
  - 6. Alcohol
  - 7. Maternal hypercalcemia
  - 8. Neonatal hypocalcemia
- E. Autoimmune destruction of parathyroid glands
  - 1. Autoimmune hypoparathyroidism
  - 2. Autoimmune polyglandular syndrome, type 1 (APECED, MIM 240300)
- F. Idiopathic hypoparathyroidism
  - 1. Autosomal recessive (MIM 241400)
  - 2. X-linked (MIM 307700)
- G. Embryologic defects in parathyroid gland development
  - 1. DiGeorge syndrome (del 22q or TBX1 mutation); DGS1; MIM 188400
  - 2. DiGeorge syndrome (del 10p) DGS2; MIM 601362
  - 3. Velocardiofacial syndrome (del 22q); MIM 192430
    - a. Kenny-Caffey and Sanjad-Sakati syndromes (TBCE, MIM 244460)
- H. Defective synthesis of parathyroid hormone (MIM 168450)
  - 1. Autosomal dominant mutation in prepro-PTH gene
  - 2. Autosomal recessive mutation in prepro-PTH gene
- I. Metabolic defects and mitochondrial neuromyopathies
  - 1. Kearn-Sayre syndrome
  - 2. Person syndrome
  - 3. tRNA *leu* mutations
- J. Resistance to PTH
  - 1. Pseudohypoparathyroidism type 1a (MIM 103580)
  - 2. Pseudohypoparathyroidism type 1b
  - 3. Pseudohypoparathyroidism type 1c
  - 4. Pseudohypoparathyroidism type 2

APECED, Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; *DGS,* DiGeorge syndrome; *MIM,* designator that represents an autoimmune gene mutation; *prepro-PTH,* preproparathyroid hormone; *PTH,* parathyroid hormone; *TBCE,* tubulin folding cofactor E.

From Levine MA. Hypoparathyroidism and pseudohypoparathyroidism. In DeGroot LJ, Jameson, JL, eds. *Endocrinology*. 5th ed, vol 2. Philadelphia: Saunders; 2006.

Pseudohypoparathyroidism is a rare phenomenon representative of several congenital, endocrinologic disorders in which tissue resistance to PTH is present. The classic form of this disorder is *Albright hereditary osteodystrophy* (AHO). Patients with AHO have short stature, mental retardation, brachydactyly, and PTH resistance (elevated PTH levels). Another form of AHO, called pseudopseudohypoparathyroidism, does not have PTH dysfunction. Although the clinical course for these diseases may be variable and, in some cases, is protracted, AHO usually is associated with a shortened life expectancy. Treatment is primarily supportive (Levine, 2006).

HYPERPHOSPHATEMIA

The most common cause of hyperphosphatemia, and most familiar to primary care physicians, is impaired renal function. It is also a characteristic of all forms of hypoparathyroidism from the loss of inhibitory effect of PTH on phosphate reabsorption at the proximal renal tubule (Kolon et al., 2004). High-phosphate formula provided to infants can result in hypocalcemia and tetany (Table 35-27).

HYPOPHOSPHATEMIA

Dietary causes of hypophosphatemia are virtually nonexistent, although excessive use of oral phosphate binders (aluminum and magnesium hydroxide antacids) can result in binding of phosphate in the intestine, thus preventing absorption. Generally, when use of oral antacids is excluded, the most common cause of hypophosphatemia is elevated levels of serum calcium caused by increased PTH or malignancy (Silverberg and Bilezikian, 2006). Hypophosphatemia, in association with hypocalcemia, is usually attributable to renal wasting or seen in severe illness. One form of infant hypophosphatemic rickets is transmitted as an autosomal dominant trait (Table 35-28).

Table 35-27 Causes of Hyperphosphatemia

Impaired renal phosphate excretion	Renal insufficiency
	Tumoral calcinosis
	Hypoparathyroidism, pseudohypoparathyroidism
	Acromegaly
	Etidronate
	Heparin
Increased extracellular phosphate	Rapid administration of phosphate (IV, oral, rectal)
	Rapid cellular catabolism or lysis
	Catabolic states
	Tissue injury
	Hyperthermia
	Crush injuries
	Fulminant hepatitis
	Cellular lysis
	Hemolytic anemia
	Rhabdomyolysis
	Cytotoxic therapy
	Transcellular shifts of phosphate
	Metabolic acidosis
	Respiratory acidosis

IV, Intravenous.

From Bringhurst FR, Leder BZ. Regulation of calcium and phosphate homeostasis. In DeGroot LJ, Jameson, JL, eds. *Endocrinology.* 5th ed, vol 2. Philadelphia: Saunders; 2006.

Table 35-28 Causes of Hypophosphatemia

IMPAIRED INTESTINAL PHOSPHATE REABSORPTION

Selective binding of dietary phosphate
- Aluminum-containing antacids

IMPAIRED RENAL TUBULAR PHOSPHATE REABSORPTION

Renal tubular disorders

Fanconi syndrome(s), other renal tubular disorders
Cystinosis
Wilson disease
Inactivating NA/P12 mutations
Dent disease
Hypophosphatemia in idiopathic hypercalciuria

Elevated PTH or PTHrP

Primary hyperparathyroidism
PTHrP-dependent hypercalcemia (malignancy)
Secondary hyperparathyroidism
- Vitamin D deficiency resistance
- Calcium starvation or malabsorption
- Bartter syndrome
- Autosomal recessive renal hypomagnesemia or hypercalciuria

Humoral phosphate-wasting syndromes

X-linked hypophosphatemic rickets
Autosomal dominant hypophosphatemic rickets
Tumor-induced osteomalacia
McCune-Albright syndrome

Other systemic disorders

Glucosuria
Hyperaldosteronism
Magnesium or potassium depletion
Amyloidosis
Renal transplantation
Rewarming, induced hyperthermia

Drugs and toxins

Ethanol
Ifosfamide
Acetazolamide
Cisplatin
Toluene
Heavy metals
Glucocorticoids
Rapamycin
Estrogens
Foscarnet
Suramin
Pamidronate

ACCELERATED PHOSPHATE REDISTRIBUTION INTO CELLS OR BONE

Acute intracellular shifts

Insulin therapy (for hyperglycemia, diabetic ketoacidosis)
IV glucose, fructose, glycerol (in NPO patients)
Catecholamines (epinephrine, albuterol, terbutaline, dopamine)
Acute respiratory alkalosis (salicylate intoxication, acute gout)
Gram-negative sepsis, toxic shock syndrome, thyrotoxic periodic paralysis
Recovery from acidosis, starvation, hypothermia

Rapid formation of new cells

Leukemic blast crisis
Bone marrow, stem cell therapy
Erythropoietin, GM-CSF therapy
Treatment of pernicious anemia
Status post–partial hepatectomy

Accelerated net bone formation

Postparathyroidectomy
Treatment of vitamin D deficiency
Early phase of bisphosphonate therapy
Osteoblastic metastases

GM-CSF, Granulocyte-macrophage-colony-stimulating factor; *IV,* intravenous; *NPO,* nothing by mouth; *PTH,* parathyroid hormone; *PTHrP,* parathyroid hormone-related protein.

Bringhurst FR, Leder BZ. Regulation of calcium and phosphate homeostasis. In DeGroot LJ, Jameson, JL, eds. *Endocrinology*. 5th ed, vol 2. Philadelphia: Saunders; 2006.

OSTEOPOROSIS AND OSTEOMALACIA

See eAppendix 35-8 online.

Summary of Additional Online Content

The following content is available at www.expertconsult.com:

eAppendix 35-1 Acromegaly and Gigantism

eAppendix 35-2 Craniopharyngiomas, Thyrotropin-Secreting Pituitary Adenomas, Gonadotropic Adenomas, and Other Adenomas

eAppendix 35-3 Isolated Aldosterone Deficiency

eAppendix 35-4 Mixed Disorder: Congenital Adrenal Hyperplasia

eAppendix 35-5 Cryptorchidism

eAppendix 35-6 Depressed Libido in Women

eAppendix 35-7 Galactorrhea and Hirsutism

eAppendix 35-8 Osteoporosis and Osteomalacia

References

The complete reference list is available at www.expertconsult.com.

Web Resources

www.aace.com/pub/guidelines American Association of Clinical Endocrinologists.

www.aafp.org/online/en/home/clinical.html The American Academy of Family Physicians maintains a website that can be accessed by members (more selection) and nonmembers with information on recommendations for clinical screening and treatment.

www.acponline.org/clinical_information/guidelines The American College of Physicians maintains this website for general information as well as specific information on disease screening.

www.endo-society.org/guidelines Direct access to current and past treatment guidelines for most endocrine-related diseases.

www.hormone.org/Resources/Patient_Guides Ready resource for current recommendations for physicians and the public for endocrine disorders.

www.jama.ama-assn.org Reference site sponsored by the American Medical Association with access to current and past *JAMA* publications, by author, subject, and so on.

www.ncbi.nlm.nih.gov/sites/entrez PubMed is a general reference source that provides search access based on subject, author, journal, and so on.

EAPPENDIX

35-8 Osteoporosis and Osteomalacia

Skeletal mass peaks around the beginning of the third decade of life, after which calcium deposition decreases steadily with advancing age. By the fifth decade of life, this process is occurring at a rate of approximately 4% per year (Perry, 2006).

With age, bone structure changes, and the direction of the change depends on which process is involved. Paget disease of the bone is caused by abnormal bone formation; loss of trabeculare bone leads to osteoporosis; and loss of bony substrate causes osteomalacia. A number of factors can impact significantly on these processes, both positively and negatively. Some are controllable and some not. Those that are controllable include decreased physical activity, decreased calcium intake, decreased sun exposure (less available vitamin D_3), smoking, and excessive alcohol use. In addition, changes in circulating levels of testosterone and estrogen, thyroxine, growth hormone, parathormone, and calcitonin can also have dramatic effect on bone metabolism. Iatrogenic causes such as use of exogenous steroids or excess thyroid hormone replacement and vascular disorders such as vasculitis and peripheral vascular disease are also important (Perry, 2006).

Pharmacologic treatments of bony demineralization, including calcitonin via nasal inhalation; parathormone via injection; oral selective estrogen receptor modulators, either oral or injectable bisphosphonates; and monoclonal antibodies such as denosumab, are all effective, albeit used in different clinical situations. It was once thought estrogen replacement therapy (HRT) was a good treatment for osteoporosis, but this has become less acceptable because of other, more significant, negative aspects to HRT. Testosterone has been shown to slow, and even reverse, bone loss in hypogonadal men.

Although the majority of demineralization of bone is a process of aging, there are some instances in which hormonal abnormalities can be the cause, so a careful review of the patient's history and symptoms and an occasional laboratory analysis in select cases is required. To monitor adequacy of treatment, bone density studies are the method of choice (Perry, 2006).

Osteoporosis in Men

Osteoporosis is a major public health problem affecting all ages, populations, and ethnic groups as well as both genders. Although a man's androgens do not wane abruptly, as occurs in menopause, men still experience clinically significant effects of osteoporosis with aging as a result of a declining bioavailable testosterone and estrogen levels. However, the risk of fracture rises in men 5 to 10 years after women (Orwoll, 1998).

The lifetime risk of nontraumatic fracture in a 60-year-old man is 25.6%, and the cumulative lifetime hip fracture risk is 17%, which carries with it a 20% first-year mortality rate (Nguyen et al., 1996). The mortality rate of older men with hip fractures is higher than that of women (Myers et al., 1991).

Approximately 90% of men with a high likelihood of osteoporosis are not investigated. About 50% of men with osteoporosis have risk factors and conditions contributing to their osteoporosis other than advancing age. These common, underlying risk factors include hypogonadism, hyperthyroidism, gastrointestinal disorders, anticonvulsant medications, excess alcohol intake, hypercalciuria, immobilization, and glucocorticoid therapy representing the most common underlying risk factors. Pharmacologic therapies such as bisphosphonates and parathyroid hormone are possible options for treatment.

The American College of Physicians recommends; clinicians periodically assess older men for osteoporosis risk factors and obtain dual-energy x-ray absorptiometry for men at increased risk of osteoporosis (Qaseem et al., 2008) Primary treatment is supplemental calcium and vitamin D (Watts et al., 2010).

KEY TREATMENT

- Estrogen replacement therapy (HRT) is no longer considered first-line therapy for women with osteoporosis because of significant cardiovascular risk (Anderson et al., 2004) (SOR: A)
- Supplemental calcium and vitamin D are first-line therapy for prevention of osteoporosis (Watts et al., 2010) (SOR: A).
- Lifestyle changes effective in prevention of osteoporosis include resistance and high-impact exercise throughout life and smoking cessation (Watts et al., 2010) (SOR: B).
- Bisphosphonates and denosumab are currently considered first-line therapy for osteoporosis (Watts et al., 2010) (SOR: A).
- Parathormone and selective estrogen receptor modulators are generally second-line therapies for osteoporosis (Watts et al., 2010) (SOR: A).
- Calcitonin is the last line of therapy for osteoporosis (Watts et al., 2010) (SOR: C).
- Primary treatment is supplemental calcium and vitamin D_3 (Watts et al., 2010) (SOR: A).

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