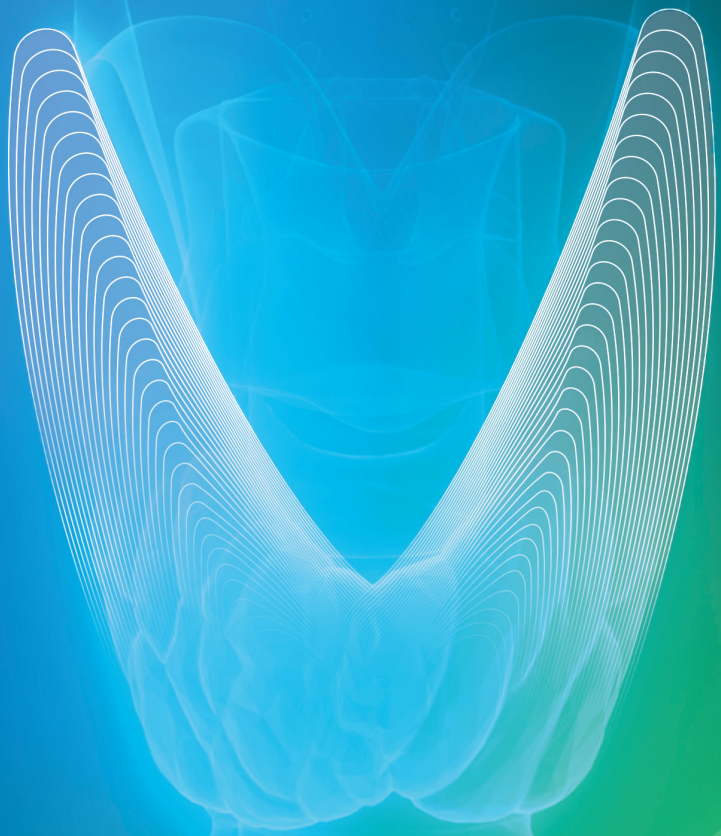
LEARNING GUIDE

THYROID



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ABOUT THIS LEARNING GUIDE

INTENDED AUDIENCE

This Learning Guide serves the basic educational needs of health care professionals involved with laboratory medicine, obstetrics, gynecology, and endocrinology.

Anyone associated with thyroid function testing will find this monograph of even greater interest.

Laboratorians, and those who use laboratory services, will find this guide useful. This includes but is certainly not limited to laboratory technicians and technologists, supervisors and managers, nurses, suppliers, and other physician office and laboratory support personnel.

HOW TO USE THIS LEARNING GUIDE

There are five sections that comprise this Learning Guide. Each section contains the topic overview, definition, and key concept review. The Key Concept Review section quickly transitions you into the significant elements of the topic discussion.

CONTENTS

INTRODUCTION

LEARNING GUIDE

Thyroid disease is the most prevalent endocrine disorder known. The onset of thyroid disease is often misunderstood by the patient. This is because the clinical manifestations of thyroid dysfunction vary considerably among patients in their characteristics and severity. In addition, the development of the signs and symptoms is often a slow and insidious process. The misdiagnosis of thyroid disease as other conditions often occurs because of the variability and overlap in clinical signs and symptoms. Successful diagnosis and management of thyroid disease require close collaboration between the physician, clinical laboratory, and the patient. The treatment of thyroid disease depends on many factors, including the type and severity of the thyroid disorder and the age and overall health of the patient. Treatment will be specific to each individual.

This Learning Guide provides an overview of thyroid gland function and the diseases and treatments associated with thyroid gland dysfunction.

SECTION 1

THE ENDOCRINE SYSTEM AND THE THYROID GLAND

LEARNING OBJECTIVES

After completing this section, you should be able to:

1. Define and describe the function of the endocrine system.
2. Explain the negative feedback mechanism.
3. Describe the function of the thyroid gland.
4. Identify laboratory tests used in the assessment of thyroid function.

DEFINITION, FUNCTION, AND COMPONENTS

The endocrine system is essential for normal growth and development, reproduction, and homeostasis (maintaining a constant internal environment).[1]

KEY CONCEPT REVIEW

A REGULATORY SYSTEM

The endocrine system interacts with the nervous system to detect environmental changes and to direct the body's response to these changes. The endocrine system functions by releasing hormones from certain organs into the bloodstream. These hormones regulate, via stimulation or inhibition, specific body activities. Certain disorders and diseases of the endocrine system, such as diabetes mellitus and thyroid disease, are due to alterations in hormone production and can cause serious health problems.

DEFINITION AND FUNCTION OF THE ENDOCRINE SYSTEM

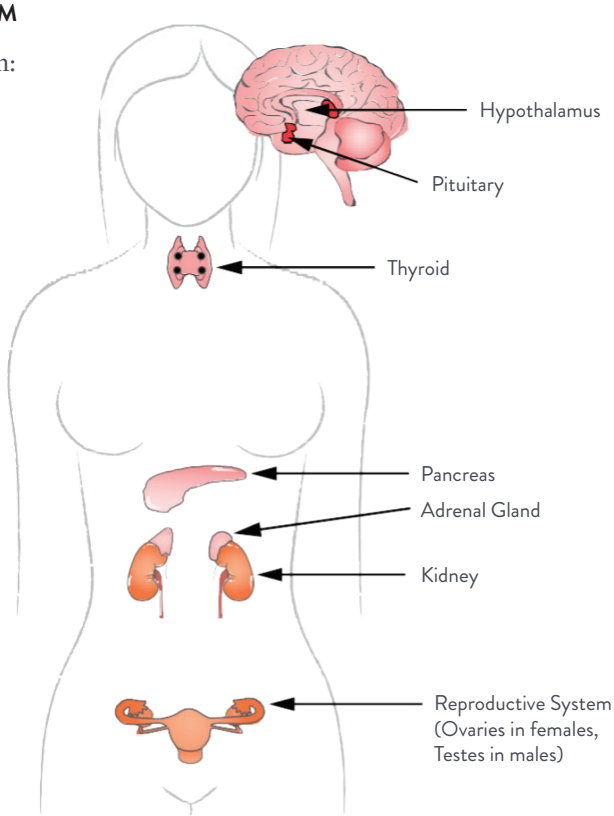
The endocrine system, in conjunction with the nervous system:

- Regulates almost all homeostatic and metabolic activities
- Sets the pace of growth and development
- Influences behavior
- Controls reproductive function

COMPONENTS OF THE ENDOCRINE SYSTEM

Some of the components of the endocrine system are glands that form discrete organs:

- Hypothalamus
- Pituitary gland
- Thyroid gland
- Parathyroid glands
- Adrenal glands
- Islets of Langerhans (pancreas)
- Sex glands or gonads (testes in males, ovaries in females)



DEFINITION AND FUNCTION OF HORMONES

Hormones are chemical substances secreted by the endocrine glands and carried by the blood to regulate the functions of tissues and organs elsewhere in the body.

There are three types of hormones:

- Steroids, which are structurally based on cholesterol and include cortisol, aldosterone, androgens (male hormones), estrogens (female hormones), progesterone, and testosterone
- Amines, which include thyroid hormones and adrenomedullary hormones
- Proteins and peptides, which include, among others, pituitary, parathyroid, and pancreatic hormones

MODES OF ACTION

When hormones are released into the bloodstream, they circulate throughout the body and are recognized by target cells in specific organs. When the hormone reaches a target cell, it can bind to receptor sites as one means of action. That combination of hormone and receptor usually triggers a series of activities within the cell.

REGULATION MECHANISMS

The endocrine system regulates the amount of hormone produced so that just enough is available to meet the physiological need. Regulation is achieved by a complex process called feedback. In the endocrine system, negative feedback is the major means of regulation. With negative feedback, an increase in the circulating level of a hormone inhibits the further secretion of that hormone (Figure 1-1). Conversely, a drop in the level of the hormone in the blood leads to an increase in the secretion of the hormone. Both of these occur via alterations in the regulatory hormones affecting the primary endocrine organ/gland.

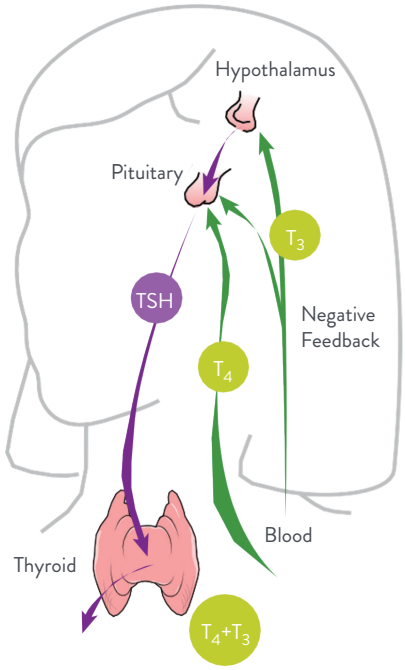


FIGURE 1-1. Positive and Negative Feedback

THE HYPOTHALAMUS AND PITUITARY GLAND

The hypothalamus controls many functions of the nervous system by its effects on the pituitary gland of the endocrine system.

The pituitary gland secretes hormones that regulate many body processes, including growth, reproduction, and a number of metabolic activities.

KEY CONCEPT REVIEW

THE HYPOTHALAMUS

The hypothalamus is located at the center of the underside of the brain. The hypothalamus is responsible for regulating:

- Food intake
- Water balance
- Sleep
- Wakefulness
- Sexual rhythms

It also plays an important role in the regulation of hormone levels.

HORMONE RELEASE

Upon stimulation by nerve impulses from the central and autonomic nervous systems, the hypothalamus releases two types of hormones:

- Hormones that signal the anterior lobe of the pituitary gland to release or inhibit specific hormones
- Hormones that are sent to the posterior lobe of the pituitary gland for storage and subsequent release

PITUITARY GLAND

The pituitary gland is the only endocrine gland that can stimulate other endocrine glands to produce their own particular hormones. It lies at the base of the brain beneath the hypothalamus and consists of two lobes—the anterior lobe and the posterior lobe.

TROPIC HORMONES

The anterior lobe produces four tropic hormones. These hormones stimulate their target endocrine gland to produce its hormones.

TSH

TSH (thyroid-stimulating hormone, or thyrotropin) is the tropic hormone that stimulates the basic activities of the thyroid gland—production and secretion of thyroxine and triiodothyronine and the growth of new thyroid cells. Without TSH, the thyroid gland stops secreting hormones and atrophies.

THE THYROID GLAND

The thyroid gland secretes thyroid hormones, thyroxine (T4) and triiodothyronine (T3), that regulate metabolism, oxygen consumption of cells, cholesterol levels, and growth and development in children.

THYROID GLAND LOCATION AND STRUCTURE

The thyroid gland, located just below the larynx in the neck, consists of two lateral lobes, one on each side of the trachea, connected by a thin isthmus (Figure 1-2). When the body requires thyroid hormones, the pituitary secretes TSH, which stimulates the thyroid to convert thyroglobulin into the active hormone form.

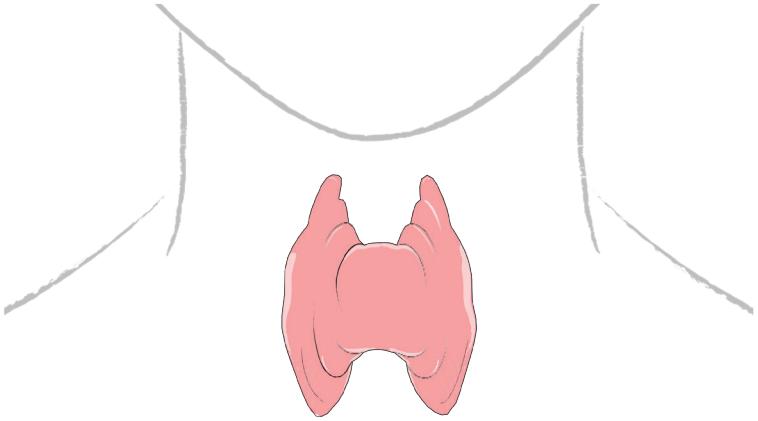


FIGURE 1-2. The Thyroid

THYROID HORMONES

T4 and T3 hormones stimulate metabolic activity and increase oxygen consumption, heat production, heart rate, gastrointestinal movement, and brain activity. They also influence the growth and development of the musculoskeletal and nervous systems.

The amount of T4 and T3 hormones in the blood is regulated by negative feedback as follows: When T4 and T3 levels are low, the hypothalamus releases TRH, which stimulates the secretion of TSH in the pituitary. TSH causes T4 and T3 to be released from the thyroid.

Rising thyroid hormone levels in the blood then inhibit the action of TRH, so the pituitary gland decreases TSH secretion, and the thyroid gland slows hormone secretion.

CALCITONIN

Calcitonin is produced by the parafollicular cells in the thyroid gland. This hormone plays a role in calcium and phosphate metabolism (regulation of bone metabolism).

LABORATORY TESTS

Blood tests to measure thyroid function are based on the feedback relationship between the hypothalamus, pituitary, and thyroid (also called the "HPT axis").

Thyroid-stimulating hormone (TSH) measurement is the single most reliable test for evaluating thyroid function or symptoms of hypo- or hyperthyroidism in people with a functioning HPT axis. TSH measurement is also used to monitor the treatment of thyroid disorders.

Thyroxine (T4) may be measured as either the total or free hormone. It is most often used to help diagnose and determine the severity of hyper- or hypothyroidism and to monitor treatment of these conditions. It is often ordered in conjunction with TSH or as a follow-up test after an abnormal TSH result. Most T4 (99.98 percent) circulates bound to protein. Only the non-protein bound ("free") T4 is biologically active. Usually, the measurement of free hormone is a more relevant but more variable indicator of thyroid function.

Triiodothyronine (T3) may be measured as either the total or free hormone. It is most often used to help diagnose hyperthyroidism and is usually ordered as a follow-up test to an abnormal TSH and T4 (free or total). Most T3 (99.7 percent) circulates bound to protein. Only the non-protein bound ("free") T3 is biologically active. Usually, the measurement of free hormone is a more relevant indicator of thyroid function.

Anti-thyroperoxidase antibodies (anti-TPO or TPOAb) are most often measured to help diagnose and monitor autoimmune thyroid disease. TPOAb is also measured as a risk factor for a variety of conditions, including autoimmune thyroid disease, thyroid dysfunction during pregnancy, and postpartum thyroid disease.

Thyroglobulin (Tg) is most often measured as a tumor marker in the diagnosis, treatment, and management of thyroid cancer. Because autoantibodies against Tg (TgAb, anti-Tg) can interfere with Tg measurements, TgAb should be tested along with Tg. Anti-thyroglobulin antibodies, TgAb, may also be measured to diagnose and monitor autoimmune thyroid disease.

TSH receptor antibodies (TRAb) are usually measured to investigate the etiology (i.e., origin) of hyperthyroidism and to monitor treatment of the disease. These can be stimulating or inhibiting types of antibodies.

T-Uptake tests have been used for many years to estimate protein binding of thyroid hormones, particularly before the development of "free" hormone tests. Uptake tests measure thyroid hormone binding capacity of serum and, along with measurement of total T4, allow calculation of the "free thyroxine index" (FTI).

It should be noted that abnormalities in hypothalamic and/or pituitary function may result in diagnostically misleading thyroid results. Also, evaluation of thyroid function in hospitalized patients can be complicated by other illnesses and medications. In these cases, interpretation of thyroid function tests is best done by an endocrinologist.

OTHER TESTS

Physicians also use a variety of other tests to assess thyroid function. These include radioactive iodine (RAI) uptake, thyroid scan, thyroid ultrasound, and fine needle aspiration (FNA) biopsy.

QUIZ QUESTIONS

THE ENDOCRINE SYSTEM AND THE THYROID GLAND

1. Name four key components of the endocrine system:

2. Match the term with the correct definition:

A	**TSH**	1	Most often used to help diagnose hypothyroidism or hyperthyroidism, ordered as a follow-up to abnormal TSH result
B	**T3**	2	Often measured in connection with thyroglobulin testing and may be measured to diagnose autoimmune thyroid disease
C	**T4**	3	Often measured as a tumor marker in the diagnosis, treatment, and management of thyroid cancer
D	**Tg**	4	Most often used to help diagnose hyperthyroidism, ordered as a follow-up to abnormal TSH and T4 results
E	**TgAb**	5	Most reliable test for evaluating symptoms of hypo- or hyperthyroidism

3. Match the word with the correct definition

A	**Hypothalamus**	1	Stimulates other endocrine glands to produce their own hormones
B	**Pituitary Gland**	2	Converts thyroglobulin into active hormone when stimulated by TSH
C	**Thyroid Gland**	3	Regulates food intake, water balance, and sleep

SECTION 2

HYPOTHYROIDISM

OVERVIEW

Hypothyroidism is a condition in which the body lacks sufficient thyroid hormone. For various reasons, the thyroid gland may fail to produce healthy levels of these hormones. This can manifest as fatigue, heart problems, difficulty concentrating, or increased intolerance to cold.[2]

LEARNING OBJECTIVES

After completing this section, you should be able to describe the following:

1. Prevalence of hypothyroidism
2. Symptoms of hypothyroidism
3. Various causes of hypothyroidism
4. Laboratory tests and other approaches for diagnosing hypothyroidism
5. Options available for treating patients with hypothyroidism

PREVALENCE

Investigators who have measured the rate of hypothyroidism in different populations around the world have found a range of rates[4] depending on the location, the definition of hypothyroidism, local diet, and the characteristics of the population studied.[5] However, a review of 12 studies found that thyroid gland failure occurs in about 5 percent of the general population. Most studies report higher prevalence rates of hypothyroidism in women[6] and those of increasing age,[2] with rates as high as 24 percent in women older than 60 years.[2]

SYMPTOMS

Symptoms can vary from patient to patient; however, the most common symptoms and signs of hypothyroidism (in descending order of frequency) include the following:[2,7]

SYMPTOMS

- Tiredness, weakness
- Dry skin
- Feeling cold or cold intolerance
- Hair loss
- Difficulty concentrating and poor memory
- Constipation
- Weight gain with poor appetite
- Dyspnea (shortness of breath)
- Hoarseness
- Menorrhagia (later oligomenorrhea or amenorrhea)
- Paresthesia
- Depression

SIGNS

- Cool peripheral extremities
- Puffy face, hands, and feet (myxedema)
- Bradycardia (slow heart rate)
- Peripheral edema
- Delayed tendon reflex relaxation
- Carpal tunnel syndrome
- Serious cavity effusions
- Hyperlipidemia (problems with lipid levels, such as excess low-density lipoprotein [LDL] cholesterol)

The onset of hypothyroidism symptoms is often undetected. In fact, patients may only become aware of symptoms after they have restored normal thyroid hormone levels following treatment.[1] Some patients with hypothyroidism present with a goiter – an enlarged thyroid gland – rather than the symptoms described previously. The goiter may not be large but is usually irregular and firm in consistency.

For patients with hypothyroidism, nail growth is often retarded, and hair is dry and brittle and falls out easily. Other common features associated with hypothyroidism include constipation and weight gain (despite a poor appetite). Libido is decreased in both sexes, fertility is reduced, and the incidence of miscarriages is increased.

Hypothyroidism has also been shown to have effects on the cardiovascular system. Myocardial contractility and pulse rate are reduced, leading to reduced stroke volume and bradycardia (reduced heart rate). Increased peripheral resistance may be accompanied by hypertension (high blood pressure). Blood flow is diverted from the skin, which results in cooler extremities.

A hoarse voice that occurs in some patients with hypothyroidism reflects the effects of fluid accumulation in the vocal cords due to hypothyroidism. Also, puffiness in the face and other parts of the body, a sign of edema, can be a sign of untreated hypothyroidism.

CAUSES

Common causes of hypothyroidism include the following:

- **Autoimmune hypothyroidism.** Autoimmune hypothyroidism occurs when a person's immune system recognizes thyroid gland tissues as foreign and mounts an attack on them.[3] This condition may be associated with a goiter (Hashimoto's or goitrous thyroiditis) or minimal residual thyroid tissue (atrophic thyroiditis). It is more common in women (4 per thousand of the population) than in men (1 per thousand, Figure 2-1).[2] Because the autoimmune process gradually reduces thyroid function, there is often a phase of compensation when normal thyroid hormone levels are maintained by a rise in thyroid-stimulating hormone (TSH). This phase is called subclinical or mild hypothyroidism. Subclinical hypothyroidism is found in 6 to 8 percent of women (10 percent of whom are over the age of 60) and 3 percent of men.[2] In these patients, free T4 levels often fall, and TSH levels increase over time, leading to *clinical or overt hypothyroidism*.

RATE OF AUTOIMMUNE HYPOTHYROIDISM BY GENDER

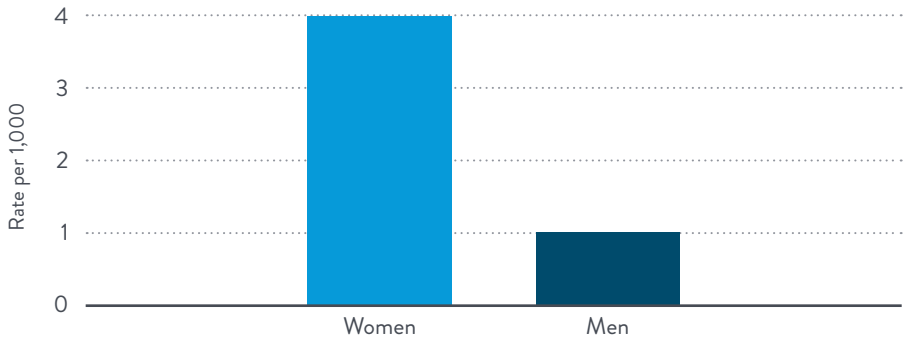


FIGURE 2-1. Autoimmune hypothyroidism: women versus men.

- **Surgical removal of part or all of the thyroid gland (thyroidectomy).**[2] The thyroid gland may be surgically removed for thyroid cancer or benign nodular disease-causing symptoms. Once the thyroid gland is removed, the body no longer has tissues capable of producing thyroid hormone. This results in hypothyroidism because of the complete reduction in thyroid hormone production (if the entire thyroid gland is removed) or substantial reduction in hormone (if part of the thyroid is removed).
- **Radiation treatment.** Some patients receive treatment with radioactive iodine (^{131}I), which is used to destroy thyroid tissue (for example, as treatment for someone with hyperthyroidism[3]). The desired destruction of thyroid tissue results in a new problem—a lack of healthy thyroid tissue to produce normal levels of thyroid hormone. Another type of radiation that can damage the thyroid is radiation therapy for cancers of the head, neck, or chest. Such treatments can reduce or eliminate normal thyroid function.
- **Congenital hypothyroidism.** Hypothyroidism occurs in about 1 in 4,000 newborns. This condition may be transient, especially if the mother has TSH-receptor-blocking antibodies or has received antithyroid drugs; however, permanent hypothyroidism occurs in the majority of infants with hypothyroidism. Neonatal hypothyroidism is caused by thyroid gland dysgenesis (problems with organ development) in 80 to 85 percent of cases. Inborn errors in thyroid hormone synthesis occur in 10 to 15 percent of cases and are TSH receptor antibody-mediated in 5 percent of affected newborns (Figure 2-2).[2] Most babies with congenital hypothyroidism appear normal at birth, yet permanent neurological damage can result if the condition is not identified and treated.[2] Developed countries have neonatal screening programs to detect babies with this condition to prevent the severe neurological consequences of untreated congenital hypothyroidism.

CAUSES OF CONGENITAL HYPOTHYROIDISM

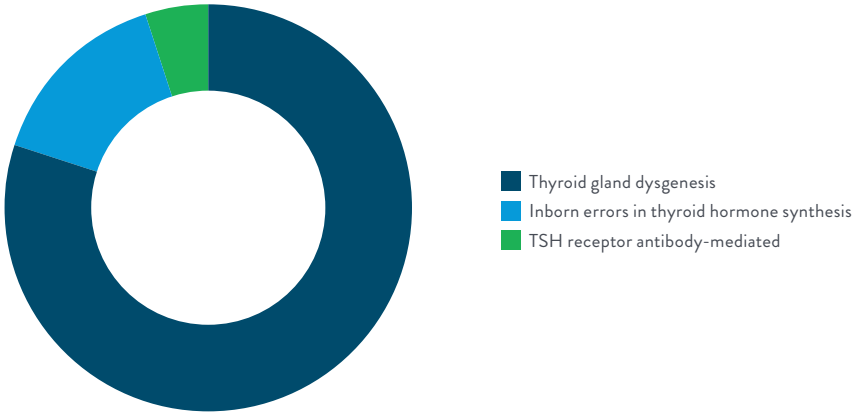


FIGURE 2-2. Causes of congenital hypothyroidism.

- **Thyroiditis.** This is an inflammation of the thyroid gland, usually associated with an autoimmune condition or an infection, such as a viral, bacterial, or fungal infection.[2,3]
- **Medications.** Hypothyroidism has been associated with the use of several drugs, including amiodarone (a medication used for irregular or rapid heartbeat), interferon alpha, interleukin-2, and lithium.

- **Iodine deficiency or excess.** Iodine deficiency is a common cause of hypothyroidism in developing countries.[2] This can cause endemic goiter and cretinism (a condition of severely stunted physical and mental growth due to untreated congenital deficiency of thyroid hormone) in communities that do not consume adequate levels of iodine in the diet. This has become increasingly less frequent in the developed world following public health measures that increase iodine intake (such as the addition of iodized salt.) Paradoxically, chronic excess iodine can also induce hypothyroidism and is responsible for hypothyroidism in up to 13 percent of patients treated with amiodarone.[2]
- **Damage to the pituitary gland.** Because the pituitary gland (in the brain) directs the production of thyroid hormone by the thyroid gland via TSH, damage to the pituitary gland by a tumor, radiation, surgery or trauma can also interfere with the normal function of the thyroid gland.

DIAGNOSIS/TESTING

An important part of managing a patient with hypothyroidism is diagnosis and testing. Hypothyroidism is diagnosed through a combination of physical examination and laboratory evaluation. A physical evaluation is an important part of the diagnosis of hypothyroidism. The physical evaluation consists of an examination of the shape, size, and feel of the thyroid itself and an assessment of signs of abnormal thyroid function. According to the American Association of Clinical Endocrinologists, appropriate laboratory evaluation is critical to establish the diagnosis and cause of hypothyroidism.[7]

- **Thyroid-stimulating hormone (TSH).** In most cases, a normal level of TSH (also called thyrotropin) excludes a primary abnormality in thyroid function. A normal TSH level for adults is between 0.4 and 4.12 μIU/mL,[8] according to the National Academy of Clinical Biochemistry (NACB) guidelines, although the American Association of Clinical Endocrinologists (AACE) encourages clinicians to consider treatment for patients who test outside the boundaries of a narrower margin, based on a TSH level target of 0.3 to 3.04 μIU/mL. A TSH measurement significantly above the normal level is considered evidence of hypothyroidism, as the pituitary releases more TSH in an attempt to raise thyroid hormone in the bloodstream to normal levels. Patients whose serum TSH levels exceed 10 mIU/L are at increased risk for heart failure and cardiovascular mortality, and should be considered for treatment with L-thyroxine.[7] The finding of an elevated TSH level may be followed by measurements of circulating thyroid hormone to confirm and determine the security of a diagnosis of hypothyroidism.
- **Free T3 (FT3) and Free T4 (FT4).** T3 and T4 circulate in the blood as either free or protein-bound hormones. Only a very small amount of the T3 (0.2 to 0.4 percent) and T4 (0.03 percent) in circulation are unbound (or free) hormones. However, it is important to measure the levels of free hormones because they are physiologically active. Assays have been designed that are specific for FT3 and FT4. Clinical or overt hypothyroidism causes decreased thyroid hormone levels, so patients with this disorder are likely to have values below the reference ranges.[8]
- **Total T3 (TT3) and Total T4 (TT4).** These tests measure the total levels of these two thyroid hormones in the serum. However, T3 and T4 are both highly protein-bound, and several factors—including illness, medications, and genetics—can have an impact on protein binding. Because of this, it is useful to measure the free or unbound levels of the hormone, which more closely indicate the level of biologically available hormone.

- **Anti-TPO and anti-Tg antibodies.** Most patients with autoimmune thyroid disease have antibodies for thyroid peroxidase (TPO) and/or thyroglobulin (Tg). It is acceptable for clinicians to measure only anti-TPO antibodies because most patients with anti-TPO antibodies will also have antibodies to Tg, although the reverse is less common.[2,3] Also, the role of anti-Tg antibodies in thyroid disease is still unclear.[8] The anti-TPO antibody test is considered the most sensitive test for detecting autoimmune thyroid disease; anti-TPO antibodies are typically the first abnormality to appear in the course of developing hypothyroidism secondary to Hashimoto's thyroiditis. When anti-TPO antibodies are measured by a sensitive immunoassay, >95 percent of patients with Hashimoto's thyroiditis have detectable levels of anti-TPO antibodies.[8]
- **T-uptake.** This test reflects the level of thyroxine-binding globulin (TBG) that is bound by T4.[9]

TREATMENT OF HYPOTHYROIDISM

After describing the causes and diagnosis of hypothyroidism, the final topic we will discuss is the treatment of patients with hypothyroidism. While hypothyroidism cannot be cured, it can be managed. The goal of the treatment of patients with hypothyroidism is to restore thyroid hormone levels to normal levels. This is accomplished by providing levothyroxine (LT4).[3] In patients with no thyroid function, the average replacement dose of levothyroxine is 1.6 μg/kg body weight/day (typically, 100 to 150 μg). In patients with some thyroid function, lower replacement doses may be sufficient to manage the condition.

Doses of LT4 are adjusted on the basis of the patient's TSH levels. The goal is to achieve normal TSH levels, ideally in the lower half of the reference range. The clinical effects of LT4 replacement are gradual, and full relief from symptoms may not occur until 3 to 6 months after normal TSH levels are restored. A TSH level between 0.5 and 2.0 μIU/mL is generally considered the therapeutic target for a standard LT4 replacement dose for hypothyroidism.[8] Once full replacement is achieved and TSH levels are stable, patients should receive follow-up TSH measurements at least annually. In patients receiving L-thyroxine treatment for hypothyroidism, serum TSH should be remeasured with 4-8 weeks of initiation of treatment with drugs that decrease the bioavailability or alter the metabolic disposition of the L-thyroxine dose.[7] It is important for patients to maintain ongoing adherence to therapy.

QUIZ QUESTIONS

HYPOTHYROIDISM

1. Name four symptoms of hypothyroidism:

   _____

   _____

   _____

   _____

2. Fill in the blanks for each test:

   A. A TSH measurement _____ the normal level indicates possible hypothyroidism.

   B. When measuring FT3/FT4, patients with hypothyroidism are likely to have values _____ reference ranges.

   C. T3 and T4 circulate in the blood as either _____ or protein-bound hormones.

3. True or False:

   A. Hypothyroidism is a condition in which the body has excess levels of thyroid hormones.

   B. The most common cause of congenital hypothyroidism is thyroid gland dysgenesis.

   C. When evaluating hypothyroidism, it is important to measure the levels of free hormones versus protein-bound hormones.

   D. A common symptom of hypothyroidism is heat intolerance.

SECTION 3

HYPERTHYROIDISM

OVERVIEW

An excess level of thyroid hormones is called thyrotoxicosis. The major causes of thyrotoxicosis include thyroiditis and hypothyroidism caused by Graves' disease, toxic multinodular goiter, and toxic **adenomas.** In hyperthyroidism, the thyroid gland produces excess levels of thyroid hormone.

LEARNING OBJECTIVES

After completing this section, you should be able to describe the following:

1. Symptoms of hyperthyroidism
2. Causes of hyperthyroidism
3. Prevalence of hyperthyroidism
4. Laboratory tests and other approaches for diagnosing hyperthyroidism
5. Treatment options for patients with hyperthyroidism

SYMPTOMS

The signs and symptoms (in descending order of frequency) are shown below.[2]

SYMPTOMS

- Hyperactivity, irritability, dysphoria
- Heat intolerance and sweating
- Palpitations
- Fatigue and weakness
- Weight loss with increased appetite
- Hyperdefecation
- Polyuria (frequent urination)
- Oligomenorrhea, loss of libido

SIGNS

- Tachycardia (rapid heartbeat); atrial fibrillation in the elderly
- Tremor
- Goiter
- Warm, moist skin
- Muscle weakness, proximal myopathy
- Lid retraction or lag
- Gynecomastia (breast enlargement in males)

Many of the signs and symptoms of hyperthyroidism stem from the excessive production of heat and increased motor and sympathetic nervous system activity associated with this disorder.[3]

CAUSES AND PREVALENCE

Let's review the causes and prevalence of hyperthyroidism.

- In 80 percent of people with hyperthyroidism (Figure 3-1),[2] the cause of the disorder is Graves' disease. Graves' disease is much more common in women than in men. Graves' disease is an autoimmune disorder caused by thyroid-stimulating immunoglobulin (TSI)—antibodies that bind to thyroid-stimulating hormone (TSH) receptors on the thyroid gland and stimulate the thyroid to produce excess levels of thyroid hormones.[3]
- Although much less frequent, another cause of hyperthyroidism is toxic adenoma (2 percent) or toxic multinodular goiter (15 percent). In these conditions, one or more nodules in the thyroid grow and increase their activity to the point where they release excess levels of thyroid hormone.[3]
- Other causes: in some cases, thyrotoxicosis is caused by thyroiditis (1 percent), a condition in which the thyroid gland leaks thyroid hormone as the result of a viral infection, injury, or other cause. Also, some individuals may develop thyrotoxicosis if they consume excess levels of thyroid hormone.

CAUSES OF HYPERTHYROIDISM/THYROTOXICOSIS

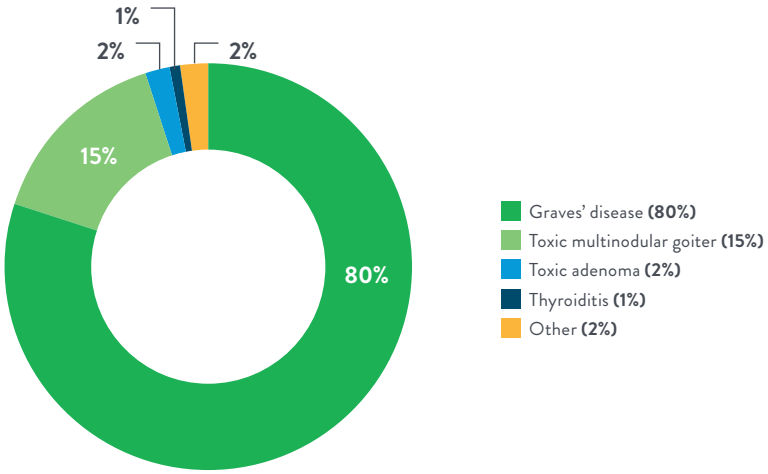


FIGURE 3-1. Causes of hyperthyroidism.

DIAGNOSIS/TESTING

A diagnosis of hyperthyroidism is confirmed by measurement of TSH, then thyroid hormones T4 and T3 (Figure 3-2).

- **Thyroid-stimulating hormone (TSH).** In most cases, a normal TSH level excludes a primary abnormality in thyroid function. A normal TSH level for adults is between 0.4 and 4.0 μIU/mL[8] according to the NACB guidelines, although the American Association of Clinical Endocrinologists (AACE) encourages clinicians to consider treatment for patients who test outside the boundaries of a narrower margin, based on a TSH level target of 0.3 to 3.04 μIU/mL. In patients with hyperthyroidism, the TSH level is generally low or undetectable, while total and free T4 levels are elevated. If TSH levels suggest an overactive thyroid gland, the patient may receive a thyroid scan to determine if the entire gland is overactive or whether the patient has a toxic nodular goiter or thyroiditis.
- **Free T3 (FT3) and Free T4 (FT4).** Measuring the free hormone can be utilized to assist in the diagnosis of hyperthyroidism. In patients with Graves' disease, FT3 is typically elevated to a greater degree than FT4. In contrast, levels of FT4 are elevated to a greater degree than FT3 in patients who have taken excessive levels of thyroid hormone.
- **Total T3 (TT3) and Total T4 (TT4).** Measurements above the normal reference range of these hormones suggest thyrotoxicosis. Total T3 measurements may be valuable when hyperthyroidism is suspected, and the free T4 estimate is normal (see below).
- **TSH-R-Ab (TRAb).** In Graves' Disease, measurement of TSH-R-Ab is recommended for an accurate diagnosis/differential diagnosis, prior to stopping antithyroid drug (ATD) treatment and during pregnancy. TSH-R-Ab are specific biomarkers for Graves' Disease. Most immunoassays today use a competitive-binding assay and measure what are referred to as TSH-R binding inhibitory immunoglobulins (TBII). Binding assays only report the presence or absence of TSH-R-Ab and their concentrations, but do not indicate their functional activity. A meta-analysis of 21 studies showed that the overall pooled sensitivity and specificity of the serum TSH-R-Ab concentration measured with second- and third-generation binding assays were 97% and 98%, respectively.[21]

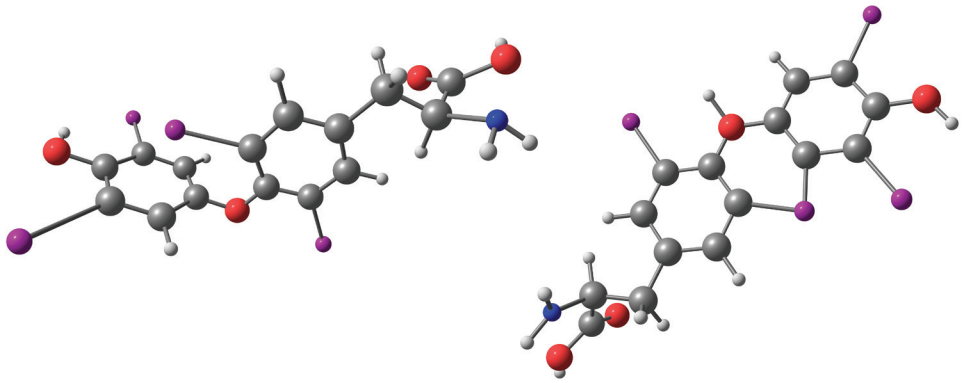


FIGURE 3-2. T4 (left) and T3 (right) molecules.

- **T-uptake.** This test reflects the level of thyroxine-binding globulin (TBG) that is bound by T4. Reference values are 27 to 37 percent for males, 20 to 37 percent for females.[9] Uptake assays are of greatest value when used in conjunction with a serum total T4 assay to provide the free thyroid index (FTI).

A physical examination is also important for the diagnosis of hyperthyroidism. A physical examination of a patient with hyperthyroidism often will show an enlarged thyroid gland and a rapid pulse. There may also be moist, smooth skin and many of the other symptoms listed above. Some patients with Graves' disease experience lid retraction, which may present as a startled appearance.[2]

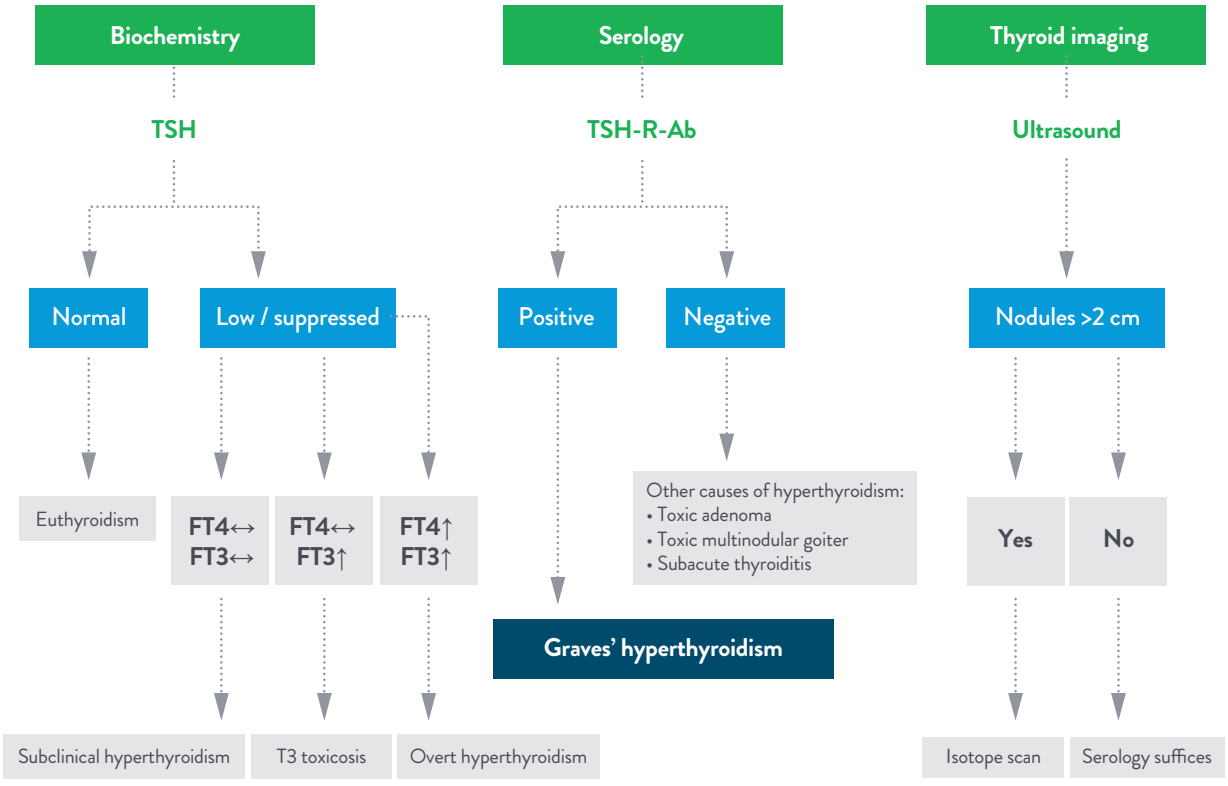


FIGURE 3-3. Algorithm for investigating a patient with suspected Graves' hyperthyroidism.[21]

TREATMENT

The hyperthyroidism of Graves' disease is treated by reducing thyroid hormone synthesis in the thyroid gland. This can be accomplished by using antithyroid drugs or by reducing the amount of functioning thyroid tissue with radioiodine (^{131}I) treatment or by thyroidectomy (all or partial removal of the thyroid gland with surgery).

- The main antithyroid drugs are thionamides (e.g., propylthiouracil, carbimazole, and methimazole). These drugs inhibit the oxidation and organification of iodine. They also reduce thyroid antibody levels by mechanisms that remain unclear.[2]
- Radioiodine is also used for treatment because it causes progressive destruction of thyroid cells. Thyroid cells need iodine to make thyroid hormones, so they take up radioiodine from the bloodstream. The radioactive iodine used in the treatment of hyperthyroidism is taken by mouth.[3] Over time, the radioiodine damages the cells that absorbed it, causing them to shrink and produce less thyroid hormone. Radioiodine can be used as initial treatment or for relapse after a trial of antithyroid drugs. Many patients treated with radioiodine become hypothyroid and are treated with thyroid hormone supplementation.
- Thyroidectomy (surgery to remove all or part of the thyroid) is another option for the treatment of hyperthyroidism, especially for patients who relapse with antithyroid drugs and who do not wish to receive radioiodine. After the thyroid gland tissue is removed, the patient is likely to have low levels of thyroid hormone and require treatment with thyroid hormone supplementation.

QUIZ QUESTIONS

HYPERTHYROIDISM

1. Name four signs of hyperthyroidism:

_____

_____

_____

_____

2. Fill in the blanks for each test:

   A. In patients with hyperthyroidism, TSH level is generally _____.

   B. In patients with hyperthyroidism, FT4 is typically _____ normal levels.

   C. A _____ TSH level for adults is between 0.4 and 4.0 μIU/mL.

3. True or False:

   A. Thyrotoxicosis is the excess level of thyroid hormones.

   B. The most common cause of hyperthyroidism is toxic multinodular goiter.

   C. A common symptom of hyperthyroidism is hyperactivity.

SECTION 4

THYROID FUNCTION IN PREGNANCY

OVERVIEW

In this section, we will discuss the importance of accurate assessment of thyroid function during pregnancy to prevent both maternal and fetal complications. The normal physiological changes that occur during pregnancy can make interpretation of tests for thyroid disease challenging. Therefore, laboratory measurement of thyroid function plays an important role in the assessment of maternal thyroid health.

LEARNING OBJECTIVES

After completing this section, you should be able to describe the following:

1. Maternal thyroid function and fetal development
2. Pregnancy and thyroid function
3. Maternal hypothyroidism and hyperthyroidism
4. The diagnosis of thyroid dysfunction in pregnancy
5. Treatment of thyroid disease during pregnancy

MATERNAL THYROID FUNCTION AND FETAL DEVELOPMENT

A healthy thyroid is important for both mother and fetus. This is especially true during the first trimester when the developing fetus depends entirely on the mother for thyroid hormones;[10] therefore, maternal thyroxine, T4 (Figure 4-1) is critical for proper fetal development. Adequate maternal iodine intake is also required during pregnancy to ensure that the maternal thyroid gland will produce adequate levels of thyroid hormones for both mother and fetus. Accurate assessment of thyroid function during pregnancy is important to prevent both maternal and fetal complications. However, the normal physiological changes that occur during pregnancy can make interpretation of tests for thyroid disease challenging.[11]

PREGNANCY AND THYROID FUNCTION

Even in a normal pregnancy, the pregnancy itself produces profound physiologic changes that can have an impact on maternal thyroid function. The main factors that affect thyroid function in pregnancy are:

- A transient increase in human chorionic gonadotropin, hCG (Figure 4-2),[2] a hormone produced by the fetus and placenta during the first trimester, which stimulates the thyroid-stimulating hormone receptor (TSH-R). The rise in circulating hCG levels during the first trimester of pregnancy is accompanied by a reciprocal decline in TSH levels, which persists into the middle of pregnancy.

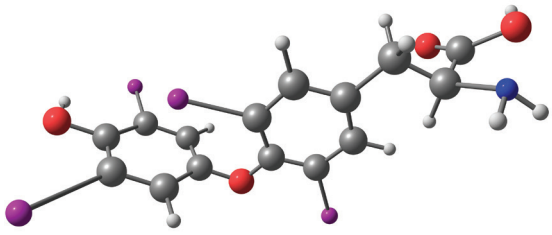


FIGURE 4-1. A T4 molecule.

FIGURE 4-2. Human chorionic gonadotropin (hCG).

- The estrogen-induced rise in thyroid-binding globulin (TBG—a protein that transports the majority of thyroid hormones [68 percent of T4 and 80 percent of T3]) during the first trimester, which is sustained during pregnancy.[11] Also, TBG increases its half-life during pregnancy from 15 minutes to 3 days.[11]
- Alterations in the immune system, which can lead to the onset, exacerbation or amelioration of an underlying autoimmune thyroid disease.
- Increased urinary iodine excretion, which can cause impaired thyroid hormone production in people who live in areas of marginal iodine sufficiency.

MATERNAL HYPOTHYROIDISM

Maternal hypothyroidism is a condition that occurs in 0.3 to 0.7 percent of pregnant women.[11] This incidence is less than that of the general population due to the association between hypothyroidism and decreased fertility. Maternal hypothyroidism is an important issue because it is associated with an increased risk of developmental delay in the offspring.[2] In many cases, an accurate laboratory assessment of maternal thyroid function is needed to distinguish thyroid disorders from the symptoms attributed to the pregnancy itself.[10,12]

MATERNAL HYPERTHYROIDISM

The incidence of hyperthyroidism in pregnant women has been estimated to be 0.2 percent.[11] Most of these women will have symptoms before the pregnancy, but some will show symptoms only after they become pregnant. As with nonpregnant women, the most common cause of hyperthyroidism in pregnant women is Graves' disease, which accounts for 85 to 90 percent of all cases. The hCG-induced changes in thyroid function can also result in transient gestational hyperthyroidism and/or hyperemesis gravidarum, a condition characterized by severe nausea and vomiting and risk of volume depletion. Diagnosis and treatment of hyperthyroidism during pregnancy is important because untreated hyperthyroidism can lead to adverse obstetrical outcomes, including first-trimester spontaneous abortions, high rates of stillbirths and neonatal deaths, and an increased rate of low birth weight infants, preterm delivery, fetal or neonatal hyperthyroidism, and intrauterine growth retardation.[11] As with hypothyroidism, diagnosis of hyperthyroidism is complicated by the fact that healthy pregnant women exhibit some of the same symptoms as those with hyperthyroidism. Because of this, diagnosis of hyperthyroidism during pregnancy needs to be made based on laboratory testing and careful clinical observations.[11]

DIAGNOSIS OF THYROID DYSFUNCTION IN PREGNANCY

The Endocrine Society has developed guidelines for screening pregnant women for thyroid dysfunction. They recommend case-finding among women at high risk of thyroid dysfunction, including women with a history of thyroid disease, type 1 diabetes, a prior history of miscarriage or preterm delivery symptoms of thyroid dysfunction, goiter, or thyroid antibodies.[13] However, relying solely on case-finding may result in clinicians missing a significant number of women with thyroid dysfunction. In a study by Vaidya et al., investigators found that only testing high-risk pregnant women would result in failure to identify about one-third of the women with hypothyroidism.[14] Therefore, evaluation and testing of all pregnant women should be considered.

Laboratory measurement of thyroid function plays an important role in the assessment of maternal thyroid health.[10] Pregnant women can have their thyroid function assessed in the same ways as nonpregnant women. The major tests for thyroid function are the following:

- **Thyroid-stimulating hormone (TSH).** A finding of a normal TSH level generally excludes a primary abnormality in thyroid function. However, TSH levels generally decrease in pregnancy during the first trimester (due to the influence of increased hCG). In most pregnancies, this decrease in TSH remains within the healthy reference interval.[11] If hCG levels are markedly increased, then hCG-induced thyroid stimulation can occur, decreasing TSH levels and increasing thyroid hormone concentrations.

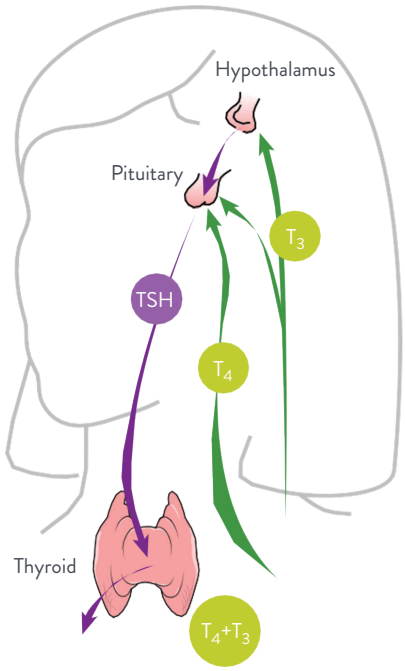


FIGURE 4-3. The thyroid gland's production of thyroid hormones is triggered by thyroid-stimulating hormone (TSH), which is made by the pituitary gland.

- **Total T3 (TT3) and Total T4 (TT4).** These tests measure the total levels of these two thyroid hormones in the blood (serum). However, TT4 and TT3 are often increased during pregnancy and may be outside the healthy reference range.[11]
- **Free T3 (FT3) and Free T4 (FT4).** The effect of pregnancy on FT4 and FT3 levels remains controversial. Pregnant women, on average, have lower free hormone concentrations at term than nonpregnant women. It is recommended that due to the variation in results of FT4 assays, method-specific and trimester-specific ranges of serum FT4 should be established.[18]
- **Anti-Tg and anti-TPO antibodies.** It has been found that the presence of antibodies to TPO is associated with an increased risk of miscarriage, preterm birth, and maternal postpartum thyroid disease.10 Women with a TSH level >3.0 μIU/mL are more likely to be TPO-antibody positive.[10] The prevalence of TPO antibodies is higher in women and increases with age, and common in women of child-bearing age. Most patients with autoimmune thyroid disease have antibodies for thyroglobulin (Tg) and/or thyroid peroxidase (TPO). It is acceptable to measure only TPO antibodies because most patients with TPO antibodies will also have antibodies to Tg, although the reverse is less common.[2,12] If a pregnant woman is negative for these antibodies, then she does not have autoimmune thyroid disease.

MATERNAL CONDITION	THYROID-STIMULATING HORMONE	FREE THYROXINE	FREE THYROXINE INDEX	TOTAL THYROXINE	TRIIODOTHYRONINE	RESIN TRIIODOTHYRONINE UPTAKE
Hyperthyroidism	Decrease	Increase	Increase	Increase	Increase or no change	Increase
Hypothyroidism	Increase	Decrease	Decrease	Decrease	Decrease or no change	Decrease
Normal pregnancy	Decrease	No change	No change	Increase	Increase	Decrease

FIGURE 4-4. Changes in thyroid function test results during uncomplicated pregnancy and in pregnant women with thyroid disease.[22]

TEST	NONPREGNANT	FIRST TRIMESTER	SECOND TRIMESTER	THIRD TRIMESTER
Thyroid-stimulating hormone (mIU per L)	0.3 to 4.3	0.1 to 2.5	0.2 to 3.0	0.3 to 3.0
Thyroxine-binding globulin (mg per dL)	1.3 to 3.0	1.8 to 3.2	2.8 to 4.0	2.6 to 4.2
Thyroxine, free (ng per dL)	0.8 to 1.7	0.8 to 1.2	0.6 to 1.0	0.5 to 0.8
Thyroxine, total (mcg per dL)	5.4 to 11.7	6.5 to 10.1	7.5 to 10.3	6.3 to 9.7
Triiodothyronine, free (pg per mL)	2.4 to 4.2	4.1 to 4.4	4.0 to 4.2	Not reported
Triiodothyronine, total (ng per dL)	77 to 135	97 to 149	117 to 169	123 to 162

FIGURE 4-5. Trimester-specific reference ranges for common thyroid tests.[22]

TREATMENT

Adequate iodine levels should be consumed by women during pregnancy. Appropriate treatment with levothyroxine for hypothyroidism has been shown to reduce miscarriages and other consequences of untreated thyroid disease in pregnant women when given during the early stages of pregnancy.[15] Propylthiouracil is the preferred agent for the treatment of hyperthyroidism during the first trimester of pregnancy. Consideration should be given to switching to methimazole after the first trimester, and the dosage should be adjusted to maintain a serum FT4 level in the upper one-third of the normal range.[22]

QUIZ QUESTIONS

THYROID FUNCTION IN PREGNANCY

1. Name the four main factors that affect thyroid function in pregnancy:

_____

_____

_____

_____

2. Fill in the blanks for each test:

   A. TSH levels generally _____ during the first trimester of pregnancy.

   B. TT3 and TT4 levels generally _____ during pregnancy.

   C. Maternal hypothyroidism is a condition that occurs in _____ to _____ of pregnant women.

SECTION 5

NODULAR THYROID DISEASE, THYROID CANCER, THYROID EMERGENCIES

OVERVIEW

In this section, we will discuss further conditions affecting the endocrine system. Thyroid nodules are characterized by the disorderly growth of thyroid cells, occurring in 25 percent of adults. Thyroid cancer is the most common type of cancer of the endocrine system. Thyroid storm is a rare but life-threatening rise in thyroid hormones.

LEARNING OBJECTIVES

After completing this section, you should be able to discuss the symptoms, causes, diagnosis, and treatment of the following:

1. Thyroid nodules, which occur in 25% of adults
2. Thyroid cancer, the most common type of cancer of the endocrine system
3. Thyroid storm, also called thyrotoxic crisis, is a rare but life-threatening rise in thyroid hormones

NODULAR THYROID DISEASE

This is a common condition, occurring in up to 25 percent of adults. Thyroid nodules may be solitary or multiple, and functional or nonfunctional.

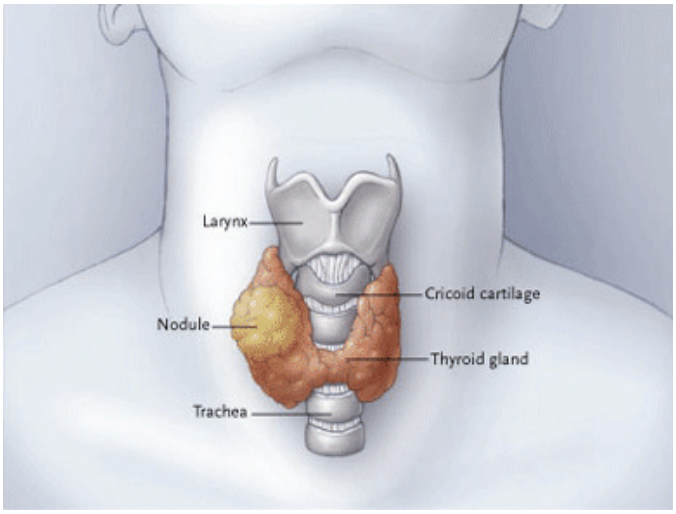


FIGURE 5-1. A thyroid gland showing a thyroid nodule.

SYMPTOMS

The following is a list of common signs and symptoms of nodular thyroid disease:

SYMPTOMS

- Lump or nodule in the thyroid
- Hoarseness
- Pain in the neck, jaw, or ear
- Difficulty swallowing
- Shortness of breath
- Dysphonia (change of voice tone)

SIGNS

- Goiter
- Palpable growth/nodule

This condition is characterized by the disorderly growth of thyroid cells, often combined with the gradual development of fibrosis (the development of excess fibrous tissue[2]). The majority of thyroid nodules are harmless—they do not cause any symptoms. Thyroid nodules may be discovered when a patient notices a lump in the neck while looking in a mirror or during a routine physical examination. Some patients with thyroid nodules complain of neck, jaw, or ear pain, while others may experience some difficulty swallowing. Thyroid nodules become a problem because sometimes nodules produce thyroid hormone beyond the needs of the individual, resulting in hyperthyroidism.

CAUSES

In general, it is not known what causes normal thyroid tissue to develop into nodules. However, the prevalence of thyroid nodules increases with age, with about 50 percent of people having some sort of thyroid nodules by the time they reach 60 years of age.[3]

DIAGNOSIS

Although some patients may feel or see a thyroid nodule in the mirror, most nodules are discovered by physicians during a routine medical examination.[3] The physician may ask the patient to swallow while he or she examines the thyroid because a nodule in the thyroid gland will often move up or down during swallowing. Some nodules are discovered incidentally during other radiologic studies, such as ultrasound or computed tomography of the neck or chest.

Once a nodule is identified, the physician will seek to determine if it is malignant and/or associated with thyroid dysfunction. Possible tests for this include the following:

- **Thyroid function tests (TSH, T4, T3).** If levels are normal, then thyroid nodules are assumed to be functioning normally.
- **Fine needle aspiration (FNA) biopsy.** A thyroid function test cannot determine if a nodule is benign or malignant. For this determination, a patient will need to receive an FNA biopsy, which is more sensitive for distinguishing between benign and malignant thyroid nodules.[3] In this procedure, the physician inserts a very thin needle into the nodule and removes a small sample of cells. Often, the physician will use ultrasound to guide the placement of the needle. Several samples may be taken; then, these samples are sent to a laboratory and analyzed under a microscope by a pathologist, a specialist who generally can determine by the appearance of cells whether they are benign or malignant.
- **Ultrasonography.** This is an imaging technique that uses high-frequency sound waves to produce images that can be examined on a screen or printed (Figure 5-2). This technology can also be used to distinguish cysts on the thyroid from solid nodules and as a guide for performing an FNA biopsy (as noted earlier).

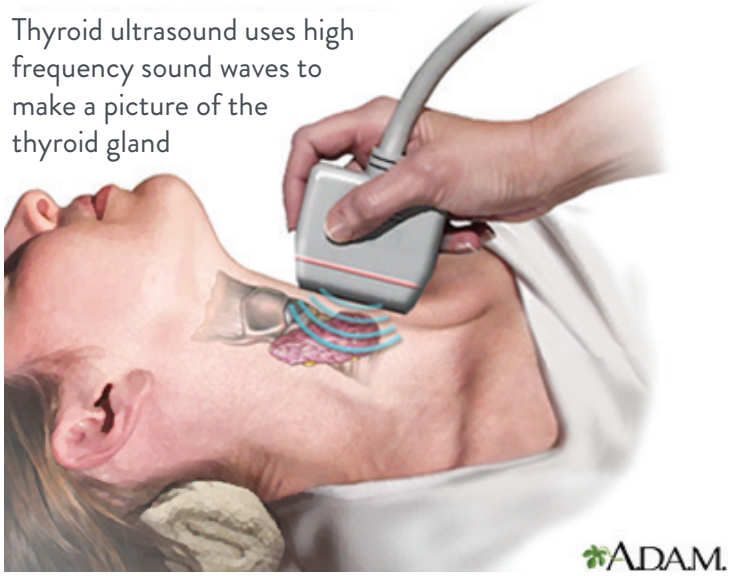


FIGURE 5-2. Ultrasound of the thyroid gland.

- **Thyroid scan.** For this procedure, radioactive material is administered by mouth or vein. The patient lies on a table while a nuclear scanner creates an image of the thyroid based on the absorption of radioactive iodine by the thyroid. Nodules that produce excess thyroid hormone are detected by the scan because they take up more of the radioactive material than normal thyroid tissue. Nonfunctioning thyroid nodules do not appear on the scans. Nodules that produce excess thyroid hormone are nearly 100 percent benign; those with some function or no function must be assessed further, as they are potentially malignant.

TREATMENT

If a nodule is benign upon examination, further immediate treatment may not be required. Benign nodules should be followed with repeat examinations 6 to 18 months following initial FNA biopsy. Patients with growing nodules that are benign after repeat biopsy should be considered for continued monitoring or intervention with surgery based on symptoms and clinical concern.[19]

THYROID CANCER

Thyroid carcinoma (cancer) is the most common malignancy of the endocrine system.[2] The incidence of thyroid cancer is higher in females and varies in different parts of the world—with an incidence of 18.4 per 100,000 population among females in North America, to a low of 1.0 per 100,000 population in Middle Africa (Figure 5-3).[16] Some types of thyroid cancer are generally curable, and the prognosis is good for patients identified with early-stage disease.[2]

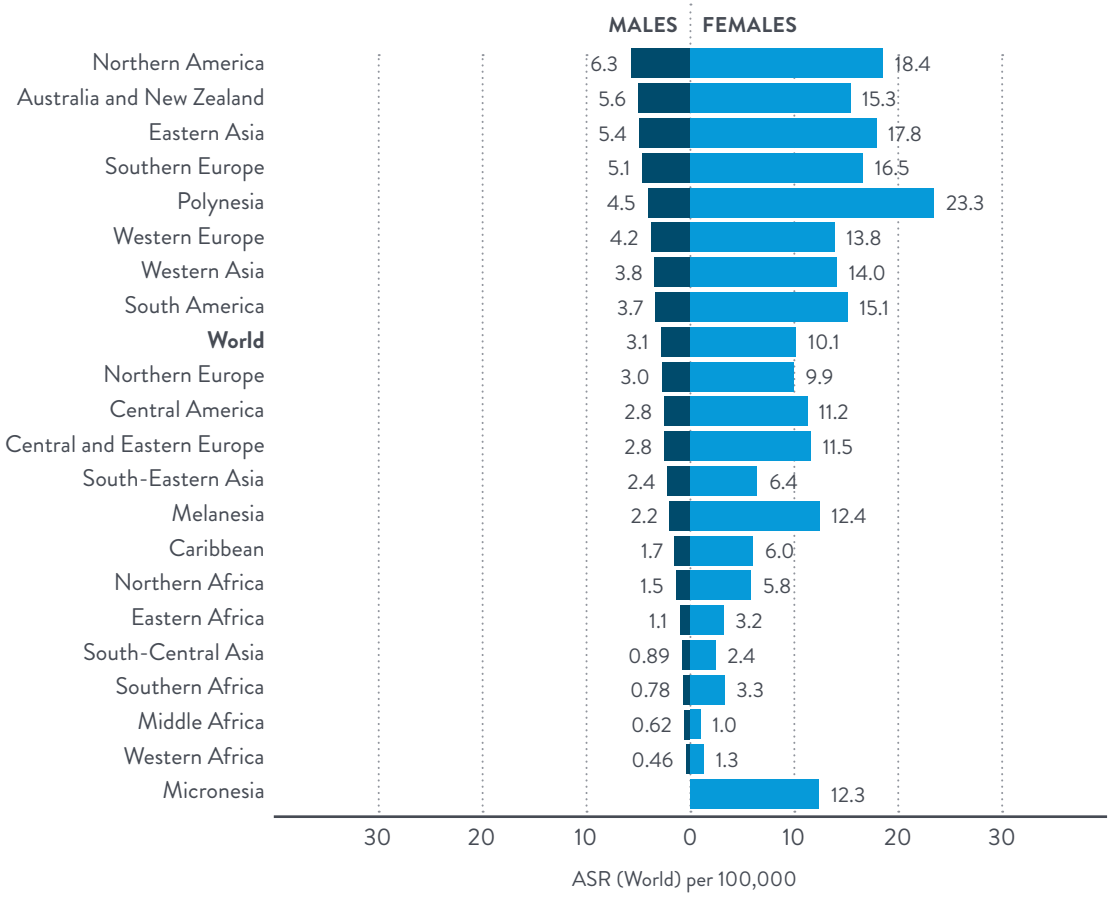


FIGURE 5-3. World incidence rates of thyroid cancer by gender and region 2020 estimates.[16]

SYMPTOMS

Thyroid cancer displays similar signs and symptoms as nodular thyroid disease. Additional signs of thyroid cancer are enlarged lymph nodes in the neck.

CAUSES

For many individuals, the causes of thyroid cancer are not known. However, thyroid cancer is more common in people with a history of exposure of the thyroid gland to radiation.[2] For example, during the 1940s and 1950s, some countries used potentially dangerous levels of radiation—including X-rays—to treat various conditions, including acne, inflamed tonsils, and an enlarged thymus gland.[2] Exposure to this radiation could potentially cause thyroid cancer to develop in some exposed individuals many years later. Thyroid cancer can also be caused by the absorption of radioactive iodine following a nuclear power plant accident, such as the 1986 Chernobyl nuclear plant explosion because this radioactive iodine accumulates in the thyroid gland. The risk of developing thyroid cancer after exposure to radioactive iodine is higher in children.[17]

DIAGNOSIS

For most patients, diagnosis of thyroid cancer is based on a fine needle biopsy (Figure 5-4) of a thyroid nodule or by examination of a nodule removed by surgery. The cells obtained from a fine needle biopsy are examined by a pathologist under a microscope and checked for cancer cells. About 95 percent of solitary thyroid nodules are benign.

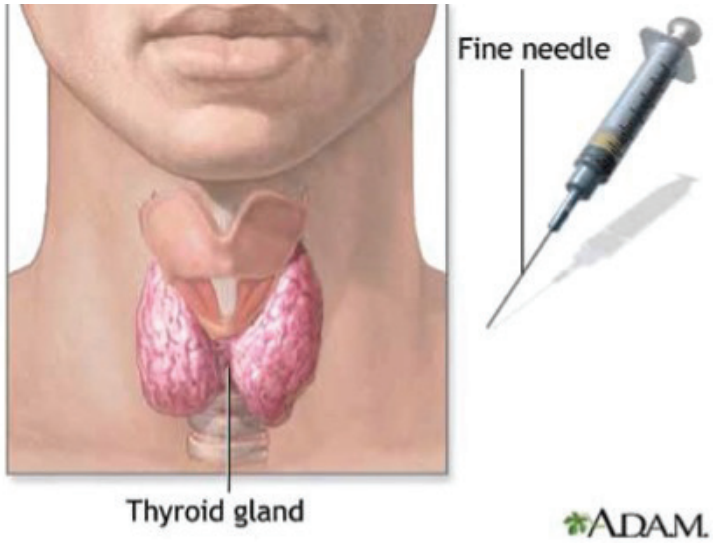


FIGURE 5-4. A fine needle biopsy (also called a fine needle aspiration biopsy) is used to obtain cells from suspected thyroid cancer for analysis.

OTHER TESTS FOR THYROID CANCER

- Physical exams can be used to detect thyroid cancer. Thyroid nodules—which may be cancerous—may be palpable, allowing for early detection and further analysis.
- Blood tests (such as the Thyroglobulin [Tg] test), which indicate the presence of active thyroid tissue. Thyroid function tests (TSH, T4, T3) to determine if the gland is functioning normally.
- Screening with iodine radioisotopes because the thyroid gland actively absorbs iodine. By measuring the amount of radioactivity that is taken up by the thyroid gland (radioactive iodine uptake, or RAIU), clinicians can determine whether the gland is functioning normally. Nonfunctioning thyroid tissue may be a sign of thyroid cancer, although a fine needle biopsy is needed to confirm this diagnosis.

TREATMENT

Three approaches are commonly used for treating patients with thyroid cancer: surgery, thyroid-stimulating hormone (TSH) suppression therapy, and radioiodine treatment.

- **Surgery.** Well-differentiated thyroid cancers can be surgically excised (removed). Lymph node spread of cancer should be assessed before and at the time of surgery, and any involved nodes should be removed. Near-total thyroidectomy (removal of most of the thyroid gland) is preferred in most patients.[2]
- **TSH suppression therapy.** Because thyroid cells are TSH-responsive, suppression of TSH with levothyroxine (thyroid hormone) is an important part of cancer treatment. The goal of treatment is to suppress TSH as much as possible without causing unnecessary side effects from excess thyroid hormone. Consistent treatment with levothyroxine may thus help prevent the recurrence of thyroid cancer. Patients treated with TSH suppression therapy will generally require ongoing monitoring. Evidence of successful suppression of TSH is found by testing the patient's TSH levels and/or free thyroxine (FT4) levels. Normal levels of TSH are listed above; the reference range for FT4 is 0.7 to 1.8 ng/dL.
- **Radioiodine treatment.** Even though thyroid cancer cells are cancerous, they may still absorb iodine. Because of this fact, radioactive iodine (^{131}I) can be used to kill them. Treatment with radioactive iodine can be useful after thyroidectomy because substantial amounts of thyroid tissue may still remain, particularly in the thyroid bed and surrounding the parathyroid glands.[2]

THYROID EMERGENCIES

Thyroid storm, also called thyrotoxic crisis, is a rare but life-threatening exacerbation of hyperthyroidism—or excess levels of thyroid hormone.[2] Myxedema crisis refers to a rare but life-threatening form of hypothyroidism.[2]

The symptoms of thyroid storm include fever, delirium, seizures, coma, vomiting, diarrhea, and jaundice. The mortality rate due to cardiac failure, arrhythmia, or hyperthermia is as high as 30 percent, even with treatment.

The symptoms of myxedema crisis are impaired cognition, severe hypothermia, hypoventilation, hypoglycemia, and hypotension. The mortality rate for this condition is also very high.

CAUSES

Thyrotoxic crisis is usually precipitated by acute illness (e.g., stroke, infection, trauma, diabetic ketoacidosis), surgery (especially on the thyroid), or radioiodine treatment of a patient with partially treated or untreated hyperthyroidism.[2] These conditions cause thyroid hormone levels to rise suddenly to dangerous levels. Myxedema crisis is usually induced by an infection, acute illness (cardiac, respiratory, or neurologically based), cold exposure, or drug use.[2]

DIAGNOSIS

Because both conditions are life-threatening emergencies, they must be recognized and treated solely on clinical grounds since laboratory confirmation often cannot be obtained in a timely manner.

Patients with thyroid storm typically appear markedly hypermetabolic, with high fevers, tachycardia, nausea, vomiting, tremulousness, agitation, and psychosis. Late in the progression of the disease, some patients may become stuporous or comatose with hypotension. Patients with myxedema crisis have impaired cognition, ranging from confusion to a coma. Late in the disease, the patient may be hypothermic.

TREATMENT

Management of thyroid storm requires intensive monitoring and supportive care, identification and treatment of the precipitating cause, and measures that reduce thyroid hormone synthesis. Large doses of propylthiouracil (600 mg loading dose and 200 to 300 mg every 6 hours) should be given orally or by nasogastric tube or rectum. The drug's inhibitory action on T4 to T3 conversion makes it the antithyroid drug of choice for treating the patient with thyroid storm. Additional therapeutic measures include glucocorticoids (e.g., dexamethasone, 2 mg every 6 hours), antibiotics, cooling, oxygen, and intravenous fluids.[2]

Management of myxedema crisis requires large doses of levothyroxine intravenously. An initial dose of levothyroxine sodium (400 mcg) should be given intravenously, followed by 50 to 100 mcg daily. Additional therapeutic measures may be required, depending on the disease complications, including applying warm blankets, intubation, and treatment for infection.[2]

QUIZ QUESTIONS

NODULAR THYROID DISEASE, THYROID CANCER, THYROID EMERGENCIES

1. Name four signs and symptoms of thyroid cancer:

2. Name the three treatments for thyroid cancer:

3. Match the diagnosis technique for nodular thyroid disease with the correct definition:

A **Routine medical examination**	1 If in normal ranges, the thyroid nodules are confirmed to be functioning normally
B **Thyroid function tests**	2 A procedure that examines a nuclear image of the thyroid after observing the thyroid absorption of radioactive material
C **FNA biopsy**	3 Used to determine if a nodule is benign or malignant by removing small samples of cells from the nodule using a thin needle
D **Ultrasonography**	4 Used to discover the presence of nodules by observing how the thyroid gland moves during swallowing
E **Thyroid scan**	5 An imaging technique using high-frequency sound waves to make images of the thyroid gland, and can be used to distinguish cysts on the thyroid from nodules

GLOSSARY, APPENDIX, AND REFERENCES

GLOSSARY

ADENOMA | A benign tumor in which the tumor cells form glands or glandlike structures.

ADRENAL GLANDS | A pair of endocrine organs that produce steroids such as sex hormones, hormones concerned with metabolic functions, and epinephrine. They are located above the kidneys.

BIOPSY | Process of removing tissue from patients for diagnostic examination.

BRADYCARDIA | Slowness of the heartbeat, usually defined as a rate under 60 beats/minute.

CALCITONIN | A peptide hormone produced by the parathyroid, thyroid, and thymus glands; it increases the deposition of calcium and phosphate in bone and lowers the level of calcium in the blood.

CARCINOMA | The most commonly occurring kind of cancer; any various types of benign or malignant tumors derived from epithelial cells.

CONGENITAL HYPOTHYROIDISM | Lack of thyroid secretion beginning at birth.

DIABETES MELLITUS | A chronic metabolic disorder in which the use of carbohydrates is impaired.

DYSGENESIS | Defective development.

DYSPNEA | Shortness of breath, usually associated with disease of the heart or lungs.

EDEMA | An accumulation of an excessive amount of fluid in cells or intercellular tissues.

ENDOCRINE SYSTEM | A system of glands, each of which secretes a type of hormone directly into the bloodstream to regulate the body.

FIBROSIS | Formation of fibrous tissue as a reactive process, as opposed to formation of fibrous tissue as a normal constituent of an organ or tissue.

GOITER | Enlargement of the thyroid gland.

GYNECOMASTIA | Excessive development of the male mammary glands.

HASHIMOTO'S THYROIDITIS | Diffuse infiltration of the thyroid gland with lymphocytes, resulting in diffuse goiter, progressive destruction of the parenchyma, often leading to hypothyroidism.

HOMEOSTASIS | The state of equilibrium in the body with respect to various functions and to the chemical compositions of the fluids and tissues.

HORMONE | A chemical substance secreted into the body fluids by one cell or a group of cells that exerts a physiological effect on other cells in the body.

HUMAN CHORIONIC GONADOTROPIN (hCG) | A hormone released by the placenta during pregnancy. The primary function of hCG is to ensure the female body does not initiate menstruation once implantation of the fertilized egg has occurred. Most pregnancy tests detect this hormone in either urine or serum to confirm pregnancy. hCG may also be administered to induce ovulation, mimicking the luteinizing hormone (LH) surge.

HYPERLIPIDEMIA | Elevated levels of lipids in the blood.

HYPERTENSION | High blood pressure, arbitrarily defined as systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg.

HYPERTHYROIDISM | An abnormality of the thyroid gland in which secretion of thyroid hormone is increased and no longer under the regulatory control of hypothalamic-pituitary centers.

HYPOTHALAMUS | Endocrine tissue which releases gonadotropin-release hormone (GnRH) which, in turn, regulates and controls hormones released by the pituitary gland. The hypothalamus is located at the base of the brain.

ISLETS OF LANGERHANS | The regions of the pancreas that contain insulin-secreting cells.

MENORRHAGIA | Abnormally heavy and prolonged menstrual period at regular intervals.

MYXEDEMA | Hypothyroidism characterized by relatively hard edema of subcutaneous tissue, with increased content of mucins in the interstitial fluid; characterized by somnolence, slow mentation, dryness and loss of hair, increased fluid in body cavities such as the pericardial sac, subnormal temperature, hoarseness, muscle weakness, and slow return of a muscle to the neutral position after a tendon jerk; usually caused by removal or loss of functioning thyroid tissue.

OLIGOMENORRHEA | Abnormally infrequent or scanty menstrual flow.

OVARY | The essential female reproductive organ that produces eggs and female sex hormones. There are usually two ovaries.

PARESTHESIA | A spontaneous abnormal, usually nonpainful sensation (e.g., burning, prickling).

PITUITARY GLAND | A small endocrine organ that produces various hormones which directly affect basic bodily functions and exert a controlling or regulating influence on other endocrine organs.

POLYURIA | Excessive excretion of urine.

RADIOACTIVE IODINE | The iodine radioisotopes ^{131}I, ^{125}I, or ^{123}I used as tracers in biology and medicine.

STEROID | Compounds of 17-carbon 4-ring composition including various hormones.

STEROID HORMONES | Any of the hormones with the characteristic ring structure of steroids, including sex hormones, cortisone, and adrenocortical hormones. Steroid hormone names often end in "-one" and "-ol" suffixes as in testosterone and estradiol.

TACHYCARDIA | Rapid beating of the heart conventionally applied to rates over 100 beats per minute.

TESTIS | The male reproductive gland in which sperm develop. Usually paired, the testis develops from the genital ridges of the embryo and normally descends into the scrotum before or shortly after birth.

THYROGLOBULIN (Tg) | A protein that contains precursors of thyroid hormone usually stored in the colloid within the thyroid follicles.

THYROIDECTOMY | Removal of the thyroid gland.

THYROID GLAND | A gland located in the neck that converts thyroglobulin into the active hormone form. The gland controls metabolic activity by secreting the thyroid hormones thyroxine (T4) and triiodothyronine (T3), and by producing and releasing calcitonin.

THYROIDITIS | Inflammation of the thyroid gland.

THYROID PEROXIDASE (TPO) | An enzyme expressed mainly in the thyroid that liberates iodine for addition onto tyrosine residues on thyroglobulin for the production of thyroxine (T4) or triiodothyronine (T3), thyroid hormones.

THYROID-STIMULATING HORMONE (TSH) | A peptide hormone synthesized and secreted by cells in the anterior pituitary gland, which regulates the endocrine function of the thyroid gland.

THYROID-STIMULATING IMMUNOGLOBULIN (TSI) | In Graves' disease, the antibodies to TSH receptors in the thyroid gland, causing hyperthyroidism.

THYROID STORM | Thyrotoxic crisis.

THYROTOXICOSIS | The overactive thyroid state produced by excessive quantities of endogenous or exogenous thyroid hormone.

THYROXINE (T4) | The main hormone produced by the thyroid gland, acting to increase metabolic rate and regulating growth and development.

THYROXINE-BINDING GLOBULIN (TBG) | Protein that binds with thyroid hormone in circulation.

TRIIODOTHYRONINE (T3) | A thyroid hormone exerted by the thyroid gland which exerts the same biologic effects as thyroxine but, on a molecular basis, is more potent, and its onset is more rapid.

TROPIC HORMONES | Those hormones of the anterior lobe of the pituitary that affect the growth, nutrition, or function of other endocrine glands.

TSH RECEPTOR | A structural protein molecule on the cell surface or within the cytoplasm that binds to a specific factor, such as a drug, hormone, antigen, or neurotransmitter.

ULTRASONOGRAPHY | The location, measurement or delineation of deep structures by measuring the reflection or transmission of high frequency or ultrasonic waves. Computer calculation of the distance to the sound-reflecting or absorbing surface plus the known orientation of the sound beam gives a two-dimensional image.

ULTRASOUND | A technique for viewing internal organs using reflected high-frequency sound waves.

APPENDIX: QUIZ ANSWERS

SECTION 1 **THE ENDOCRINE SYSTEM AND THE THYROID GLAND**

1. Hypothalamus, pituitary gland, thyroid gland, parathyroid gland, adrenal glands, islets of Langerhans or pancreas, sex glands (testes or ovaries)
2. A. – 5
   B. – 4
   C. – 1
   D. – 3
   E. – 2
3. A. – 3
   B. – 1
   C. – 2

SECTION 2 **HYPOTHYROIDISM**

1. Tiredness, weakness, dry skin, feeling cold, hair loss, difficulty concentrating, poor memory, constipation, weight gain, dyspnea, hoarse voice, menorrhagia, paresthesia, impaired hearing, depression
2. A. – Above
   B. – Below
   C. – Free
3. A. – False
   B. – True
   C. – True
   D. – False

SECTION 3 **HYPERTHYROIDISM**

1. Tachycardia, tremor, goiter, warm and moist skin, muscle weakness, lid retraction or lag, gynecomastia
2. A. – Low
   B. – Above
   C. – Normal
3. A. – True
   B. – False
   C. – False

SECTION 4 **THYROID FUNCTION IN PREGNANCY**

1. A transient increase in hCG, a rise in TBG during the first trimester, alterations in the immune system, increased urinary iodine excretion
2. A. – Decrease
   B. – Increase
   C. – 0.3 percent, 0.7 percent

SECTION 5 **NODULAR THYROID DISEASE, THYROID CANCER, THYROID EMERGENCIES**

1. Lump or nodule in the thyroid, hoarseness, pain in the neck/jaw/ear, difficulty swallowing, tickle in the throat, shortness of breath
2. Surgery, TSH suppression therapy, radioiodine treatment
3. A. – 4
   B. – 1
   C. – 3
   D. – 5
   E. – 2

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