Ann is a 27-year-old woman with no significant health problems who complains of having some strange sensations and is wondering whether she is having a stroke. She had a baby 11 months ago, and is tired, but expected that with nighttime feedings. Now she has occasional numbness and tingling in her ring finger and thumb on her right hand, in her left foot, and on the right side of her face. She sometimes feels unusually weak and can’t open baby food jars. She stopped breastfeeding months ago, yet her menses has not returned. She denies postpartum depression or anxiety, headaches, gait, speech, or vision changes, concentration problems, or falls. She reports that her lab work during her pregnancy was normal, and her obstetrician referred her to primary care for evaluation of her sporadic symptoms.

On exam, Ann appears quite well, and is alert with normal vital signs. Her thyroid is slightly enlarged without nodules. The remaining physical exam is normal, including intact sensation in all extremities with monofilament testing and vibratory sense, equal motor strength, intact cranial nerves, and normal balance. A full set of lab tests are ordered before she leaves the clinic. Her lab results are as follows: thyroid-stimulating hormone (TSH) 66.8 microIU/mL (normal 0.3 to 4.0 microIU/mL) and her free thyroxine (free T4) 2.5 (normal 10 to 27 pmol/L). All other lab results are normal, with the exception of very mild anemia. Follow-up lab testing also reveals elevated thyroperoxidase antibody levels, suggestive of autoimmune hypothyroidism.1

Disorders of thyroid function are one of the most commonly encountered endocrine abnormalities in primary care. Hypothyroidism can yield serious clinical consequences but is readily treatable. Approximately 11 million people are affected with hypothyroidism every year in the United States, representing about 4% to 10% of the population, and over 18% are over the age of 65. Women develop hypothyroidism 10 times more often than men, and the risks of developing it escalate with age among both men and women.1,2 Studies of the incidence of autoimmune hypothyroidism reveal that women develop it at a rate of 350/100,000/year and men at a rate of 80/100,000/year.3

Pathophysiology
Thyroid hormones are regulated by the hypothalamic-pituitary-thyroid axis (see Hypothalamic-pituitary-thyroid feedback system). The hypothalamus secretes thyrotropin (TRH), which is carried via the hypothalamic portal vein to bind with TRH receptors. There it stimulates genes that express TSH beta subunit synthesis. Mature TSH is secreted from the pituitary gland, which maintains balance by providing the stimulus for synthesis and secretion of the thyroid hormones thyroxine (T4) and triiodothyronine (T3). TSH levels and circulating T4 and T3 exist in an inverse relationship such that low levels of T4 and T3 cause TSH to...
Hypothyroidism: An evidence-based approach to a complex disorder

rise. The higher levels of TSH will stimulate the release of thyroid hormones.1,4 T4 is the main thyroid hormone that is converted into T3 in peripheral organs. Approximately 100 to 125 nmol of T4 is released daily, and its half-life is 7 to 10 days. Although it is the metabolically active hormone, T3 is released in minute amounts only.5,6

Thyroid hormone is highly active metabolically and necessary for most bodily functions such as growth and development and maintenance of homeostasis (see Control of thyroid function). Thyroid hormone deficiency results in a wide variety of effects that are caused by myxedematous infiltration of glycosaminoglycans. When glycosaminoglycans accumulate in vital areas, they interfere with normal organ function. Consider the example of myxedematous infiltration of the heart, which can lead to decreased contractility, cardiomegaly, pericardial effusion, bradycardia, and decreased cardiac output. In other areas, myxedema can cause gastroparesis, delayed puberty, anovulation, infertility, insulin resistance, and increased levels of total cholesterol.5

Histologic changes associated with autoimmune disease of the thyroid lead to chronic gland inflammation with progressive destruction of tissue. Widespread lymphocytes and plasma cells are eventually replaced by fibrosis and trophic thyroid follicles.5

Causes of hypothyroidism
Thyroid disorders that lead to low levels of thyroid hormones are classified as either primary or secondary hypothyroidism, and primary disorders present with a full spectrum of severity ranging from very mild to overt disease.1 Worldwide, the most common cause of hypothyroidism is iodine deficiency; but the most common cause of primary hypothyroidism in the United States is Hashimoto disease, an autoimmune thyroiditis associated with high titers of antithyroid peroxidase (anti-TPO) or antimicrosomal antibodies in up to 95% of those affected.2 Lymphocytic infiltration of the gland progressively destroys functional thyroid tissue. It is interesting to note that patients with one autoimmune disorder such as type 1 diabetes mellitus are at higher risk for developing another, and approximately 10% of patients with type 1 diabetes mellitus will develop autoimmune thyroiditis and should be monitored for goiter development.5,7

Other common causes of primary hypothyroidism include surgical removal of the thyroid gland, thyroid ablation with radioactive iodine, external radiation, low or high levels of iodine, temporary inflammation of the thyroid gland, too little thyroid medication, and exposure to some pharmacologic agents such as amiodarone, lithium, thalidomide, and stavudine.5,7

Postpartum thyroiditis occurs in 5% to 8% of women in a general population and up to 25% of women with type 1 diabetes.2,6 In Ann’s case, autoimmune thyroiditis is the culprit, and it can either be transient (2 to 4 months) or permanent. Antithyroid antibodies will be elevated, and thyroperoxidase antibody, TSH, and free T4 levels should

Hypothalamic-pituitary-thyroid feedback system

be used to confirm diagnosis. The presence of anti-TPO antibodies at high levels during pregnancy are 97% sensitive and 91% specific for postpartum autoimmune thyroid disease.\(^5,6\)

Secondary or central hypothyroidism results from pituitary-based deficiencies of TRH-stimulating hormone or TRH-releasing hormone. These disorders are rare and are related to impaired stimulation of the thyroid gland at the hypothalamus or pituitary level. The most common cause of central hypothyroidism is pituitary adenoma, but other causes include Sheehan syndrome, traumatic brain injury, space-occupying lesions, radiation, growth hormone therapy, subarachnoid hemorrhage, or gene mutation.\(^4\) Sheehan syndrome is a rare occurrence of postpartum hemorrhage that leads to ischemic necrosis of the pituitary. Usually, the patient develops panhypopituitarism (56% to 84% of
cases) and selective hormone deficiencies such as growth hormone. Women with Sheehan syndrome often will develop lactation failure, amenorrhea, adrenal insufficiency, and central hypothyroidism.8

Screening
Population screening for thyroid disorders is somewhat controversial. Many expert groups have offered screening guidelines.7,9–14 (See Professional organization recommendations for thyroid screening). Although recommendations for routine screening vary, most groups recommend screening individuals who display symptoms or who are at high risk for developing hypothyroidism such as pregnant women, women with dementia, and those with unexplained lab results such as hypercholesterolemia, anemia, or elevated creatine phosphokinase. Due to issues of costs, questionable gains in quality-adjusted life years, and insufficient evidence, general population screening is not recommended by all groups.1

Interestingly, the American Association of Clinical Endocrinologists (AACE)7 recommends routine screening for all pregnant women, but the United States Preventive Services Task Force (USPSTF)10 and the American Congress of Obstetricians and Gynecologists (ACOG)14 have not endorsed routine screening.

Signs and symptoms
As seen in the case study, clinical presentation is highly variable. Classic symptoms of hypothyroidism are sometimes subtle and develop slowly. They include fatigue, weakness, dry skin, constipation, heavier bleeding with menstruation, brittle hair, alopecia, weight gain, edema, sensitivity to cold, facial edema, and slowing of physical activity in general (See Signs and symptoms of hypothyroidism). Carpal tunnel-like symptoms with numbness and tingling in the hands and generalized arthralgia can occur, as in Ann’s case. Later symptoms include decreased taste, hoarseness, hand and feet edema, slow speech, skin thickening, and thinning of eyebrows.1,5,7 Autoimmune thyroiditis is often accompanied by unique signs and symptoms such as fullness sensation in the throat, thyroid enlargement, exhaustion, neck pain or sore throat, and low-grade fever.1

Because signs and symptoms of hypothyroidism often mimic other comorbid conditions, it can be difficult to make an accurate diagnosis. Consider Ann’s case. She presented with tingling in various extremities and menstrual disorder. Other coexisting conditions frequently encountered—hypercholesterolemia, menstrual changes, infertility, arthritis–like pains around joints, and depression—can complicate a clear diagnosis of hypothyroidism.5,7

Physical exam findings
The thyroid gland should be examined for size, texture, nodularity, and tenderness. The right lobe may be somewhat larger than the left lobe, and the volume will vary with the patient’s size, gender, and age. It is rubbery but smooth when nodules are absent. When a nodule is discovered, it is likely that other occult nodules are present in up to 50% of patients. Thyroid nodules can be associated with hypothyroidism, but they are not always encountered.5

Pain in the thyroid area is likely associated with thyroiditis. Recall that the thyroid is best examined with the clinician behind the patient, palpating the thyroid gland as he or she is swallowing. Offer the patient water to ensure that swallowing occurs effectively. Other signs to look for include brittle nails, pale or dry skin, cool skin, edema, and thin or brittle hair. More severe cases may reveal slowed speech and movements, weight gain, bradycardia, coarse facial features, goiter, decreased BP, pericardial effusion, nonpitting edema (myxedema), hyporeflexia, and ataxia. A chest X-ray may reveal an enlarged heart.1,5
Signs and symptoms of hypothyroidism

- Cold intolerance
- Hypothermia
- Fatigue, loss of energy, sleepiness
- Lethargy
- Decreased appetite
- Goiter
- Slowed speech
- Jaundice
- Dry skin,
- Coarse brittle hair, hair loss
- Decreased perspiration
- Weight gain
- Fullness in throat
- Hoarseness
- Decreased hearing
- Blurred vision
- Periorbital edema
- Dull facial expression
- Mental slowing
- Depression
- Paresthesias
- Hyporeflexia
- Slowed movements
- Bradycardia
- Decreased BP
- Constipation
- Menstrual abnormalities, infertility
- Arthralgia
- Edema of the lower extremities
- Myxedema

Diagnostic findings

As in Ann's case, lab evaluation establishes the diagnosis. Additional lab work will help pinpoint the etiology as well. The third-generation TSH is the most sensitive and is considered the single best screening test for hypothyroidism. However, its usefulness with diagnosing and titrating medication is controversial among experts. The normal reference range varies among labs, with some reporting a low range of 0.3 to 4.12 microIU/mL. The AACE reports a normal range for TSH as 0.3 to 4.0 microIU/mL. TSH levels peak in the evening and are at their lowest in the afternoon. The TSH also varies greatly with imposed physiologic conditions such as severe stress, illness, trauma, and low energy intake. If the TSH is elevated, a total T4 should be measured along with binding proteins.

The free T4 has become increasingly more popular because it measures unbound or free hormone levels; however, it is unreliable with severe illness. In fact, TSH testing is discouraged among severely ill patients because the findings are difficult to interpret. Often, the TSH, T4, and T3 levels are markedly abnormal, suggesting secondary hypothyroidism, but are not necessarily related to a thyroid disorder. Instead, the abnormal findings are more indicative of abnormalities in the hypothalamic-pituitary axis, referred to as "euthyroid sick syndrome." AACE recommends that treatment is deferred for TSH values less than 10 microIU/mL unless thyroid disorder is coexistent.

Free T4 level should be done in conjunction with the TSH because it is the cause of hypothyroidism. A high TSH and low free T4 is associated with classic primary hypothyroidism, but a low TSH and low free T4 is associated with secondary hypothyroidism. Note that T3 is not helpful with diagnosing hypothyroidism.

Measuring thyroid antibodies (antimicrosomal or anti-TPO antibodies) and antithyroglobulin (anti-Tg) may be helpful in determining the etiology of hypothyroidism or with predicting a future occurrence.

Other lab findings may include mild anemia, increased cholesterol, increased liver enzymes, increased prolactin, and hyponatremia. Imaging studies of the neck and thyroid can detect infiltrative disease or nodules, but they have little use in hypothyroidism. Fine needle biopsy of nodules is recommended. Radioactive iodine uptake (RAIU) and thyroid scanning are not useful with hypothyroidism because they require endogenous functioning of the thyroid gland to provide diagnostic information.

Subclinical hypothyroidism

Another scenario is commonly encountered: mildly increased TSH and normal free T4. This condition is subclinical hypothyroidism and represents another controversial area among expert panels. Although it may herald thyroid failure, it can occur without symptoms, often discovered with routine lab work. It is fairly common (1% to 10% of the adult population) among women, aging adults, and those with a higher iodine intake.

The most common cause of subclinical hypothyroidism is Hashimoto disease, and the conversion to overt hypothyroidism ranges from 3% to 20%. Patients at higher risk for developing overt disease include those with positive antibodies and/or goiter.

The data for treating patients with TSH levels between 5 and 10 microIU/mL are conflicting. Several studies demonstrate reduction in cardiovascular risk factors such as improving lipid profiles, but patients with TSH levels markedly above 10 microIU/mL were mistakenly included in the analy-
Treatment

AACE urges treatment for patients with TSH levels greater than 10 microIU/mL. The goals for treatment include restoring normal thyroid hormone levels, relieving symptoms, preventing neurologic complications in newborns and children, and reversing other metabolic abnormalities associated with hypothyroidism. It is also recommended that patients with subclinical hypothyroidism are closely monitored for conversion to hypothyroidism. Thyroid hormone administration will supplement or replace the inadequate production of T4.

The types of pharmacologic agents available for thyroid replacement include both synthetic and natural combinations of T3 (liothyronine) and T4 (levothyroxine) and desiccated natural thyroid. Levothyroxine is considered the drug of choice for replacement therapy because it is dosed once daily, offers reliable results, is chemically stable, has a long half-life, and is inexpensive.

To initiate therapy, clinicians need to tailor the treatment plan for the individual patient because even small changes in dose can rapidly shift a patient from a euthyroid state. The starting dose may range from 12.5 mcg to full replacement therapy of 1.6 mcg/kg based on age, weight, presence of associated disorders, cardiac status, and severity and duration of hypothyroidism. It is recommended to start at a low dose (12.5 to 25 mcg) and titrate slowly every 6 to 8 weeks until the TSH reaches 0.3 to 3.0 microIU/mL. Clinical benefit is noted within 3 to 5 days and will level off in 6 to 8 weeks. More conservative management is recommended for patients who are elderly, and have heart failure, angina, or anxiety. Overall, a higher TSH initially will mandate a slower titration schedule.

Patients should be monitored for effects of too much thyroid replacement, including tachycardia, palpitations, nervousness, sleeplessness, tremors, and chest pain. In this case, the dose should be lowered immediately and the patient should be monitored more closely until stable. After the TSH is stabilized, maintenance therapy should be continued with annual or semiannual TSH testing. An exception includes a demonstrative change in patient status or symptoms such as pregnancy or severe illness.

Complication: Myxedema coma

Myxedema coma is a rare, life-threatening emergency that can occur in long-standing, untreated hypothyroidism. Although more common decades ago, data suggest that severe hypothyroidism with resultant myxedema coma may be detected earlier and managed more aggressively than in the past because the incidence and mortalities have dropped.

Typical symptoms include lethargy and weakness, below normal body temperature, low BP, low blood glucose, weight gain, myxedema (thickened, nonpitting edema), changes to soft tissues of lower extremities and some internal organs, decreased breathing, and slow cognitive functioning to unresponsiveness. Lab studies reveal hypnatremia, hypoglycemia, hypercapnia, hypoxia, elevated TSH, low FT4, and low T3 resin uptake. Imaging studies may reveal pericardial effusion and acute ileus, and an ECG will show bradycardia with possible T-wave abnormalities and electrical alternans if effusion is present.

This condition represents a severe emergency with an estimated mortality as high as 20%. The patient should be hospitalized for intensive care such as possible ventilator support, I.V. thyroid medication, hemodynamic support, and interventions to raise core body temperature. I.V. T4 replacement via slow infusion followed by a daily dosage is often necessary, and some patients will require glucocorticoid replacement if adrenal insufficiency is also present. Long-term management will include identifying the etiology and underlying conditions, careful titration.

Adverse outcomes associated with hypothyroidism

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<tr>
<th>Maternal outcomes</th>
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Maternal outcomes

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Adverse outcomes associated with hypothyroidism

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situation of thyroid medication, and prevention of further occurrence.22

Special populations
Pregnancy
Hypothyroidism in pregnancy is associated with many poor maternal and fetal outcomes such as preeclampsia, spontaneous abortion, abnormal fetal brain development, and fetal mortality (see Adverse outcomes associated with hypothyroidism). Because even mild hypothyroidism can lead to adverse fetal results, it needs to be detected and managed carefully.2,3,7,8,22 In general, increased dosage requirements for pregnant women with hypothyroidism should be anticipated, especially during the first two trimesters. During the first trimester, thyroid hormones are supplied exclusively by the mother and will cross the placenta, so maintenance of normal levels is necessary to ensure proper fetal neural growth. During and after the second trimester, thyroid hormones are supplied by both mother and fetus but primarily from the mother.7,22 At the confirmation of pregnancy, the T4 dose should be augmented by 30% and serial TSH levels should be measured every 3 to 4 weeks thereafter. The TSH level of less than 2.5 microIU/mL is the goal of therapy during pregnancy.5,7,8

The AACE supports TSH testing in high-risk pregnant women, and if elevated, levothyroxine therapy should be initiated. Pregnant women with subclinical hypothyroidism should be monitored closely for the high probability of subsequent clinical hypothyroidism.8

Children
Hypothyroidism in children represents a special challenge because of the critical role thyroid hormones play in neurologic development.23 The congenital low or absent levels of thyroid hormone may result in cretinism, and neonatal hypothyroidism accounts for the most preventable cause of intellectual disability. Consequently, TSH levels warrant careful monitoring during pregnancy and for neonatal screening.22,23

As a protective mechanism for the newborn, TSH levels surge during the first hour after birth. T4 levels are stimulated to rise to ensure myelinization of the central nervous system; they rapidly decline by 1 week of age to normal levels. Because of their immature hypothalamic-pituitary-ovary axis, preterm infants have smaller increases in TSH and T4 concentrations.23

Sporadic cases of congenital hypothyroidism account for over 85% of cases and the other 15% are hereditary.23 Approximately 1 in 4,000 newborns are diagnosed annually with a higher incidence occurring among females.23 Delays in diagnosis will lower the intelligence quotient accordingly, and early detection is important.23 Because T4 will cross the placenta, newborns with congenital hypothyroidism will possess 25% to 50% of normal T4. Signs and symptoms of hypothyroidism can include an open posterior fontanels, lethargy, hypotonic posture, hoarse cry, feeding problems, constipation, dry skin, and hypothermia.21,24

Newborn screening includes an initial T4 level in all 50 states, and some states are now using more sensitive TSH testing. Subclinical hypothyroidism in infants merits treatment for at least the first 3 years because thyroid hormone is very critical to adequate myelinization.25

Treatment goals are to keep the T4 level in the upper half of the normal range for the child’s age to ensure normal growth and cognitive outcome. Oral levothyroxine is recommended. The more rapidly replaced, the better the overall neurologic outcome for the infant.21 The American Academy of Pediatrics (AAP) screening recommendations include measuring T4 and TSH levels as follows:

• At 2 to 4 weeks after starting T4 treatment
• Every 1 to 2 months during first 6 months
• Every 3 to 4 months between 6 months and 3 years
• Every 6 to 12 months until growth is complete
• 2 weeks after any change in dose.

More frequent intervals as necessary for abnormal results.

Infants treated early can be expected to have normal growth and development, especially when compared with infants born before newborn screening was instituted. Untreated infants often display significantly lower intelligence quotients and may have other neurologic problems with gross and fine motor coordination, ataxia, altered muscle tone, strabismus, decreased attention span, and speech problems.

Teaching parents and caregivers about the importance of complying with treatment is mandatory. Levothyroxine orally needs to be taken as a tablet, crushed and mixed with milk, formula, or water, and it should not be taken with calcium or soy products because they can interfere with its absorption.22
**Elderly**

The signs and symptoms of hypothyroidism may be very subtle or mistakenly attributed to normal aging changes. Fatigue and weakness are common presentations and are associated with many other conditions. Other symptoms such as dry skin, alopecia, weight gain, and sensitivity to cold are often present as well. Taking a careful history can assist with making the correct diagnosis and helping to avoid erroneous diagnoses of heart failure, dementia, or depression.7,21

The treatment goals are similar for the older adults, but some extra precautions should be taken. The replacement dose of levothyroxine is started at a lower dose of 12.5 to 25 mcg each day with reassessment of levels every 6 to 8 weeks until TSH is normalized. For patients with known cardiovascular disease, the dose needs to be monitored very carefully to avoid adverse reactions such as tachycardia, hypertension, angina, and myocardial infarction.7

**Patient teaching**

Patient teaching includes cautioning patients to continue taking thyroid replacement as directed and reassuring him or her that it can take several weeks to notice improvement in symptoms. Most likely, taking thyroid replacement will continue for life. If the brand of medication changes, the patient needs to call so that TSH can be checked again. Thyroid medication needs to be taken the same time each day on an empty stomach, at least 1 hour before other medications. Significant interference with absorption can occur when taken with calcium, iron, vitamins, some antacids, colestipol, or other medications that bind bile acids or fiber supplements. Patients should report adverse reactions such as tachycardia, tremulousness, or rapid weight loss, which may be associated with too high dose of thyroid replacement.5,7

**Maintain an index of suspicion**

The majority of cases of primary hypothyroidism can be detected, treated, and monitored by primary care providers. Having a high index of suspicion is appropriate for early detection of thyroid failure in high-risk individuals. Assessment and treatment of hypothyroidism can be more complicated when vulnerable populations or patients with complex issues are encountered. AACE provides evidence-based guidelines for managing the disorder, and referral to an endocrinologist is often indicated for extreme cases. Treatment of subclinical hypothyroidism remains controversial, yet all patients warrant close monitoring, and practice recommendations exist for these cases as well. 2

**REFERENCES**


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