Learning Objectives

After participating in this educational activity, participants should be better able to

1. Recognize the common and less common signs and symptoms of thyroid disorders and have a low index of suspicion for patient work-up
2. Prescribe thyroid replacement therapy according to relevant guidelines, and follow up with patients regularly, adapting treatment and doses as needed
3. Identify pregnant women at high risk of thyroid dysfunction who would benefit from screening, and follow relevant guidelines when managing patients with hypothyroidism who become pregnant
Overview
The thyroid gland impacts nearly all of the body's metabolic processes, and its disorders cover a wide range of diseases. These conditions are usually seen first in primary care settings, but they frequently go undiagnosed. With proper diagnosis, however, thyroid disorders can usually be well managed. This activity will focus on the diagnosis of the under- and overactive thyroid and the details of thyroid replacement therapy.

Case Study: Carol
Carol is a 46-year-old who complains of fatigue, weight gain, hair loss, dry skin, and heavy but regular menses. Her previous medical history is positive for hyperlipidemia. Physical examination, including pelvic exam, is normal. Her complete blood count (CBC) is within normal limits (WNL).

You first recommend
A. Dermatology consult for her hair and skin concerns
B. Pelvic ultrasound
C. Thyroid stimulating hormone (TSH) test
D. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) tests
E. All the above

Carol’s symptoms are complex, multidimensional, multifactorial, and subtle, like many patients in primary care.

While clearly there are several possible causes for her complaints, she presents with many nonspecific clues that her thyroid may be underactive and should be assessed. The clues that raise the suspicion of hypothyroidism in any include fatigue, constipation, hair loss, dry skin, weight gain, heavy menses, and hyperlipidemia.[1]

Prevalence
Hyperthyroidism and hypothyroidism are common problems in primary care that can have lifelong consequences if not properly managed. About 5% of U.S. adults report having thyroid disease or taking thyroid medication.[2]

The problem becomes even more prevalent in older populations. In a large study, 2,799 well-functioning adults, aged 70 to 79, participated in thyrotropin, free thyroxine, and total cholesterol testing. See Table 1 for the reported history of hyperthyroidism and hypothyroidism in those individuals.[3]
Etiology of Hyperthyroidism and Hypothyroidism

Hyperthyroidism has many causes, but Graves’ disease, an autoimmune disorder, is the most common primary reason.[1] It is associated with the development of long-acting thyroid stimulating antibodies. Thyroid nodules (single or multiple) may produce excess thyroid hormones leading to thyrotoxicosis. Finally, the excessive iatrogenic and exogenous dosing of the thyroid hormone supplement levothyroxine (LT4) is a common reason for hyperthyroidism.

Likewise, subclinical hyperthyroidism is most often caused by release of excess thyroid hormone by the gland or by excessive iatrogenic or exogenous thyroid supplementation.

The most common cause of hypothyroidism in the United States is Hashimoto’s thyroiditis, also known as chronic lymphocytic thyroiditis. Hashimoto’s thyroiditis holds a special significance in medical history as it is the first recognized autoimmune disorder. The presence of antithyroid peroxidase (antiTPO) antibodies or antimicrosomal antibodies (AMA) in the blood helps make the diagnosis. Prior treatment for Graves’ disease with surgery or radioiodine is another common reason for low thyroid function.

Worldwide, iodine deficiency remains the most common cause of hypothyroidism, but is uncommon in North America due to the widespread availability of iodized table salt. Some clinicians worry that the move to “organic natural” salt may lead to a resurgence in thyroid disease.

The term subclinical hypothyroidism refers to patients who have only an elevated TSH and a normal T4 level.[4]

Symptoms

Hyperthyroidism

The correlation between the degree of elevation in thyroid hormone concentration and clinical signs and symptoms of hyperthyroidism is modest. The signs and symptoms of overt hyperthyroidism and subclinical hyperthyroidism are alike (Table 2).
### Hypothyroidism

The symptoms of both hypothyroidism and subclinical hypothyroidism are often subtle and nonspecific (Table 3).

#### Table 2. Overt Hyperthyroidism and Subclinical Hyperthyroidism Signs & Symptoms

<table>
<thead>
<tr>
<th>Hypothyroidism</th>
<th>Subclinical Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervousness and irritability</td>
<td>Exertional intolerance and dyspnea</td>
</tr>
<tr>
<td>Palpitations and tachycardia</td>
<td>Menstrual disturbance (decreased flow)</td>
</tr>
<tr>
<td>Heat intolerance or increased sweating</td>
<td>Impaired fertility</td>
</tr>
<tr>
<td>Tremor</td>
<td>Mental disturbances (anxiety)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Sleep disturbances (including insomnia)</td>
</tr>
<tr>
<td>Alterations in appetite</td>
<td>Changes in vision, photophobia, eye irritation, diplopia, or exophthalmos (with Graves’ disease)</td>
</tr>
<tr>
<td>Frequent bowel movements or diarrhea</td>
<td>Fatigue and muscle weakness</td>
</tr>
<tr>
<td>Dependent lower extremity edema</td>
<td>Thyroid enlargement (depending on cause)</td>
</tr>
<tr>
<td>Sudden paralysis</td>
<td>Pretibial myxedema (in patients with Graves’ disease)</td>
</tr>
</tbody>
</table>

#### Table 3. Hypothyroidism and Subclinical Hypothyroidism Signs & Symptoms

<table>
<thead>
<tr>
<th>Hypothyroidism</th>
<th>Subclinical Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Memory and mental impairment</td>
</tr>
<tr>
<td>Weight gain from fluid retention (but usually not morbid obesity)</td>
<td>Decreased concentration</td>
</tr>
<tr>
<td>Dry skin and cold intolerance</td>
<td>Depression[4]</td>
</tr>
<tr>
<td>Yellow skin</td>
<td>Irregular or heavy menses and infertility</td>
</tr>
<tr>
<td>Coarseness or loss of hair</td>
<td>Myalgias</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Goiter</td>
<td>Macrocytic anemia[5]</td>
</tr>
<tr>
<td>Reflex delay, relaxation phase</td>
<td>Bradycardia and hypothermia</td>
</tr>
<tr>
<td>Ataxia</td>
<td>Myxedema fluid infiltration of tissues</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
</tr>
</tbody>
</table>
Case Study (cont)
Carol’s laboratory tests show a TSH of 11 mU/L (normal 0.5-5.0) and free thyroxine (FT4) of 0.8 ng/dl (normal 0.7-2.0). You tell her
A. She has hypothyroidism but as her FT4 is within normal range, treatment is not indicated
B. She has hypothyroidism and would likely benefit from replacement therapy
C. She has subclinical hypothyroidism and, while treatment is best avoided now, she needs to be closely monitored
D. She has subclinical hypothyroidism and would likely benefit from replacement therapy
E. She needs further testing including a free triiodothyronine (FT3) before you can make any recommendations

Diagnosis

Hyperthyroidism
The most important development to aid in the diagnosis of hyperthyroidism has been the widespread use of the sensitive TSH (sTSH) assays or sometimes called high sensitivity-TSH (HS-TSH). The sTSH assays refer to a TSH assay with a functional sensitivity of 0.03 mU/L or less. All cases of hyperthyroidism of any cause (except the rare cases of excess TSH production) result in a lower than normal or undetectable TSH level. Patients with overt hyperthyroidism will also, by definition, have an elevated FT4 and/or FT3. It is not necessary that both be high to make the diagnosis.

Generally, the sTSH assay is your single best screening test for hyperthyroidism, and, in most clinical situations, the serum TSH is the most sensitive test for detecting mild (subclinical) thyroid hormone excess or deficiency. The one exception is in monitoring patients with unstable thyroid states including those with recently treated hyperthyroidism or those who have been receiving excess thyroid hormone replacement where serum thyroxine (T4) measurement more accurately indicates the current thyroid status than does the serum TSH. TSH or thyrotropin is a peptide manufactured in the anterior pituitary. When functioning properly, it is regulated through a negative feedback loop based on T3 and T4 concentrations and so lags behind those levels when changes are rapid or recent.

The most controversial area of diagnosis and management is subclinical disease. When suspecting subclinical hyperthyroidism, the best single test is the sTSH. The finding of undetectable levels or levels of less than 0.02 mU/L or 0.03 mU/L, but with normal values of FT3 and FT4, makes the diagnosis. It is important to remember that both overt and subclinical disease may lead to characteristic signs and symptoms and that subclinical hyperthyroidism is a risk factor for atrial fibrillation.
**Hypothyroidism**

Primary hypothyroidism manifests by both an elevated serum TSH and a low serum FT4. In the much less common secondary (pituitary) or tertiary (hypothalamic) causes of hypothyroidism, the FT4 is low and the TSH is not appropriately elevated. Imaging of the hypothalamus and pituitary gland is required in all such patients with suspected central hypothyroidism to rule out hypothalamic and pituitary tumors.

Review of the literature favors treatment of subclinical hypothyroidism diagnosed with an elevated TSH but with normal FT4, especially when the patient is symptomatic or has a TSH greater than 10 mU/L.[7]

**Case Study (cont)**

Carol is very concerned about the cost of her medications and asks if you can prescribe a generic thyroid medication. You explain that

A. All prescriptions, generic or branded, are equally therapeutic
B. Although there are some slight differences in the absorption and therapeutic equivalence of the various formulations, they are not clinically significant
C. There is no difference in the cost of generic and branded levothyroxine
D. There is significant concern about the variability in the therapeutic equivalence among the available levothyroxine products that might complicate therapy and demand closer monitoring
E. There is significant concern about the variability in the therapeutic equivalence among the available levothyroxine products, but since there is a large safety margin in dosing, the laboratory values are less important than how she feels on the replacement therapy

**Treatment**

**Hypothyroidism and Subclinical Hypothyroidism**

The most common and recommended standard of care for thyroid replacement is the use of oral LT4. LT4 should be taken on an empty stomach, ideally an hour before breakfast,[8] due to some products (eg, coffee, antacids, and calcium) that may interfere with absorption.[9] It is always best to consult the package insert regarding any known interactions.

The average replacement dose is 112 mcg or 1.6 mcg/lb/day in a 154 lb male. In young healthy adults, there is no need to start therapy at a low dose and titrate up. The full anticipated dose could be the starting dose. However, in patients older than 50 or 60, depending on comorbidities, it is advised to start at a lower dose of 25 mcg or 50 mcg a day. Because it is known that T4 increases myocardial oxygen demand and the risk of angina and arrhythmias, in patients with coronary artery disease, it is best to be cautious and start at the low dose of 25 mcg daily.
Many patients may start to feel better in as soon as two weeks, but for others it can take months, and responses may be incremental rather than dramatic.

After initiating replacement therapy, thyroid function tests do not reach their new steady state until after six weeks, so a follow-up visit should be scheduled then. The FT4 will climb first and then the TSH will start to fall. The serum TSH level and an FT4 estimate may be included in the assessment. If levels are still subtherapeutic, then an increase dose of 12 to 25 mcg daily is appropriate. Once the TSH and FT4 levels are in the normal range, the frequency of visits and laboratory work can be decreased. Although care for each patient is different, a follow-up visit in six months and then annually is common practice. Over and under treating are significant dangers in replacement therapy; as with blood pressure or diabetes, patients need to be followed and monitored.

Another area of controversy in treatment is the issue of bioavailability, bioequivalence, and therapeutic equivalence. The American Association of Clinical Endocrinologists (AACE) advocates the use of a branded preparation of levothyroxine and is at odds with the U.S. Food and Drug Administration (FDA) on how different formulations of LT4 are approved as equivalent.[10] The FDA bases its approval of the available generic and the five branded LT4 preparations on only total T4 measurements and not TSH levels. The FDA uses Area Under Curve (AUC) and maximum concentration (Cmax) determinations in normal subjects with normal thyroid function as its measure of bioavailability. The FDA then equates this to bioequivalence and therapeutic equivalence. Moreover, it accepts any and all formulations that deviate from each other by less than 25% but greater than 12.5% as equivalent.[11]

Not surprisingly, brands vary significantly in their bioavailability. The Sandoz generic LT4 product is 12.5% more bioavailable than Synthroid® (Abbott Laboratories), but is 2.3% less bioavailable than Levoxyl® (King Pharmaceuticals).[12] The concern is that even small changes in thyroxine can cause important changes in serum TSH. The difference between the available prescription doses of 125 mcg and 137 mcg is only 9%. The AACE argues that, based on how the FDA measures, bioequivalence is not the same as therapeutic equivalence. To further complicate the issue, there is no standard LT4 for comparison with the various formulations of LT4.

Once generic substitution has occurred, refills with any of the generic formulations (some of which are rated as noninterchangeable with one another) may occur.[10] Therefore, the AACE recommends that the best choice would be for the patient to receive the same brand of LT4 throughout treatment.

At a minimum, a joint statement from the Endocrine Society, American Thyroid Association (ATA), and AACE has recommended monitoring of thyroid function tests whenever a change in LT4 preparation has occurred.[13] In other words, a change in the manufacturer of an LT4 preparation should be managed as any other dose modifications with appropriate laboratory monitoring of thyroid function six weeks later and dosage adjustment as necessary.
The FDA however does not agree. It still hosts the following statement from 1997 on its website. David G. Orloff, MD, the then Director, Division of Metabolic and Endocrine Drug Products, stated, “... the ‘risks’ of alterations in thyroid balance associated with switching LT4 brands (based on FDA designations) are no different than the ‘risks’ of refilling a prescription of the same brand.” He went on to say that there is no scientific evidence of risk or harm. He makes the following arguments:\[14\]:

- Pharmacists’ substitution is not evidence of risk
- Patients may not know it is not evidence of risk
- Patients may not have had their TSH checked in temporal relation to such a switch is not evidence of risk
- Anecdotes of changes in thyroid status after a switch are not evidence of risk
- No formal studies of differences in “efficacy” within vs across products have been conducted

Yet another controversy is the role of T3 in replacement therapy. There has been increased interest in the role of combination therapy of T3 plus T4 since the publication of a small five-week study in the *New England Journal of Medicine*.\[15\] The study found significantly improved mood with the addition of T3. A subsequent meta-analysis of more than 1,200 patients randomized to LT4 monotherapy or combination therapy with T3 showed no difference in body pain, depression, anxiety, fatigue, quality of life, body weight, or lipids.\[16\] There is just not enough evidence to know which patients with hypothyroidism, if any, would be better treated with a combination of T4 plus T3 rather than with T4 alone.

These are the same issues associated with the use of desiccated thyroid (a mixture of T3 and T4 made from porcine thyroid glands), which is not considered the standard of care for therapy. Synthetic T4 alone is the recommended therapy by the AACE.\[17\] T3 levels may fluctuate widely and T4 levels may remain low, so it is critical for those few patients who insist on a natural product that the TSH and not the T4 be used for monitoring therapy. There are, however, clinicians who continue to prescribe and confirm the safety and efficacy of naturally desiccated thyroid (NDT). The clinicians state that the desiccated thyroid drugs are MORE stable and reliable and vary less in strength from batch to batch than the synthetic ones. They are far closer in range than Synthroid or levothyroxine, and NDT contains a full spectrum of thyroid hormones: T4, T3, and also T2 and T1.\[18\] In addition, the synthetic formula lacks calcitonin which is present in natural thyroid and usually lacking in patients after total thyroidectomy, which removes the parathyroid glands.

Thyroid hormone is highly protein bound so anything that changes the amount of binding hormones and drugs that compete for binding may change the amount of available free thyroid hormone. The thyroid replacement dosage must be changed in response to alterations in binding status.

High estrogen states such as pregnancy (dealt with in the next section), oral contraceptive use, or postmenopausal estrogen replacement causes an increase in serum binding proteins, so the dose of
LT4 must be increased. In contrast, low androgens, nephrosis, protein-losing enteropathies, cirrhosis, and even simple aging may decrease levels of thyroid binding proteins, and so require a reduced dose.[19]

The list of medications that require monitoring of thyroid function is extensive and the mechanism of actions is variable. A partial list of well-studied common drugs includes the following:

- Iodine and iodide-containing drugs such as radiographic contrast (may cause both hypothyroidism and hyperthyroidism weeks later)
- Lithium (therapeutic levels cause thyroid enlargement in half the patients and hypothyroidism in 20%, may also cause hyperthyroidism)
- Oral tyrosine kinase inhibitors (blocks clearance)
- Proton pump inhibitors
- Concomitant use of calcium carbonate and of bile acid sequestrants (interfere with absorption)
- Most selective estrogen receptor modulators (SERMs), anabolic steroids, and glucocorticoids (decrease protein binding so dose may need to be reduced)
- Amiodarone (can cause both hypothyroidism and hyperthyroidism by different mechanisms)
- Phenobarbital, rifampin, phenytoin, and carbamazepine (increase the metabolism of T4 and T3 so patients on T4 supplementation may need higher dosages)
- Beta adrenergic antagonists including high-dose propranolol (inhibit T3 production)
- Some nonsteroidal anti-inflammatory drugs (NSAIDs) including salicylates, and heparin, and furosemide (decrease T4 binding) and dopamine (suppresses TSH)[20]

When adding or subtracting any new medication for a patient on thyroid replacement it is always a good practice to check for any known interactions and monitor accordingly.

Finally, while there may be a difference between the pricing of generic and branded LT4, the small cost difference may be something some patients are willing to put up with in order to avoid the controversy of dose fluctuations and the need for more frequent follow-up.

The treatment of hyperthyroidism and other thyroid conditions is beyond the scope of this review.
Pregnancy

Case Study: Carol/Sarah
Carol says her 23-year-old daughter Sarah is trying to get pregnant and asks your advice about screening her for thyroid disease. You tell her that

A. It is recommended that all women be screened for low thyroid in the first trimester and her daughter is no exception

B. It is recommended that all women be screened for low thyroid before conception and her daughter is no exception

C. Because she has a family history of thyroid disease, she should be screened

D. Thyroid function tests are unreliable in pregnancy and if she is not screened before conception, she should wait until postpartum to be tested

E. Screening is not indicated in the absence of any suggestive symptoms

Risks
Avoiding maternal and fetal hypothyroidism is critical because of the potential damage to fetal neural development. The mother with uncontrolled hypothyroidism is at higher risk for anemia, myopathy, congestive heart failure, preeclampsia, placental abnormalities, low birth weight infants, and postpartum hemorrhage.

Fetal tachycardia, fetal hyperthyroidism, small for gestational-age babies, prematurity, preeclampsia, and stillbirths may accompany maternal thyrotoxicosis.[21,22]

Physiology
The effects of pregnancy on the thyroid gland and thyroid function are profound. Thyroid size increases approximately 10% to 15% during pregnancy in patients who live in countries where there is adequate intake of iodine and by 20% to 40% in areas where there is iodine deficiency. T4 and T3 production increases by 50%. The daily iodine requirement goes up by 50% due to the increased T4 production and the increased renal clearance. The serum thyrotropin drops the most in the first trimester under the impact of placental human chorionic gonadotropin (hCG), which itself has a weak thyrotropic effect.

Putting all these together explains why it might help to view pregnancy as a thyroid stress test.

Screening
While universal screening of pregnant woman is temptingly simple, according to the Clinical Guidelines Subcommittee of The Endocrine Society, there is insufficient data to make the recommendation.[23]
Instead, there are suggested indicators for targeted thyroid case finding in pregnancy, where the incidence of clinical hypothyroid disease is high and benefit of therapy is clear. There are also conditions that screening may be considered since the incidence might be enough but no known benefit of treatment has yet been determined (Table 4).

### Table 4. Screening for Thyroid Disease\(^{[23]}\)

<table>
<thead>
<tr>
<th>Suggested indicators for targeted thyroid case finding in pregnancy, where the incidence of clinical hypothyroid disease is high and benefit of therapy is clear, women with:</th>
<th>The following conditions screening may be considered since the incidence might be high enough but no known benefit of treatment has yet been determined:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A history of hyperthyroid or hypothyroid disease, postpartum thyroiditis, or thyroid lobectomy</td>
<td>• A prior history of preterm delivery</td>
</tr>
<tr>
<td>• A family history of thyroid disease</td>
<td>• Infertility should have screening with TSH as part of their infertility work-up</td>
</tr>
<tr>
<td>• A goiter</td>
<td>• Prior therapeutic head or neck irradiation</td>
</tr>
<tr>
<td>• Thyroid antibodies (when known)</td>
<td>• Other autoimmune disorders</td>
</tr>
<tr>
<td>• Symptoms or clinical signs suggestive of thyroid under function</td>
<td>• Women with recurrent pregnancy loss</td>
</tr>
</tbody>
</table>

When indicated, screening should begin with checking a TSH level using a gestational age-dependent standard (see below) preferably performed before conception.

**Laboratory Findings**

As mentioned, your laboratory should provide pregnancy and, preferably, trimester specific ranges of normal for all thyroid tests. If your laboratory does not provide trimester specific normals, the following levels for TSH mU/L can be used\(^{[24]}\):

- First trimester 0.1 to 2.5
- Second trimester 0.2 to 3.0
- Third trimester 0.3 to 3.0

Generally because thyroid binding globulin (TBG) is higher, the total T4 may also be higher because the total T4 reflects the increased protein binding in pregnancy.\(^{[25,26]}\) The FT4 however is more likely to be normal; although, some studies suggest an increase or even decrease.\(^{[27-29]}\)
The way FT4 is measured is important and must be considered in management. The high level of TBG renders many methods of testing for FT4 unreliable in pregnancy. The preferred procedure in calculating serum FT4 during pregnancy is measurement of T4 in the dialysate or ultrafiltrate of serum samples employing online extraction/liquid chromatography/tandem mass spectrometry, but this is expensive and not always available. If your laboratory uses another method of measuring FT4, then the recommendation is to rely on the serum TSH as a more accurate indication of thyroid status in pregnancy.[30]

**Treatment**

Strong consideration should be given to having the patient consult with an endocrinologist experienced in managing thyroid disorders in pregnancy.

Historically, propylthiouracil (PTU) has been the drug of choice to treat hyperthyroidism in pregnancy. Although the drug is category D in pregnancy (positive evidence of human fetal risk),[31] the evidence of it being a teratogen is unclear, and the ATA states that the benefits of treatment outweigh the risks.[32] The lowest possible effective dose should be used.

The following treatment recommendations for hypothyroidism are taken directly from The Thyroid Dysfunction during Pregnancy and Postpartum Guideline Task Force (Table 5).[23]
Table 5. Hypothyroidism Treatment Recommendations

- 1.1.1. Both maternal and fetal hypothyroidism are known to have serious adverse effects on the fetus. Therefore maternal hypothyroidism should be avoided.
- 1.1.2. If hypothyroidism has been diagnosed before pregnancy, we recommend adjustment of the preconception thyroxine dose to reach a TSH level not higher than 2.5 μU/mL prior to pregnancy.
- 1.1.3. The T4 dose usually needs to be incremented by 4-6 wk gestation and may require a 30%-50% increase in dosage.
- 1.1.4. If overt hypothyroidism is diagnosed during pregnancy, thyroid function tests (TFTs) should be normalized as rapidly as possible. Thyroxine dosage should be titrated to rapidly reach and thereafter maintain serum TSH concentrations of less than 2.5 μU/mL in the first trimester (or 3 μU/mL in the second and third trimester) or to trimester-specific normal TSH ranges. Thyroid function tests should be remeasured within 30-40 days.
- 1.1.5. Women with thyroid autoimmunity who are euthyroid in the early stages of pregnancy are at risk of developing hypothyroidism and should be monitored for TSH elevation above the normal range.
- 1.1.6. Subclinical hypothyroidism (serum TSH concentration above the upper limit of the reference range with a normal free T4) has been shown to be associated with an adverse outcome for both the mother and offspring. T4 treatment has been shown to improve obstetrical outcome but has not been proved to modify long-term neurological development in the offspring. However, given that the potential benefits outweigh the potential risks, the panel recommends T4 replacement in women with subclinical hypothyroidism.
- Women in the childbearing age should have an average iodine intake of 150 μg per day. During pregnancy and breastfeeding, women should increase their daily iodine intake to 250 μg on average.

Summary

Thyroid disease may present in subtle ways and demand nuanced diagnosis and management, especially in pregnancy. By understanding the basic underlying physiology and pharmacology, providers can sort out the complexity, manage the controversies, and make the best choices for their patients.
References

4. McDermott MT, Ridgway EC. Subclinical hypothyroidism is mild thyroid failure and should be treated. *J Clin Endocrinol Metab.* 2001;86(10):4585-4590.


