The Subtleties and Controversies of Thyroid Disease Management

Brian Koffman, MDCM, DCFP, DABFM, MS Ed
Chief Medical Officer, CLL Society (CLLSociety.org)
Retired Clinical Professor
Department of Family Medicine
Keck School of Medicine, USC Family Practice
Learning Objectives

▪ Recognize the common and less common signs, symptoms and associated conditions of thyroid disorders, both clinical and subclinical, and have a low index of suspicion for patient work-up

▪ Prescribe and monitor thyroid replacement therapy according to relevant guidelines

▪ Identify pregnant women at high risk of thyroid dysfunction who would benefit from screening and indicated treatment
Savannah Smith: 1st Visit for WWE

- Savannah Smith
  - 54-year-old female presents for annual well woman exam (WWE)
  - Your medical assistant advises you to be prepared for multiple concerns
    - Fatigue
    - Dry skin
    - Hair loss
    - Constipation
    - Weight gain
    - Heat intolerance
    - Numbness and tingling in both hands
Physiology
Thyroid System

Hypothalamus

- Thyrotropin-releasing hormone (TRH)
- Thyroid-stimulating hormone (TSH)

Anterior pituitary gland

Negative feedback

Thyroid gland

Thyroid hormones (T3 and T4)

- Increased metabolism
- Growth and development
- Increased catecholamine effect
Definitions and Diagnosis
Definitions and Diagnosis Underactive

- **Hypothyroidism**
  - Primary: high serum thyrotropin (TSH) and a low serum free thyroxine (FT4)
  - Secondary and Tertiary (central): low FT4 and TSH not elevated

- **Subclinical Hypothyroidism**
  - Only an elevated TSH with a normal FT4 level

- Both overt and subclinical disease can be symptomatic

Definitions and Diagnosis Overactive

- Hyperthyroidism
  - Usually excess production of free thyroid hormones (either T3 or T4 or both) in serum with suppressed HS-TSH or highly sensitive (3rd generation) TSH (<0.01mU/L)
  - Most patients with Graves or a nodular goiter have higher increases in T3 than T4
  - TSH induced hyperthyroidism with high or normal TSH is very rare, usually from a pituitary adenoma or resistance to feedback of T3 and T4

- Thyrotoxicosis includes hyperthyroidism but also excess release of hormone in thyroiditis or excess exogenous T4

- Subclinical Hyperthyroidism (SH)
  - Low or undetectable (HS-TSH) but normal range for both triiodothyronine (T3) and free thyroxine (FT4)

- Both overt and sub-clinical disease may lead to characteristic signs and symptoms

Prevalence
Prevalence

NHANES III: 13,344 people (54% female) without known thyroid disease had TSH, T4, thyroglobulin antibodies, and thyroid peroxidase antibodies measured

- Hypothyroidism in 4.6% (0.3% overt and 4.3% subclinical)
- Hyperthyroidism was found in 1.3% (0.5% overt and 0.7% subclinical)
- Serum thyroid peroxidase antibody concentrations elevated in 11%

Higher Prevalence in 70-79 Years Old

<table>
<thead>
<tr>
<th>Hyperthyroidism and Hypothyroidism Study Results</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Black women</td>
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<tr>
<td>White women</td>
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<tr>
<td>Black men</td>
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<tr>
<td>White men</td>
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- 3 to 8 times more common in women than men
- Mean TSH is lower in blacks than whites or Hispanics
- Mean TSH rises as we age

Etiology
Etiology of Hypothyroidism

- Hashimoto’s Thyroiditis (Chronic Lymphocytic Thyroiditis)
  - Most common in the USA
  - Historic Note: 1st discovered Auto-Immune Disorder
  - Diagnosed with antithyroid peroxidase (antiTPO) antibodies or antimicrosomal antibodies (AMA)

- Post Treatment Graves’ Disease
  - No function after radiation or surgery

- Iodine Deficiency
  - Most common worldwide associated with a goiter
  - Rare in North America but ? re-emergence with “natural” salt

- Hypothalamic-pituitary Disease (secondary or central)

Etiology of Hyperthyroidism

- **Graves’ Disease**
  - Most common
  - Auto-immune: long-acting thyroid stimulating antibodies (LATS)

- **Thyroid Nodules**
  - “Toxic” nodules (become autonomous)
  - Benign or malignant, single or multiple
  - Toxic nodular goiter - most common cause in the elderly

Etiology of Hyperthyroidism

- Excessive Thyroid Supplementation
  - Iatrogenic
  - Exogenous
- Thyroiditis (excessive release, not production)
  - Early Hashimoto’s, radiation, palpation, post partum
- Rare Causes: pituitary adenoma, teratomas

Etiology of Subclinical Hyperthyroidism Exogenous

- 10,000,000 Americans and 200,000,000 worldwide take thyroid hormone
- All are at risk for subclinical hyperthyroidism, whether intentional or unintentional
- In patients on LT4 (levothyroxine), up to 25% may have low TSH
  - Associated with lower bone density
  - Associated with atrial fibrillation
- BUT subclinical hyperthyroidism is the goal of thyroid hormone therapy in thyroid cancer, in some thyroid nodules, multinodular or diffuse goiters, or a history of head and neck irradiation
Symptoms
### Hypothyroidism Symptoms

<table>
<thead>
<tr>
<th>Hypothyroidism and Subclinical Hypothyroidism Signs &amp; Symptoms</th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>Memory and mental impairment</td>
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<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</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</td>
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<tr>
<td>Reflex delay, relaxation phase</td>
<td>Bradycardia and hypothermia</td>
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<tr>
<td>Ataxia</td>
<td>Myxedema fluid infiltration of tissues</td>
</tr>
<tr>
<td>Constipation</td>
<td>Carpal Tunnel Syndrome</td>
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</tbody>
</table>
Sir William Osler

The Model for Sherlock Holmes?

“Listen to the patient. They are telling you the diagnosis.”

- Walked into the muggy ward when the yet to be examined new patient was not in her bed
- Asked the students “Where is the hypothyroid patient?”
- How did he diagnose the unseen, unmet patient?
Sir William Osler

The Model for Sherlock Holmes?

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- Walked into the muggy ward when the yet to be examined new patient was not in her bed
- Asked the students “Where is the hypothyroid patient?”
- How did he diagnose the unseen, unmet patient?
  - Extra blankets
  - Bed undisturbed
  - Hair loss and flaked skin on the pillows
  - Clothes suggesting obesity

ELEMENTARY, MY DEAR WATSON
# Hyperthyroid Symptoms

<table>
<thead>
<tr>
<th>Overt Hyperthyroidism and Subclinical Hyperthyroidism Signs &amp; Symptoms</th>
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<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>
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<tr>
<td>Heat intolerance or increased sweating</td>
<td>Impaired fertility</td>
</tr>
<tr>
<td>Tremor and proximal muscle weakness</td>
<td>Mental disturbances (anxiety)</td>
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<tr>
<td>Weight loss</td>
<td>Sleep disturbances (including insomnia)</td>
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<tr>
<td>Alterations in appetite</td>
<td>Changes in vision, photophobia, eye irritation, diplopia, or exophthalmos (with Graves’ disease), lid lag, “stare”</td>
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<tr>
<td>Frequent bowel movements or diarrhea</td>
<td>“Apathetic thyrotoxicosis” with asthenia</td>
</tr>
<tr>
<td>Dependent lower extremity edema</td>
<td>Thyroid enlargement (depending on cause)</td>
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<tr>
<td>Sudden paralysis</td>
<td>Pretibial myxedema (in patients with Graves’ disease)</td>
</tr>
<tr>
<td>Bone loss and increased fracture risk</td>
<td>Atrial fibrillation (w/u new onset AF for thyroid disease)</td>
</tr>
</tbody>
</table>
Work-Up
Hypothyroidism Work-Up

- History
  - Radiation and Surgery
  - Infections
    - TB, Pneumocystis carinii
  - Infiltrative Disease
    - Riedel's, leukemia, scleroderma, hemochromatosis
  - Meds
    - Lithium
    - Prednisone
    - Metformin
    - Androgens and Anabolic Steroids
    - Heparin
    - Tyrosine Kinase Inhibitors
    - Interferon, Interleukin
    - Amiodarone (3 mg iodine per 100 mg)
Hypothyroidism Work-Up

- Physical
  - +/- Goiter
  - Slowed movement and speech
  - Hoarse voice
  - Bradycardia
  - Carotenemia
  - Hung deep tendon reflex
  - Coarse skin
  - Puffy eyes and faces
  - Enlarged tongue
  - Galactorrhea
  - Diastolic Hypertension
Hypothyroidism Work-Up

- **Lab**
  - TSH, FT4
  - No need to check thyroid antibodies
  - CBC, CMP, lipids

- **Imaging**
  - No need for thyroid imaging unless abnormal palpations or pain
  - No need of pituitary MRI unless signs of central hypothyroidism (<1%)
Savannah: Follow-up Visit 1 Week Later

- Savannah returns after WWE and lab work is back
  - VS: Hgt: 5’4” Wgt: 157 lbs BMI: 26.95 (overweight)
  - T 97.6, BP 130/92, P 60
  - Normal exam except bilateral Tinel’s at wrists (no goiter, eye changes, edema or hung reflexes)
  - ECG, cardiac stress test, mammography, colonoscopy, all WNL

- LAB
  - CBC, CMP, UA all WNL
  - Lipids: LDL cholesterol: 135, otherwise OK
  - TSH: 8.8 (N = 0.5 to 5), FT4: 0.9 (N = 0.7 to 2)

WNL, within normal limits
Hyperthyroid Work-Up

- **History**
  - Thyroiditis including trauma
  - Meds
    - Amiodarone
    - Iodine

- **Physical**
  - Hyperactivity and rapid speech
  - Stare (lid retraction) and lid lag
  - Sweaty
  - Fine hair
  - Tachycardia and Atrial Fibrillation
  - Hypertension
  - Hyperreflexia
  - Muscle weakness
  - Tremor

- **Thyroid**
  - Size, nodularity, tenderness
Hyperthyroidism Work-Up

- **Lab**
  - 3rd generation TSH (<0.05 mU/L)
  - T4 (RIA), FT4, T3 (RIA), FT3
  - CBC, CMP

- **Biotin**
  - 5-10 mg/d can give false ↓TSH and ↑T3, T4

- **Imaging (only if dx is uncertain)**
  - Radioiodine uptake and scan
    - If high, increased production such as Graves’ or nodule(s)
    - If low, thyroiditis or source is outside of thyroid (struma ovarii or exogenous)

Radioiodine Scan

Treatment
Savannah: Follow-up Visit 10 Months Later

- Little change in symptoms or TSH at 6 weeks
- LT4 increased to 0.125 to get TSH down <5.0
- Feeling better with TSH of 3.2 at 6 month recheck
- Lab and prescription unchanged
- Returns early for her annual check complaining of recently feeling less energetic
Controversy
Hypothyroidism and Subclinical Hypothyroidism

- Decision to treat subclinical disease is controversial and should be individualized
  - Recommended if TSH >10 or patient is symptomatic
  - Lower risk of cardiovascular outcomes
  - Individual decision when no symptoms of TSH only slightly elevated
  - 2-4% a year progress to clinical disease without treatment
  - No apparent benefits in >65 yrs old with subclinical hypothyroidism

- Levothyroxine (LT4) is the recommended replacement
- Average replacement dose is 112 mcg/daily or 1.6 mcg/Kg/day

1. Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism  D.J. Stott et al, N Engl J Med 2017;376:2534-44.
Special Cases and Considerations
Hypothyroidism and Subclinical Hypothyroidism

- In some older patients and those with CAD start at 25 or 50 mcg as T4 increases myocardial $O_2$ demands and risk of angina and arrhythmia
- Take on empty stomach (ideally 1 hour before breakfast)
- Coffee, antacids, and calcium interfere with absorption

CAD, coronary artery disease
Hypothyroidism and Subclinical Hypothyroidism

- Patients may feel better as soon as two weeks, but it can take months
- Changes are often incremental, not dramatic
- Takes 6 weeks to see blood levels change
- FT4 rises first, TSH is slower to fall
- Recheck FT4 and TSH at 6 weeks
- If still sub-therapeutic, increase by 12.5 or 25 mcg, and recheck in 6 weeks
- Once stable, check every 6 months for first year, then annually
Controversy
Bioavailability, Bioequivalence, Therapeutic Equivalence

The American Association of Clinical Endocrinologists (AACE)
- Advocates the use of a single consistent branded LT4
- Need to measure Area Under Curve (AUC) and maximum concentration (Cmax) in thyroid patients to equate
- Need to measure TSH to equate
- Bioavailability ≠ bioequivalence ≠ therapeutic equivalence
- Up to 25% variation found between products, but change from 125 mcg and 137 mcg is only 9%
- At minimum need to measure thyroid function at 6 weeks if brand changed (same as if dose changed)

US Food and Drug Administration (FDA)
- Does not see any risk with brand switching
- Uses AUC and Cmax determinations in normal subjects with normal thyroid function for bioavailability
- Bases approval of all generics and the 5 branded LT4 on only total level of T4 but not TSH
- Accepts formulations that deviate from each other by < 25% but > 12.5% as equivalent

Controversy
T3 and “Natural” Therapy

Arguments PRO and CON for T3 Supplementation

- The thyroid produces both T3 and T4
- LT4 therapy has no T3
- Patients on T4 alone have higher than normal T4/T3 ratios
- Peripheral conversion of T4 to T3 may be inadequate in some patients → tissues have deficient T3 level
- So is T4 monotherapy = “Tissue hypothyroidism”
- BUT T3 has short half life, may need extended release
- Data do not support the use of T3 or dessicated thyroid
Controversy
T3 and “Natural” Therapy

- N Eng J Med 1999
  - Mood better with T3: 7 of 8 tests P<0.04
  - No difference in:
    - Neuropsychological tests
    - BP and serum lipids

- Eur J Endocrinol 2009
  - 49% preferred combination of T4 and T3 and 15% T3 alone, 36% had no preference
  - BUT: Meta-analysis of >1,200 patients randomized to LT4 monotherapy or combination therapy with T3 showed no difference in body pain, depression, lipids, anxiety, fatigue, quality of life, body weight

Controversy

T3 and “Natural” Therapy

- 1891: Dr. George Murray 1st used sheep thyroid extract to successfully treat his patient with myxedema for 28 years
- Same issues with naturally desiccated thyroid or NDT (a mixture of T3 and T4 made from porcine or beef thyroid glands) as there are with T3
- Must use TSH for monitoring
- NDT contains all thyroid hormones: T4, T3, T2, and T1 and calcitonin which is present in natural thyroid
- Synthetic T4 alone is the recommended therapy by AACE daily dose of 100 μg of LT4 = biologic activity to 101 mg of NDT

Protein Binding

- Thyroid hormone is highly protein bound so changes in the amount of binding protein and drugs that compete for binding change the amount of available active free thyroid hormone.

- The thyroid replacement dosage must be changed in response to alterations in binding status.

- **HIGH BINDING**: High estrogen states (pregnancy, oral contraceptive use, or postmenopausal estrogen replacement), so the dose of LT4 must be increased.

- **LOW BINDING**: Low androgens, nephrosis, protein-losing enteropathies, cirrhosis, and aging may decrease levels of thyroid binding proteins, and so require a reduced dose.
Drug Interactions
Multiple Complex Mechanisms of Actions

- 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%, but may also cause hyperthyroidism)
- Oral tyrosine kinase inhibitors (blocks clearance)
- Proton pump inhibitors
- Concomitant use of calcium, iron, and bile acid sequestrants (interfere with absorption)
Drug Interactions
Multiple Complex Mechanisms of Actions

- Selective estrogen receptor modulators (SERMs), anabolic steroids, and glucocorticoids (decrease protein binding so dose may need to be reduced)
- Amiodarone (multiple causes for both hypothyroidism and hyperthyroidism)
- Phenobarbital, rifampin, phenytoin, and carbamazepine (increase the metabolism of both T4 and T3 so patients on T4 supplementation may need higher dosages)
- Beta adrenergic antagonists including high-dose propranolol (inhibit T3 production)
- NSAIDs including salicylates, heparin, and furosemide (decrease T4 binding)
- Dopamine (suppresses TSH)
Graves’ Disease Treatment
2 Step Process

- >95% satisfaction with all three therapy choices but relapse risk higher with medication
- **1st STEP:** Rapid amelioration of symptoms with a beta-blocker
  - Palpitations, tachycardia, anxiety, tremor, heat intolerances
- **2nd STEP:** Decreasing thyroid hormone synthesis
  1. Thionamide
    - Methimazole (preferred)
    - Propylthiouracil (PTU) avoid due to **Black Box:** hepatoxicity
    - Inhibit the enzyme thyroid peroxidase
  2. Radioiodine ablation
    - 60% of endocrinologists prefer to treat with a capsule of I131 in the USA
    - 6-18 weeks to work, worsening of Graves' ophthalmopathy, 21% relapse
  3. Surgery
    - 1% use, lowest relapse (6%) surgical risk (recurrent laryngeal nerve injury)
    - Obstructive goiter or suspicious nodule, ophthalmopathy, contraindications to meds or radioiodine

- 3-8 weeks to work, often a step before permanent ablation, but may be well tolerated long term – 37% relapse after discontinuation
In 1866, Samuel David Gross said, "If a surgeon should be so foolhardy as to undertake it [thyroidectomy] ... every step of the way will be environed with difficulty, every stroke of his knife will be followed by a torrent of blood, and lucky will it be for him if his victim lives long enough to enable him to finish his horrid butchery."
Controversy
Subclinical Hyperthyroidism Treatment

- Treat if high risk patient
  - > 65-years-old
  - Heart disease (heart function and rate varies with TSH even in normal range)
  - Osteoporosis
- Treat low risk if TSH value is <0.1 mU/mL
- Same treatment options as in Graves’

Prevalence of Thyroid Nodules and Cancer

- 2.4-fold increase between 1973 and 2002 in thyroid cancer with >50% found in nodules < 2cm
- Palpable nodules in 10% of women and 2% of men
- With US (ultrasound) 50% of all of us have at least 1 nodule
- 20% to 48% of patients with one palpable nodule have multinodular changes on US
- 4%-6.5% are cancerous of which 80% well differentiated that usually has a benign course
- Non palpable, multiple and incidentalomas have the same risk

American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS et al Thyroid. 2009;19(11):1167.
Primary Care Work-up of Thyroid Nodules

- **WU:** Hx, Px, TSH, US, then FNA (fine needle aspirate for cytology)
- **Hx, Px, US** determine who gets a FNA; FNA who gets surgery
- **High risk Hx, Px** and US findings suggesting the need for FNA
  - **Hx:** Male, Age <20 or >60?, FH of thyroid cancer, Hx of any cancer or local radiation
  - **Px:** hard, fixed, or rapidly growing, cervical nodes, vocal palsy, >4cm
  - **US:** Suspicious findings more important than size: microcalcifications, hypoechoic, increased nodular vascularity, solid, irregular margins
    - Most spongiform and purely cystic nodules (no mural component) do not need a biopsy
  - **TSH:** if low and no high risk findings, and scan shows “hot”, nodule, no need for FNA
  - **TSH:** if high, increased risk of thyroid cancer
- **FNA:** Sensitivity 83% Specificity 92% PPV 75% False - 5% False + 5%

American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS et al Thyroid. 2009;19(11):1167.
Pregnancy
Pregnancy

- Maternal and fetal hypothyroidism associated with risks to fetal neural development

- Maternal hypothyroidism at increased risk for anemia, myopathy, congestive heart failure, preeclampsia, placental abnormalities, low birth weight infants, and postpartum hemorrhage

- Maternal thyrotoxicosis is associated with fetal tachycardia, fetal hyperthyroidism, small for gestational-age babies, prematurity, preeclampsia, and stillbirths

Pregnancy is a “Thyroid Stress Test”

- Thyroid size increases 10% to 15% during pregnancy in patients who live in countries with adequate iodine and by 20% to 40% where there is an iodine deficiency
- T4 and T3 production increases by 50%
- The daily iodine requirement goes up by 50% due to > T4 production and > renal clearance
- WHO recommends 250 mcg of iodine daily
- TSH drops the most in the first trimester under the impact of placental human chorionic gonadotropin (hCG), which itself has a weak thyrotropic effect → possible transient hyperthyroidism
- Thyroid Binding Globulin (TBG) increases

Controversy Screening

- American Thyroid Association, American College of Obstetricians and Gynecologists, and The Endocrine Society all recommend targeted rather than universal screening
- BUT may miss 1/3 pregnancy with hypothyroidism

**Screening for Thyroid Disease**

*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:*

<table>
<thead>
<tr>
<th>Suggested Indicators</th>
<th>Other Indicators</th>
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<tbody>
<tr>
<td>A history of hyperthyroid or hypothyroid disease, postpartum thyroiditis, or thyroid lobectomy</td>
<td>Type 1 diabetes</td>
</tr>
<tr>
<td>A family history of thyroid disease</td>
<td>Other autoimmune disorders</td>
</tr>
<tr>
<td>A goiter</td>
<td>Infertility should have screening with TSH as part of their infertility work-up</td>
</tr>
<tr>
<td>Thyroid antibodies (when known)</td>
<td>Prior therapeutic head or neck irradiation</td>
</tr>
<tr>
<td>Symptoms or clinical signs suggestive of thyroid under function</td>
<td>A prior history of preterm delivery</td>
</tr>
</tbody>
</table>

*The following conditions screening may be considered since the incidence might be high enough but no known benefit of treatment has yet been determined:*

- Women in whom the last delivery was preterm
- Women with recurrent pregnancy loss

Abalovich M, et al. *J Clin Endocrinol Metab.* 2007;92(8 Suppl);S1-S47.
Lab Findings

- Lab should provide pregnancy and trimester specific ranges of all thyroid tests
- If not provided, then for TSH use
  1. First trimester 0.1 to 2.5
  2. Second trimester 0.2 to 3.0
  3. Third trimester 0.3 to 3.0
- TBG is higher so total T4 is higher as total T4 reflects the increased protein binding in pregnancy
- FT4 however is more likely to be normal but can be technically difficult to accurately measure

Controversy
Management Consult an Experienced Endocrinologist

- Hyperthyroidism
  - hCG-mediated hyperthyroidism is usually transient and does not require treatment
  - Methimazole is preferred to PTU except during the first trimester of pregnancy. Methimazole is more teratogenic
  - Surgery if thionamide is contraindicated

- Hypothyroidism
  - New guidelines suggest rapid dose escalation in pregnancy to avoid prolonged fetal exposure to underactive thyroid levels

PTU, propylthiouracil
Controversy
Management Consult an Experienced Endocrinologist

- Subclinical Hypothyroidism
  - Lower pregnancy risk than with overt disease
  - RX with LT4 may improve baby's neuro development
  - The Thyroid Dysfunction during Pregnancy and Postpartum Guideline Task Force recommends treatment

- Elevated antithyroid peroxidase antibody (TPO antibodies) in euthyroid pregnant patients
  - Increased risk of fetal loss, perinatal mortality, and large-for-gestational-age
  - High risk to become hypothyroid, so need monitoring
  - LT4 may lower miscarriage rates
  - ATA does not recommend for or against treatment
### 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 $\mu U/mL$ 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 $\mu U/mL$ in the first trimester (or 3 $\mu U/mL$ 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 $\mu g$ per day. During pregnancy and breastfeeding, women should increase their daily iodine intake to 250 $\mu g$ on average.

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Abalovich M, et al. *J Clin Endocrinol Metab.* 2007;92(8 Suppl);S1-S47.
Best Practices Pearls

▪ Have a low threshold to test for thyroid disease
▪ Treatment of both subclinical and overt disease should be individualized and monitored
▪ Manage issues around variable therapeutic equivalence of levothyroxine products
▪ Appropriately counsel, screen, and monitor thyroid function in pregnancy to improve outcomes