Session 5: Thyroid Disorders: From the Obvious to the Obscure

Learning Objectives

1. Describe the spectrum of the signs and symptoms of thyroid disease - from subclinical hypothyroidism to life-threatening thyrotoxicosis.
2. Understand the diagnostic and management considerations for special patient populations commonly seen in primary care practice.
Session 5

Thyroid Disorders: From the Obvious to the Obscure

Faculty

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Dr. Carl Malchoff is an endocrinologist and professor of medicine at the University of Connecticut Health Center. He is the director of the endocrine neoplasia program within the Neag Comprehensive Cancer Center and director of the diabetes education program.

Dr. Malchoff received his PhD and MD from the University of Rochester, New York, in 1978. He received his residency training in internal medicine and fellowship training in both endocrinology and metabolism at the University of Virginia, Charlottesville.

He has published over 45 peer reviewed manuscripts and over 35 invited reviews. He has a general interest in the molecular pathogenesis of tumors of the thyroid, adrenal, and pituitary glands. Specific research interests include familial papillary thyroid carcinoma, autoimmunity in thyroid cancer, and primary aldosteronism.

He is an active member of the Endocrine Society, American Association of Clinical Endocrinologists, and the American Thyroid Association.

Faculty Financial Disclosure Statement
The presenting faculty reports the following:

Dr. Malchoff has no financial relationships to disclose.
Session 5:
3:00 PM - 4:00 PM
Thyroid Disorders:
From the Obvious to the Obscure
Carl D. Malchoff, MD

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Demographic Question
How many patients with thyroid disorders (hyper- or hypothyroid) do you see each week?
1. None
2. 1 - 5
3. 6 - 15
4. 16 - 25
5. Over 25

Outcomes Question #1
A 52-year-old man comes in for evaluation of worsening palpitations over the past 2 months.
A thyroid panel reveals ↓ TSH, ↑ FT4, ↑ T3
What is his likely diagnosis ?
1. Hypothyroidism
2. Overt thyrotoxicosis
3. Subclinical hyperthyroidism
4. Thyroid cancer

Outcomes Question #2
Your patient has recently been diagnosed with Graves’ disease and begun on therapy with methimazole (MMU). She calls to announce that she is 6 weeks pregnant and is experiencing some heat intolerance and palpitations.
TFTs: serum TSH=0.1 uIU/ml (0.4-4.2 uIU/mL); FT4 =2.2 ng/dL(0.8-1.8 ng/dL)
What would be an appropriate next step ?
1. Start thyroid hormone therapy to keep the fetus euthyroid
2. Stop MMI and start propylthiouracil (PTU) therapy
3. Increase the MMI dose targeting a normal range serum TSH
4. Stop MMI and monitor for symptoms
Outcomes Question #3

Which of the following is TRUE regarding hypothyroidism?

1. Patients usually present with specific symptoms
2. Combination T4/T3 is the preferred treatment for most patients
3. Some patients with an elevated TSH may not benefit from thyroid hormone treatment
4. All of the above

Goiters and Nodules

• Goiter: definition: enlargement of the thyroid gland which causes swelling in the neck
  – Endemic goiter: enlargement a response to a lack of iodine
  – Sporadic goiter: hyperplastic or neoplastic overgrowth
  • Toxic nodular goiter: autonomous thyroid hormone production
  • Exophthalmic goiter (Graves’ disease) associated with hyperthyroidism
• Thyroid Nodule: area of different contour or consistency on palpation with differing echotexture on sonographic examination

Thyroid Nodule Prevalence

• By age 30, ~20% of the population has a thyroid nodule (women > men)
  • Likelihood of malignancy is higher in the extremes of age (< 20 years, > 70 years)
  • Lifetime likelihood is ~60%

Thyroid Nodule Laboratory Diagnosis

• TSH
  – Suppressed C/W thyrotoxicosis
    • Malignancy unlikely
  – Elevated C/W hypothyroidism

RADIONUCLIDE SCANNING

Indication:
• Thyroid nodules identification (TSH < normal)
• 99mTc (False +s), 131-I (Rads) or 123-I (Std)

Risk Factors for malignancy: Patient History

• Surgical diagnosis of thyroid cancer in contralateral lobe
• Ionizing Irradiation (XRT) as child/adolescent
• Calcitonin > 100 pg/mL
• PET positive thyroid nodule
• Low dietary iodine intake
• Thyroid cancer in first degree relative

Thyroid Ultrasound

Indication: normal to ↑TSH
• Defines a distinct nodule vs. abnormal parenchyma
• Role to guide FNA (cystic, posterior)
• Nodule selection within a MNG
• Useful in f/u of low risk patient, incidentaloma

• MRI / CT SCANNING
  – Offer little in pre-operative diagnosis
  – Contrast administration may delay Dx &/or Rx


Who Should Be Biopsied?

<table>
<thead>
<tr>
<th>Feature</th>
<th>Size Threshold</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid Nodule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AND hypoechoic</td>
<td>&gt; 1 cm</td>
<td>B</td>
</tr>
<tr>
<td>AND iso- or hyperechoic</td>
<td>≥ 1-1.5 cm</td>
<td>C</td>
</tr>
<tr>
<td>Mixed cystic-solid nodule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WITH suspicious feature</td>
<td>≥ 1.5-2.0 cm</td>
<td>B</td>
</tr>
<tr>
<td>W-OUT suspicious feature</td>
<td>≥ 2.0 cm</td>
<td>C</td>
</tr>
<tr>
<td>Spongiform nodule</td>
<td>≥ 2.0 cm</td>
<td>C</td>
</tr>
<tr>
<td>Purely Cystic nodule</td>
<td>Not indicated</td>
<td>E</td>
</tr>
</tbody>
</table>

B = Recommend fair evidence, C = Recommend expert opinion, E = Recommend against


High Risk Features and Biopsy

<table>
<thead>
<tr>
<th>Feature</th>
<th>Size Threshold</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcalcifications</td>
<td>≥ 1 cm</td>
<td>B</td>
</tr>
<tr>
<td>High-Risk History*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With suspicious feature</td>
<td>&gt; 5 mm</td>
<td>A</td>
</tr>
<tr>
<td>W-OUT suspicious feature</td>
<td>&gt; 5 mm</td>
<td>I</td>
</tr>
<tr>
<td>Abnormal Cervical LN</td>
<td>All</td>
<td>A</td>
</tr>
</tbody>
</table>

* FHx Thy Ca (1°), Hx XRT/Ion Irrad. (child), Surg. Dx Thy Ca, PET pos. nodule, Calcitonin > 100 pg/ml, RET pos., MEN, FMTC

A = Strongly recommend, B = Recommend fair evidence, I = Neither for or against


FNA Malignancy Prediction with Bethesda System

- Category         | Malignant risk | What next?     
- Non-Diagnostic   | 1-4%           | Re-do (U/S)    
- Benign           | 0-3%           | Clinical F/U   
- Atypical         | 5-15%          | Re-do (U/S)    
- Follicular Neoplasm | 15-30%     | Lobectomy      
- Suspect malignancy | 60-75%   | Total Tx       
- Malignant         | 97-99%         | Total Tx       

FNA = fine needle aspiration

Case 2: Next Steps

ECG Results:
Atrial fibrillation with ventricular response of 110 BPM

Lab Results:
- TSH <0.05 (0.4-4.2 mIU/mL)
- FT4 2.1 (0.8-1.8 ng/dL)
- TT3 345 (80-200 ng/dL)

Case 2

- 72-year-old man presents with worsening palpitations over 2 months
- ROS: 14 lb weight loss over last 6 months, recent insomnia
- PE:
  - BP 152/84, Pulse 112 BPM, irregular
  - Eyes: alert stare present
  - Thyroid: Palpable 3.5 cm left nodule, freely movable
  - Cor: Irregularly irregular rhythm, no M/G/R
  - Lungs: bibasilar rales
  - LE: 1+ edema

What additional work-up is needed?

Question

Which of the following is TRUE?

1. All thyroid nodules should be surgically removed
2. A nodule in a patient with a suppressed serum TSH should be biopsied
3. "Hot" nodules are not likely malignant but may necessitate treatment of thyrotoxicosis
4. Thyroid nodules can not occur in the setting of Graves’ disease
Case 2

What is the most likely diagnosis in this patient?

1. Euthyroid with thyroid cancer
2. Thyrotoxicosis due to toxic nodule
3. Hypothyroidism with asymmetric thyroid enlargement
4. Pituitary tumor producing a thyroid stimulator

Clinical Evaluation

- Comprehensive H&P, VS: PR, BP, RR, BMI
- Thyroid: +/- tender, symmetry, nodularity
- Gen PE: Pulmonary, Cardiac, Neurologic
- +/- Edema, eye signs, pretibial myxedema
- Biochemical evaluation:
  - TSH most sensitive and specific (intact pituitary)
  - FT4 and TT3 simultaneously with high suspicion
- Otherwise reflex FT4 and TT3 for suppressed TSH

Determination of Etiology

- Radioactive Iodine uptake (RAIU)
  - Should be performed when the clinical presentation is not diagnostic of Graves’ disease
  - Exception
    - Pregnancy
    - Obvious signs and symptoms of Graves’ disease
- Radioactive iodine thyroid scan
  - Should be added in the presence of thyroid nodularity

RAIU & Differential Diagnosis

<table>
<thead>
<tr>
<th>↓ TSH, nl to ↑ FT4, nl to ↑ TT3</th>
<th>(RAIU/Scan)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves’ disease (TRAb), hCG mediated</td>
<td>↑/ diffuse</td>
</tr>
<tr>
<td>Nodular hyperthyroidism</td>
<td>↑/ nodular</td>
</tr>
<tr>
<td>Iodine induced hyperthyroidism</td>
<td>↓/ no-vis.</td>
</tr>
<tr>
<td>Subacute Thyroiditis (+/- pain, p-partum)</td>
<td>↓/ no-vis.</td>
</tr>
<tr>
<td>Ectopic Thyrotoxicosis (ectopic uptake)</td>
<td>↓/ no-vis.</td>
</tr>
<tr>
<td>Exogenous thyrotoxicosis (↑ thyroglobulin)</td>
<td>↓/ no-vis.</td>
</tr>
<tr>
<td>Normal to elevated TSH, ↑ FT4, ↑ TT3</td>
<td>↑/ diffuse</td>
</tr>
<tr>
<td>Thyroid hormone resistance, TSH pituitary adenoma, heterophilic antibodies to TSH</td>
<td></td>
</tr>
</tbody>
</table>

Management of Hyperthyroidism

- Symptomatic Management:
  - Beta-adrenergic blockade
  - For elderly, resting HR >90, coexistent CV Disease
  - All with symptomatic thyrotoxicosis
- Thyroid storm: Rare life-threatening syndrome of exaggerated clinical manifestations of thyrotoxicosis
  - Antithyroid drugs to decrease TH production
  - Systemic support for hyperthermia and hypovolemia
  - Beta blockers tissue effects of excess circulating TH
  - Identify and treat precipitating illness
- Directed Interventions based on etiology

Thyroid Hormone Regulation

TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone (thyrotropin)
**Who Should be Treated?**

- Overt hyperthyroidism due to Graves’
  - Treatment with any of the following
    - 131-I, antithyroid medication (ATD), thyroidectomy
- Overt hyperthyroidism due to TMNG/ TA
  - Treatment with any of the following
    - 131-I, thyroidectomy, ATD (occasionally)
- Subclinical hyperthyroidism?

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**Subclinical Thyrotoxicosis Rx?**

<table>
<thead>
<tr>
<th>Factor</th>
<th>TSH (&lt;0.1 mUL)</th>
<th>TSH (0.1 – 0.5 mUL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65</td>
<td>Yes</td>
<td>Consider treating</td>
</tr>
<tr>
<td>Age &lt;65 with comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>Yes</td>
<td>Consider treating</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Menopausal</td>
<td>Consider treating</td>
<td>Consider treating</td>
</tr>
<tr>
<td>Hyperthyroid symptoms</td>
<td>Yes</td>
<td>Consider treating</td>
</tr>
<tr>
<td>Age &lt;65, asymptomatic</td>
<td>Consider treating</td>
<td>No</td>
</tr>
</tbody>
</table>

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**Antithyroid Drug Comparison – MMI and PTU**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Methimazole</th>
<th>Propylthiouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacology</td>
<td>Inhibits intra-thyroidal hormone synthesis</td>
<td>Impact on peripheral thyroxine to T3 conversion</td>
</tr>
<tr>
<td>Impact on peripheral thyroxine to T3 conversion</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Indications</td>
<td>Yes</td>
<td>Selectively and in those who are intolerant of methimazole</td>
</tr>
<tr>
<td>Graves’ disease with hyperthyroidism or toxic multinodular goiter for whom surgery or radioactive iodine therapy is not an appropriate treatment option</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Adverse Effects**

- Congenital defects especially in first trimester (category D)
- Agranulocytosis
- Rare reports of liver toxicity in adults
- Liver toxicity in adults, children, and in utero
- Agranulocytosis

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**PTU Black Box Warning**

**WARNING:** Severe liver injury and acute liver failure, in some cases fatal, have been reported in patients treated with propylthiouracil. These reports of hepatic reactions include cases requiring liver transplantation in adult and pediatric patients.

Propylthiouracil should be reserved for patients who can not tolerate methimazole and in whom radioactive iodine therapy or surgery are not appropriate treatments for the management of hyperthyroidism.

Because of the risk of fetal abnormalities associated with methimazole, propylthiouracil may be the treatment of choice when an antithyroid drug is indicated during or just prior to the first trimester of pregnancy.

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**Anti-Thyroid Drug Recommendations**

- **PTU** not be considered 1st line ATD therapy
  - MMI preferred in children and adults
- **PTU** may be considered over MMI:
  - **1st Trimester of pregnancy**
    - Until more is known with potential MMI embroyopathy
    - Consider switch to MMI in 2nd and 3rd to ↓ risk liver dz
  - **In Thyroid Storm**
    - Advantage T4→T3 conversion inhibition
    - Reaction to MMI (NOT AGRANULOCYTOSIS) in whom 131-I or surgery are not possible

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**When to Refer**

- Patients with persistent TSH suppression
  - To determine etiology of finding
  - To determine indications for treatment
- Adults: overt & subclinical hyperthyroidism
- Children/ Adolescents with hyperthyroidism
- Patients with thyrotoxicosis during pregnancy
- Patients with GD and ophthalmopathy
**Case 3**

- A 36-year-old woman with complaints of
  - Inability to lose weight
  - Dysphoria
  - Cold intolerance over 6 months
- Saw OB/GYN 2 months ago who ordered "lab tests" but patient did not follow up
- PE: BP: 136/88 mmHg, P 68,
  - BMI 29 kg/m²
  - 25-35 gram firm thyroid
    - No nodules palpable
  - Obese abdomen without striae

**Laboratory Evaluation:**
- CBC WNL
- Na 136, K 4.1, Cl 101, CO₂ 24, BUN 14, Cr 0.9
- T Chol 212 mg/dL, LDL 163 mg/dL
- Thyroid panel
  - TSH 8.6 uIU/mL (6/27) (at the OB’s office)
  - TSH 9.1 uIU/mL (8/29)
  - FT4 1.0 mcg/dL (8/29)
  - Anti TPO Ab 18.6 IU/mL (+)

**Clinical Diagnosis:** Subclinical hypothyroidism

**Hypothyroidism**

**Overt:** Elevated TSH, low FT4
- Obvious but non-specific symptoms
- Cardiovascular manifestations
  - ↑ CVD risk, Hypertension, Hyperlipidemia, CHF
- Pulmonary, Musculoskeletal, Neurologic and Psychiatric
- Skin/connective tissue, Renal/electrolyte abnormalities
- Gastrointestinal/liver, Hematologic and Hemostatic
- Pituitary and adrenal dysfunction

**Subclinical:** Elevated TSH, normal FT4
- Little to no symptoms
- Milder metabolic changes

**Hypothyroid Etiology**

- Iodine deficiency (most common world wide)
- Chronic autoimmune thyroiditis (Hashimoto’s)
  - More frequent in women than men
  - Increases in frequency with age
- Iatrogenic
  - 131-I or surgical treatment of hyperthyroidism
  - After external beam irradiation of the thyroid
  - Drugs: thionamides, lithium, amiodarone, interferon-alpha, interleukin-2, tyrosine kinase inhibitors (sunitinib)
- Central hypothyroidism: insufficient active TSH
  - Tumors: pituitary, hypothalamus
  - Infiltrative, inflammatory, surgical, irradiation

**Who to Treat**

- TSH > 10 mIU/ml considered for Rx
  - Due to risk of CHF and CV mortality
- TSH > upper “normal” & < 10 mIU/ml
  - Treatment based on individual factors
    - Symptoms c/w hypothyroidism
    - Positive TPO antibodies
    - ASCVD, CHF or risk of same
- Thyroid hormones should NOT be used to treat “hypothyroid symptoms” without biochemical confirmation of hypothyroidism

**But What is an Upper Normal TSH?**

**NHANES III:** 4.12 mU/L (Thyroid risk free)¹

**NHANES III:** Age adjusted (Thyroid risk free)²

<table>
<thead>
<tr>
<th>Age group</th>
<th>97.5 centiles</th>
<th>% &gt; 4.5 mU/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–29 years</td>
<td>3.56 mIU/liter</td>
<td>2.4%</td>
</tr>
<tr>
<td>70–79 years</td>
<td>5.9 mIU/liter</td>
<td>9.9%</td>
</tr>
<tr>
<td>&gt;80 years</td>
<td>7.49 mIU/liter</td>
<td>12.0%</td>
</tr>
</tbody>
</table>

¹ Hallowell JG et al. 2002 JCEM 87:489-99
² Surks et al. 2007 JCEM 92: 4575-4582

Hypothyroid symptoms should NOT be treated with thyroid hormone replacement therapy without biochemical confirmation of hypothyroidism.

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Which patients with a “normal” TSH should be considered for treatment?

- Women who are pregnant
  - 1st Trimester TSH > 2.5 mIU/L
  - 2nd Trimester TSH > 3.0 mIU/L
  - 3rd Trimester TSH > 3.5 mIU/L
- Women of child bearing age who are pregnant or planning pregnancy
  - Including those with assisted reproduction
  - When there are positive TPO-abs, or history of miscarriage or previous hypothyroidism, TSH > 2.5

What Should We Treat With?

- Hypothyroidism should be treated with L-thyroxine monotherapy
- The evidence does NOT support using L-thyroxine and L-triiodothyronine (T4/T3) combinations to treat hypothyroidism
- L-thyroxine and L-triiodothyronine combinations should NOT be administered to pregnant women or those planning pregnancy

Therapy Targets for LT4 Replacement

- Replacement Doses: 1.6-1.7 mcg/kg/day (0.8 mcg/lb.)
  - Lower start doses: elderly, those with symptomatic CAD (12.5-15 mcg/d)
  - Initial full replacement for younger and asymptomatic individuals
- Best outcomes when taken fasting, with water only, 30-60 minutes before breakfast or at bedtime 4 hours after last meal
- Check TSH 4-8 Weeks after start, change of dose or product
  - Titrate TSH into the “normal range”
  - Pregnancy Goal
    - 1st Trimester < 2.5 mIU/L
    - 2nd Trimester < 3.0 mIU/L
    - 3rd Trimester < 3.5 mIU/L

When to Refer for Hypothyroidism

- Children and infants
- When difficult to render and maintain euthyroidism
- Pregnancy and pre-pregnancy planning
- Patients with cardiac disease
- Presence of goiter, nodule or other structural issue
- Presence of pituitary or adrenal disease
- Unusual constellation of thyroid function tests
- Unusual causes of hypothyroidism

Outcomes Question #1

A 52-year-old man comes in for evaluation of worsening palpitations over the past 2 months. A thyroid panel reveals ↓ TSH, ↑ FT4, ↑ T3.

What is his likely diagnosis?

1. Hypothyroidism
2. Overt thyrotoxicosis
3. Subclinical hyperthyroidism
4. Thyroid cancer

Outcomes Question #2

Your patient has recently been diagnosed with Graves’ disease and begun on therapy with methimazole (MMU). She calls to announce that she is 6 weeks pregnant and is experiencing some heat intolerance and palpitations. TFTs: serum TSH=0.1 uIU/ml (0.4-4.2 uIU/mL); FT4 =2.2 ng/dL(0.8-1.8 ng/dL)

What would be an appropriate next step?

1. Start thyroid hormone therapy to keep the fetus euthyroid
2. Stop MMI and start propylthiouracil (PTU) therapy
3. Increase the MMI dose targeting a normal range serum TSH
4. Stop MMI and monitor for symptoms
Outcomes Question #3

Which of the following is TRUE regarding hypothyroidism?

1. Patients usually present with specific symptoms
2. Combination T4/T3 is the preferred treatment for most patients
3. Some patients with an elevated TSH may not benefit from thyroid hormone treatment
4. All of the above