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 Peter Singer is currently professor of clinical medicine, and chief of clinical endocrinology at the Keck School of Medicine at the University of Southern California (USC). Dr Singer was born and raised in San Francisco and received his medical degree from the University of California at San Francisco (UCSF). He then did a rotating internship at Los Angeles County General Hospital (now, LAC+USC Medical Center), followed by two years in military service, including a year as a battalion doctor in Vietnam. After the service, he returned to Los Angeles and completed a medical residency and endocrine fellowship at USC.

Dr Singer has had an active clinical practice for 40 years, with an emphasis on thyroid conditions. He has approximately 100 peer reviewed publications, book chapters, and abstracts.

Dr Singer is past president of the American Thyroid Association and has been on the board of directors of the American Association of Clinical Endocrinologists (AACE) since 2008. In 2004, he received the outstanding clinical endocrinologist award from AACE.

Dr Singer spends his spare time as chairman of the Board of East Meets West and, in 2011, was honored by the Ministry of Health of Vietnam for his more than 20 years of humanitarian assistance to that country. Peter Singer is married to Marjorie Kagawa, a professor of public health and Asian American studies at University of California Los Angeles (UCLA). Despite the academic and athletic rivalry between USC and UCLA, Peter and Margie have managed to set aside their differences, have two grown kids, and a son who is assistant professor of medicine at UCSF, and a daughter who is expecting Margie and Peter’s second grandchild.

Faculty Financial Disclosure Statement

The presenting faculty reports the following:

Dr Singer is a consultant for Abbvie Pharmaceuticals
Thyroid Disorders: From the Obvious to the Obscure

SPEAKERS
Peter A. Singer, MD

Learning Objectives
• Describe the spectrum of the signs and symptoms of thyroid disease – from subclinical hypothyroidism to life-threatening thyrotoxicosis
• Understand the diagnostic and management considerations for special patient populations commonly seen in primary care practice

First, a few words about physiology

Thyroid Hormone Regulation

TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone (thyrotropin); T3 = triiodothyronine; T4 = thyroxine

Goiters and Nodules
• Goiter definition: any enlargement of the thyroid gland.
  - Endemic goiter; enlargement a response to a lack of iodine-rare in US born individuals.
  - 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 of a nodule is ~60%

Detected by ultrasound/autopsy
- Detected by palpation

Types of Thyroid Nodules

- Benign (90%)
  - Colloid, hyperplastic
  - Hashimoto’s
  - Cysts
  - Follicular adenoma
  - Hurthle cell lesion

- Malignant (<10%)
  - Papillary cancer
  - Follicular cancer
  - Medullary cancer
  - Anaplastic cancer
  - Thyroid lymphoma
  - Metastatic

Degree of Clinical Concern for Carcinoma in a Thyroid Nodule Based on History and Physical Exam

**Less Concern**
- Chronic stable exam
- Evidence of a functional disorder (e.g., Hashimoto’s toxic nodule)
- Multinodular gland without dominant nodule?

**More Concern**
- Age <20, >60 years
- Males
- Rapid growth, pain
- History of radiation therapy
- Family history thyroid cancer
- Hard, fixed lesion
- Lymphadenopathy
- Vocal cord paralysis
- Size >4 cm
- Tracheo-esophageal pressure (e.g., stridor, dysphagia)

Thyroid Cancer - 2013

By the numbers (estimated)
- 60,220 new cases
- 3x more common in women
- 45,310 women; 14,910 men
- More lethal in men
- Deaths: 1,040 women, 810 men

Incidence peaks earlier in women (diagnosed in 4th-5th decades) than in men (diagnosed in 6th-7th decades)

Thyroid Nodule Laboratory Diagnosis

- TSH

Papillary Thyroid Cancer Tumor Size in USA

- % of tumors ≤1 cm: 49%
- % of tumors ≤2 cm: 87%
- % of tumors >2 cm: 13%

Thyroid Nodule Laboratory Diagnosis

**TSH Concentration & Risk of Malignancy**

<table>
<thead>
<tr>
<th>TSH (mIU/L)</th>
<th>Adjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.4</td>
<td>1</td>
</tr>
<tr>
<td>0.4-0.9</td>
<td>2.31</td>
</tr>
<tr>
<td>1.0-1.7</td>
<td>3.72</td>
</tr>
<tr>
<td>1.8-5.5</td>
<td>5.88</td>
</tr>
<tr>
<td>&gt;5.5</td>
<td>11.8</td>
</tr>
</tbody>
</table>

*P < 0.05


**Thyroid Nodule Laboratory Diagnosis**

- **TSH**
  - Suppressed C/W thyrotoxicosis
  - Malignancy unlikely
  - Elevated C/W hypothyroidism

**Radionuclide Scanning**

- Thyrotoxic nodule identification (TSH < normal)
- 99mTc (False +s), 131-I (Rads) or 123-I (Std)
- Does not ddx B9 from Ca, unless TSH <


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**Thyroid Ultrasound**

**Indication:** normal to ↑ TSH

- Defines a distinct nodule vs. abnormal parenchyma
- Role to guide FNA (cystic, posterior)
- MNG nodule selection
- Useful in f/u of low risk patient, incidentaloma

- **MRI / CT Scanning**
  - Offer little in pre-operative diagnosis


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**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


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**FNA Malignancy Prediction with Bethesda System**

<table>
<thead>
<tr>
<th>Category</th>
<th>Malignant risk</th>
<th>What next?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Diagnostic</td>
<td>1-4%</td>
<td>Re-do (U/S)</td>
</tr>
<tr>
<td>Benign</td>
<td>0-3%</td>
<td>Clinical F/U</td>
</tr>
<tr>
<td>Atypical</td>
<td>5-15%</td>
<td>Re-do (U/S)</td>
</tr>
<tr>
<td>follicular Neoplasm</td>
<td>15-30%</td>
<td>Lobectomy</td>
</tr>
<tr>
<td>Suspicious malignancy</td>
<td>60-75%</td>
<td>Total Tx</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99%</td>
<td>Total Tx</td>
</tr>
</tbody>
</table>

FNA = fine needle aspiration


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**Thyroid Nodule Work-up**

- TN (palpation/imaging) >1-1.5 cm

- He and Physical Serum TSH

- Low TSH

- Ultrasound Scan

- Not >50% cystic nor posterior

- Not >50% cyst or posterior

- Elevated TSH

- Normal TSH

- Poly of U/S Guided FNA

- U/S Guided FNA (see text)

- Results

- FNA not indicated

Cooper, et al. Thyroid. 2006;16(2):1-33
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 right nodule, freely movable
• Cor: Irregularly irregular rhythm, no M/G/R
• Lungs: bibasilar rales
• LE: 1+ edema

What additional work-up is needed?

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)

Thyrotoxicosis (T-Tox)

Definition: Thyroid hormone (TH) excess (+/- symptoms)
– Without regard to source
  • Prefomed TH passively released from the thyroid, i.e. thyroiditis with destruction
  • Exogenous TH administration

– Hyperthyroidism
  • Thyroid hormone production by the thyroid
  • Thyroid stimulated by trophic factors
  • Constitutive activation of thyrocytes
– Autonomous excessive TH synthesis and release

Thyrotoxicosis Classification and Etiology

• Classification: all may have signs & symptoms1
  – Overt T-Tox: ↓TSH, ↑FT4, ↑T3
  – Subclinical T-Tox: ↓TSH, normal FT4 and T3

• Etiology:
1. Graves’ disease (GD), autoimmune, stimulating TSH-receptor antibodies (TRAbs)
2. Toxic Nodular disease, growth and autonomy
  • Multinodular (TMNG) or Adenoma (TA)
  • TAs have somatic TSH receptor activating mutations
3. Both susceptible to iodine induced T-Tox
4. TMNG Incidence increases with age and in Iodine deficiency

3. Painless and Subacute Thyroiditis (SAT)
– Inflammation of thyroid tissue → TH release
– Painful SAT: post viral → fever, thyroid pain
– Painless SAT underlies 10% “hyperthyroidism”2
  • Occurs postpartum (PPT), with lithium4, cytokines (Interferon alpha), and 5-10% of amiodarone6
  – Usually resolves to euthyroidism

Excess Thyroid Hormone Manifestations

• Increased thermogenesis and metabolic rate
• Reduced cholesterol and vascular resistance
• Profound effects on cardiovascular system
  – a fibrillation, embolic events, CV collapse, death
• Other complications of untreated thyrotoxicosis
  – Weight loss, weakness and myopathy, osteoporosis
• Signs & symptoms (S/S) of overt and subclinical
  – Similar, differing only in magnitude
  – Only moderate correlation elevation of TH and S/S
• Elderly may exhibit fewer hyperadrenergic signs
  – “apathetic” with depressed mood and more arrhythmias

Thyrotoxicosis Etiology Continued

Clinical Evaluation

• Comprehensive H&P
  – 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 elevated (except in subclinical)


Determination of Etiology

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


Hyperthyroidism-Differential Diagnosis

Hyperthyroidism-Differential Diagnosis

Management of Hyperthyroidism

• Symptomatic management:
  – Beta-adrenergic blockade
    • For elderly, resting HR >90, coexistent CV Disease
    • All with symptomatic thyrotoxicosis
• Directed Interventions based on Etiology


Treatment Options

• 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 (suppressed TSH and nl thyroid hormone levels)

Subclinical Thyrotoxicosis Rx?

<table>
<thead>
<tr>
<th>Factor</th>
<th>TSH (&lt;0.1 mU/L)</th>
<th>TSH (0.1 – 0.5 mU/L)</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>

Comparing MMI and PTU

<table>
<thead>
<tr>
<th>Factor</th>
<th>MMI</th>
<th>PTU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response time</td>
<td>Faster</td>
<td>Slower</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Dose-related, rare effects less common</td>
<td>? Dose-related, hepatitis, vasculitis</td>
</tr>
<tr>
<td>Compliance</td>
<td>Better</td>
<td>Worse</td>
</tr>
<tr>
<td>Effect on RAI</td>
<td>No effect</td>
<td>Decreases effect</td>
</tr>
<tr>
<td>Cost (monthly)</td>
<td>$62 for 30 mg; $21 for 30 mg</td>
<td>$22 for 300 mg</td>
</tr>
</tbody>
</table>

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 cannot 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.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/006188s021s022lbl.pdf

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 embryopathy
    - Consider switch to MMI in 2nd and 3rd to ↓ risk liver dz
  - **In Thyroid Storm**
    - Advantage T4→T3 conversion inhibition
    - **Reaction to MMI** (NOT AGRANULOCTOSIS) in whom 131-I or surgery are not possible


Case 3

- A 36-year-old woman with complaints of
  - Inability to lose weight
  - Fatigue, “brain fog”
  - Cold intolerance
- Saw OB/GYN 2 months ago who ordered “lab tests” but patient did not follow up
- PE: BP:136/88, P 68,
  - Hgt: 5’ 4”, Wgt 186 lb, (BMI 32 kg/m²)
  - 25-35 gram firm, diffuse thyroid
  - Obese abdomen without striae

But What is an Upper Normal TSH?

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

NHANES III: Age adjusted (Thyroid risk free):

<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 mU/liter</td>
<td>2.4%</td>
</tr>
<tr>
<td>70-79 years</td>
<td>5.9 mU/liter</td>
<td>9.9%</td>
</tr>
<tr>
<td>&gt;80 years</td>
<td>7.49 mU/liter</td>
<td>12.0%</td>
</tr>
</tbody>
</table>

Not all elevations of TSH levels = Hypothyroidism!!!!

2. Surks  et al. 2007JCEM 92: 4575–4582

Case 3

- 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 tests
    - TSH 8.6 ulU/mL (6/27) (at the OB’s office)
    - TSH 9.1 ulU/mL (8/29)
    - FT4 1.0 mcg/dL (8/29)
    - Anti TPO Ab 18.6 IU/mL (+)

Clinical Diagnosis: Subclinical hypothyroidism (elevated TSH with normal FT4)
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

Hypothyroidism Epidemiology

<table>
<thead>
<tr>
<th>TSH &gt; 4.5</th>
<th>TSH &gt; 5.0</th>
<th>TSH &gt; 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclinical</td>
<td>Overt</td>
<td>Females</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hypothyroidism Etiology

- Iodine deficiency (most common world wide)  
- Chronic autoimmune thyroiditis (Hashimoto’s)  
  - More frequent in women than men (80% / 20%)  
  - 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-alfa, interleukin-2, tyrosine kinase inhibitors (sunitinib)  
- Central hypothyroidism: insufficient active TSH  
  - Tumors: pituitary, hypothalamus  
  - Infiltrative, inflammatory, surgical, irradiation

Whom 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

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
Thyroid Hormone Therapy Considerations

- In 2004, the FDA approved generic substitution for branded levothyroxine products.
- ATA, TES, AACE opposed decision, as the evaluation process allows products differing by 12.5% or more in bioavailability to be designated as interchangeable.
- ATA, TES, AACE Recommend that we should:
  - Alert patients that preparations may be switched at pharmacy
  - Encourage patients to ask to remain on the same preparation at every pharmacy refill
  - Make sure that patients understand the need to have their TSH retested and dosing readjusted every time their levothyroxine preparation is switched

Thyroid Hormone Therapy Considerations

http://www.thyroid.org/thyroxine-products-joint-position-statement/

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 (12.5-25 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

Frequency of sampling

<table>
<thead>
<tr>
<th>Pregnancy</th>
<th>Goal</th>
<th>Frequency of sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Trimester</td>
<td>&lt; 2.5 mIU/L</td>
<td>Q 4 weeks 1st 1/2</td>
</tr>
<tr>
<td>2nd Trimester</td>
<td>&lt; 3.0 mIU/L</td>
<td>&gt; X 1 @ 26-32 wks</td>
</tr>
<tr>
<td>3rd Trimester</td>
<td>&lt; 3.5 mIU/L</td>
<td></td>
</tr>
</tbody>
</table>


When to Consider Referral

- 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


Last case—72 year old woman with hypothyroidism

- Had symptoms of depression, poor appetite, weight loss, of 6 months duration. He husband passed away shortly before her symptoms began.
- Despite her young age, her family made arrangements for assisted living.
- Her alert physician obtained TFT’s:
  - TSH 19.2; FT4 0.8 (0.8-1.8)

72-year-old woman with hypothyroidism

- L-T4, 0.025 mg/d and the dose titrated over the next 3 months to 0.075 mg/d
- TSH 1.2; FT4 1.4
- She felt much better!


Thank you!

Questions?