Thyroid Disorders
Giuseppe Barbesino, MD

22nd Annual Northeast Regional Nurse Practitioner Conference – May 6-8, 2015
DISCLOSURES

• Advisory Board Member for Akrimax.
• There has been no commercial support or sponsorship for this program.
• The program co-sponsors do not endorse any products in conjunction with any educational activity.
Boston College Connell School of Nursing Continuing Education Program is accredited as a provider of continuing nursing education by the American Nurses Association Massachusetts, an accredited approver by the American Nurses Credentialing Center’s Commission on Accreditation.
SESSION OBJECTIVES

• Describe the key aspects of thyroid physiology.
• Interpret thyroid function tests.
• Summarize the workup of hyperthyroidism and hypothyroidism as well as treatment.
• Explain the diagnostic work-up of thyroid nodules.
Objectives

• Review key aspects of thyroid physiology
• Ordering and interpreting thyroid function tests
• Diagnostic workup of hyperthyroidism
• Diagnostic workup of hypothyroidism, and treatment, with special reference to pregnancy
• Diagnostic work-up of thyroid nodules
HYPERTHYROIDISM
Case 1:

- 25M with no PMHx presents with a 10lb weight loss, feeling on edge, trouble concentrating.

- Additional history
  - Appetite normal to increased
  - Increased frequency of bowel movements
  - + palpitations
  - + trouble sleeping
  - + irritability
  - + exercise intolerance
  - Symptoms for ~3 months

- Family history:
  - Sister takes thyroid hormone
Case 1:

- Exam:
  - T = 97.6  P112, regular, BP 136/66
  - Gen: thin man in NAD, somewhat on edge
  - HEENT: notable stare, no conjunctival injection, periorbital edema or proptosis
  - Neck: symmetric goiter, nontender, 30gm, no audible thyroid bruit, + palpable pyramidal lobe
  - CV: regular tachycardia
  - Pulm: CTA-B
  - Abdomen: no organomegaly, NTND
  - Ext: thin, 2+ peripheral pulses, no LEE
  - MSK: mild (4+) proximal muscle weakness
  - Neuro: fine resting tremor, brisk DTRs
Thyroid Physiology

From DPC Online
The thyroid is simple…

Thyroxine (T4)

Triiodothyronine (T3)
Thyroid hormones

- T3 = active hormone, shorter half life

- T4 = predominant circulating hormone, longer half life
Thyroid hormone metabolism

Thyroid gland

T4 → T3 by deiodinases

T3 → T4 by deiodinases

UDP glucuronyltransferases
Circulating thyroid hormone forms

TT4

FT4

- Free
- Albumin
- TTR
- TBG
Thyroid Hormone Action

- Mediated by nuclear hormone receptors
Thyroid hormones

• T4 – thyroxine
  • higher affinity for TBG –
  • ~10% cleared per day
  • $T_{1/2} = \sim 7\text{ days}$

• T3 – triiodothyronine
  • lower affinity for TBG
  • 60% turnover per day
  • $T_{1/2} = 0.75\text{ days}$
End organ effects -1

- **Brain/Nervous System:**
  - Neurogenesis (Cretinism)
  - Catecholamine sensitivity

- **Vascular:**
  - Increased heart contractility via α-MHC, β-adrenergic receptors
  - Increased cardiac O$_2$ consumption
  - Vasodilation of vascular smooth muscle (NO$_2$)

- **Metabolic:**
  - Increase lipolysis
  - Increased thermogenesis
  - Insulin resistance (and turnover)
End organ effects -2

- **Skeletal Muscle**
  - Increased adrenergic tone

- **Adrenal**:
  - Cortisol metabolism

- **Bone**
  - Increased bone turnover (hypercalcemia, osteopenia)

- **Blood**
  - Turnover of vitamin-K dependent clotting factors

- **Reproductive**
  - Conversion of testosterone (gynecomastia)
  - Altered LH/FSH pulses (GnRH signaling)
Thyroid Physiology
Control and regulation of thyroid function

pituitary/hypothalamus (TRH)
Evaluation of thyroid function

- **Laboratory:**
  - TSH – best test (mU/mL)
  - Free T₄ – “free” fraction of circulating T₄ (ng/mL)
  - Total T₃ (ng/dL)
  - Total T₄ (μg/dL)
  - T₃ Resin Uptake – free T₄ index

- **Imaging:**
  - Radioactive Iodine uptake and scan (¹²³I)
  - Thyroid ultrasound
    - Role beyond thyroid nodule evaluation only in special circumstances
Thyrotoxicosis

- Overt thyrotoxicosis:
  - Low/undetectable TSH
  - High free T4, T4, or T3

- Subclinical hyperthyroidism:
  - Low/undetectable TSH
  - Normal free T4, T3 WNL
Case 1: thyrotoxicosis

• Labs:
  • TSH <0.01 (0.4-5)
  • FT4 4.2 (0.8-1.8)
  • Total T3 570 (60-181)

• Diagnosis
  • Thyrotoxicosis

• Etiology?
Hyperthyroidism: differential diagnosis

- TSH independent autonomous hormone production
  - Graves’ disease
  - Hyperfunctioning thyroid nodules
    - Single/multiple
  - hCG-mediated – gestational trophoblastic disease
  - Struma ovarii (extremely rare)
  - Metastatic thyroid cancer (extremely rare)
- Release of stored hormone
  - Thyroiditis
    - Painless/painful
  - Amiodarone
- Exogenous administration of hormone
  - Factitious hyperthyroidism
- TSH-dependent thyrotoxicosis – Pituitary tumors
Graves’ disease
Toxic Nodules
Thyroiditis
Destructive thyroiditis

- Painful subacute thyroiditis
- Painless subacute thyroiditis
  - Sporadic
  - Postpartum
- Palpation thyroiditis (surgery)
- Radiation thyroiditis
- Amyloidosis
- Pneumocystis thyroiditis
- Malignant pseudothyroiditis (mets)
Destructive thyroiditis – natural history

Functional test

- Radioiodine uptake and scan
  - Graves’ disease
  - Toxic adenoma
  - Thyroiditis
  - Toxic nodular goiter

- Need simultaneous TSH measurement for accurate interpretation

Thyrotoxicosis: clinical clues

- Pathognomonic for Graves’
  - Ophthalmopathy – conjunctival injection, periorbital edema, proptosis
  - Dermopathy (rare)
  - Thyroid bruit

- Clinical pearl: it’s not thyroiditis if symptoms and/or thyrotoxicosis lasts more than 3-4 months
Thyrotoxicosis: diagnostic testing

- Antibody testing: ruling Graves’ diseases in or out
  - Thyroid stimulating immunoglobulins (TSI)
  - Thyrotropin binding inhibitory immunoglobulins (TBII)
  - Specificity and sensitivity >95%

- TPO (thyroid peroxidase) antibody can be positive in any autoimmune thyroid disease, therefore is not useful in thyrotoxicosis -> do not order
TSH receptor antibody in GD

Ota et al., Clin.Endocrinol, 2007
Thionamides

Propylthiouracil

Methimazole

Effect of thionamides
Graves’ disease – medical therapy

• Goals
  • Control of thyroid hyperfunction
    • Inhibit thyroid hormone synthesis: thionamides
  • Inhibit thyroid hormone effects on target organs: beta-blockers
    • Propranolol 20-80 MG TID
    • Atenolol (daily dosing) – 25-50mg, goal HR <90

• Cure
  • Natural history of TSI
    • Treatment for ~1 year then withdrawal
    • 40-50% in remission
    • 50% of these will relapse – long term remission in ~25%
  • Surgery
  • Radioactive iodine
# Methimazole vs PTU

<table>
<thead>
<tr>
<th>Reaction</th>
<th>PTU</th>
<th>MMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor Reactions (fever, rash)</td>
<td>1-5%</td>
<td>1-5%</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>0.2-.5%</td>
<td>0.2-.5%</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>hepatitis</td>
<td>cholestasis</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>ANCA +</td>
<td>very rare</td>
</tr>
<tr>
<td>Teratogenicity</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Nakamura et al, JCEM 2007, 92:2157
Special Scenarios

• Pregnancy:
  • PTU may be preferred due to MMI embryopathy (choanal atresia and aplasia cutis) during first trimester.
  • Decline in autoimmunity may enable reduction or discontinuation of medication (likely relapse in post-partum period).
Graves’ – definitive therapy

- **Radioactive Iodine – $^{131}$I**
  - Successful in ~85% of patient with a single dose
  - Contraindications:
    - Pregnancy
    - Lactation
    - Inability to comply with radiation safety guidelines
    - Moderate to severe ophthalmopathy

- **Surgery (total thyroidectomy)**
  - Adverse effects:
    - 1-3% chance of recurrent laryngeal nerve injury, hypoparathyroidism
  - Surgical expertise (volume) important
  - Very large goiter, MNGs
  - Pregnant with allergy to ATDs
HYPOTHYROIDISM
Hypothyroidism

- Overt hypothyroidism:
  - Elevated TSH
  - Low free T4, T4, or T3

- Subclinical hypothyroidism:
  - Elevated TSH
  - Free T4, T3 WNL

- TSH level correlates with degree of hypothyroidism
Hypothyroidism - Manifestations

- Goiter
- Cold intolerance
- Constipation
- Fatigue, lethargy
- Weight gain
- Coarse hair
- Brittle nails
- Dry skin
- Bradycardia

- Hypertension
- Menstrual irregularities (polymenorrhea)
- Infertility
- Elevated cholesterol
- Psychiatric abnormalities
- Pericardial effusion
- Ventricular arrhythmias

- Hypos of hypothyroidism: hyponatremia, hypotension, hypoventilation, hypothermia, hypometabolism
Hypothyroidism - etiology

- Hashimoto’s thyroiditis - Most common
- Hashimoto’s thyroiditis - Second most common
- Hashimoto’s thyroiditis – Third most common

- Prior thyroid surgery
- Radioactive iodine treatment
- External radiation

- Drugs (amiodarone, lithium, TKIs)
- Congenital hypothyroidism
  - Thyroid dysgenesis
  - Enzymatic defects
- Mutant TSH receptor
- TSH receptor antibodies (inhibitory)
Hashimoto’s thyroiditis

- Chronic autoimmunity to thyroid
- Common in iodine sufficient areas
- Thyroid peroxidase antibody positive (TPO) in >90% of cases
- Can be associated with other autoimmune diseases
- Goitrous, or atrophic
  - Typical exam, a rubbery moderately enlarged thyroid
# Hashimoto’s thyroiditis - variable clinical course

<table>
<thead>
<tr>
<th>Course</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euthyroid</td>
<td>No treatment, except in pregnancy</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>Levothyroxine if &lt;60 y/o Consider monitoring in &gt;60y/o</td>
</tr>
<tr>
<td>Overt hypothyroidism</td>
<td>Levothyroxine</td>
</tr>
<tr>
<td>Transient thyrotoxicosis, followed by transient or permanent hypothyroidism</td>
<td>Treat thyrotoxic symptoms, Treat hypothyroidism if permanent</td>
</tr>
</tbody>
</table>
TPO antibodies in thyroid disease
T3 in hypothyroidism

Normal

Hypo

Exogenous T4

Peripheral tissues

Peripheral tissues

TSH

T4

T3

T3

TSH

T4
Hypothyroidism – treatment

- Levothyroxine (LT4)
  - Standard of care
  - ~1.4 mcg/kg/d
  - Single daily dose, but adjust based on T½ - weekly dosage
  - Empty stomach
  - Generics are fine in my experience, but opinions vary

- Liothyronine (LT3)
  - No proven benefit, additional risks
  - Not routinely used -> can be tested in addition to T4 in select individuals
  - Used in psychiatry

- Dessicated animal thyroid (Armour)
  - Contains both LT4 and LT3, with supraphysiologic T3
  - Difficult titration
  - It is a form of thyroid replacement
Changes in TSH after changes in T4 dose

Causes of thyroxine ineffectiveness

Reduced absorption

- Calcium
  - Moderate
- Iron
  - Major
- Multivitamins
  - Variable
- Cholestyramine
  - Major
- PPI
  - Minor
- GI disease
  - Celiac disease
  - RYGBP

Increased metabolism

- Rifampin
- Dilantin
- Phenobarbital
- TKIs
THYROID PHYSIOLOGY AND THYROID DISEASE IN PREGNANCY
Reciprocal changes in TSH and HCG during pregnancy

Glinoer et al. JCE&M, 1990
Changes in TBG levels during pregnancy

Glinoer et al. JCE&M, 1990
Effects of pregnancy on total and free T4
Effects of normal pregnancy on thyroid function tests

- Lower TSH
- Higher TT4, TT3
- Normal FT4
Hypothyroidism and Pregnancy:
Need for Increased doses of T4

Alexander et al. NEJM, 2004
Hypothyroidism in Pregnancy: Long Term Effects on the Offspring

Haddow et al., NEJM 1999
Hypothyroidism in Pregnancy: Long Term Effects on the Offspring

![Bar graph showing IQ scores for Hypothyroid, Hypothyroid + T4, and Controls. The graph indicates lower IQ scores for the Hypothyroid group compared to Hypothyroid + T4 and Controls.]

Haddow et al., NEJM 1999
Hypothyroidism and Pregnancy: key points

• Pre-conception TSH should be >0.3-<2.5 mU/L
• Euthyroid women with Hashimoto’s thyroiditis may benefit from treatment even when euthyroid.
• Test TSH FT4 immediately (4-6 wks)
• Expect increased need of T4 (50%) early
• Monitor every 4-6 weeks
• Return to pre-pregnancy T4 dose after delivery
THYROID NODULES
Current Thyroid Cancer Trends in the United States

Welch & Davies, JAMA Otolaryngol Head Neck Surg., 2014
Prevalence of Thyroid Incidentalomas Detected on Ultrasonography

<table>
<thead>
<tr>
<th>Author (Reference), Location</th>
<th>Study Year</th>
<th>Frequency Range of Ultrasonographic Equipment</th>
<th>Purpose of Examination</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horlocker et al. (22), United States</td>
<td>1981–1984</td>
<td>10 MHz</td>
<td>Hyperparathyroidism</td>
<td>46 %</td>
</tr>
<tr>
<td>Stark et al. (23), United States</td>
<td>1981–1982</td>
<td>10 MHz</td>
<td>Hyperparathyroidism</td>
<td>40 %</td>
</tr>
<tr>
<td>Carroll (21), United States</td>
<td>1981</td>
<td>7.5 MHz</td>
<td>Carotid ultrasonography</td>
<td>13 %</td>
</tr>
<tr>
<td>Ezzat et al. (24), United States</td>
<td>1993</td>
<td>10 MHz</td>
<td>Prospective</td>
<td>67 %</td>
</tr>
<tr>
<td>Brander et al. (25), Finland</td>
<td>1989–1990</td>
<td>7.5 MHz</td>
<td>Prospective</td>
<td>27 %</td>
</tr>
<tr>
<td>Woestyn et al. (26), Belgium</td>
<td>1984–1985</td>
<td>5.5 MHz</td>
<td>Prospective</td>
<td>19 %</td>
</tr>
<tr>
<td>Tomimori et al. (27), Brazil</td>
<td>1995</td>
<td>7.5 MHz</td>
<td>Prospective</td>
<td>17 %</td>
</tr>
</tbody>
</table>

Tan, G. H. et al., 1997
Incidence of Malignancy in Solitary and Multiple Thyroid Nodules-US

Frates et al., 2006
Incidence of Malignancy in Thyroid Nodules According to Nodule Size

Frates et al., 2006

The bar graph shows the percentage of malignant thyroid nodules across different size categories:
- 11-14 mm: Approximately 10%
- 15-19 mm: Approximately 8%
- 20-24 mm: Approximately 12%
- 25-29 mm: Approximately 10%
- >29 mm: Approximately 14%

As the nodule size increases, the percentage of malignant nodules also increases.

Frates et al., 2006
Malignancy Rates in Subcentimetric Nodules

Papini et al., 2002
Impact of Tumor Size on Papillary Thyroid Cancer Mortality

Hay et al., 1993
A typical US report

• Left lobe:
  – 0.9 x 0.7 x 1.2 cm hypoechoic nodule in the lower pole.
  – 1.4 x 1.3 x 1.6 cm isoechoic nodule with central flow in the midpole
  – 0.3 x 0.6 x 0.9 cm nodule with microcalcifications in the upper pole

• Right lobe:
  – 3.3 cm partially cystic nodule in the lower pole
  – 2.1 x 2.1 x 1.8 cm solid isoechoic nodule in the upper lobe
Evaluation of thyroid nodules: role of fine needle aspiration biopsy

- Office procedure, local anesthesia, virtually with no risk
- False negative results: 2-4%
- False positive results: almost nil
- Non-diagnostic: 5-15%
- Indeterminate: 15-25%
First Rule: Only Cold Nodules Should Be Considered for FNA

Corollarium: always order a TSH!
Risk Assessment In Thyroid Nodules

Risk of Malignancy in Thyroid Nodule

\[ \times \]

Mortality from Thyroid Malignancy

\[ = \]

Mortality from Thyroid Nodules
Value of some U/S features in predicting malignancy in thyroid nodules.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Specificity</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent Halo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrolcific.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microcalcific.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoechoic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Hypoechoic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irreg. Margins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central Flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taller Than Wide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Specificity:

- Absent Halo: 25%
- Macrolcific: 50%
- Microcalcific: 75%
- Hypoechoic: 25%
- Very Hypoechoic: 50%
- Irreg. Margins: 75%
- Central Flow: 25%
- Taller Than Wide: 50%
# Nodule Features Associated With Benignity

<table>
<thead>
<tr>
<th>Feature</th>
<th>Malignant/Total</th>
<th>Malignancy Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spongiform</td>
<td>0/210</td>
<td>0%</td>
</tr>
<tr>
<td>Cyst with Colloid Clot</td>
<td>0/53</td>
<td>0%</td>
</tr>
<tr>
<td>Giraffe</td>
<td>0/23</td>
<td>0%</td>
</tr>
<tr>
<td>White knight</td>
<td>0/17</td>
<td>0%</td>
</tr>
<tr>
<td>Red Light</td>
<td>15/52</td>
<td>28.8%</td>
</tr>
<tr>
<td>Hypoechoic</td>
<td>14/45</td>
<td>31.1%</td>
</tr>
<tr>
<td>Isoechoic without Halo</td>
<td>2/37</td>
<td>5.4%</td>
</tr>
<tr>
<td>Isoechoic with Halo</td>
<td>4/42</td>
<td>9.5%</td>
</tr>
<tr>
<td>Ring of Fire</td>
<td>4/10</td>
<td>40%</td>
</tr>
<tr>
<td>Other</td>
<td>1/12</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

Bonavita et al., 2008
ATA recommendations for FNA of thyroid nodules

<table>
<thead>
<tr>
<th>Size (cm)</th>
<th>&lt;1</th>
<th>1-1.5</th>
<th>1.6-2.0</th>
<th>&gt;2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almost never</td>
<td>If highly suspicious on U/S</td>
<td>If moderately suspicious on U/S</td>
<td>If not purely cystic</td>
<td></td>
</tr>
</tbody>
</table>

- Familial syndromes
- H/O neck XRT
- Microcalcifications
- Deeply hypoechoic
- Solid
- Hypoechoic
- Spongiform
THANK YOU!