Common Endocrine Disorders in Pregnancy

Justin Moore, MD
disclosures

None
Learning points

• hCG is similar to TSH, and with certain glycosylation, has a high affinity for the TSH receptor

• In cases of a suppressed TSH in pregnancy, even in the first trimester, measurement of TSH receptor antibodies (TRAb or TSI) may be useful

• Don’t use nuclear medicine studies in pregnancy

• Propylthiouracil (PTU) is probably the first-trimester treatment of choice in pregnancy, and methimazole (MMI) thereafter
Learning points

• Both MMI and PTU are safe at usual doses for breastfeeding
• Thyroid nodules discovered in pregnancy should—at minimum—be evaluated with thyroid ultrasound and measurement of TSH
• Definitive treatment of thyroid cancer can be delayed until after parturition in most pregnant women
• Delay radioactive iodine for 6-8 weeks after discontinuation of lactation
• Delay pregnancy 6-12 months after exposure to therapeutic doses of $^{131}$I
Case 1

• 18 yr old G1P0 (1 prior TAb) female presented to PCP with complaints of peripheral edema and fatigue
• Pregnancy test positive
• PRN furosemide prescribed
• Four weeks later, pt re-presents with advancing tachycardia, weight loss
• Routine labs drawn, pt transferred urgently to tertiary care center
  – TSH reportedly undetectable, T4 “high.”
• Once at tertiary care center, received iodine for CT angiogram of chest (showed small pulmonary nodules; below)
• Thyroid function testing repeated:
  – TSH undetectable
  – T4 26.2 µg/dL (4.5 - 12.5)
• hCG 1.2 million IU/l
Diagnosis?

- Metastatic choriocarcinoma
- So why was she hyperthyroid?
Learning point

- hCG is similar to TSH, and especially with certain glycosylation, has a high affinity for the TSH receptor

Endocr Rev 1997, PMID: 9267761
TSH vs. hCG in Gestation

Human Reproduction Update 2004, PMID: 15073140
## hCG Concentration in Singlet vs. Twin Pregnancies

<table>
<thead>
<tr>
<th></th>
<th>Mean hCG</th>
<th>Duration of hCG Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singlet Pregnancies</td>
<td>65,500 +/- 7600 U/Liter</td>
<td>&lt;1 week</td>
</tr>
<tr>
<td>Twin Pregnancies</td>
<td>171,000 +/- 12,500</td>
<td>Up to 6 weeks</td>
</tr>
</tbody>
</table>

 Clin Endocrinol 1997, PMID: 9274703
Case 2

- 22 yr old G1P0 female at 14 2/7 weeks presents with tremor
- Diffuse goiter, fine resting tremor
- Wt stable since first positive pregnancy test
- Some nausea, rare vomiting
- TSH 0.02 mIU/l, FT4 1.9 ng/dl
- No history of thyroid disease
<table>
<thead>
<tr>
<th>Reference</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haddow et al. (13)</td>
<td>0.94 (0.08–2.73)</td>
<td>1.29 (0.39–2.70)</td>
<td>--</td>
</tr>
<tr>
<td>Stricker et al. (14)</td>
<td>1.04 (0.09–2.83)</td>
<td>1.02 (0.20–2.79)</td>
<td>1.14 (0.31–2.90)</td>
</tr>
<tr>
<td>Panesar et al. (15)</td>
<td>0.80 (0.03–2.30)</td>
<td>1.10 (0.03–3.10)</td>
<td>1.30 (0.13–3.50)</td>
</tr>
<tr>
<td>Soldin et al. (16)</td>
<td>0.98 (0.24–2.99)</td>
<td>1.09 (0.46–2.95)</td>
<td>1.20 (0.43–2.78)</td>
</tr>
<tr>
<td>Bocos-Terraz et al. (17)</td>
<td>0.92 (0.03–2.65)</td>
<td>1.12 (0.12–2.64)</td>
<td>1.29 (0.23–3.56)</td>
</tr>
<tr>
<td>Marwaha et al. (18)</td>
<td>2.10 (0.60–5.00)</td>
<td>2.40 (0.43–5.78)</td>
<td>2.10 (0.74–5.70)</td>
</tr>
</tbody>
</table>

*Median TSH in mIU/L, with parenthetical data indicating 5th and 95th percentiles (13,15,18) or 2.5th and 97.5th percentiles (14,16,17).*

Thyroid 2011, PMID: 21787128
Hyperthyroidism Etiologies in Pregnancy

• Graves Disease the most common (>80%)
  – Peak incidence of Graves’ in second through fourth decade parallels reproductive years

• hCG-associated
  – Hydatidiform mole
  – Choriocarcinoma
  – Transient hyperthyroidism of hyperemesis gravidarum (THHG)

Thyroid 2011, PMID: 21787128
Transient Hyperthyroidism of Hyperemesis Gravidarum

- Up to 50% of all women with hyperemesis gravidarum are hyperthyroid
- Usually transient, resolving by 18 weeks’ gestation

“Recommendation 25
The appropriate management of women with gestational hyperthyroidism and hyperemesis gravidarum includes supportive therapy, management of dehydration, and hospitalization if needed.
Level A-USPSTF

Recommendation 26
ATDs are not recommended for the management of gestational hyperthyroidism.
Level D-USPSTF”

Thyroid 2011, PMID: 21787128
How do we diagnose thyroid disease and not just hCG-related changes?

- “Any subnormal serum TSH value should be evaluated in conjunction with serum FT4. The diagnosis of clinical hyperthyroidism is confirmed in the presence of a suppressed or undetectable serum TSH and an elevated FT4.”

- “In the presence of a suppressed serum TSH in the first trimester (TSH <0.1 mIU/L), a history and physical examination are indicated...Measurement of TT3 and TRAb may be helpful in establishing a diagnosis of hyperthyroidism. (Level B-USPSTF)”

Thyroid 2011, PMID: 21787128
Learning point

• In cases of a suppressed TSH in pregnancy, even in the first trimester, measurement of TSH receptor antibodies may be useful
Learning point

• Don’t use radioactive iodine in pregnant women
Case 2 (cont.)

• TSH receptor antibodies are positive at a high titer
• Could this lead to a poor pregnancy outcome?
Risks of Thyrotoxicosis & Pregnancy

- Low birth weight (OR 9.2, 95% CI 5.5–16; PMID 11298089)
- Prematurity (OR 16.5, 95% CI 2.1–130; PMID 11071676)
- Eclampsia (OR 4.7, 95% CI 1.1–19.7; PMID 1379702)
- Miscarriage
- Small for gestational age in untreated versus treated Graves (26.7 vs 7.7%; PMID 1379702)
- Neonatal hyperthyroidism
- Advanced bone age
- Craniosyostoses

How should the patient be treated?
Antithyroid drugs

- Cross placenta liberally (MMI > PTU)
- But so does TSI
MMI: Aplasia Cutis

Also:

Choanal atresia

Esophageal atresia

Tracheo-esophageal fistula
As such... Learning point

- “PTU is preferred for the treatment of hyperthyroidism in the first trimester. Patients on MMI should be switched to PTU if pregnancy is confirmed in the first trimester. Following the first trimester, consideration should be given to switching to MMI. Level I-USPSTF”

Thyroid 2011, PMID: 21787128
Why not PTU for the entire pregnancy?

Information for Healthcare Professionals - Propylthiouracil-Induced Liver Failure

FDA ALERT [06/04/2009]:

FDA is notifying healthcare professionals of the risk of serious liver injury, including liver failure and death, with the use of propylthiouracil in adult and pediatric patients.

Reports to FDA’s Adverse Event Reporting System (AERS) suggest there is an increased risk of hepatotoxicity with when compared to methimazole. Although both propylthiouracil and methimazole are indicated for the treatment of hyperthyroidism due to Graves’ disease, healthcare professionals should carefully consider which drug to initiate in a patient recently diagnosed with Graves’ disease. Physicians should closely monitor patients on propylthiouracil therapy for symptoms and signs of liver injury, especially during the first six months after initiation of therapy. Propylthiouracil and methimazole were approved in 1947 and 1950, respectively.

FDA has identified 32 AERS cases (22 adult and 10 pediatric) of serious liver injury associated with propylthiouracil use. Of the adult cases, 12 deaths and 5 liver transplants occurred. Among the pediatric patients, 1 case resulted in death and 6 in liver transplants.

In contrast, for methimazole 5 AERS cases of serious liver injury were identified. All five cases were in adult patients and 3 resulted in death.

In general, propylthiouracil is considered second-line drug therapy except in patients who are allergic to or intolerant of methimazole. Rare cases of embryopathy, including aplasia cutis, have been reported with use of methimazole during pregnancy, while no such cases have been reported with propylthiouracil use. Thus, propylthiouracil may be more appropriate for patients with Graves’ disease who are in their first trimester of pregnancy.

On April 18, 2009, FDA held a public workshop with the American Thyroid Association (ATA) to discuss propylthiouracil-related hepatotoxicity. FDA is continuing to monitor these serious reported adverse events and working to make changes to the propylthiouracil prescribing information, particularly for use in pediatric patients. Also, the ATA plans to update its treatment guidelines for Graves’ disease in the upcoming months.

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandPro-

viders/DrugSafetyInformationforHealthcareProfessionals/ucm162701.htm
The patient is started on 15 mg methimazole daily

• How often should the patient have her thyroid labs re-checked, and what is the goal of therapy?

“Recommendation 30
In women being treated with ATDs in pregnancy, FT4 and TSH should be monitored approximately every 2–6 weeks. The primary goal is a serum FT4 at or moderately above the normal reference range.
Level B-USPSTF”

Thyroid 2011, PMID: 21787128
Case 1 (continued)

- The patient’s MMI dose is gradually titrated to 5 mg daily by delivery.
- Delivers at 39 1/7 uneventfully.
- She wishes to breastfeed.
- What is the appropriate drug to use during lactation?
Thyrotoxicosis & Lactation

• ATD generally don’t get into breast milk in meaningful concentrations unless taken at relatively high doses:
  • PTU > 450-600 mg/d
  • MMI > 20 mg/d

• Take ATD dose just *after* breast-feeding
  • Should provide 3-4h interval before the patient lactates again
“Recommendation 35

MMI in doses up to 20–30mg/d is safe for lactating mothers and their infants. PTU at doses up to 300 mg/day is a second-line agent due to concerns about severe hepatotoxicity. ATDs should be administered following a feeding and in divided doses.

Level A-USPSTF”

Thyroid 2011, PMID: 21787128
Learning point

• Antithyroid drugs, given in divided doses following feedings, are generally safe in lactation
Case 3

• A 22 year old G1P0 female at 14 weeks gestation presents with a newly discovered neck lump
• Physical examination is consistent with a thyroid nodule

What two diagnostic procedures are obligatory in this patient?
Learning point: If a thyroid nodule is present or suspected, obtain a TSH level and a thyroid ultrasound.

“Recommendation 46

The optimal diagnostic strategy for thyroid nodules detected during pregnancy is based on risk stratification. All women should have the following: a complete history and clinical examination, serum TSH testing, and ultrasound of the neck.

Level A-USPSTF”

Thyroid 2011, PMID: 21787128
Ultrasound reveals a 2.1 cm hypervascular lesion in the mid-right pole

• What should be done with this lesion?
<table>
<thead>
<tr>
<th>Nodule sonographic or clinical features</th>
<th>Recommended nodule threshold size for FNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk history&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥5 mm&lt;br&gt;Recommendation A</td>
</tr>
<tr>
<td>Nodule WITH suspicious sonographic features&lt;sup&gt;b&lt;/sup&gt;</td>
<td>≥5 mm&lt;br&gt;Recommendation A</td>
</tr>
<tr>
<td>Nodule WITHOUT suspicious sonographic features&lt;sup&gt;b&lt;/sup&gt;</td>
<td>≥5 mm&lt;br&gt;Recommendation I</td>
</tr>
<tr>
<td>Abnormal cervical lymph nodes</td>
<td>All&lt;sup&gt;c&lt;/sup&gt;&lt;br&gt;Recommendation A</td>
</tr>
<tr>
<td>Microcalcifications present in nodule</td>
<td>≥1 cm&lt;br&gt;Recommendation B</td>
</tr>
<tr>
<td>Solid nodule</td>
<td></td>
</tr>
<tr>
<td>AND hypoechoic</td>
<td>≥1 cm&lt;br&gt;Recommendation B</td>
</tr>
<tr>
<td>AND iso- or hyperechoic</td>
<td></td>
</tr>
<tr>
<td>Mixed cystic–solid nodule</td>
<td>≥1.5–2.0 cm&lt;br&gt;Recommendation B</td>
</tr>
<tr>
<td>WITH any suspicious ultrasound features&lt;sup&gt;b&lt;/sup&gt;</td>
<td>≥1.5–2.0 cm&lt;br&gt;Recommendation B</td>
</tr>
<tr>
<td>WITHOUT suspicious ultrasound features</td>
<td>≥2.0 cm&lt;br&gt;Recommendation C</td>
</tr>
<tr>
<td>Spongiform nodule</td>
<td>≥2.0 cm&lt;sup&gt;d&lt;/sup&gt;&lt;br&gt;Recommendation C</td>
</tr>
<tr>
<td>Purely cystic nodule</td>
<td>FNA not indicated&lt;sup&gt;e&lt;/sup&gt;&lt;br&gt;Recommendation E</td>
</tr>
</tbody>
</table>

<sup>a</sup>High-risk history: History of thyroid cancer in one or more first degree relatives; history of external beam radiation as a child; exposure to ionizing radiation in childhood or adolescence; prior hemithyroidectomy with discovery of thyroid cancer, ¹⁸F-DG avidity on PET scanning; MEN2/FMTC-associated RET protooncogene mutation, calcitonin >100 pg/mL. MEN, multiple endocrine neoplasia; FMTC, familial medullary thyroid cancer.

<sup>b</sup>Suspicious features: microcalcifications; hypoechoic; increased nodular vascularity; infiltrative margins; taller than wide on transverse view.

<sup>c</sup>FNA cytology may be obtained from the abnormal lymph node in lieu of the thyroid nodule.

<sup>d</sup>Sonographic monitoring without biopsy may be an acceptable alternative (see text) (48).

<sup>e</sup>Unless indicated as therapeutic modality (see text).
Fine Needle Aspiration

“Recommendation 48
Thyroid or lymph node FNA confers no additional risks to a pregnancy.
Level A-USPSTF

Recommendation 49
Thyroid nodules discovered during pregnancy that have suspicious ultrasound features, as delineated by the 2009 ATA guidelines, should be considered for FNA. In instances in which nodules are likely benign, FNA may be deferred until after delivery based on patients’ preference.
Level I-USPSTF”

Thyroid 2011, PMID: 21787128
Further evaluation by FNA and ultrasound reveals a 2.1 cm papillary cancer without obvious lymphadenopathy of the neck.

What treatment should be offered now?
Learning point: for low-risk cancers, the patient may elect to wait until after delivery for thyroidectomy

“Recommendation 51
Because the prognosis of women with well-differentiated thyroid cancer identified but not treated during pregnancy is similar to that of nonpregnant patients, surgery may be generally deferred until postpartum.

Level B-USPSTF”

Thyroid 2011, PMID: 21787128
The patient delivers at term uneventfully and undergoes a near-total thyroidectomy one month later. She is breastfeeding and wishes to continue.

- How should her radioiodine dose be timed in regards to her breastfeeding?
<table>
<thead>
<tr>
<th>Factors</th>
<th>Description</th>
<th>Expected benefit</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Decreased risk of death</td>
<td>Decreased risk of recurrence</td>
</tr>
<tr>
<td>T1</td>
<td>1 cm or less, intrathyroidal or microscopic multifocal</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>1–2 cm, intrathyroidal</td>
<td>No</td>
<td>Conflicting data</td>
</tr>
<tr>
<td></td>
<td>&gt;2–4 cm, intrathyroidal</td>
<td>No</td>
<td>Conflicting data</td>
</tr>
<tr>
<td></td>
<td>&gt;4 cm</td>
<td>No</td>
<td>Conflicting data</td>
</tr>
<tr>
<td></td>
<td>&lt;45 years old</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>≥45 years old</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Any size, any age, minimal extrathyroidal extension</td>
<td>No</td>
<td>Inadequate data</td>
</tr>
<tr>
<td>T4</td>
<td>Any size with gross extrathyroidal extension</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nx,N0</td>
<td>No metastatic nodes documented</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>&lt;45 years old</td>
<td>No</td>
<td>Conflicting data</td>
</tr>
<tr>
<td></td>
<td>&gt;45 years old</td>
<td>Conflicting data</td>
<td>Conflicting data</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis present</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Because of either conflicting or inadequate data, we cannot recommend either for or against RAI ablation for this entire subgroup. However, selected patients within this subgroup with higher risk features may benefit from RAI ablation (see modifying factors in the text).
RECOMMENDATION 74

(a) Radioactive iodine should not be given to nursing women. Depending on the clinical situation, RAI therapy could be deferred until a time when lactating women have stopped breast-feeding for at least 6–8 weeks.

Recommendation rating: B

(b) Dopaminergic agents might be useful in decreasing breast exposure in recently lactating women, although caution should be exercised given the risk of serious side effects associated with their routine use to suppress postpartum lactation.

Recommendation rating: C

Thyroid 2009, PMID: 19860577
Finally…the patient receives 30 mCi I$^{131}$ with good results. She wishes to conceive, and wonders when she and her husband could resume unprotected intercourse.

**RECOMMENDATION 73**

Women receiving RAI therapy should avoid pregnancy for **6–12 months**.

Recommendation rating: C

Thyroid 2009, PMID: 19860577
Conclusions

• hCG is similar to TSH, and with certain glycosylation, has a high affinity for the TSH receptor
• In cases of a suppressed TSH in pregnancy, even in the first trimester, measurement of TSH receptor antibodies (TRAb or TSI) may be useful
• Don’t use nuclear medicine studies in pregnancy
• Propylthiouracil (PTU) is probably the first-trimester treatment of choice in pregnancy, and methimazole (MMI) thereafter
Conclusions

• Both MMI and PTU are safe at usual doses for breastfeeding
• Thyroid nodules discovered in pregnancy should—at minimum—be evaluated with thyroid ultrasound and measurement of TSH
• Definitive treatment of thyroid cancer can be delayed until after parturition in most pregnant women
• Delay radioactive iodine for 6-8 weeks after discontinuation of lactation
• Delay pregnancy 6-12 months after exposure to therapeutic doses of I$^{131}$
Questions?

• jmoore7@kumc.edu