Thyroid Disease in Pregnancy

Justin Moore, MD
Case 1

- 22 yr old G1P0 female at 14 2/7 weeks presents with tremor
- Weight 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
Case 1

- 22 yr old G1P0 female at 14 2/7 weeks presents with tremor
- Weight 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 2. Sample Trimester-Specific Reference Intervals for Serum TSH

<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).
Transient Hyperthyroidism of Hyperemesis Gravidarum

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

Recommendation 25: manage hyperthyroidism due to hyperemesis gravidarum with supportive therapy (Level A-USPSTF)

Recommendation 26: don’t use anti-thyroid drugs (Level D-USPSTF)

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

- Subnormal TSH plus elevated FT4 = clinical hyperthyroidism
- In the first trimester, a TSH < 0.1 mIU/L plus an elevated FT3 and positive TSH receptor antibodies (TRAb or TSI) is consistent with Graves disease (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
Case 1 (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 (PMID: 11272098)
- 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

Radiographics 2000, PMID 10992014
Methimazole: Aplasia Cutis

Also:

Choanal atresia

Esophageal atresia

Tracheo-esophageal fistula
• PTU preferred in the first trimester
• If on methimazole, switch to PTU if pregnancy is confirmed in the first trimester
• Following the first trimester, consideration should be given to switching to methimazole (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.

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: FT4 and TSH should be monitored approximately every 2–6 weeks. Goal is a serum FT4 at or moderately above the reference range. Level B-USPSTF”

Thyroid 2011, PMID: 21787128
Case 1 (continued)

• The patient’s methimazole 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

• Both methimazole and PTU are present in breast milk
• No alterations in thyroid function in 159 neonates nursed between weeks 3 and 8 by moms treated with PTU (50–300 mg/d) and methimazole (5–20 mg/d)

J Pediatr Endocrinol Metab 2003, PMID: 14714745
Recommendation 35:
- **Methimazole** in doses up to 20–30mg/d is safe
- **PTU** at doses up to 300 mg/day is a second-line agent due to concerns about severe hepatotoxicity
- Give following feedings 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 2

• 32 year old G0 with a history of Hashimoto’s disease has a TSH of 1.5 uIU/mL and desires pregnancy
  – 125 mcg LT4 daily, taken appropriately
• How should we counsel her about her thyroid replacement as it relates to her pregnancy?
<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Pregnancy</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>38</th>
<th>P Value by ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyrotropin (µU/ml)</td>
<td>1.0±1.14</td>
<td>4.2±3.8</td>
<td>2.3±3.2</td>
<td>1.3±1.5</td>
<td>1.0±0.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Free thyroxine index</td>
<td>8.8±1.2</td>
<td>7.8±1.8</td>
<td>8.9±1.5</td>
<td>8.5±1.7</td>
<td>8.5±1.8</td>
<td>0.33</td>
</tr>
<tr>
<td>Thyroid hormone-binding ratio</td>
<td>1.0±0.1</td>
<td>0.8±0.1</td>
<td>0.7±0.05</td>
<td>0.6±0.06</td>
<td>0.6±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thyroxine dose (fraction of dose before pregnancy)</td>
<td>1.00±0</td>
<td>1.29±0.25</td>
<td>1.48±0.18</td>
<td>1.48±0.15</td>
<td>1.47±0.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>55±24</td>
<td>1100±400</td>
<td>7000±2800</td>
<td>13,500±3500</td>
<td>20,400±4200</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
THERAPY Trial

- **P:** 60 women with treated hypothyroidism seeking pregnancy.
- **I:** Increase LT4 by two tablets/wk
- **C:** Increase LT4 by three tablets/wk
- **O:** Thyroid function testing biweekly through midpregnancy and at 30 weeks gestation

JCEM 2010, PMID: 20463094
Results:

• TSH suppressed below 0.5 mIU/liter in 8/25 women in the 2 tabs/week group.

• TSH suppressed below 0.5 mIU/liter in 15/23 women in the 3 tabs/week group (P < 0.01).

• Risk of suppressed TSH was significantly increased in:
  – Athyreotic patients (OR = 3.3; 1.1-11.1)
  – Prepregnancy TSH < 1.5 mIU/liter (OR = 4.6; 1.3-16.2)
  – Prepregnancy LT4 dose ≥ 100 mcg/d (OR = 7.2; 1.7-30.6).

• However, if a trimester-specific TSH lower reference range of 0.1 mIU/liter was used, only two patients (8%) in the 2 tabs/week group required a dose reduction.
Learning Point

• In women on a stable levothyroxine dose, a dose increase of 2 tabs/week at the time of the first positive pregnancy test generally results in acceptable TSH levels throughout the pregnancy.