NEWBORN FEMALE WITH GOITER

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CHIEF COMPLAINT

• 35 6/7 week F with goiter, born to a mother with Graves' disease (GD)
HPI

- 35 6/7 week F born to a 25 yo G3P2 mother with GD
  - Managed with PTU during pregnancy
  - Infant delivered by scheduled C-section for fetal goiter
    - Noted on 32w ultrasound
    - Confirmed on fetal MRI at 35 wks GA
  - No complications with delivery
    - Apgars at 1 and 5 min were 9 and 9
REVIEW OF SYSTEMS

- **Constitutional:** - appetite change, unexpected weight change, fever, irritability. + *feeding well*
- **Endo:** + *hypoglycemia*, good UOP
- **HEENT:** - ocular discharge
- **CVS:** - BP instability
- **GI:** + passed meconium
- **Skin:** - rash
OTHER HISTORY

• **PMH:** Goiter
• **PSH:** None
• **FH:** GD- mother
• **SH:** Will live at home with mother, mother’s boyfriend, and older brother
• **Allergies:** NKDA
• **Meds:** None
PHYSICAL EXAM

- **Vitals**: T 36.9, HR 130, BP 59/30, RR 34, Wt 2.85 kg (55%ile), Lt 44 cm (10%ile), HC 33.5 cm (25%ile)
- **General**: well-appearing, NAD, non-dysmorphic
- **HEENT**: AFSOF, pink MMM, PERRL, no midline defects
- **Neck**: +goiter (smooth, mobile, no nodules, 6x1.5 cm), isthmus 1 cm in length
- **CV/Resp/Chest**: RRR, C TAB
- **GU**: nL external, prepubertal genitalia
- **Neuro**: alert, no focal deficits, nL reflexes, nL suck, slightly decreased tone
- **Skin**: warm, dry
LABS/IMAGING

- TSH 8.08 (1.3-16 mcU/mL)
- Total T4 16.0 (8.2-19.9 mcg/dL)
- Free T4 2.84 (0.86-4.46 ng/dL)
- Total T3 207 (89-405 ng/dL)
- TG Ab 1 (<0.4 KU/mL)
- TPO Ab 30 (<0.4 KU/mL)
- TSI <1.0 (<1.3)
- TRAb <1.0 (<1.75 IU/mL)

- Fetal MRI: **Bilateral prominence** of homogeneous T2-low and T1-high signal tissue in the region of the thyroid. This is **compatible with fetal goiter**. The gland measures approximately **42 x 24 mm in transaxial dimension**. Sagittal imaging reveals the airway to be patent and fluid-filled from the oral cavity to the lungs.
CLINICAL OBJECTIVES

1. Review fetal thyroid physiology and affects of ATDs
2. Discuss fetal goiter development
3. Identify the association between maternal TFTs and fetal goiter development
4. Examine the relationship between maternal PTU dose and fetal goiter development
FETAL THYROID FUNCTION

- Fetus begins to metabolize thyroid hormones early in the 1st trimester
  - Production and secretion reach appreciable levels in the 2nd trimester
- Until then, the fetus is dependent on the maternal supply
- At term $\geq 30\%$ of the fetal thyroid hormones are of maternal origin
  - Due to preferential placental deiodination (by type 3 deiodinases) of T4 to rT3 → preventing fetal hyperthyroidism
ATD AFFECT ON THYROID FUNCTION

- ATDs cross the placenta and block the activity of fetal thyroid peroxidase
  - And also peripheral deiodination with maternal PTU tx → increased risk fetal hypothyroidism and goiter
- Likely have no direct effect on the fetus prior to onset of fetal thyroid function
  - Iodide uptake and colloid formation begin at 11 weeks GA
FETAL AND NEWBORN TFTs

- TSH
- T₃
- T₄

Graph showing changes in TSH, T₃, and T₄ levels with gestational age and post-birth.
## TFTs BY AGE

<table>
<thead>
<tr>
<th>Gestation (weeks)</th>
<th>Age of specimen</th>
<th>Free T4 (ng/dL)</th>
<th>T4 (microgram/dL)</th>
<th>T3 (ng/dL)</th>
<th>TSH (mU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23-27 weeks</td>
<td>Cord</td>
<td>1.28 ± 0.4</td>
<td>5.4 ± 2.0</td>
<td>20 ± 15</td>
<td>6.8 ± 2.9</td>
</tr>
<tr>
<td></td>
<td>7 d</td>
<td>1.47 ± 0.6</td>
<td>4.0 ± 1.8</td>
<td>33 ± 20</td>
<td>3.5 ± 2.6</td>
</tr>
<tr>
<td></td>
<td>14 d</td>
<td>1.45 ± 0.5</td>
<td>4.7 ± 2.6</td>
<td>41 ± 25</td>
<td>3.9 ± 2.7</td>
</tr>
<tr>
<td></td>
<td>28 d</td>
<td>1.50 ± 0.4</td>
<td>6.1 ± 2.3</td>
<td>63 ± 27</td>
<td>3.8 ± 4.7</td>
</tr>
<tr>
<td>28-30 weeks</td>
<td>Cord</td>
<td>1.45 ± 0.4</td>
<td>6.3 ± 2.0</td>
<td>29 ± 21</td>
<td>7.0 ± 3.7</td>
</tr>
<tr>
<td></td>
<td>7 d</td>
<td>1.82 ± 0.7</td>
<td>6.3 ± 2.1</td>
<td>56 ± 24</td>
<td>3.6 ± 2.5</td>
</tr>
<tr>
<td></td>
<td>14 d</td>
<td>1.65 ± 0.4</td>
<td>6.6 ± 2.3</td>
<td>72 ± 28</td>
<td>4.9 ± 11.2</td>
</tr>
<tr>
<td></td>
<td>28 d</td>
<td>1.71 ± 0.4</td>
<td>7.5 ± 2.3</td>
<td>87 ± 31</td>
<td>3.6 ± 2.5</td>
</tr>
<tr>
<td>31-34 weeks</td>
<td>Cord</td>
<td>1.49 ± 0.3</td>
<td>7.6 ± 2.3</td>
<td>35 ± 23</td>
<td>7.9 ± 5.2</td>
</tr>
<tr>
<td></td>
<td>7 d</td>
<td>2.14 ± 0.6</td>
<td>9.4 ± 3.4</td>
<td>92 ± 36</td>
<td>3.6 ± 4.8</td>
</tr>
<tr>
<td></td>
<td>14 d</td>
<td>1.98 ± 0.4</td>
<td>9.1 ± 3.6</td>
<td>110 ± 41</td>
<td>3.8 ± 9.3</td>
</tr>
<tr>
<td></td>
<td>28 d</td>
<td>1.88 ± 0.5</td>
<td>8.9 ± 3.0</td>
<td>120 ± 40</td>
<td>3.5 ± 3.4</td>
</tr>
<tr>
<td>≥37 weeks</td>
<td>Cord</td>
<td>1.41 ± 0.3</td>
<td>9.2 ± 1.9</td>
<td>60 ± 35</td>
<td>6.7 ± 4.8</td>
</tr>
<tr>
<td></td>
<td>7 d</td>
<td>2.70 ± 0.6</td>
<td>12.7 ± 2.9</td>
<td>148 ± 50</td>
<td>2.6 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>14 d</td>
<td>2.03 ± 0.3</td>
<td>10.7 ± 1.4</td>
<td>167 ± 31</td>
<td>2.5 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>28 d</td>
<td>1.65 ± 0.3</td>
<td>9.7 ± 2.2</td>
<td>176 ± 32</td>
<td>1.8 ± 0.9</td>
</tr>
</tbody>
</table>
CLINICAL OBJECTIVES

1. Review fetal thyroid physiology and affects of ATDs
2. Discuss fetal goiter development
3. Identify the association between maternal TFTs and fetal goiter development
4. Examine the relationship between maternal PTU dose and fetal goiter development
FETAL GOITER DEVELOPMENT

Mother
- Stimulatory TSH receptor antibodies
  - Stimulation of TSH receptor
    - Increased thyroid hormone levels
      - Hyperthyroidism
      - Goiter
      - Risk of: Polyhydramnios, Premature labor, Airway obstruction

Placenta
- ATD treatment
  - Blockage of deiodination and TPO activity
    - Decreased thyroid hormone levels
      - Hypothyroidism
      - Goiter

Fetus
- Inhibitory TSH receptor antibodies
  - Blockage of TSH receptor
    - Decreased thyroid hormone levels
      - Hypothyroidism
Antithyroid drug-induced fetal goitrous hypothyroidism

Sofie Bliddal, Åse Krogh Rasmussen, Karin Sundberg, Vibeke Brocks and Ulla Feldt-Rasmussen

- 48 case reports and 7 larger studies from 1980-2009
- Group A (n=23) PO maternal ATD + intra amniotic LT4
- Group B (n=25) PO maternal ATD
- Fetal goiter detected at ~29 wks GA in 23 pregnancies

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mat. TSH &gt;2.5 mU/L</td>
<td>7/11</td>
<td>1/7</td>
</tr>
<tr>
<td>Low Mat. FT4</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>+TRAb</td>
<td>9/14</td>
<td>5/12</td>
</tr>
<tr>
<td>Avg PTU dose</td>
<td>289 mg/d</td>
<td>222.8 mg/d</td>
</tr>
<tr>
<td>Fetal TSH</td>
<td>9.7–1,640 mU/L (avg 38.0)</td>
<td>40.2–56 mU/L</td>
</tr>
<tr>
<td>Goiter at birth</td>
<td>7/17</td>
<td>6/13</td>
</tr>
<tr>
<td>Neonatal hypothyroidism</td>
<td>6/22</td>
<td>8/22</td>
</tr>
</tbody>
</table>
CONCLUSIONS

- No correlation with goiter development and duration of maternal GD or PTU dose
- Maternal hypothyroxinemia seems to be the most reliable maternal indicator of fetal hypothyroidism
- After dx of fetal hypothyroidism, PTU dose should be adjusted to maintain maternal FT4 within trimester-specific reference ranges
  - Group A: Decrease in goiter size in 0.5-2.5 wks
  - Group B: Decrease in goiter size in 1-9 wks
Management of neonates born to women with Graves’ disease: a cohort study
Alix Besançon¹, Jacques Beltrand¹,², Isabelle Le Gac¹, Dominique Luton³ and Michel Polak¹,²

- Prospective study of 68 neonates born to mothers with GD from 1999-2002
  - Avg ages at enrollment = 33 yrs and GA 17 weeks
- Inclusion criteria: GD diagnosed by an endocrinologist
- Mothers: monthly TFTs
  - ATD dose adjusted to maintain FT4 at upper limit of nL
- Neonates: Cord blood sampling at time of delivery, day 7, 15, and 30
## CLINICAL PRESENTATION

<table>
<thead>
<tr>
<th></th>
<th>TRAB⁻ve/ATD⁻ve (n=27)</th>
<th>TRAB⁻ve/ATD⁺ve (n=8)</th>
<th>TRAB⁺ve/ATD⁺ve (n=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine fetal death</td>
<td>0</td>
<td>0</td>
<td>1 (35 WG, due to fetal hyperthyroidism)</td>
<td></td>
</tr>
<tr>
<td>Preterm birth (&lt;37 WG)</td>
<td>3</td>
<td>1 (after fetal blood sampling)</td>
<td>5</td>
<td>(NS)</td>
</tr>
<tr>
<td>Very premature birth (&lt;32 WG)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>(NS)</td>
</tr>
<tr>
<td>Low BW (&lt;10th percentile)</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td>0.27 (NS)</td>
</tr>
<tr>
<td>Birth length (&lt;10th percentile)</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>(NS)</td>
</tr>
<tr>
<td>Abnormal symptoms</td>
<td>2⁵⁺</td>
<td>0</td>
<td>5⁶⁺</td>
<td>(including one with tetralogy of Fallot, one with left ventricular hypertrophy and pericardial detachment, and one with ventricular dysfunction)</td>
</tr>
<tr>
<td>Clinical goiter</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>0.02</td>
</tr>
<tr>
<td>Goiter (ultrasonography)</td>
<td>3</td>
<td>4</td>
<td>13</td>
<td>1 (NS)</td>
</tr>
<tr>
<td>Congenital heart defects (echocardiography)</td>
<td>2 (PFO in premature infants)</td>
<td>3 (two atrial septal defects and one ventricular septal defect)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Other congenital birth defects</td>
<td>1 congenital pulmonary airway malformation</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bone maturation⁷⁺</td>
<td>0</td>
<td>0</td>
<td>1 (9 cases, due to fetal hyperthyroidism)</td>
<td></td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
TRAb TITERS

- Intrauterine death
- Newborns treated by ATDs for neonatal hyperthyroidism
CONCLUSIONS

Mother:
• +TRAb \( \rightarrow \) increased risk of hyperthyroidism in the neonate
• –TRAb (+/– ATD tx) \( \rightarrow \) neonatal euthyroidism

Neonate (cord blood sampling):
• +TRAb \( \rightarrow \) sig risk of neonatal hyperthyroidism
• –TRAb \( \rightarrow \) standard follow-up w/o extra TFT monitoring
• No correlation between TFTs and postnatal risk of hyperthyroidism
• Rapid FT4↑ during the 1st postnatal wk may predict hyperthyroidism
  • consider ATD tx
NEONATAL GOITER AFTER MATERNAL PTU THERAPY

Burrow GN. J Clin Endocrinol Metab 1965.
BACK TO OUR PATIENT...
# FOLLOW-UP LABS

<table>
<thead>
<tr>
<th>Age</th>
<th>2 days</th>
<th>14 days</th>
<th>10 wks</th>
<th>3.5 mos</th>
<th>5.5 mos</th>
<th>12 mos</th>
<th>NL 1-11 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>8.08</td>
<td>2.59</td>
<td>2.06</td>
<td>1.96</td>
<td>1.29</td>
<td></td>
<td>0.9-7.7</td>
</tr>
<tr>
<td>TT4</td>
<td>16.0</td>
<td>11.1</td>
<td>10.9</td>
<td>10.3</td>
<td>0.72</td>
<td></td>
<td>6.1-14.9</td>
</tr>
<tr>
<td>FT4</td>
<td>2.84</td>
<td>2.03</td>
<td>1.59</td>
<td>1.49</td>
<td>1.80</td>
<td>1.69</td>
<td>0.48-2.34</td>
</tr>
<tr>
<td>TT3</td>
<td>207</td>
<td>166</td>
<td>199</td>
<td>158</td>
<td>160</td>
<td></td>
<td>85-250</td>
</tr>
</tbody>
</table>

- Goiter <0.5 cm
- Goiter 6 cm
- Thyroid not palpable
GROWTH

Weight

Length
SUMMARY

- Ob to inform endo if h/o maternal GD
- Adult endo to inform peds endo for neonatal w/u
- For maternal GD: TRAb testing in the 3rd trimester
  - If positive, consider checking for TRAb on cord blood
- Neonates born to TRAb+ mothers should also have TFTs checked at birth and repeated between days 3-5 or sooner if +symptoms
  - Consider ATD tx if maternal FT4 >2.5 ng/dL
REFERENCES