INFANT OF A MOTHER WITH GRAVES DISEASE

Endorama
May 14th, 2015
Carmen Mironovici, M.D.
Chief Complaint

- Newborn born to a mother with autoimmune hyperthyroidism
HPI

- Male infant born at 39w 2d gestation via C/S to a 32 year-old G2P2002 mother

- Pregnancy: uncontrolled maternal Graves, high thionamide doses; also GBS + (s/p PCN x6 doses intrapartum)
  - Labor induced due to uncontrolled Graves
  - C/S delivery due to failure to dilate, prior C/S

- Fetal U/S: no goiter

- APGARS: 9 at 1 min and 9 at 5 min of life
- AGA: Birth weight 3340 g (75% ile), length 50 cm (75% ile), HC 35 cm (75% ile)
Maternal History

• Graves disease dx’d 8/2013 (+ antibodies by maternal report)
  • Methimazole 30 mg/day
• Switched to PTU 150 mg BID at initial prenatal visit (Nigeria)
• Prenatal care: Initially in Nigeria; UCMC after 28 weeks *(2/18/15)*
• 3/27/15 (at 34+5/7 wks): TSH <0.01, FT4 4.21
  • Had run out of PTU 2 weeks prior; restarted on 3/28/15
  • 4/1/15 – primary OB saw labs, asked patient to come to L&D
• 4/2/2015: TSH <0.01, FT4 4.33, TT4 >24, TT3 223 → L&D 4/2
  • -> endo consult (thank you, Drs. O’Sullivan and Sargis)
    • PTU dose increased to 200 mg q8h
• 4/15/15: TSH 0.01 and FT4 2.78
• 4/26/15 (39 weeks gestation): induction of labor given uncontrolled thyrotoxicosis → failure to dilate → repeat C/S
# Maternal TFTs

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</thead>
<tbody>
<tr>
<td><strong>FT4 (ng/dL)</strong></td>
<td>0.65-1.07</td>
<td>4.21 (H)</td>
<td>4.33 (H)</td>
<td>2.78 (H)</td>
<td>2.45 (H)</td>
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<tr>
<td><strong>TSH (mIU/mL)</strong></td>
<td>0.3-3.0</td>
<td>&lt; 0.01 (L)</td>
<td>&lt; 0.01 (L)</td>
<td>0.01 (L)</td>
<td>&lt; 0.01 (L)</td>
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<tr>
<td><strong>TSI</strong></td>
<td>&lt;=1.3</td>
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<td>3.5 (H)</td>
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<tr>
<td><strong>Total T4 (ug/dL)</strong></td>
<td>7.5-14</td>
<td>&gt;24.0 (H)</td>
<td>&gt;24.0 (H)</td>
<td>22.2 (H)</td>
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<tr>
<td><strong>Total T3 (ng/dL)</strong></td>
<td>120-197</td>
<td>223 (H)</td>
<td>226 (H)</td>
<td>177</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Admitted for IOL</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
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<tr>
<td><strong>Constitutional:</strong> No fever, no fatigue</td>
<td><strong>EYES:</strong> Bulging</td>
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<tr>
<td><strong>Endo:</strong> No polys</td>
<td><strong>GU:</strong> breast development</td>
<td></td>
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<tr>
<td>No heat/cold intolerance (beyond neonate norms)</td>
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<tr>
<td><strong>HENT:</strong> No neck swelling</td>
<td><strong>Skin:</strong> + Jaundice <em>(G6PD deficiency, bili stable, no phototherapy)</em></td>
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<td><strong>Resp:</strong> Negative</td>
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<tr>
<td><strong>CV:</strong> No tachycardia</td>
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<tr>
<td><strong>GI:</strong> No abdominal pain or distention</td>
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<tr>
<td><strong>MSI:</strong> No joint swelling</td>
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<tr>
<td><strong>CNS:</strong> No irritability, no weakness</td>
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</tbody>
</table>
Physical Exam

• Vitals: T 98.4F; HR 124/min; RR 35/min; BP 74/42; SaO₂: 94%
• W: 3295 g (62%ile); L: 50 cm (75%ile); HC: 36 cm (75%ile)
• HENT: AFOSF; no craniosynostosis. No macroglossia.
• Eyes: Exophtalmos B/L. Baby able to close eyes. No significant chemosis. + Scleral icterus.
• Neck: No goiter
• CV: RRR, Normal S1, S2
• Chest: Tanner III breast development with milky breast discharge B/L. Compressed breast tissue: 4 cm B/L
• Abdominal: no umbilical hernia
• GU: Normal circumcised male external genitalia. Tanner 1 male genitalia, pubic hair. Testes descended in scrotum bilaterally.
• Skin: warm, dry, mild jaundice
• Neuro: no jitteriness, no irritability, no lethargy
WHAT ARE THE POSSIBLE HPT AXIS PERTURBATIONS IN THIS INFANT?
A priori: Possible HPT axis perturbations infant

- Fetal &/or neonatal hyperthyroidism (neonatal Graves)
  - Transplacental TSI transfer

- Fetal &/or neonatal (primary) hypothyroidism:
  - Transplacental transfer of blocking TSH-R Abs
  - Overtreatment of mother → transplacental thionamide transfer → suppression of infant HPT axis

- Central hypothyroidism
  - Maternal thyrotoxicosis → impaired maturation of HPT axis

Stagnaro-Green A et al. ATA Guidelines for Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum. Thyroid 2011
• WHAT LABS DO YOU WANT TO GET?
# Initial Labs

<table>
<thead>
<tr>
<th></th>
<th>Reference Range</th>
<th>4/29/15 11:30</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FT4 (ng/dL)</strong></td>
<td>Cord blood: 1.41 +/-0.39</td>
<td>1.07</td>
</tr>
<tr>
<td><strong>TSH (mIU/L)</strong></td>
<td>Cord blood: 6.7 +/- 4.8</td>
<td>0.59 (L)</td>
</tr>
<tr>
<td><strong>Total T4 (mcg/dL)</strong></td>
<td>Cord: 9.2 +/- 1.94</td>
<td>8.5</td>
</tr>
<tr>
<td><strong>Total T3 (ng/dL)</strong></td>
<td>Cord: 60 +/- 34</td>
<td>84</td>
</tr>
</tbody>
</table>

TSH rec Abs: pending
ASSESSMENT?
Thyroid function fetal and neonatal life

Pollak M. et al, Best Practice & Research Clinical Endocrinology & Metabolism, 2004
## Complete lab evaluation

<table>
<thead>
<tr>
<th>Test</th>
<th>Ref Range (cord blood and DOL 7: thyroidmanager.org)</th>
<th>4/29/15 11:30 HrOL 24</th>
<th>4/30/15 13:11 HrOL 50 (DOL 2) (breastfed)</th>
<th>5/2/15 05:59 DOL 4 (formula)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT4 (ng/dL)</td>
<td>Cord blood: 1.41+/−0.39 ; DOL 7: 2.7</td>
<td>1.07</td>
<td>1.01 (L)</td>
<td>0.83 (L)</td>
</tr>
<tr>
<td>TSI</td>
<td>&lt;=1.3</td>
<td>4.4 (H)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRAB (iU/L)</td>
<td>0.00-1.75</td>
<td>13 (H)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>Cord blood: 6.7±4.8 Post-TSH surge: up 60-70 DOL 7: 2.6+/− 1.8</td>
<td>0.59 (L)</td>
<td>0.86 (L)</td>
<td>2.43</td>
</tr>
<tr>
<td>Total T4 (mcg/dL)</td>
<td>Cord: 9.2+/− 1.94 DOL 7: 12.6+/−2.87</td>
<td>8.5</td>
<td>8.7</td>
<td>7.1 (L)</td>
</tr>
<tr>
<td>Total T3 (ng/dL)</td>
<td>Cord: 60+/− 34 DOL 7: 147+/− 50</td>
<td>84</td>
<td>86 (L)</td>
<td>75 (L)</td>
</tr>
</tbody>
</table>
INTERPRETATION OF LABS AND PLAN?
Our assessment

- Neonatal Graves
  - Transplacental TSI transfer

- Primary hypothyroidism:
  - Transplacental transfer of blocking TSH-R Abs
  - Overtreatment of mother → transplacental thionamide transfer → suppression of infant HPT axis

- Central hypothyroidism
  - Maternal thyrotoxicosis → impaired maturation of HPT axis
Interim plan

• Baby in house extra days while mother in MICU → Reassess baby’s TFTs in 48 hr to determine if T4, T3 are recovering

• If T4 and/or T3 remain low, plan to initiate L-T4 replacement

• Given the presence of maternal TSI in the baby’s blood, he remains at risk for developing neonatal Graves disease

• Monitor the baby for s/s of hyper- and hypothyroidism

• Ophthalmology exam

• Mother cannot breastfeed at present
Questions

1) What is the mechanism for development of central hypothyroidism in infants of mothers with GD?
Neonatal Central Hypothyroidism in infants of mothers with Graves

- First reported in 1988; incidence: 1 per 35,000 neonates (Kempers MJ et al. JCEM 88 (12), 2003)
- Usually seen in 1st week of life following uncontrolled maternal thyrotoxicosis
  - leads to a hyperthyroid fetal environment
  - During the period of fetal and neonatal hyperthyroidism, TSH secretion is suppressed
  - Secondary hypothyroidism (+/- preceded by neonatal thyrotoxicosis) may be seen until pituitary TSH secretion is restored
  - Likely cause: excess maternal T4, not transplacentally-transferred TSH receptor antibodies (Higuchi et al. 2007)
- Case reports of neonates with low TSH, low normal/normal FT4 levels in cord blood which subsequently declined to subnormal levels on serial monitoring (at DOL 4-7). (Higuchi et al, 2007; Yamanda et al. 2008)
Neonatal Central Hypothyroidism

• Only a minority of newborns from mothers with Graves disease develop central hypothyroidism
  (Uenaka M et al. Eur J of Reprod Biology, 2014)
• Fetal thyroxine may be elevated due to passive transfer of maternal thyroxine during the last trimester leading to suppression of fetal pituitary-thyroid axis
• After birth, high levels of thyroid hormones produced by fetal thyroid as a result of passively transferred TRAb may also impair the fetal hypothalamic-pituitary thyroid system
  (Ogilvy-Stuart A L et al. Paed Child Health. 2007)
Questions

1) What is the mechanism for development of central hypothyroidism in infants of mothers with GD?

2) What is the timeline of HPT axis recovery?
### Cases of Central Hypothyroidism related to Maternal Thyrotoxicosis

<table>
<thead>
<tr>
<th>Gestational Age, wk</th>
<th>Birth Weight, g</th>
<th>Maternal Graves’ Disease, Onset, Control at Delivery</th>
<th>Thyrotoxicosis, Duration</th>
<th>TRAb (TSAb), %</th>
<th>Hypothyroidism, Onset, Recovery</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>1152</td>
<td>Pregestation, poor</td>
<td>2 d</td>
<td>16</td>
<td>12 d, 6 mo</td>
<td>Case 1</td>
</tr>
<tr>
<td>30</td>
<td>1620</td>
<td>Pregestation, poor</td>
<td>2 d</td>
<td>88.7</td>
<td>16 d, 15 mo</td>
<td>Ref 7</td>
</tr>
<tr>
<td>31</td>
<td>1474</td>
<td>Pregestation, poor</td>
<td>3 mo</td>
<td>(2438)</td>
<td>7 mo, &gt;18 mo</td>
<td>Ref 9</td>
</tr>
<tr>
<td>33</td>
<td>2016</td>
<td>23 wk gestation, partial</td>
<td>—</td>
<td>45.2</td>
<td>0 d, 24 mo</td>
<td>Ref 11</td>
</tr>
<tr>
<td>34</td>
<td>2455</td>
<td>Pregestation, partial</td>
<td>—</td>
<td>42.7</td>
<td>4 d, 13 mo</td>
<td>Case 2</td>
</tr>
<tr>
<td>36</td>
<td>3250</td>
<td>Pregestation, partial</td>
<td>—</td>
<td>ND</td>
<td>4 d, &gt;4 mo</td>
<td>Ref 8</td>
</tr>
<tr>
<td>37</td>
<td>3244</td>
<td>31 wk gestation, good</td>
<td>—</td>
<td>20.3</td>
<td>2 d, 20 mo</td>
<td>Case 3</td>
</tr>
<tr>
<td>38</td>
<td>2735</td>
<td>Pregestation, poor</td>
<td>—</td>
<td>Negative</td>
<td>4 d, &gt;3 mo</td>
<td>Ref 8</td>
</tr>
<tr>
<td>38</td>
<td>3490</td>
<td>Around delivery, poor</td>
<td>—</td>
<td>Negative</td>
<td>7 d</td>
<td>Ref 8</td>
</tr>
</tbody>
</table>

Higuchi R et al. Pediatrics, 2005
Questions

1) What is the mechanism for development of central hypothyroidism in infants of mothers with GD?

2) What is the timeline of HPT axis recovery?

3) If + TSI, what are the chances of developing neonatal Graves?
Prediction of neonatal hyperthyroidism in infants born to mothers with Graves

- Measurement of TSH receptor Abs in infants born to mothers with Graves would predict the development of neonatal hyperthyroidism.
- In 50% infants with +TSI, clinical and biochemical signs of hyperthyroidism developed between 1 - 29 days of age.
- The development of hyperthyroidism could not be predicted by initial measurements of serum T4, FT4, T3 or TSH.

TSH Rec Abs in pregnancy

Mestman JH. Best Practice & Research Clin Endocrinol & Metab, 2004
Back to our patient

- Mother transferred from MICU to floor DOL 5, discharged (at her insistence) the following day (Sunday)
- Got baby into clinic DOL 8
- Clinically stable – vitals: T 36.6 C, HR 128, RR 44, doing fine, feeding Enfamil
  - Physical exam
    - exophthalmos, chemosis, jaundice
    - Unrelated: gynecomastia, galactorrhea
- Wants to go back to Nigeria at month’s end
## Follow-up labs

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<tbody>
<tr>
<td>FT4 (ng/dL)</td>
<td>DOL 7: 2.7 +/- 0.57</td>
<td>0.75</td>
<td>0.85</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>DOL 7: 2.6+/-. 1.8</td>
<td>3.02</td>
<td>5.46</td>
</tr>
<tr>
<td>Total T4 (mcg/dL)</td>
<td>DOL 7: 12.6+/-. 2.87</td>
<td>6.4</td>
<td>7.0</td>
</tr>
<tr>
<td>Total T3 (ng/dL)</td>
<td>DOL 7: 147+/-. 50</td>
<td>84</td>
<td>146</td>
</tr>
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</table>
Conclusions

• Neonatal central hypothyroidism can be caused by insufficient treatment for maternal hyperthyroidism during pregnancy

• High levels of serum thyroxine in the maternal circulation cross the placenta and affect the pituitary, with suppression of TSH levels in fetuses

• It is usually detected during first week of life

• Recovery of the HPT axis varies from months to years
References

- Higuchi R, Miyawaki M, Kumagai T, Okutani T. Central hypothyroidism in infants who were born to mothers with thyrotoxicosis before 32 weeks’ gestation: 3 cases. Pediatrics 2005; 115; e623