Neonatal Graves Disease: A Case Study

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Disclosures

- No disclosures
- No discussion of off label medication or treatment

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Learning Objectives

- Discuss pathophysiology of neonatal Graves disease (GD)
- Review maternal and newborn monitoring for neonates born to mothers with GD
- Discuss medication management and lab monitoring for neonates born to mothers with GD
- Demonstrate the need for APRNs in caring for these high risk neonates

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Neonatal Graves Disease

- Estimated 0.1% - 0.4% of pregnant women have GD
- Only 0.6% - 1% of children born to these women will have hyperthyroidism
- Transient neonatal hyperthyroidism is rare, affecting 1:50,000 neonates

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Transient Maternal Antibodies

- Most cases of neonatal GD due to transfer of maternal thyroid stimulating immunoglobulins (TSIs) to fetus
  - Stimulates fetal thyroid by activation of thyroid stimulating hormone receptors (TSH-R)
  - Creates increase in thyroid hormone secretion → leads to thyrotoxicosis
  - Occurs first in utero, then postnatally until maternal antibodies have cleared infant's circulation

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Maternal Risk Factors

- Hyperthyroidism diagnosed during pregnancy
- Women with known GD on anti-thyroid drug (ATD) therapy during pregnancy
- Known remission after ATD therapy
- History of RI-ablation (RAI) or thyroidectomy

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Case Study

- Baby born at 35 weeks GA to mother with known history of hypothyroidism, s/p RAI for GD
- Newborn period c/b respiratory distress requiring CPAP in first 24 hours of life, cardiomegaly, hypotension, and initial feeding without return to birth weight
- NBS performed x2 (first performed at < 24 hours of life so not valid); repeat "normal"

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Case Study

- Persistent tachycardia and tachypnea; 1.5 weeks of life had thyroid labs drawn
  - Free T4 > 8 ng/dL (normal for age is < 2.0); TSH suppressed
- On call endocrinologist notified and recommended start of methimazole compounded at 3 mg/ml at 0.14 ml by mouth Q 8 hours (0.5 mg/kg)
- TSI positive at 4.7; TRAB positive at 9.08 (reference range 0 -1.75)

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Typical Clinical Presentation

- IUGR
- Fetal tachycardia
- Premature birth frequent
- Goiter
- Affects both sexes equally
- Signs appear several days after birth, particularly if mother is on ATD during pregnancy
- In utero: if both TSHR-blocking antibodies and TSIs present in neonate → may be euthyroid

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Diagnosis of Neonatal GD

- Free T4, Total T3, and TSH
  - Even if normal initially, repeat 3-7 days later
  - May have delayed appearance of hyperthyroidism particularly if mother on ATDs and cleared after 3 days
- TSI to determine autoimmune origin
- Anti-TSHR antibodies

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Treatment of Neonatal GD

- Methimazole: ATD of choice
  - Dosing: 0.5 to 1 mg/kg/day, divided in 2 doses
- Propylthiouracil (PTU): concern for liver toxicity particularly in pediatrics
- Propranolol may be considered to restore normal HR

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Monitoring of Neonatal GD

- Should initially be monitored clinically/biochemically weekly
- Tapering of ATDs and B-blockers can be initiated as:
  - Free T4 and T3 values fall in the lower ½ of normal range for age
- Serum TSH may be suppressed 1-2 months
- Treatment should be maintained as long as TSIs detectible (usually 3-12 weeks)
- May apply "block and replace" approach
  - ATD and levothyroxine
- Treatment required for 1 month on average

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Initial Consultation - 4 weeks

- At 4 weeks of age (2 weeks post D/C from NICU)
  - Continues on methimazole 0.21 ml or 0.42 mg Q6 hours (2mg/1 ml)
  - Thyroid labs:

	Value	Reference Range
TSH	0.02	0.3 – 4.5 uIU/mL
Free T4	1.0	0.7 – 1.5 ng/dL

  - Impression: TSH low, Free T4 normal
  - Plan: No change in methimazole. Repeat thyroid labs at end of week

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Lab monitoring- 5 weeks

	Value		Reference Range
	5 weeks	4 weeks	
TSH	<0.01 (L)	0.02	0.5-6.0 mU/L
Free T4	0.73 (L)	1.0	(0.76 - 1.46 ng/dL)

- Impression: Becoming hypothyroid
- Plan: Decrease methimazole to 0.42 mg TID (0.21 ml). Repeat thyroid labs in 1 week.

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Lab monitoring- 6 weeks

	Value			Reference
	6 weeks	5 weeks	4 weeks	
TSH	0.08(L)	<0.01 (L)	0.02	0.5-6.0 mU/L
Free T4	0.38 (L)	0.73 (L)	1.0	0.76-1.46 ng/dL
T3 Total	54			105-269 ng/dL

- Impression: Hypothyroid. Presumably has metabolized maternal GD antibodies
- Plan: Discontinue methimazole. Repeat thyroid labs in 1 week.

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Lab monitoring- 7 weeks

	Value				Ref Range
	7 weeks	6 weeks	5 weeks	4 weeks	
TSH	0.95	0.08(L)	<0.01 (L)	0.02	0.5-6.0 mU/L
Free T4	0.37 (L)	0.38 (L)	0.73 (L)	1.0	0.76-1.46
T3 Total	64	54			105-269 ng/dL

- Impression: Remains hypothyroid off all methimazole at this time although total T3 is improving.
- Plan: Start 25 mcg of levothyroxine. Repeat labs in 1 week.

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Lab monitoring- 8 weeks

	Value					Reference Range
	8 weeks	7 weeks	6 weeks	5 weeks	4 weeks	
TSH	0.28 (L)	0.95	0.08(L)	<0.01 (L)	0.02	0.50 - 6.00 mU/L
Free T4	1.04	0.37 (L)	0.38 (L)	0.73 (L)	1.0	0.76 - 1.46 ng/dL
T3 total		64	54			

- Impression: Free T4 has now normalized.
- Plan: Continue levothyroxine at 25 mcg. Repeat labs in 2 weeks.

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Lab monitoring- 10 weeks

	Value						Reference Range
	10 wk	8 wk	7 wk	6 wk	5 wk	4 wk	
TSH	0.01	0.28 (L)	0.95	0.08(L)	<0.01 (L)	0.02	0.50 - 6.00 mU/L
Free T4	1.17	1.04	0.37 (L)	0.38 (L)	0.73 (L)	1.0	0.76 - 1.46 ng/dL
T3 total			64	54			

-Impression: Free T4 normal. TSH low.

-Plan: Levothyroxine may not be needed now that she is recovering.

- Reduce levothyroxine to 12.5 mcg daily
- Repeat labs in 2 weeks

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Lab monitoring- 3 months of age

	Value							Ref Range
	3 mo	10 wk	8 wk	7 wk	6 wk	5 wk	4 wk	
TSH	0.28	0.01	0.28 (L)	0.95	0.08(L)	<0.01 (L)	0.02	0.50 - 6.00 mU/L
Free T4	1.05	1.17	1.04	0.37 (L)	0.38 (L)	0.73 (L)	1.0	0.76-1.46 ng/dL
T3 total	133			64	54			105-269 ng/dL

-Impression: Lab results show normal Free T4 on reduced dose of levothyroxine. TSH remains mildly low but improving.

-Plan: DC levothyroxine. Repeat labs in 2 weeks.

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Lab monitoring- 3.5 months

	Value		Reference Range
	3.5 mo	3 mo	
TSH	1.0	0.28	0.50 - 6.00 mU/L
Free T4	0.90	1.05	0.76 - 1.46 ng/dL
T 3		133	

-Impression: Off all meds (methimazole and levothyroxine). Labs now normal.

-Plan: Remain off treatment. Clinic follow up in 1 month.

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4.5 months of age-clinic visit

	Value			Reference Range
	4 mo	3.5 mo	3 mo	
TSH	0.58	1.0	0.28	0.50 - 6.00 mU/L
Free T4	0.98	0.90	1.05	0.76 - 1.46 ng/dL
T3			133	

-Impression: Thyroid labs NORMAL. Baby is doing well developmentally.

-Plan: Follow up for regular WCC. Return to endocrine clinic for further endocrine concerns.

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Discussion

- Maternal antibodies typically cleared in infant after 3-12 weeks
- Can be assessed by TSI in infant
- Although most cases of neonatal GD transient, treatment is required to avoid:
  - Short-term complications (e.g. heart failure)
  - Long term complications (e.g. craniosynostosis, cognitive impairment)

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Maternal Screening/Treatment

- PTU preferred in 1st trimester (risk of aplasia cutis congenital, other malformations)
- 2nd/3rd trimester: transition to methimazole
- Maternal screening of TSI at 22-26 weeks gestation
  - If positive TSI, monthly US to detect fetal goiter
- **REMEMBER**: elevated TSIs may persist in 10% of women after thyroidectomy; 40% of women after RAI

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Conclusions

- The overall population-to-pediatric endocrinologist ratio within 20 miles: 39,492:1
- New patient appointments can be 2-3 months out (or more)
- While neonatal GD is rare: care is urgent with frequent lab monitoring
- APRNs can and do assist with management of rare thyroid disorders

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References

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Questions