THYROID DISEASE IN PREGNANCY: IS IT INCREASING?

Antepartum and Intrapartum Management Conference
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DISCLOSURES

• I have nothing to disclose

OBJECTIVES

• Review thyroid physiology in pregnancy
• Define thyroid pathophysiology
  – Hypothyroidism
    • Subclinical hypothyroidism
  – Hyperthyroidism
• Outline pregnancy management

THYROID PHYSIOLOGY

• Thyroid gland
  – Metabolism, growth, cognition, cardiovascular
    • Thyroxin (T4)
    • Triiodothyronine (T3)
  – Calcium homeostasis
    • Calcitonin

Ain et al. Endocrinol Metab 1987;65:689
THYROID CHANGES IN PREGNANCY

• Increased thyroxine-binding globulin (TBG)
  – Estrogen → 2x increase TBG
  – Increased serum total T4 & total T3
• TSH-receptor stimulated by hCG
  – Common alpha subunits
  – Homology between beta subunits
  – 10-20% pregnancies subclinical hyperthyroidism
    • Transiently low or undetectable TSH in the 1st trimester

Glinoer D. Endocr Rev 1997;18:404

THYROID LAB ISSUES IN PREGNANCY

• Free T4 assay may not be reliable
• Serum total T4 & T3 in pregnancy
  – 1.5X higher than non-pregnant women
  – TBG excess


IODINE NEEDS IN PREGNANCY

• Higher iodine needs in pregnancy
  – Increased thyroxine (T4) production
• IOM 2006
  – 220 mcg pregnancy
  – 290 mcg lactation
• ATA 2011
  – 150 mcg in prenatal vitamins
• Excessive iodine detrimental
  – Fetal hypothyroidism → fetal goiter
  – Upper limit of benign intake 600-1100 mcg daily

Stagnaro-Green et al. Thyroid 2001;21(10):1081

TRIMESTER SPECIFIC TSH (mIU/L)
NORMAL REFERENCE RANGES

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Lower limit</th>
<th>Upper limit</th>
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Dashe et al. Obstet Gynecol 2005;106:753

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GOITER IN PREGNANCY

- 10-40% thyroid enlargement
- Increased iodine excretion in urine
- Low risk iodine deficiency in U.S.


FETAL THYROID

- Fetal TSH production begins @10-12 wks
- Thyroid hormone production @18-20 wks
- Maternal thyroid hormone placental transport
  - Newborns with congenital absence of thyroid
    - 20-50% thyroid hormone levels of normal newborns
  - TSH receptor antibodies can cause fetal disease
    - Both hyper and hypothyroidism
  - Little Maternal TSH crosses to fetus
  - TRH can cross the placenta & stimulate fetal TSH

Burrow et al. NEJM 1994;331:1072

HYPOTHYROIDISM

- Globally → iodine deficiency #1 cause
- In the U.S. → Hashimoto’s most common
  - Chronic autoimmune thyroiditis
- Other etiologies
  - Treated Grave’s
  - Pituitary or hypothalamus disorders
- Diagnosis
  - Elevated TSH + decreased FT4

Stagnaro-Green et al. Thyroid 2001;21(10):1081

HYPOTHYROIDISM CLINICAL PICTURE

- U.S. prevalence 0.1-2.0%
  - 5Xs greater in women
  - 0.3-0.5% of screened pregnant women
- Symptoms
  - Weight gain
  - Fatigue
  - Constipation
  - Cold intolerance

Stagnaro-Green et al. Thyroid 2001;21(10):1081
HYPOTHYROIDISM PREGNANCY OUTCOMES
• Increased risk of adverse pregnancy outcomes
  – Infertility
  – Miscarriage
  – Preeclampsia
  – Placental abruption
  – Preterm delivery
  – NRFHT
  – Cesarean
  – Low birth weight
  – Postpartum hemorrhage
  – Child neuropsychological & cognitive impairment

Casey et al. Obstet Gynecol 2006;108:1283

SUBCLINICAL HYPOTHYROIDISM
• Diagnosis
  – Elevated TSH but normal FT4
  – General population prevalence 4-10%
    • 2.0-2.5% of screened pregnant women in the U.S.
• Controversial whether impacts pregnancy


RCT CRITIQUE
• Screened and Rx’d too late in GA?
• Age 3 too early for neurocognitive testing?
• 24% lost to follow up rate too high?
• More RCTs needed
• NICHD MFMU Network TSH trial pending
  – Thyroid therapy for mild thyroid deficiency in pregnancy
  – Follow up to age 5

Lazarus et al. NEJM 2012; 366:493

• RCT levothyroxine for SCH in pregnancy
  – 22,000 screened women, median 12w3d
  – TSH 3.8 screened v. 3.2 control
  – 390 LT4 150mcg v. 404 control, median 13w3d Rx
  – IQ no different age 3
    • Mean IQ 99.2 v. 100.0, IQ <85 12.1% v. 14.1%
HYPERTHYROIDISM

• Diagnosis
  – TSH<0.1 mIU/L & elevated FT4 +/- elevated FT3
  – TSH as low as 0.03-0.1 may still be physiologic
• Grave’s most common
  – Thyrotropin receptor antibody (TRAb)
  – Thyroid stimulating immunoglobulins (TSI)
• hCG mediated
  – No need to treat
• Toxic multinodular goiter
• Toxic adenoma
• Struma ovarii

Bahn et al. Thyroid 2011;21(6):593

HYPERTHYROIDISM CLINICAL PICTURE

• Prevalence general population 1.3%
  – More common in women 5:1
    • Older women 4:5
  – Uncommon in pregnancy
    • 0.1-0.4% of all pregnancies
• Symptoms
  – Overlap with pregnancy
    • Tachycardia, heat intolerance, increased perspiration
  – Anxiety
  – Tremor
  – Unexplained weight loss
  – Goiter & ophthalmopathy (Grave’s)

Krassas Endocr Rev 2010;31:702

HYPERTHYROIDISM PREGNANCY OUTCOMES

• Increased risk of adverse pregnancy outcomes
  – Miscarriage
  – Preeclampsia
  – IUFD
  – IUGR & low birth weight
  – Preterm labor/preterm delivery
  – Maternal CHF
  – Thyroid storm

Miller et al. Obstet Gynecol 1994;84:946

FETAL THYROID DISEASE

• Pregnant women with Grave’s
  – 1-5% newborns hyperthyroid
    • Fetal tachycardia
    • Fetal goiter, advanced bone age, craniosynostosis
    • IUGR
    • Hydrops
  – Trans-placental TSH receptor stimulating Abs
  – Higher risk with higher maternal titers

Weetman AP. NEJM 200;343:1236
CONGENITAL HYPOTHYROIDISM

• Agenesis or dysgenesis of the fetal thyroid
• Congenital dyshormonogenesis
• Iodine deficiency in endemic areas

THYROID PEROXIDASE ANTIBODIES

• Euthyroid but +TPO Abs
  – Adverse pregnancy outcomes
    • Miscarriage risk 2-3X higher
    • Preterm birth 2X higher
    • Perinatal mortality
    • Large for gestational age
  – 20% develop subclinical hypothyroidism

Thangaratinam et al. BMJ 2011;342:d2616

POSTPARTUM THYROIDITIS

• Transient hyperthyroidism within 1 year
• Prevalence 4.1%
  – 0.2% related to Grave’s disease
• Sometimes followed by hypothyroidism
  – Transient or permanent (rare)


THYROID STORM

• Life threatening
• Clinical presentation
  – Hyperpyrexia: T>103F/39.4C
  – CV dysfunction: tachycardia, CHF
  – Altered mental status
  – Goiter
  – Elevated FT4 +/- elevated FT3 + low TSH

ACOG Practice Bulletin 148, April 2015
RISK FACTORS FOR THYROID STORM

- Long standing untreated hyperthyroidism
- Precipitated by an acute event
  - Surgery
  - Trauma
  - Infection
  - Acute iodine load
  - Irregular or discontinuation of antithyroid Rx
  - PARTUITION

Sheffield et al. AJOG 2004;190:211

AUDIENCE QUESTION #1
Do you universally order TSH with 1st tri labs?

A. Yes
B. No
C. Sometimes

AUDIENCE QUESTION #2
34yo G1P0 @12 wks - TSH is 3.5 but FT4 normal

Do you start levothyroxine?
A. Yes
B. No
C. Maybe – counsel patient 1st
D. Don’t know

UNIVERSAL TSH SCREENING CONTROVERSIAL

- ACOG, ATA and Endocrine Society
  - Not universal but yes targeted
- ATA says screen pregnant women if:
  - Age >30
  - Infertility
  - Symptoms
  - Type I Diabetes
  - Morbid obesity (BMI ≥ 40 kg/m²)
  - History of PTD or recurrent miscarriage
  - Family or personal history of thyroid disease
  - History of head or neck radiation
  - From an area where iodine deficiency is endemic

ACOG Practice Bulletin 148 April 2015
ARGUMENTS IN FAVOR OF SCREENING

• Risk based TSH screening
  – Misses 1/3rd of women with hypothyroidism
• Treatment might increase IQ of offspring
  – Becomes cost-effective?

HYPOTHYROIDISM MANAGEMENT

• Medication
  – Thyroid hormone (T4) replacement
  – 30-50% increased need in pregnancy
    • As soon as UPT+ → double dose 2 days a week
• Lab surveillance
  – TSH & FT4 every trimester for dose adjustments
  – TSH & FT4 four weeks after dose adjustment
• Fetal surveillance
  – Usual obstetric care

Stagnaro-Green et al. Thyroid 2001;21(10):1081

HYPERTHYROIDISM MANAGEMENT

• Medication
  – PTU 1st tri → methimazole 2nd & 3rd tri
  – PTU risk of maternal hepatic failure
  – Methimazole risk of fetal aplasia cutis
  – Minimal dose needed
  – Beta blockers
• Lab surveillance
  – Goal = upper limit of normal FT4
  – Check FT4 every 4 weeks for dose adjustments
• Fetal surveillance
  – 3rd tri serial growth sonograms + antenatal testing

FDA WARNING

Stagnaro-Green et al. Thyroid 2001;21(10):1081

TPO ANTIBODY MANAGEMENT

• Levothyroxine for euthyroid women?
  – Not universally screening for TPO Abs
  – Treat if recurrent miscarriage?
  – Monitor TSH in pregnancy

Negro et al. J Clin Endocrinol Metab 2006;91:2587
THYROID NODULES

• Evaluation
  – TSH & FT4
  – Thyroid ultrasound
  – No thyroid radionuclide scanning
  – Yes FNA
  – If rapid growth or compressive symptoms:
    • Surgery ideally in 2nd trimester

Haugen et al. Thyroid 2016;26:1

THYROID CANCER

• Thyroid nodules → 12-43% cancer
• Diagnosis in pregnancy no impact on prognosis
• Slow growing so can delay surgery until postpartum
  – No negative impact on prognosis
• Suppressive thyroid hormone therapy
  – Goal TSH 0.1–1.5 mIU/L
• Thyroid ultrasound every trimester
  – Surgery in 2nd trimester if rapid growth
• Increased surgical complications in pregnancy
  – Hypoparathyroidism, hypocalcemia
  – Recurrent laryngeal nerve injury


HISTORY OF TREATED THYROID CANCER

• If radioiodine treatment:
  – Delay pregnancy 6 months
  – Might need additional radiation treatment
• No increased risk of recurrence in pregnancy
• If persistent disease & pregnant:
  – Thyroid ultrasound & thyroid labs every trimester
• Thyroid hormone suppression therapy
  – Increase dose needs in pregnancy
  – Check TSH every 4 weeks for dose adjustments


THYROID STORM MANAGEMENT

• ICU + endocrine consult
  – High mortality rate 8-25%
• Beta blocker – propranolol
  – BP & heart rate control
• Thionamide - PTU 200mg q4hrs
  – Blocks new hormone synthesis
  – PTU preferred because blocks T4 → T3
• Iodine solution 1 hour AFTER PTU given
  – Blocks thyroid hormone release
  – Delay to avoid it used as substrate for new hormone

THYROID STORM CONTINUED

- Glucocorticoids – IV hydrocortisone 100mg q8
  - Reduce T4 → T3 conversion
  - Vascular stability
  - Prevent adrenal insufficiency
- Bile acid sequestrant – cholestyramine 4g QID
  - Decrease enterohepatic recycling of thyroid hormones
- Balance of IVFs v. lasix
- May need digoxin
- Acetaminophen but avoid NSAIDs
  - Aspirin can ↓ protein binding + thus ↑ serum T4 & T3


CONCLUSION

- Is thyroid disease increasing in pregnancy?
  - Depends
    - Universally screening?
    - Subclinical hypothyroidism is clinically significant?

THANK YOU

- Ingrid Block-Kurbisch, Endocrinologist