

# OVERVIEW OF THYROID DISEASE IN PREGNANCY

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# OUTLINE

- ⦿ Thyroid physiology
- ⦿ Hyper and Hypothyroidism
- ⦿ Postpartum thyroiditis
- ⦿ Screening guidelines

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Management of Thyroid Dysfunction during Pregnancy and Postpartum

An Endocrine Society Clinical Practice Guideline

# CASE

28 year old G1P1 -now 13 months postpartum  
Planning another pregnancy.

She had hyperthyroidism diagnosed 8 months postpartum—but was symptomatic earlier.

Clinical exam-hyperthyroid, diffuse goiter  
-no eye signs

# CASE

What is the most likely diagnosis?

1. Postpartum thyroiditis
2. Graves Disease

What are the expected results of-

1. Thyroid scan and 24 hour I-131 uptake test
2. Thyroid antibodies

# CASE

How would you treat and monitor her now?  
During and after pregnancy?

1. Medications
2. Lab tests
3. Fetal/neonatal monitoring

# CASE

3 years later she returns at 8 weeks gestation and is on thyroxine replacement therapy.

How do you advise re-

1. Dose of synthroid
2. TSH and fT4 targets
3. Fetal risks

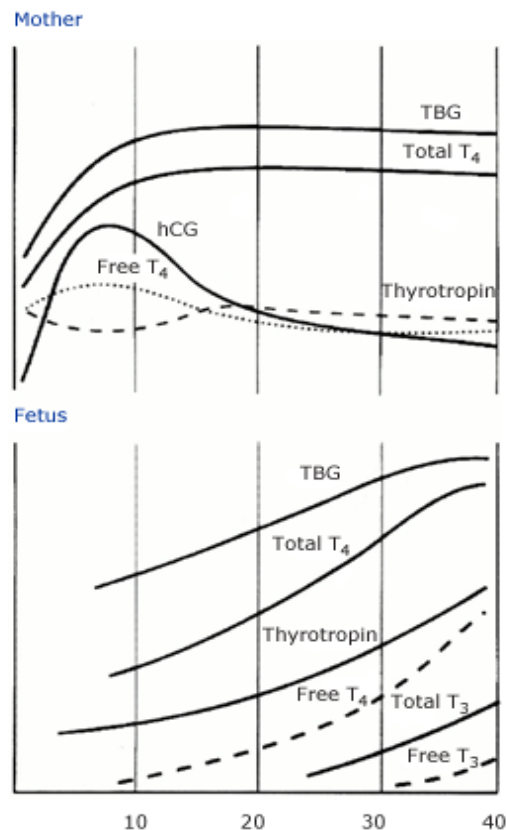
# FETAL THYROID PHYSIOLOGY

- Fetal thyroid begins trapping iodine at 10-12 weeks, but TSH stimulated synthesis and release of T4 and T3 occurs later after 20 weeks
- Maternal fT4 and fT3 cross the placenta to some extent (important before 20 weeks)
- Maternal TSH-receptor antibodies (stimulatory and inhibitory) can cross the placenta, but TSH does not

# MATERNAL THYROID PHYSIOLOGY

- ◉ Serum TBG concentrations rise almost 2X with resultant increase in TT4 and TT3, but not fT4 or fT3
- ◉ TSH levels fall mid-late first trimester coincident with rising hCG
- ◉ 10-12% of normal women have transiently “low” TSH levels when hCG are peaking.
- ◉ First trimester fT4 levels increase over nonpregnant reference range, then fall to 30% below the nonpregnant range.

# MATERNAL AND FETAL THYROID REGULATION



- Maternal TSH(thyrotropin) falls as hCG rises
- Fetal fT<sub>4</sub> is maternally derived before 20 weeks
- Fetal fT<sub>4</sub> gradually rises in response to fetal TSH after 20 weeks

\*Burrow et al NEJM 1994;331:1072

# HYPERTHYROIDISM IN PREGNANCY

- Prevalence 0.1-0.4% pregnant women
- TSH <0.01 mU/L with Normal(subclinical) or High fT4 or fT3(overt)
- Graves disease accounts for 85% of cases
- Toxic MN goiter, autoimmune thyroiditis
- Up to 60% of women with hyperemesis gravidarum have subnormal TSH and nearly 50% have an elevated Ft4

# GRAVES DISEASE VS GESTATIONAL THYROTOXICOSIS

- ◉ Clinical signs of thyrotoxicosis
- ◉ Diffuse goiter
- ◉ Eye signs
- ◉ TSH receptor antibodies +
- ◉ Minimal signs of hyperthyroidism
- ◉ Minimal thyroid enlargement
- ◉ Absent eye signs
- ◉ TSH receptor antibodies -

GRAVES'

GESTATIONAL THYROTOXICOSIS

# GRAVES DISEASE

- TRAbs present which can stimulate and inhibit the TSH-R (TSH binding inhibitory immunoglobulins)
- Most assays do not differentiate stimulatory from inhibitory antibodies
- 1-5% of neonates have neonatal Graves, especially if TSI >5 IU\*
- The incidence of neonatal Graves is not directly related to maternal thyroid function

\*Peleg et al Obstet and Gynecol 2002,99:1040

# FETAL AND NEONATAL GRAVES

- Signs include tachycardia, growth restriction, goiter—cardiac failure.
- Clinical diagnosis may be difficult-umbilical cord sampling may be needed
- Treatment-maternal thionamide therapy
- Signs may be delayed onset(day 10-20)if mother was treated with a thionamide during pregnancy
- Spontaneously resolves in 3-12 weeks

FETAL

NEONATAL

# MATERNAL HYPERTHYROIDISM

## COURSE AND TREATMENT

- ⦿ Graves disease typically exacerbates in the first trimester, gradual improvement during pregnancy and exacerbation shortly after delivery
- ⦿ PTU and methimazole inhibit thyroid peroxidase (hence synthesis of T4 and T3)
- ⦿ PTU also inhibits T4→T3 conversion
- ⦿ Placental transfer of both drugs occurs, yet fetal thyroid status is not strictly correlated with maternal doses
- ⦿ MMI-aplasia cutis, choanal/esophageal atresia

# THERAPY AND MONITORING

- PTU 25-100 mg q8h or MMI 7.5-30 mg/d-dose tapered based on fT4 level (not TSH)
- I-131 contraindicated (wait 6 mths to conceive)
- TSH and fT4 tests monthly-maintain fT4 in upper 1/3 of N range (less fetal hypothyroidism)\*
- Fetal US monthly after 20 weeks when TRAbs positive/unknown in any women with past Graves disease or when thionamides are used

\*Momatani et al 1986 NEJM 315

# MATERNAL HYPERTHYROIDISM- ADVERSE OUTCOMES

- Subclinical hyperthyroidism is not associated with adverse outcomes in pregnancy\*
  - Overt hyperthyroidism conveys risk relative to disease control
1. miscarriage
  2. premature labor
  3. stillbirth
  4. preeclampsia
  5. heart failure
  6. Fetal and neonatal thyrotoxicosis or hypothyroidism

\*Casey et al Obstet and Gynecol  
Vol 107, No2, Part 1, Feb 2006

# RECOMMENDATIONS AND SUMMARY

## HYPERTHYROIDISM

- Subnormal TSH in pregnancy requires evaluation—esp differentiation of Graves from gestational thyrotoxicosis
- Subclinical hyperthyroidism does not require treatment(monitering needed)
- Overt hyperthyroidism should be treated with ATD therapy,aim for fT4 in upper nonpregnant range
- PTU first line over MMI
- TRAbs should be measured before or by the end of the second trimester(all Graves pts)

# RECOMMENDATIONS AND SUMMARY

## HYPERTHYROIDISM

- ⦿ I-131 is absolutely contraindicated
- ⦿ Fetal US monthly from 20 weeks if TRAb+ or ATD therapy (goiter, growth, hydrops, cardiac failure)
- ⦿ Umbilical cord sampling when clinical status uncertain, and management would change
- ⦿ All neonates born to Graves mothers should be evaluated for thyroid dysfunction
- ⦿ Gestational hyperthyroidism with  $fT4 >$  upper N pregnancy value and  $TSH < 0.1 \mu U/ml$  and clinical signs may require treatment

# HYPOTHYROIDISM IN PREGNANCY

- Overt hypothyroidism is uncommon 0.3-0.5% pregnancies
- Subclinical hypothyroidism 2-3%
- The most common cause worldwide is iodine deficiency (ID)
- Autoimmune thyroiditis is the most common cause in North America (+ antiperoxidase ab in 5-15% of women of childbearing age)
- Other causes-post I-131 or thyroidectomy

# HYPOTHYROIDISM TREATMENT IN PREGNANCY(T4)-

- ◉ Initial dose average 0.1-0.15mg/day
- ◉ Full replacement 2.0-2.4µg/kg/d
- ◉ Double the full dose for a few days if hypothyroidism is severe
- ◉ Iron supplements can inhibit absorption
- ◉ Nonpregnant women full replacement 1.7-2.0µg/kg/d
- ◉ Requirements increase 30-50% above preconception dose in pregnancy
- ◉ Increases required as early as 4-6 weeks gestation

**NEW HYPOTHYROIDISM**

**PREEXISTING HYPOTHYROIDISM**

# HYPOTHYROIDISM IN PREGNANCY- MONITORING RESPONSE TO TREATMENT

- ⦿ Measure fT4 and TSH 1 month after initiation of therapy-aiming for TSH <2.5mIU/L in the first trimester, and <3.0mIU/L in later trimesters
- ⦿ Retest every 6-8 weeks once target TSH achieved, and again postpartum
- ⦿ If hypothyroidism predates pregnancy, then immediate 30% dose increase may be done by taking 2 extra pills weekly
- ⦿ Anticipate greater incremental doses in patients without residual thyroid tissue

# HYPOTHYROIDISM ADVERSE EFFECTS

- Miscarriage
- Gestational BP
- Preterm delivery<sup>↑</sup>
- Placental abruption
- PP hemorrhage
- Cognitive impairment\* or delayed neurodevelopment\*\*
- Placental abruption\*
- Preterm delivery-34 weeks or less\*
- Neonatal ICU admission and RDS\*
- Mild reduction in global intelligence at preschool age\*\*

\* Haddow et al NEJM 1999:341:549

\*\* Pop et al Clin Endo 2003:59:282

\* Casey et al Obstet and Gynecol 2005  
Vol 105;No2:239

\*\*Rovet at al 2004 ATA Abstract

**Overt hypothyroidism**

**Subclinical Hypothyroidism**

# RECOMMENDATIONS AND SUMMARY

## HYPOTHYROIDISM

- ◉ Preconception thyroxine dose adjustment to achieve  $TSH < 2.5 \text{ mIU/L}$
- ◉ Dose incrementation is needed by 4-6 weeks gestation, possibly 30-50% increase overall
- ◉ If overt hypothyroidism (OH) is diagnosed during pregnancy, rapid dose adjustment is needed. Goals  $TSH < 2.5$  in the first trimester,  $TSH < 3$  later in pregnancy
- ◉ Thyroid function tests should be remeasured within 30-40 days.
- ◉ OH and subclinical hypothyroidism are associated with adverse obstetrical outcomes

# POSTPARTUM THYROIDITIS(PPT)

## Prevalence

- ◉ varies globally from 1.1% in Thailand to 21.1% in Canada (mean USA 7%)
- ◉ high in women with Type 1 DM 18-25%
- ◉ high in women with positive antiperoxidase abs(TPO) who were euthyroid during pregnancy

# POSTPARTUM THYROIDITIS

Presentation-within 1 year postpartum(often small firm goiter)

- ⦿ Transient hyperthyroidism alone(20-40%)
- ⦿ Transient hypothyroidism alone(40-50%)
- ⦿ Transient hyperthyroidism followed by hypothyroidism and then recovery(20-30%)

# POSTPARTUM THYROIDITIS

## TPO ANTIBODIES

Amino et al 1982 NEJM 306:849

- ◉ Incidence of PPT 5.5%
- ◉ 89.1% of PPT patients were TPO +
- ◉ 40.3% of TPO+ patients developed PPT
- ◉ 0.6% of TPO-patients developed PPT

Hidaka et al 1994 Clin Endocrinol(Oxf) 41:15

Premawardhana et al 2004 Thyroid 14:610

- ◉ 40-60% of women with TPO+ in early pregnancy develop PPT

# POSTPARTUM THYROIDITIS

## TREATMENT AND FOLLOW UP

- ⦿ Hyperthyroid phase-if symptomatic use propranolol or atenolol for up to 2 months
- ⦿ Hypothyroid phase-treat with thyroxine if
  1. Symptomatic
  2. TSH >10
  3. Planning pregnancy

Hypothyroid TSH <10 and asymptomatic, not planning pregnancy—followup TSH in 4-8 weeks

# RECOMMENDATIONS AND SUMMARY

## POSTPARTUM THYROIDITIS

- ◉ Women known to be TPO+ should have TSH test at 3 and 6 months postpartum
- ◉ The prevalence of PPT in women with Type 1 DM is 3X the general population, hence postpartum screening (TSH) is recommended at 3 and 6 months postpartum
- ◉ Women with PPT have a markedly increased risk of permanent hypothyroidism within 5-10 years. Annual TSH testing is recommended.

# RECOMMENDATIONS AND SUMMARY

## POSTPARTUM THYROIDITIS

- ⦿ Asymptomatic women with subclinical hypothyroidism (TSH<10) need retest TSH in 4-8 weeks.
- ⦿ However, if pregnancy is planned-treatment is indicated regardless of symptoms. (TSH <10)
- ⦿ Treatment is indicated if TSH>10
- ⦿ Selenium supplementation deserves further study

# AUTOIMMUNE THYROID DISEASE (AITD) AND MISCARRIAGE

- ◉ Meta-analysis of 18 case-control and longitudinal studies confirming the association between miscarriage and thyroid abs\*
- ◉ OR of 2.73(95%CI,2.2-3.4) among 8 case-control studies  
OR of 2.3(95%CI,1.80-2.95) in 10 longitudinal studies

\* Prummel and Wiersinga Eur J of Endo(2004)150:751

# EUTHYROID AUTOIMMUNE THYROID DISEASE(AITD)

- ⦿ Women undergoing IVF with positive abs have higher miscarriage rates\*
- ⦿ Euthyroid women with AITD develop impaired thyroid function-and have an increased risk of miscarriage and preterm delivery. Treatment with T4 lowers the chance of miscarriage and premature delivery\*\*

\*Stagnaro-Green and Glinoe Best Prac Res Clin Endo Metab  
2004:18:167

\*\*Negro et al 2006 JCEM 91(7):2587

# RECOMMENDATIONS AND SUMMARY

## AUTOIMMUNE THYROID DISEASE

- Although a positive association exists between the presence of thyroid antibodies and pregnancy loss-universal screening for abs cannot be recommended at this time
- Only one adequately designed intervention trial has demonstrated a decrease in miscarriage rate in thyroid ab+ euthyroid women---more study is needed.

# ENDOCRINE SOCIETY

## TARGETED PERIPARTUM THYROID SCREENING (TSH)

- ⦿ Symptoms or signs suggestive of thyroid disease
- ⦿ Past history of hyper or hypothyroidism
- ⦿ Type 1 Diabetes; other autoimmune diseases
- ⦿ Past head/neck irradiation
- ⦿ Prior miscarriage, preterm labor or infertility
- ⦿ Family history of thyroid disease
- ⦿ Presence of a goiter
- ⦿ Women with positive thyroid abs(when known)

# SCREENING-UNIVERSAL OR TARGETED

Vaidya et al JCEM 2007 92(1)203

1540 consecutive pregnancies demonstrated that targeted screening (personal or family history of thyroid disease or other autoimmune disorder) found only 2/3 women with TSH  $>4.2$  mU/L

# PERIPARTUM THYROID SCREENING - UNIVERSAL SCREENING STUDY

Controlled Antenatal Thyroid Screening  
Study(CATS) Lazarus et al 2005 J Clin Pathol 58:449

22,000 singleton pregnancies < 16 weeks  
TSH, fT4 tests - assayed or frozen (untested)

Treat with thyroxine if TSH > 97.5<sup>th</sup> percentile  
or fT4 < 2.5<sup>th</sup> percentile

Outcome - IQ age 3

# SUMMARY

- Overt hyperthyroidism in pregnancy requires treatment, but subclinical hyperthyroidism does not (it should be followed closely).
- Both overt and subclinical hypothyroidism in pregnancy should be treated.
- Women with preexisting hypothyroidism, should increase their dose of thyroxine as soon as pregnancy is confirmed.
- Women with PPT should be treated for hypothyroidism if symptomatic, TSH > 10 or planning pregnancy.

# SUMMARY

- ⦿ Population reference ranges for TSH, fT4 and fT3 that are gestational age specific need to be established. In their absence, target TSH should be  $<2.5-3.0 \mu\text{U/ml}$  and fT4 in the upper 1/3 nonpregnant reference range.
- ⦿ Targeted screening of TSH is currently recommended, however screening for TPO abs is not (need interventional studies).
- ⦿ Patients already known to be TPO+ should have TSH and fT4 screening q3mths during and after pregnancy.