Thyroid disease during pregnancy

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2017 Guidelines updated the prior guidelines from 2011

2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum

Erik K. Alexander,1 Elizabeth N. Pearce2,3 Gregory A. Brent4 Rosalind S. Brown4 Herbert Chen5 Chrysoula Dosiou6 William A. Grobman7 Peter Laurberg8,9 John H. Lazarus7 Susan J. Mandel10 Robin P. Peeters11 and Scott Sullivan12
Overview

1. Pregnancy induced thyroid changes
2. Autoimmune Thyroid disease
3. Hypothyroidism
4. Hyperthyroidism

Pregnancy-induced changes in thyroid gland

- Moderate enlargement
- Glandular hyperplasia
- Increased vascularity
 Thyroid Physiology During Pregnancy

1. TBG ↑ (2-fold)
2. Total T4 & T3 ↑
3. HCG stimulates TSH-receptor
4. Decrease in iodide

*Casey et al, Obstet Gynecol 2006.*

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Normal Pregnancy and TSH

1. TSH decreases in the 1st trimester.
2. LLN decreases modestly in all populations. ULN decreases varies per race/ethnic group.

*Casey et al, Obstet Gynecol 2006.*

*Weeke J et al, Acta Endocrinologica 1982. Figure: Casey and Leveno.*
# Ethnicity & TSH changes during pregnancy

<table>
<thead>
<tr>
<th>Gestational trimesters</th>
<th>TSH (mIU/l)</th>
<th>Percentiles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>2.5th</td>
</tr>
<tr>
<td>nonpregnancy</td>
<td>153</td>
<td>0.50</td>
</tr>
<tr>
<td>1st trimester</td>
<td>168</td>
<td>0.93</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>168</td>
<td>0.95</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>169</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Manufacturer's nonpregnant adult reference interval is 0.35–5.50 mIU/l

Li C et al, JCEM 2014
Marwaha RK et al, BJOG 2008
Mannisto et al, Thyroid 2011

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# TSH in normal pregnancy

- Ideally, use population-based, trimester specific reference range for TSH.
- If unavailable:

  1\textsuperscript{st} trimester = LLN decrease by 0.4 mU/L
  ULN decrease by 0.5 mU/L*  
  (Corresponds to ULN=4.0 mU/L)

*Change from 2011 ATA Guidelines
Normal Pregnancy and thyroxine

1. Free T4: poor accuracy during pregnancy
   - ft4 by equilibrium dialysis, LC/MS-OK

2. Total T4 more accurate
   - Pregnancy specific reference range
   - If calculated: 5% per week \( \uparrow \) starting week 7–16
   - Wk 16 and later: 50% increase

\(^1\) Weke J et al, Acta Endocrinologica 1982

Normal Pregnancy and T4

\[ \begin{array}{|c|c|c|c|}
\hline
\text{Total T4 (TT4)} & \text{Free T4 Index} & \text{FT4 Immunoassay (A)} & \text{FT4 Immunoassay (B)} \\
\hline
\end{array} \]

\[ \begin{array}{|c|c|c|c|}
\hline
\text{TT4/FT4}\, \text{ng/dL} & \text{FT4 Immunoassay (A)} & \text{FT4 Immunoassay (B)} \\
\hline
\end{array} \]

* \( p < 0.05 \)

\(^2\) Lee RH et al, AJOG 2009
Summary

- Pregnancy alters TFTs
- Use pregnancy specific, population-specific TSH when possible
- TSH upper limit: $<4.0$
- Use Total T4 (with trimester specific reference)

Overview

1. Pregnancy induced thyroid changes
2. Autoimmune Thyroid disease
3. Hypothyroidism
4. Hyperthyroidism
Case

- ID/HPI: 35 yo Caucasian female referred by reproductive endocrinology for evaluation of thyroid tests. She plans to undergo IVF within the next 6 mths.
- PMH: Hashimoto’s
- MEDS: PNV
- S/FHX: mother with Hashimoto’s, on LT4
- PEX: Normal. Thyroid gland is normal in size, not enlarged, no nodules.
- Labs: TSH 3.0, fT4 1.1, TPO ab 550

Risks during pregnancy? Any treatment?

Autoimmune Thyroid Disease

- +Thyroid autoantibodies in 2-17% of pregnant women
- Euthyroid women with +TAb: check TSH at time of pregnancy and q4wks until mid-pregnancy

Frequency distribution of TSH at EGA=11 wks
+TAb=87 women, control ~Tab=550 women

1 Glinoer JCEM 1994; 2 Negro R et al, JCEM 2006
Risk of subclinical hypothyroidism in pregnant women with autoimmune thyroid disease

- 19% of women with +TAb develop elevated TSH (>4.5) during pregnancy

Negro R et al, JCEM 2006

Is +TAb associated with adverse pregnancy outcomes in euthyroid women?

- + association with sporadic pregnancy loss (OR=2-2.5) 1,2
- + likely association with recurrent pregnancy loss (OR=1.5-2.3) 3,4
- + association w/preterm delivery (OR=1.4-2.9) 5-7

Miscarriage in euthyroid pregnant women with +Tab

Stagnaro-Green et al, JAMA 1990

Negro R et al, JCEM 2006

Does LT4 treatment of euthyroid pregnant women with +Tab reduce risk?

- Interventional study data is scarce (1-4)
- Insufficient data to treat newly pregnant women +Tab euthyroid women.
- ATA: treat euthyroid women with prior h/o miscarriage and +TAb (weak rec, low quality evidence)

Negro R et al, JCEM 2006

Lepoutre T et al Gynecol Obstet Invest 2012;
Vaquero E et al, Am J Reprod Immunol 2000;
Nazapour et al, Eur J Endo 2017

Fig 1. – Miscarriage rate in thyroid autoantibody-positive women vs thyroid autoantibody-negative women.

Fig 4. Percentage of miscarriages (top) and premature deliveries (bottom) in group A (TPOAb+ treated with LT4), group B (TPOAb-), and group C (TPOAb+), α, P < 0.05; α, P < 0.01.
LT4 treatment in +TPO Ab

- Randomized, prospective
- +TPO (euthyroid or SCH) vs TPO- controls
- Many maternal and fetal outcomes
- Preterm birth is the only outcome that changed significantly

Nazarpour et al, Eur J Endo 2017

What about fertility & autoimmune thyroid disease ??

- Overt hypothyroidism → LT4
  1
- Subclinical hypothyroidism and –TAb → consider LT4 if attempting natural conception
  2,3
- Euthyroid with +Tab attempting natural pregnancy → unclear

1 ATA 2017 Guidelines
3- Yoshioka W et al. Endocr J 2015
Assisted Reproductive Technology (ART) and Autoimmune Thyroid Disease

- Subclinical Hypothyroidism + ART $\rightarrow$ LT4

- TSH $>2.5$ + ART $\rightarrow$ Consider LT4

- Euthyroid, +TAb and ART $\rightarrow$ Insufficient evidence *

**Goal TSH $<2.5$**


Overview

1. Pregnancy induced thyroid changes
2. Autoimmune Thyroid disease
3. Hypothyroidism
4. Hyperthyroidism
Hypothyroidism during pregnancy

- ~2-3% of women of child-bearing age (1)
- Definition: “TSH > ULN of the pregnancy & population-specific reference range” (ATA 2017)
- Overt vs subclinical hypothyroidism

**If pregnancy specific TSH unavailable, then ULN of ~ 4.0 (decrease by ~0.5 from non-pregnant)**

Risk of overt hypothyroidism

- Retrospective and case-control studies show that hypothyroidism has negative effects on pregnancy and fetal health.
- Pregnancy: Pregnancy loss, premature birth, low birth weight, gestational hypertension
- Fetal thyroid: begins to function at EGA 12 weeks. Dependent on maternal T4 until 18-20 wks.
- Fetus: poor neurocognitive/physical development (cretinism).

Risk of hypothyroidism on fetus

- Retrospective study
- LT4 tx vs untreated
- IQ: 7 pts less at age 7-9 yo

Haddow et al NEJM 1999 Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child.

Treatment of overt hypothyroidism

- Overt hypothyroidism should be treated during pregnancy with levothyroxine.
Subclinical Hypothyroidism

- Worse pregnancy outcomes (pregnancy loss) (1-3)
- Worse perinatal outcomes (premature delivery, placental abruption) (1-3)
- Neurocognitive outcomes in offspring – possible

### Table from: 1--Chan S and Boelaert K. Clin Endocrinol 2015. 2 – Maraka et al, Thyroid 2016. 3–ATA Guidelines

Does treatment of SCH improve outcomes?

Retrospective Study
51 hypothyroid, pregnant women
(16 overt, 35 SCH)

Abalovich et al, Thyroid 2002
LT4 treatment in +TPO women – euthyroid and subclinical hypothyroidism

- Randomized, prospective
- +TPO (euthyroid or SCH) vs TPO- controls
- Baseline: 25% SCH 2nd/3rd Trimester: 40%
- Preterm birth decreased significantly with LT4

![Graph showing preterm delivery and neonatal admission rates with and without LT4 treatment]

Nazarpour et al, Eur J Endo 2017

Subclinical Hypothyroidism & Neurocognitive Outcomes

![Image of the New England Journal of Medicine]

Antenatal Thyroid Screening and Childhood Cognitive Function

Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy
When to treat pregnant women with subclinical hypothyroidism?

- Check TPO Ab status if TSH > 2.5
- TSH > ULN and +TPO Ab $\rightarrow$ LT4
  TSH > 10 and – TPO Ab $\rightarrow$ LT4
- TSH > 2.5 and +TPO Ab $\rightarrow$ consider LT4
  TSH > ULN and – TPO Ab $\rightarrow$ consider LT4
- TSH normal and – TPO AB $\rightarrow$ No LT4

LT4 in hypothyroid women who become pregnant

- Most women taking LT4 require increased dose during pregnancy.
- TIMING: Increased requirement for thyroxine occurs as early as EGA 4-6 wks. $^{1,2}$
- AMOUNT: Increase LT4 by average of 30%$^{1-3}$

When pregnancy is first confirmed, tell patient to take 2 additional LT4 tabs per week.

$^{1}$Alexander et al, NEJM 2004; $^{2}$ATA Guidelines 2017; $^{3}$Abalovic Thyroid 2010
Overview

1. Pregnancy induced thyroid changes
2. Autoimmune Thyroid disease
3. Hypothyroidism
4. Hyperthyroidism

Hyperthyroidism

- **Thyrotoxicosis**: Clinical syndrome of hypermetabolism due to supraphysiological fT4 and/or fT3 serum levels.
- **Hyperthyroidism**: Hyperfunction of the thyroid gland causing thyrotoxicosis (Grave’s, MNG, toxic adenoma)
- **Thyroiditis**: Passive release of thyroid hormone causing thyrotoxicosis.
Hyperthyroidism during pregnancy

• Prevalence: 0.1-1% ¹
• Graves’ Disease: most common cause ²,³
• Identify Grave’s disease vs hCG mediated thyrotoxicosis²
• hCG mediated thyrotoxicosis ⁴:
  – Gestational transient thyrotoxicosis:2-3%. End of 1st trimester
  – Hyperemesis gravidarum:0.3-1%. Persistent N/V in 1st trimester
• Differentiating the two


Initial Evaluation of Low TSH

• 1st trimester, hCG peaks b/w EGA 7-11 wks
• TSH < reference range in up to 15% of women in first trimester ¹
• Evaluation: repeat TSH, check total T4/free T4 and T3. Evaluate for symptoms of thyrotoxicosis.

Risks of Hyperthyroidism

• Risks of uncontrolled hyperthyroidism 1-3

• Subclinical hyperthyroidism: No adverse pregnancy outcomes. 4

• Achieve euthyroidism BEFORE attempting pregnancy

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Treatment of GD Before Pregnancy

<table>
<thead>
<tr>
<th>THERAPY</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithyroid drugs</td>
<td>- Effective w/in 1-2 mths</td>
<td>- Adverse effects (mild 5-8%, severe 0.2%)</td>
</tr>
<tr>
<td></td>
<td>- May induce remission of autoimmunity (gradual)</td>
<td>- Birth defects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Relapse after drug stopped</td>
</tr>
<tr>
<td>Radioactive iodine</td>
<td>- Easy po administration</td>
<td>- Repeat tx may be needed</td>
</tr>
<tr>
<td></td>
<td>- Reduction in goiter size</td>
<td>- Increase TRAb titers after tx may worsen TAO,</td>
</tr>
<tr>
<td></td>
<td>- Relapse of hyperthyroidism rare</td>
<td>fetal risk</td>
</tr>
<tr>
<td>Thyroidectomy</td>
<td>- Definitive treatment</td>
<td>- Surgical complications (2-5%)</td>
</tr>
<tr>
<td></td>
<td>- Subsequent gradual remission of autoimmunity</td>
<td>- Lifelong LT4 tx</td>
</tr>
<tr>
<td></td>
<td>- Goiter resolves</td>
<td>- Healing/recovery from surgery</td>
</tr>
</tbody>
</table>

Adapted from: Alexander et al. ATA Guidelines. Thyroid 2017
Thionamides for Graves’ hyperthyroidism

- Mechanism: Inhibit hormone synthesis
- Dose: MMI 10-20 mg qd, PTU 200-400/day
- Advantages: Rapid effect (1-2 mths), gradual remission of autoimmunity (1,2)


Risks of Thionamides

- Side effects in 3-5%
- Mostly allergic reactions.
- Agranulocytosis in 0.15%
- Develops w/in first 90 days or re-initiation

2. Nakamura H. Analysis of 754 cases of antithyroid drug induced agranulocytosis over 30 yrs in japan. JCEM 2013 (image)
Risks of Thionamides

- Liver dysfunction in <0.1%\(^1\)
- MMI = cholestatic liver injury
  PTU = transaminitis
- PTU 3\(^{rd}\) most common drug cause of liver failure leading to transplant (1:1000 non-pregnant patients) \(^2\). Idiosyncratic\(^3\).

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Teratogenic effects of thionamides

<table>
<thead>
<tr>
<th></th>
<th>METHIMAZOLE (^1-3)</th>
<th>PROPYLTHIOURICIL (^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of birth</td>
<td>2-4%</td>
<td>2-3%</td>
</tr>
<tr>
<td>defects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth defects</td>
<td>Aplasia cutis</td>
<td>Face &amp; neck cysts (minor)</td>
</tr>
<tr>
<td></td>
<td>Choanal/esophageal atresia</td>
<td>Urinary tract abnormalities in males.</td>
</tr>
<tr>
<td></td>
<td>Abdominal wall defects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary system defects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ventral Septal defects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eye defects</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Defects mostly with exposure during EGA 6-10 wks.</td>
<td>Less severe defects. Diagnosed later in life, when complications ensued.</td>
</tr>
</tbody>
</table>

**No association with dose of ATD**

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\(^1\) Mandel SJ and Cooper DS. Use of antithyroid drugs in pregnancy and lactation. JCEM 2001.
\(^3\) - Andersen SL et al. Antithyroid drug side effects in the population and in pregnancy. JCEM 2016
Thionamides & Birth Defects

- Danish registry, 20 yrs
- 818 K children
- 812K=never ATD
- PTU=560
- MMI/CM=1100
- Switch 1st trimester=150
- No ATD pregnancy=3500

Andersen et al. JCEM 2013

Birth Defects & Timing of Thionamide

- Does MMI to PTU switch protect against birth defects?
- 8.7% of the 149 children had defects.
- MMI-associated defects were only seen if shift was >=7 wks EGA.
- PTU related defects if PTU started at EGA=6 wks.
- Shift done 20 days later from MMI→PTU.
- Rec: consider switching to PTU prior to pregnancy.

N=13

**Birth Defects & Timing of Thionamide**

![Graph showing the timing and risk of birth defects related to thionamide use.]


**How to reduce birth-defects associated with thionamides?**

1. Clear instructions to fertile women re: pregnancy (ie, test if menses missed, stop ATD & call MD) ¹

2. Limit ATD in 1st trimester (euthyroid, ATDx6 mths) ¹,²

3. If ATD stopped, check TFT every 1-2 wks ¹,²

4. If ATD continued ²:
   - Switch from MMI → PTU ASAP
   - PTU through EGA 16 wks
   - After EGA 16, ??? PTU → MMI (no rec, insufficient evidence)

5. [?? Consider MMI → PTU before pregnancy??] ¹

Fetal Thyroid Function

- Fetal thyroid is effected by: ATD & TRAb
- Once fetal thyroid is functional, it can respond to TRAb (~20 wks)
- ATD dose should be the lowest possible.

Cucci I et al. Thyroid-Stimulating Hormone Receptor Antibodies in Pregnancy: Clinical Relevance. Frontiers in Endocrinology 2017

Fetal Thyroid Function

Fetal/neonatal risks in women with prior or current GD:

- Hypothyroidism
- Hyperthyroidism (1-5%)
- Central hypothyroidism

Cucci I et al. Thyroid-Stimulating Hormone Receptor Antibodies in Pregnancy: Clinical Relevance. Frontiers in Endocrinology 2017
Effects of thionamide on fetal thyroid

- Risk of fetal hypothyroidism: Use lowest dose possible of ATD
- Maintain maternal fT4 at the upper normal to mildly thyrotoxic range.
- TT4/FT4 & TSH should be measured q2-4 wks after starting ATD, and q4 wks once at goal

Momotani N et al. NEJM 1986

TRAb & Fetal Thyroid Function

- Check TRAb in early pregnancy.
- If -TRAb and no ATD, no further testing.
- Repeat TRAb in 2\textsuperscript{nd} trimester (wk 20-23) in pt on ATD or +TRAb initially.
- TRAb 3x ULN \(\Rightarrow\) 100% SS and 43% SP for neonatal hyperthyroidism

1 Zimmerman D. Fetal and neonatal hyperthyroidism. Thyroid 1999
TRAb testing & Fetal Goiter

- Fetal U/S at end of 2nd trimester if TRAb+ or maternal hyperthyroidism is uncontrolled.
- If + fetal goiter is present, assess for fetal thyroid function.

Questions?
Summary

- Use pregnancy specific TSH, fT4, TT4 assays. TSH ULN<4.0 (rather than 2.5)
- Subclinical Hypothyroidism: assess TPO and treat based on TSH level
- Ideally, treat hyperthyroidism prior to pregnancy. Minimize use of thionamides, including PTU

Postpartum Issues

- Recurrent GD
- Breastfeeding: MMI recommended (even though it is more soluble). Take in divided doses, after feeding. If dose is <20 mg MMI daily, no effect on neonatal TFTs, growth, development (Azizi F JCEM 2000, infants/methimazole). If >20 mg, TFTs should be checked in infant at mth 1 and 3.
Nodules and DTC

- DTC: Deferring surgery until post-partum
  NOT associated with worse prognosis\(^1\)

Additional Data – Not part of talk

- Maternal Iodine deficiency – diurnal and day-to-day variation in urine iodine, so specific 24 hr urine iodine not very helpful – more population and median based. Per WHO, median Uiodine b/w 150-250=optimal iodine intake.
  NHANES 2005-2010: median UIC in pregnant women=129 (mild iodine deficiency). 1/3 of 3\(^{rd}\) trimester women had adequate Uiodine levels. NCS data – 1\(^{st}\) and 2\(^{nd}\) trimester more likely to be deficient than 3\(^{rd}\) trimester. NHANES didn’t have enough pregnant women to look at trimester data.
- IOM: RDA for iodine intake: 150 ug/d for women planning pregnancy, 220 for pregnant women, 290 for breast feeding women.
- WHO: 250 ug/d for pregnant and lactating women
Subclinical hyperthyroidism during pregnancy does not affect outcomes

Teratogenic risks of thionamides

- MMI: aplasia cutis, choanal/esophageal atresia/abdominal wall defects, eye/urinary system and ventral septal defects (1, 2). Prevalence 2-4%, esp w/exposure during EGA 6-10 wks.
- PTU: Face and neck cysts (minor defects), and urinary tract abnormalities. Prevalence 2-3%. Less severe. Diagnosed later in life, when complications ensued. (3)
- No association with dose of ATD.

1 – Clementi M et al. Treatment of hyperthyroidism in pregnancy and birthdefects. JCEM 2010
3 – Andersen et al. Birth defects after early pregnancy use of ATD: a Danish nationwide study. JCEM 2013
Fetal Thyroid Function

1 Cucci I et al. Thyroid-Stimulating Hormone Receptor Antibodies in Pregnancy: Clinical Relevance. Frontiers in Endocrinology 2017

FDA Warning - PTU

PROPYLTHIOURACIL TABLETS, USP

WARNING

Severe liver injury and acute liver failure, in some cases fatal, have been reported in patients treated with propylthiouracil. These reports of hepatic reactions include cases requiring liver transplantation in adult and pediatric patients.

Propylthiouracil should be reserved for patients who cannot tolerate methimazole and in whom radioactive iodine therapy or surgery are not appropriate treatments for the management of hyperthyroidism. Propylthiouracil may be the treatment of choice when an antithyroid drug is indicated during or just prior to the first trimester of pregnancy (see Warnings and Precautions).
Subclinical Hypothyroidism

- Another meta-analysis below.

<table>
<thead>
<tr>
<th>Pregnancy outcome</th>
<th>Pooled RR [95% CI]</th>
<th>I² (%)</th>
<th>Studies used for meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy loss</td>
<td>2.01 [1.66-2.44]</td>
<td>0</td>
<td>(6,7,10-12,14,18,20,35)</td>
</tr>
<tr>
<td>Preterm labor</td>
<td>0.93 [0.83-1.01]</td>
<td>0</td>
<td>(18,32,34)</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>1.20 [0.97-1.50]</td>
<td>39</td>
<td>(6,8,11-14,18-20,21,23-35)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>1.22 [0.84-1.78]</td>
<td>52</td>
<td>(11,12,15,18,20,21,32,33)</td>
</tr>
<tr>
<td>Preecclampsia</td>
<td>1.30 [1.00-1.68]</td>
<td>0</td>
<td>(12,13,18,21,33,34)</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>1.26 [0.90-1.81]</td>
<td>44</td>
<td>(12,14,18,20,21,32-35)</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>2.14 [1.23-3.70]</td>
<td>0</td>
<td>(12-14,18,21,32-34)</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>0.78 [0.19-3.18]</td>
<td>0</td>
<td>(14,18,34)</td>
</tr>
<tr>
<td>PROM</td>
<td>1.45 [1.04-1.95]</td>
<td>9</td>
<td>(8,14,18,32,34,35)</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>1.06 [0.94-1.19]</td>
<td>0</td>
<td>(12,13,19,20,31,32)</td>
</tr>
<tr>
<td>IUGR</td>
<td>1.70 [0.83-3.50]</td>
<td>47</td>
<td>(14,20,32-35)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>1.34 [0.98-1.82]</td>
<td>52</td>
<td>(7,11,12,14,18,19,35)</td>
</tr>
<tr>
<td>Low Apgar score</td>
<td>1.08 [0.71-1.65]</td>
<td>0</td>
<td>(11,19,34)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>1.17 [0.65-2.09]</td>
<td>43</td>
<td>(7,19,34,35)</td>
</tr>
<tr>
<td>Neomatal death</td>
<td>2.58 [1.41-4.73]</td>
<td>0</td>
<td>(7,12,18,19,34,35)</td>
</tr>
</tbody>
</table>

RR, relative risk; CI, 95% confidence interval; PROM, premature rupture of membranes; IUGR, intravenous growth restriction.

Matsum S, et al., Thyroid 2016

Changes in 2017 ATA Guidelines compared to 2011

- TSH ULN during pregnancy increased to 4.0 from 2.5 (given new data in Asia, Indian and Netherlands). Prior data mostly from US and Europe led to rec of 2.5 (1st trimester) and 3.0 (2nd and 3rd trimester)
- T4 assessment during pregnancy: Again, 2017 guidelines say use pop/trimester specific ranges. When not possible, use Tt4, and can use ULN of 50% more than normal range. Can use ft4 by equil dialysis (LC/MS/MS), but expensive.
- SCH tx or not? Previously there was infor on association b/w SCH and pregnancy outcome, but little data on whether tx made a difference. 2017 guidelines say tx MAY decrease miscarriage in TPOab + women. Rec: eval women with TSH>2.5 for TPOab status. Definitely tx if TSH>pregnancy specific range+TPOab and, if TPO Ab-, then if TSH>10. Consider in other cases
- GD: PTU may have adverse effects. 2017 stronger rec on stopping tx in women who may be stable; consider preconception surgery or RAIA.
- Universal Screening: remains a gray area.
Association of +Tab with other adverse outcomes in euthyroid women

• Besides the known preterm delivery and miscarriage, there is some data that supports increased risk of ADHD, possible autism spectrum.

• Data with respect to neurocognitive outcomes is mixed.

Variation in TSH changes with Ethnicity

<table>
<thead>
<tr>
<th>Visit</th>
<th>Gestational age</th>
<th>Ethnic group</th>
<th>n</th>
<th>2.5th</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>97.5th</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1</td>
<td>9–11 weeks</td>
<td>Combined</td>
<td>540</td>
<td>0.01 (0.01–0.02)</td>
<td>0.33</td>
<td>0.40</td>
<td>1.16</td>
<td>2.39 (2.18–2.39)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chinese</td>
<td>280</td>
<td>0.01 (0.01–0.02)</td>
<td>0.38</td>
<td>0.50</td>
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<td>1.00</td>
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</table>

Values in brackets indicate the 95% confidence intervals of the corresponding reference limits. Manufacturer’s reference interval for non-pregnant adults is 0.35–4.4 μU/L.

multiethnic population in Singapore combined of Indian, Malaysian and Chinese women. TSH lower limit is 0.01, lower than Caucasian population.

1 Ho et al. Clin Chem Med 2017
TSH during pregnancy

- N=343 pregnant Chinese women, compared to n=63 non-pregnant healthy females

Thionamides

How to reduce birth-defects associated with thionamides?

1. Restrict the use of ATDs in first trimester (weeks 6–10) of pregnancy
2. Give written instruction to fertile women treated with ATDs to:
   i) Perform a pregnancy test within a few days after the 1st day of a missed (or atypical week) menstrual period, if pregnancy is a possibility
   ii) If the pregnancy test is positive, contact physician the same day, and take no more ATDs before such contact
3. If the pregnant woman is considered in remission of Graves’ disease, observe without ATDs along with weekly thyroid function testing until second trimester
4. If an ATD is necessary in early pregnancy: use PTU
5. If future pregnancy is planned: consider shift from MMI/CMZ to PTU before pregnancy
6. Consider surgical therapy in young women with severe Graves’ disease

1 Laurberg P and Andersen SL. Eur J Endocrinol 2014.

TSH in Caucasian Pregnant W.

<table>
<thead>
<tr>
<th>Week of gestation</th>
<th>TSH percentiles (mU/L)</th>
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<tr>
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<td>2.5th  5th  25th  50th 75th  95th  97.5th</td>
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<td>2–6</td>
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<tr>
<td>17–20</td>
<td>161  0.35 0.45 0.98 1.36 1.96 2.94 3.32</td>
</tr>
</tbody>
</table>

• N=5805 women in northern Finland. TSH ranges: 0.07-3.5.

1 Mannisto T et al., Thyroid 2011
Hyperthyroidism Case

ID/HPI: 27 yo Asian female with h/o therapeutic abortion 1 yr ago found to be hyperthyroid as part of pre-pregnancy planning. She is asymptomatic and desires pregnancy soon.

PMH: Therapeutic abortion 15 wks due to cardiac defect.

Meds/FHx: No meds. FHx negative for thyroid dz.

PEX: Notable for tachycardia. No evidence of TAO. Thyroid gland 1.5x normal in size, soft.

Labs:
3/4/17: TSH 1.05
11/16/17: TSH 0.02, ft4 1.2, ft3 4.0, TPO ab 237
12/6/17: TSH 0.01, ft4 1.4, ft3 3.7, TSI 333