Thyroid dysfunction during pregnancy – current concepts and future directions

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Abbott Diagnostics Research
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Put science on your side.
Why think about thyroid dysfunction and pregnancy?

- Thyroid disorders are common in women of reproductive age
- They often go unrecognized or under-treated
- Maternal thyroid dysfunction has been associated with a wide variety of adverse outcomes for the mother and child
- Are pregnant women getting enough iodine?
- Diagnosing, treating, and monitoring thyroid dysfunction during pregnancy presents special challenges for healthcare providers
- Laboratory evaluation of maternal thyroid function requires gestational age specific reference intervals
- Conflicting professional society recommendations
- Maternal thyroid dysfunction associated with future adverse health outcomes
Prevalence of thyroid failure

- Higher in women
- Increases with age
- Common in women of child-bearing age.

Canaris, Arch Intern Med. 2000
Prevalence of TPO-Abs

- Higher in women
- Increases with age
- Common in women of child-bearing age.

Hollowell, J Clin Endo Metab 2002
Evolution of autoimmune thyroid disease

- Genetic predisposition
- Activation of autoimmune process
- TPO Ab elevation
- TSH elevation (subclinical hypothyroidism)
- Free T4 decrease (clinical hypothyroidism)

Presence of TPO-Ab is a pathologic finding

5% per year
Importance of maternal thyroid health
## Recommended dosages of daily and annual iodine supplementation (6)

<table>
<thead>
<tr>
<th>POPULATION GROUP</th>
<th>DAILY DOSE OF IODINE SUPPLEMENT (µg/d)</th>
<th>SINGLE ANNUAL DOSE OF IODIZED OIL SUPPLEMENT (mg/y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women</td>
<td>250</td>
<td>400</td>
</tr>
<tr>
<td>Lactating women</td>
<td>250</td>
<td>400</td>
</tr>
<tr>
<td>Women of reproductive age (15–49 y)</td>
<td>150</td>
<td>400</td>
</tr>
<tr>
<td>Children &lt; 2 years&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>90</td>
<td>200</td>
</tr>
</tbody>
</table>

<sup>a</sup> For children 0–6 months of age, iodine supplementation should be given through breast milk. This implies that the child is exclusively breastfed and that the lactating mother received iodine supplementation as indicated above.

<sup>b</sup> These figures for iodine supplements are given in situations where complementary food fortified with iodine is not available, in which case iodine supplementation is required for children of 7–24 months of age.
## Iodine status of pregnant women - examples

<table>
<thead>
<tr>
<th>Location</th>
<th>Median UIC</th>
<th>% &lt; 150 µg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyon, France (2012)¹</td>
<td>81 µg/L</td>
<td>~ 77%</td>
</tr>
<tr>
<td>Canberra, Australia (2010)²</td>
<td>62 µg/L</td>
<td>~ 84%</td>
</tr>
<tr>
<td>Ankara, Turkey (2012)³</td>
<td>80 µg/L</td>
<td>~ 73%</td>
</tr>
<tr>
<td>US – NHANES (2011)⁴</td>
<td>125 µg/L</td>
<td>~ 57%</td>
</tr>
<tr>
<td>Queretaro, Mexico (2011)⁵</td>
<td>273 µg/L</td>
<td>~ 32% (~ 3% &lt; 50 µg/L)</td>
</tr>
</tbody>
</table>

Women who already have compromised thyroid function (e.g., TPO-Ab) may be at even greater risk when iodine deficient.

1. Raverot, et al. Thyroid 2012
5. Garcia-Solis, et al. Thyroid (2011)
Landmark study: Haddow, NEJM 1999

- Measured TSH in stored serum samples collected during the 17th week of gestation from 25,216 pregnant women.

- Women with elevated TSH were located, and their children (now 8 to 9 years old) underwent 15 different neuropsychological tests relating to intelligence, attention, language, reading ability, school performance, and visual-motor performance.
Maternal thyroid failure and neuropsychological development of the child

• Pregnant women with untreated hypothyroidism were significantly more likely to have children with IQs < 85.

• For children whose mothers were being treated for hypothyroidism during pregnancy, the percent with IQ < 85 was not significantly different from the control.

Adapted from: Haddow, N Engl J Med. 1999

Control, n = 124
Untreated hypothyroidism, n = 48
Obstetric complications associated with maternal hypothyroidism

- Fertility problems
- Endometriosis*
- Ovarian failure*
- Miscarriage* &
- Fetal death
- Prematurity* &
- Intrauterine growth retardation*
- Hypertensive disease
- Pre-eclampsia* &
- Placental abruption*
- Fetal hyperthyroidism*

*Also associated with thyroid autoimmunity
*Also associated with maternal hyperthyroidism

Vila et al. EJE 2013
Impact of maternal thyroid dysfunction in the offspring

- Perinatal mortality*
- Decreased neuropsychological development
- Sepsis*
- Respiratory distress syndrome*

- Cardiomyopathy*
- Low birth weight*
- Large-for-gestational-age infants
- Neonatal hyperthyroidism*

*Also associated with maternal hyperthyroidism

&Also associated with thyroid autoimmunity

Vila et al. EJE 2013
TPO-Ab and risk of pre-term delivery – meta-analysis

<table>
<thead>
<tr>
<th>Study ID</th>
<th>RR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glinoer D 1994</td>
<td>2.03 (1.17, 3.53)</td>
<td>11.96</td>
</tr>
<tr>
<td>Iijima T 1997-TPOAb</td>
<td>1.31 (0.52, 3.33)</td>
<td>7.77</td>
</tr>
<tr>
<td>Negro R 2006</td>
<td>2.74 (1.62, 4.65)</td>
<td>12.25</td>
</tr>
<tr>
<td>Ghafoor F 2006</td>
<td>3.33 (2.45, 4.54)</td>
<td>14.94</td>
</tr>
<tr>
<td>Jiang YY 2011</td>
<td>1.45 (0.69, 3.04)</td>
<td>9.72</td>
</tr>
<tr>
<td>Mannisto T 2009-TPOAb</td>
<td>1.23 (0.79, 1.93)</td>
<td>13.26</td>
</tr>
<tr>
<td>Negro R 2011</td>
<td>1.09 (0.66, 1.78)</td>
<td>12.71</td>
</tr>
<tr>
<td>Namblar V 2011</td>
<td>1.54 (0.48, 4.93)</td>
<td>5.96</td>
</tr>
<tr>
<td>Ashoor G 2011-TPOAb</td>
<td>1.17 (0.64, 2.12)</td>
<td>11.42</td>
</tr>
<tr>
<td>Overall (I² = 71.6%, P = 0.000)</td>
<td>1.69 (1.19, 2.41)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis
Increased Pregnancy Loss Rate in Thyroid Antibody Negative Women with TSH Levels between 2.5 and 5.0 in the First Trimester of Pregnancy

Roberto Negro, Alan Schwartz, Riccardo Gismondi, Andrea Tinelli, Tiziana Mangieri, and Alex Stagnaro-Green

Divisions of Endocrinology (R.N.), Neonatology and Intensive Care Unit (T.M.), and Obstetrics and Gynecology (A.T.), V. Fazzi Hospital, 73100 Lecce, Italy; Department of Medical Education (A.S.), University of Illinois, Chicago, Illinois 60637; Division of Obstetrics and Gynecology (R.G.), Casa di Cura Salus, 72100 Brindisi, Italy; and Departments of Medicine and Obstetrics and Gynecology (A.S.-G.), Touro University College of Medicine, Hackensack, New Jersey 07601
Spontaneous pregnancy loss in thyroid antibody negative euthyroid women

<table>
<thead>
<tr>
<th>TABLE 1. Clinical characteristics of patients by group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A TSH &lt; 2.5</strong> (n = 3481)</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Previous babies (%)</td>
</tr>
<tr>
<td>Smoking (%)</td>
</tr>
<tr>
<td>First gynecological visit (wk)</td>
</tr>
<tr>
<td>TSH first trimester (mIU/liter), median (interquartile range)(^a)</td>
</tr>
<tr>
<td>Free T(_4) first trimester (pmol/liter)(^a)</td>
</tr>
<tr>
<td>Family history of thyroid disease (%)(^b)</td>
</tr>
<tr>
<td>Goiter (%)</td>
</tr>
<tr>
<td>Symptoms of hypo-/hyperthyroidism (%)</td>
</tr>
<tr>
<td>Type 1 diabetes/autoimmune disease (%)</td>
</tr>
<tr>
<td>Irradiation (%)</td>
</tr>
<tr>
<td>Previous miscarriage/preterm deliveries (%)</td>
</tr>
</tbody>
</table>

Demographic information, pregnancy history, clinical information, and thyroid function tests for women are broken down by group. Group A TSH levels are below 2.5 mIU/liter; group B TSH levels are between 2.5 and 5.0 mIU/liter.

\(^a\) \(P < 0.01\).
\(^b\) \(P < 0.05\).

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Spontaneous pregnancy loss

<table>
<thead>
<tr>
<th>Group A = 3.6%</th>
<th>Group B = 6.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(p &lt; 0.006)</td>
</tr>
</tbody>
</table>

Negro, et al. JCEM 2012

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**Put science on your side.**

Abbott
A Promise for Life
Abbott’s Global Thyroid Research Initiative (2003 – present)

Since 2003, over 25 papers have been published
Evaluation of maternal thyroid function
### Changes in physiology during pregnancy influence thyroid function tests

<table>
<thead>
<tr>
<th>Physiologic Change</th>
<th>Thyroid function test change</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Estrogen production</td>
<td>↑ TT4, TT3 (reference range ~ 1.5x non-pregnant levels)</td>
</tr>
<tr>
<td>↑ TBG (peak at ~ 20 weeks)</td>
<td>↓ TSH (nadir ~ 10 – 12 weeks)</td>
</tr>
<tr>
<td>↑ hCG (peak ~ 10 – 20 weeks)</td>
<td>↑ FT4 (modest) – 1(^{st}) trimester</td>
</tr>
<tr>
<td>↑ Iodine clearance, requirement</td>
<td>↓ FT4, FT3 (20 – 30% below normal mean)</td>
</tr>
<tr>
<td>↑ T4 and T3 degradation</td>
<td>Trimester specific reference ranges needed</td>
</tr>
</tbody>
</table>

Adapted from: Brent, Clin Obstet Gynecol 1997; Demers and Spencer, Thyroid 2003.
Thyroid disease and pregnancy have many signs and symptoms in common

Clinical diagnosis of thyroid disease during pregnancy can be very challenging

Fatigue
Nausea
Weight gain
Skin, hair, nail changes
Sleep disturbances
Constipation
Faintness/dizziness
Mood swings
Headaches

“It is important to diagnose hypothyroidism because of its potential adverse impact on pregnancy, and yet most patients are relatively asymptomatic … and complaints of weight gain or fatigue may be attributed to the pregnancy itself.”

Mandel, Best Practice & Research Clinical Endocrinology & Metabolism 2004
The importance of trimester specific reference intervals

Cross-sectional study, n = 2,272
Women positive for Anti-TPO and/or Anti-Tg were excluded
Gestational age specific reference intervals calculated in antibody negative women
Gestational age specific TSH values

Gestational Age (weeks)

TSH (mIU/L)

< 6 to 9
< 9 to 12
< 12 to 15
< 15 to 18
< 18 to 21
< 21 to 24
< 24 to 27
< 27 to 30
< 30 to 33
< 33 to 36
> 36 to term

Median
Upper 97.5th percentile
Lower 2.5th percentile

Non-pregnant reference limits

Stricker, Euro J Endocrinol 2007
Potential misclassification of TSH values during pregnancy

Overall, 7.3% of TSH would have been misclassified if using non-pregnant reference intervals

Stricker, Euro J Endocrinol 2007
Overall potential for misclassification of maternal thyroid function test results

Accurate classification of TFT in pregnant women requires the use of gestational age specific reference intervals

“Accurate classification of TFT in pregnant women requires the use of gestational age specific reference intervals”

Stricker, Euro J Endocrinol 2007
Study of thyroid function in pregnant and non-pregnant Mexican women
### Study population

<table>
<thead>
<tr>
<th></th>
<th>Pregnant women</th>
<th>Non-pregnant women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>660</td>
<td>104</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>25.8</td>
<td>28.6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Range</td>
<td>12 – 45</td>
<td>16 – 42</td>
</tr>
<tr>
<td>Median</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td><strong>Thyroid antibody status (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPO-Ab positive</td>
<td>7.42</td>
<td>6.73</td>
</tr>
<tr>
<td>Tg-Ab positive</td>
<td>11.06</td>
<td>13.46</td>
</tr>
<tr>
<td>TPO-Ab and/or Tg-Ab positive</td>
<td>13.48</td>
<td>14.42</td>
</tr>
<tr>
<td>TPO-Ab and Tg-Ab positive</td>
<td>5.00</td>
<td>5.77</td>
</tr>
</tbody>
</table>

<sup>a</sup>p < 0.001

Manuscript currently under review
Box-plot of TSH values

TSH (mIU/L)

Ab - Ab + Ab - Ab + Ab - Ab + Ab - Ab +
not pregnant 1st trimester 2nd trimester 3rd trimester

Manuscript currently under review
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>Median</th>
<th>2.5th</th>
<th>97.5th</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TSH (mIU/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non pregnant</td>
<td>89</td>
<td>1.84</td>
<td>1.8</td>
<td>0.53</td>
<td>4.02</td>
</tr>
<tr>
<td>First trimester (&lt;6-12)</td>
<td>178</td>
<td>1.67</td>
<td>1.44</td>
<td>0.05</td>
<td>4.79</td>
</tr>
<tr>
<td>Second trimester (&gt;12-24)</td>
<td>168</td>
<td>1.73</td>
<td>1.47</td>
<td>0.09</td>
<td>4.56</td>
</tr>
<tr>
<td>Third trimester (&gt;24 to term)</td>
<td>225</td>
<td>2.4</td>
<td>2.34**†&amp;</td>
<td>0.49</td>
<td>5.18</td>
</tr>
</tbody>
</table>

*p < 0.05 two-tailed significantly different from first trimester
†p < 0.05 two-tailed significantly different from second trimester
&p < 0.05 two-tailed significantly different from non-pregnant
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>Median</th>
<th>2.5th</th>
<th>97.5th</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Free T4 (ng/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non pregnant</td>
<td>89</td>
<td>1.09</td>
<td>1.1</td>
<td>0.83</td>
<td>1.37</td>
</tr>
<tr>
<td>First trimester (&lt;6-12)</td>
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<td>1.08</td>
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<td>0.78</td>
<td>1.39</td>
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<tr>
<td>Second trimester (&gt;12-24)</td>
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<td>1.03*&amp;</td>
<td>1.02</td>
<td>0.74</td>
<td>1.29</td>
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<tr>
<td>Third trimester (&gt;24 to term)</td>
<td>225</td>
<td>0.91*†&amp;</td>
<td>0.9</td>
<td>0.66</td>
<td>1.2</td>
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<tr>
<td><strong>Total T4 (ug/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non pregnant</td>
<td>89</td>
<td>7.21</td>
<td>7.13</td>
<td>4.45</td>
<td>10.85</td>
</tr>
<tr>
<td>First trimester (&lt;6-12)</td>
<td>178</td>
<td>9.51*&amp;</td>
<td>9.3</td>
<td>5.92</td>
<td>13.32</td>
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<tr>
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<td>168</td>
<td>10.85*&amp;</td>
<td>10.86</td>
<td>7.07</td>
<td>14.02</td>
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<tr>
<td>Third trimester (&gt;24 to term)</td>
<td>225</td>
<td>9.69*†&amp;</td>
<td>9.63</td>
<td>6.56</td>
<td>14.01</td>
</tr>
</tbody>
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& p < 0.05 two-tailed significantly different from non-pregnant
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<th>Median</th>
<th>2.5th</th>
<th>97.5th</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Free T 3 (pg/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non pregnant</td>
<td>89</td>
<td>2.41</td>
<td>2.44</td>
<td>1.71</td>
<td>3.26</td>
</tr>
<tr>
<td>First trimester (&lt;6-12)</td>
<td>178</td>
<td>3.13 &amp;</td>
<td>3.17</td>
<td>2.21</td>
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<td>225</td>
<td>2.92 **†&amp;</td>
<td>2.74</td>
<td>2.13</td>
<td>3.67</td>
</tr>
<tr>
<td><strong>Total T3 (ng/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non pregnant</td>
<td>89</td>
<td>0.99</td>
<td>0.97</td>
<td>0.63</td>
<td>1.68</td>
</tr>
<tr>
<td>First trimester (&lt;6-12)</td>
<td>178</td>
<td>1.41 &amp;</td>
<td>1.42</td>
<td>0.82</td>
<td>2.04</td>
</tr>
<tr>
<td>Second trimester (&gt;12-24)</td>
<td>168</td>
<td>1.66 **&amp;</td>
<td>1.64</td>
<td>1.16</td>
<td>2.19</td>
</tr>
<tr>
<td>Third trimester (&gt;24 to term)</td>
<td>225</td>
<td>2.06 †</td>
<td>1.48</td>
<td>1.05</td>
<td>2.01</td>
</tr>
</tbody>
</table>

*p < 0.05 two-tailed significantly different from first trimester
†p < 0.05 two-tailed significantly different from second trimester
& p < 0.05 two-tailed significantly different from non-pregnant
Identification of pregnant women with thyroid dysfunction
# Pre-existing maternal hypothyroidism

**Table 3** Aspects of thyroxine treatment of hypothyroidism in pregnancy (adapted from Abalovich et al.\(^\text{40}\)).

| Preconception: optimise therapy in patients with pre-existing disease |
| On confirmation of pregnancy, increase dose by 30–50% of preconception dose |
| Check thyroid function early in first trimester |
| Aim for TSH <2.5 mU/l in the first trimester and <3 mU/l in later pregnancy |
| Monitor thyroid function 4–6 weeks and further adjust dose |
| Higher dose requirement in post-ablative and post-surgical hypothyroidism |
| After delivery reduce thyroxine to preconception dose |
| Recheck thyroid function at 6 weeks postpartum |

**Note drug interactions:**
- (a) Drugs which impair thyroxine absorption: iron supplements, cholestyramine, calcium carbonate, soy milk
- (b) Drugs which increase thyroxine clearance: carbamazepine, rifampicin, valproate

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**Pregnant women with pre-existing hypothyroidism require close monitoring**

Lazarus, Brit Med Bulletin 2011
Abalovich, et al. JCEM 2007
Professional society guidelines – no consensus ...

<table>
<thead>
<tr>
<th>Organization</th>
<th>Thyroid Screening with TSH</th>
<th>Goal TSH During Treatment (mU/L)</th>
<th>Treatment of Subclinical Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOG⁴</td>
<td>Case finding</td>
<td>Not specified</td>
<td>Not recommended</td>
</tr>
<tr>
<td>USPSTF⁹⁶</td>
<td>Case finding</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>TES¹⁵,a</td>
<td>Case finding</td>
<td>2.5 in first trimester 3.0 in second, third trimesters</td>
<td>Recommended</td>
</tr>
<tr>
<td>AACE⁹⁷,⁹⁸</td>
<td>Routine</td>
<td>0.3–3.0</td>
<td>Recommended</td>
</tr>
<tr>
<td>BTA⁹⁹,b</td>
<td>Case finding</td>
<td>0.4–2.0</td>
<td>Recommended</td>
</tr>
</tbody>
</table>

Table 2
Opinions of professional organizations regarding thyroid disease screening and treatment in pregnancy
Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum

The American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum

Alex Stagnaro-Green (Chair),¹ Marcos Abalovich,² Erik Alexander,³ Fereidoun Azizi,⁴ Jorge Mestman,⁵ Roberto Negro,⁶ Angelita Nixon,⁷ Elizabeth N. Pearce,⁸ Offie P. Soldin,⁹ Scott Sullivan,¹⁰ and Wilmar Wiersinga¹¹

Put science on your side.
Testing women at high risk

RECOMMENDATION 76
Serum TSH values should be obtained early in pregnancy in the following women at high risk for overt hypothyroidism:

- History of thyroid dysfunction or prior thyroid surgery
- Age >30 years
- Symptoms of thyroid dysfunction or the presence of goiter
- TPOAb positivity
- Type 1 diabetes or other autoimmune disorders
- History of miscarriage or preterm delivery
- History of head or neck radiation
- Family history of thyroid dysfunction
- Morbid obesity (BMI ≥ 40 kg/m²)
- Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast
- Infertility
- Residing in an area of known moderate to severe iodine insufficiency

Level B-USPSTF

Dissent from one committee member: There is no good evidence that improved maternal or perinatal outcomes will be obtained if the criteria for thyroid function screening were different for a pregnant than a nonpregnant population. Correspondingly, criteria for screening pregnant women should not differ from the nonpregnant population.

Stagnaro-Green, Thyroid 2011
A trial that screens women preconception and then randomizes women with SCH or isolated hypothroixinemia and Tab+ euthyroid women to either a treatment or no treatment arm is needed.

Another well powered, prospective, randomized interventional trial of LT4 in euthyroid patients who are TPOAb+ for the prevention of spontaneous abortion and preterm delivery.

Stagnaro-Green, Thyroid 2011
RECOMMENDATION 72
There is insufficient evidence to recommend for or against universal TSH screening at the first trimester visit. Level I-USPSTF

RECOMMENDATION 75
All pregnant women should be verbally screened at the initial prenatal visit for any history of thyroid dysfunction and/or use of thyroid hormone (LT₄) or anti-thyroid medications (MMI, carbimazole, or PTU). Level B-USPSTF

Stagnaro-Green, Thyroid 2011
Case-finding vs. universal screening

BRIEF REPORT

Detection of Thyroid Dysfunction in Early Pregnancy: Universal Screening or Targeted High-Risk Case Finding?

Bijay Vaidya, Sony Anthony, Mary Bilous, Beverley Shields, John Drury, Stewart Hutchison, and Rudy Bilous

Department of Endocrinology (B.V., B.S.), Peninsula Medical School, Royal Devon & Exeter Hospital, Exeter EX2 5DW, United Kingdom; and Departments of Endocrinology (S.A., M.B., R.B.), Clinical Biochemistry (J.D.), and Obstetrics (S.H.), James Cook University Hospital, Middlesbrough TS4 3BW, United Kingdom

- Prospective study, n = 1,560
- Assess efficacy of targeted high-risk screening vs. case finding for early identification of thyroid dysfunction in pregnant women
Risk factors for raised TSH at screening

- Personal history of thyroid disease
- TPO-Ab positive
- Personal history of autoimmune disorders
- Family history of thyroid disease
- South Asian ethnicity

Relative risk for elevated TSH

*** p < 0.0001
** p < 0.05

Vaidya, JCEM 2007
Limitations of case finding

Figure 2 The rates of missed diagnoses if screening were to be performed only in the high-risk population.

Wang et al., Euro J Endocrinol 2012
Can intervention improve outcomes?¹

Levothyroxine Treatment in Euthyroid Pregnant Women with Autoimmune Thyroid Disease: Effects on Obstetrical Complications

Roberto Negro, Gianni Formoso, Tiziana Mangieri, Antonio Pezzarossa, Davide Dazzi, and Haslinda Hassan

Department of Endocrinology (R.N., G.F.), Azienda Ospedaliera LE11, 73100 Lecce, Italy; Department of Obstetrics and Gynecology (T.M.), Casa di Cura “Salus”, 72100 Brindisi, Italy; Department of Internal Medicine (A.P., D.D.), Azienda Ospedaliera PR, “Di Vaiio” Hospital, 43036 Fidenza, Italy; and Endocrine Unit (H.H.), Raja Isteri Pengiran Anak Saleha Hospital, Bandar Seri Begawan, Brunei Darussalam BA 1000

- Prospective study, 984 women
- To assess if women with AITD have a higher rate of obstetrical complications and if levothyroxine (LT4) treatment provides beneficial effects.
- TPO-Ab women divided into control, and treated (LT4) groups
- Outcomes measured: rate of obstetrical complications

Negro, JCEM 2006
"LT4 treatment turned out to be extremely effective in reducing the number of miscarriages when given during the early stages of pregnancy ..."
Reduction in rate of pre-term delivery

LT4 treatment appeared to be effective in reducing miscarriages whether given before or after the first trimester of pregnancy.

Negro, JCEM 2006
Antenatal Thyroid Screening and Childhood Cognitive Function

Study design

21,846 Women were recruited and underwent randomization

10,924 Were assigned to screening group at approximately 12 wk of gestation (serum assay within approximately 1 wk)

- 499 (4.6%) Tested positive
  - 242 Had low free T₄
  - 232 Had high thyrotropin
- 25 Had low free T₄ and high thyrotropin

- 10,425 Tested negative

- 499 (4.6%) Were prescribed levothyroxine at approximately 13 wk of gestation

10,915 Had stored serum assay after delivery

- 351 (5.0%) Tested positive
  - 257 Had low free T₄
  - 254 Had high thyrotropin
  - 30 Had low free T₄ and high thyrotropin
- 10,364 Tested negative

106 Were lost to follow-up

- 90 Declined child testing
- 19 Declined child testing

390 (78.2%) of children completed psychological testing at 3 yr of age

404 (73.3%) of children completed psychological testing at 3 yr of age

Treatment group

- Women had either:
  - TSH > 97.5th percentile
  - FT4 < 2.5th percentile
  - Or both out of range
- Initial LT4 dose = 150 µg/day
- Target TSH 0.1 – 1.0 mIU/L
### Table 1. Characteristics of Women with Positive Screening Results and Their Children Who Completed Psychological Testing.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Screening Group (N = 390)</th>
<th>Control Group (N = 404)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at screening (weeks, days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>12, 3</td>
<td>12, 3</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>11, 6–13, 6</td>
<td>11, 6–13, 5</td>
</tr>
<tr>
<td>Thyrotropin (mIU/liter)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>1.5–4.7</td>
<td>1.2–4.2</td>
</tr>
<tr>
<td>Turin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>1.3–4.0</td>
<td>1.3–3.9</td>
</tr>
<tr>
<td>Free T₄†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom (pmol/liter)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>11.1</td>
<td>11.2</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>10.5–13.3</td>
<td>10.5–13.2</td>
</tr>
<tr>
<td>Turin (pg/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7.4</td>
<td>7.4</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>7.1–8.6</td>
<td>7.2–8.3</td>
</tr>
</tbody>
</table>

Lazarus et al., NEJM 2012
## Child IQ and development scores

<table>
<thead>
<tr>
<th>Test</th>
<th>Screening Group (N = 390)</th>
<th>Control Group (N = 404)</th>
<th>Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>99.2±13.3</td>
<td>100.0±13.3</td>
<td>0.8 (−1.1 to 2.6)</td>
<td>0.40</td>
</tr>
<tr>
<td>&lt;85 (% of children)</td>
<td>12.1</td>
<td>14.1</td>
<td>2.1 (−2.6 to 6.7)</td>
<td>0.39</td>
</tr>
<tr>
<td>CBCL T score‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>44.4±12.4</td>
<td>45.1±13.6</td>
<td>0.7 (−1.2 to 2.5)</td>
<td>0.49</td>
</tr>
<tr>
<td>Brief-P T score§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>40</td>
<td>40</td>
<td>0</td>
<td>0.59</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>47–55</td>
<td>47–55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. The full-scale child IQ test was standardized so that for each psychologist, the mean score among the children in the control group whom they tested was 100. In the screening group, the women were assigned to treatment with levothyroxine.

† For percentages of children with an IQ below 85, the absolute (percentage-point) differences are shown.

‡ For the CBCL, a T score above the 98th percentile is indicative of a clinically significant problem.

§ For the Brief-P, a T score above 65 is indicative of a clinically significant problem.

Lazarus et al., NEJM 2012
Possible reasons for why there was lack of benefit in the Lazarus, et al. NEJM 2012 study

- Women in this study milder hypothyroidism
- Starting treatment at median gestational age of 13 week 3 days may be too late
- Even though subgroup analysis of women treated earlier showed no benefit, the study was not sufficiently powered for this analysis
- IQ testing at age 3 may not be a sensitive reflection of thyroid hormone action on the developing fetal brain (more neurocognitive testing would be beneficial)
Question cut-off values used, given iodine deficiency in women in the UK (cut-offs would be lower in iodine sufficient women)

- Question power calculation – based on US study where women were iodine sufficient and patients had higher TSH

- Thyroid dysfunction may have been under diagnosed

**Antenatal Thyroid Screening and Childhood Cognitive Function**

TO THE EDITOR: Lazarus and colleagues (Feb. 9) administered levothyroxine to pregnant women who would have been treated (along with their respective controls). (Incidentally, the units...
Thyroid function screening in pregnancy – debate continues

Do you feel that women should have thyroid function testing performed during pregnancy?

<table>
<thead>
<tr>
<th>Expert</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>James Haddow</td>
<td>“My view is that all women should have a TSH measurement performed during pregnancy.”</td>
</tr>
<tr>
<td>Sarah Kilpatrick</td>
<td>“… routine screening is not indicated. However, it is very important to test women at high risk for thyroid disease …”</td>
</tr>
<tr>
<td>John Lazarus</td>
<td>“Because thyroid dysfunction is common in pregnancy I do think that thyroid function testing in early pregnancy is justified in all women.”</td>
</tr>
<tr>
<td>Roberto Negro</td>
<td>“Personally, I stand in favor of universal screening for thyroid disease at the beginning of pregnancy.”</td>
</tr>
</tbody>
</table>
Thyroid function and future health
Thyroid Dysfunction and Autoantibodies during Pregnancy as Predictive Factors of Pregnancy Complications and Maternal Morbidity in Later Life

Tuija Männistö, Marja Väärsmäki, Anneli Pouta, Anna-Liisa Hartikainen, Aimo Ruokonen, Heljä-Marja Surcel, Aini Bloigu, Marjo-Riitta Järvelin, and Ella Suvanto

Department of Obstetrics and Gynecology (T.M., M.V., A.-L.H., E.S.) and Institute of Health Sciences (T.M., M.-R.J.), University of Oulu, 90014 Oulu, Finland; National Institute of Health and Welfare (A.P., H.-M.S., A.B., M.-R.J.), Child and Adolescent Health and Wellbeing Unit, 90101 Oulu, Finland; Department of Clinical Chemistry (A.R.), University of Oulu, 90014 Oulu, Finland; and Department of Epidemiology and Public Health (M.-R.J.), Imperial College London SW7 2AZ, United Kingdom

- Prospective population based cohort study (NFBC 1986)
- N = 5805, with follow-up of 20 years
- Evaluated association between maternal thyroid dysfunction and/or antibodies during pregnancy and pregnancy complications or later maternal hypertension, diabetes, and thyroid disease

Mannisto, JCEM 2010
Thyroid dysfunction during pregnancy predicts future morbidity

Overt hypothyroidism – associated with subsequent maternal:

- Thyroid disease, HR = 17.7 (7.8 – 40.6)
- Diabetes, HR = 6.0 (2.2 – 16.4)

Later maternal thyroid disease associated with:

- Subclinical hypothyroidism, HR = 3.3 (1.6 – 6.9)
- TPO-Ab +, HR = 4.2 (2.3 – 7.4)
- Tg-Ab +, HR = 3.3 (1.9 – 6.0)

Mannisto, JCEM 2010
Summary

- Thyroid dysfunction is common in women of childbearing age.

- Proper maternal thyroid function is important for the health of both the mother and developing child, and maternal thyroid dysfunction is associated with multiple adverse pregnancy outcomes.

- Maternal physiology changes during pregnancy – gestational age specific reference intervals are needed for accurate interpretation of thyroid function tests.

- Maternal iodine nutrition status is critically important.

- TSH and TPO-Ab are important markers of maternal thyroid status.
Current practice guidelines recommend case-finding in high-risk populations. However case-finding may miss a significant number of women with thyroid dysfunction.

Data suggesting intervention can improve outcomes is conflicting. Further prospective studies are needed.

Pregnant women with thyroid dysfunction – particularly autoimmune thyroid disease – are at increased short/long-term risk for a variety of other co-morbid conditions.

Knowledge of maternal thyroid status can inform patient care – both now and in the future.
MUCHAS GRACIAS!
TSH based algorithm for the detection of thyroid dysfunction in pregnancy

Serum TSH determination in early gestation

First trimester reference range

Below

Above

Within

Measure total T₄ or free T₄

No further action

Hyperthyroidism

T₄ status elevated
Measure TR-Ab
TPO-Ab usually positive

Overt thyrotoxicosis
(probable cause: Graves disease)

Antithyroid drugs
Monitor TR-Ab (for risk of fetal hyperthyroidism)

Hypothyroidism

T₄ status normal
(or moderately elevated)
TPO-Ab usually negative

Subclinical thyrotoxicosis
(probable cause: gestational transient thyrotoxicosis)

No treatment needed in most cases

Hypothyroidism

T₄ status subnormal
TPO-Ab positive or negative

Subclinical hypothyroidism

Levothyroxine

TPO-Ab positive

Isolated hypo-T₄

Levothyroxine?

Glinoer and Spencer, Nat Rev Endocrinol 2010

Put science on your side.
Interpretation and management of 1st trimester thyroid function test screening

Stagnaro-Green et al., Thyroid 2011