Management of elevated TSH in pregnancy

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CONSULTANT ENDOCRINOLOGIST, ALFRED HEALTH, MELBOURNE
Why is this topic of interest to us?

- Potential adverse effects on
  - The baby’s cognitive development
  - Important pregnancy outcomes

- ATA Guidelines: 2017 vs 2011
  - Help or hindrance?
Congenital hypothyroidism

Infants

- Severe intellectual disability
- Short stature
- Coarse facial features
- Macroglossia
- Umbilical hernia
- Hypotonia
- Mild jaundice
- Poor feeding
- Constipation
An adult male from the Congo, with three women of the same age (17-20 years), all of whom are myxedematous cretins.
But what about more subtle maternal thyroid dysfunction?
Unleash the Genius within your child!

Shopfront window,
Surrey Hills, Melbourne
Heguru Method
 esp. Right Brain Education
Elevated TSH: Potential issues

- Effects on the baby’s brain
- Effects on pregnancy outcomes
  - Fetal loss
  - Premature delivery
  - Pre-eclampsia
  - Gestational hypertension
  - Gestational diabetes
  - Placental abruption
  - IUGR
  - Low birth weight
  - Neonatal death
- Effects on fertility
Fetal physiology

- Fetal thyroid begins concentrating iodine and synthesising thyroid hormones after **12 weeks** of gestation.

- **Before this time all required thyroid hormone is supplied by the mother.**
Brain development

- Neural tube development begins 3 weeks after conception
- Neuron production begins 6 weeks after conception
- By mid-gestation billions of neurons have been produced (close to lifetime maximum)

Entry of T4 and T3 into brain

- **Specific transmembrane transporters**
  - Monocarboxylate transporter 8 (Mct8)
  - Organic anion transporter polypeptide 1c1 (Oatp1c1)
Thyroid hormones are major players in brain development

- Mostly T3 via classical pathway with nuclear receptor interaction
- Non genomic effects of T4 & T3 also likely
- T3 in brain
  - Some from the circulation and some from 5’-deiodination of T4 in the astrocytes
  - Proportions depend on the developmental stage

Thyroid hormones & brain development

Specific critical time windows

Thyroid hormones are involved in:

- Neurogenesis
- Neuronal migration
- Neuronal and glial cell differentiation
- Myelination
- Synaptogenesis
TFT requests by Gestational Week – Melbourne Pathology data
Weeks 4-11 gestation: more than 1000 TFT requests every week

Total n = 22,838
(32% of the data extract)
Emergency Department Physician

I have no idea what's going to happen.

And I love it.
Emergency Department Physician

Endocrinologist

I have no idea what's going to happen.

And I love it.

Doubt & Fear
Just Ahead
Is there reason for doubt (and possibly fear) in managing high TSH in pregnancy?
NUMBER OF PARTICIPANTS IN CLINICAL STUDIES
NUMBER OF PARTICIPANTS IN CLINICAL STUDIES

- HOPE: 9541
- UKPDS: 5102
- 45: 4444
- DCCT: 1411
- IQ & L-T4 PREGNANCY TREATMENT (LAZARUS NEJM...): 794
- IQ & HIGH TSH OBSERVATIONAL STUDY (HADDOW...): 69
- PRETERM BIRTHS & SCH (LARGEST): 186
- PRETERM BIRTHS & SCH (SMALLEST): 404

NUMBER OF PARTICIPANTS IN CLINICAL STUDIES
Total of 62 women with elevated TSH
Mean TSH 13.2 mU/L
15 had TSH above 30 mU/L
Only 21 had TSH 4-10 mU/L
MATERNAL THYROID DEFICIENCY DURING PREGNANCY AND SUBSEQUENT NEUROPSYCHOLOGICAL DEVELOPMENT OF THE CHILD


<table>
<thead>
<tr>
<th>TEST</th>
<th>CHILDREN OF WOMEN WITH HYPOTHYROIDISM (N=62)</th>
<th>CONTROL CHILDREN (N=124)</th>
<th>MEAN DIFFERENCE†</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intelligence</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>WISC-III full-scale IQ score</td>
<td>103±15</td>
<td>107±12</td>
<td>−4.1±2.1</td>
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<tr>
<td>WISC-III full-scale IQ score ≤85 (%)</td>
<td>15</td>
<td>5</td>
<td>3 (1−8)</td>
<td>0.08</td>
</tr>
</tbody>
</table>
MATERNAL THYROID DEFICIENCY DURING PREGNANCY AND SUBSEQUENT NEUROPSYCHOLOGICAL DEVELOPMENT OF THE CHILD

JAMES E. HADDOW, M.D., GLENN E. PALOMARO, B.S., WALTER C. ALLAN, M.D., JOSEPHINE R. WILLIAMS, GEORGE J. KNIGHT, PH.D., JUNE GAGNON, M.A., CHERYL E. O’HEIR, M.ED., ED.S., MARVIN L. MITCHELL, M.D., ROSAIE J. HERMOSIS, M.P.H., SUSAN E. WASSERMAN, Ph.D., JAMES D. FACK, M.D., AND ROBERT Z. KLEIN, M.D.

<table>
<thead>
<tr>
<th>TEST</th>
<th>CHILDREN OF TREATED WOMEN WITH HYPOTHYROIDISM (N=14)</th>
<th>CHILDREN OF UNTREATED WOMEN WITH HYPOTHYROIDISM (N=48)</th>
<th>CONTROL CHILDREN (N=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WISC-III full-scale IQ score</td>
<td>111 0.20</td>
<td>100 0.005</td>
<td>107</td>
</tr>
<tr>
<td>WISC-III full-scale IQ score ≤85 (%)</td>
<td>0 0.90</td>
<td>19 0.007</td>
<td>5</td>
</tr>
<tr>
<td>Test</td>
<td>Children of Treated Women with Hypothyroidism (N=14)</td>
<td>Children of Untreated Women with Hypothyroidism (N=48)</td>
<td>Control Children (N=124)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------------------------------------------</td>
<td>---------------------------------------------------</td>
<td>--------------------------</td>
</tr>
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<td>100 0.005</td>
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<table>
<thead>
<tr>
<th>Test</th>
<th>Children of Treated Women with Hypothyroidism (N=14)</th>
<th>P Value†</th>
<th>Children of Untreated Women with Hypothyroidism (N=48)</th>
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<td>5</td>
</tr>
</tbody>
</table>
Maternal thyroid hormone insufficiency & IQ: A systematic review and meta-analysis

![Graph showing the association between maternal thyroid hormone insufficiency and IQ, with weights from random-effects analysis.](image)

**NOTE:** Weights are from random-effects analysis.
Maternal thyroid hormone insufficiency & IQ: A systematic review and meta-analysis
Maternal thyroid hormone insufficiency & IQ: A systematic review and meta-analysis

![Diagram showing the results of a meta-analysis on the association between maternal thyroid hormone insufficiency and IQ. The diagram includes studies by Haddow (1999), Smit (2000), Li (2010), Su (2011), Behrooz (2011), Williams (2012), Williams (2013), Chen (2015), Noten (2015), Murphy (2015), Pakkila (2015), and overall results. The overall effect size (ES) is 2.14 (95% CI: 1.20, 3.83) with a significance level of 0.000.]

NOTE: Weights are from random-effects analysis.
Maternal thyroid hormone insufficiency & IQ: A systematic review and meta-analysis

Li study: Only 18 women with subclinical hypothyroidism

Thompson W et al, Clinical Endocrinology 2018;88:575–584
Maternal thyroid hormone insufficiency & IQ: A systematic review and meta-analysis

Pre-term infants ≤ 34 weeks

Thompson W et al, Clinical Endocrinology 2018;88:575–584
Maternal thyroid hormone insufficiency & IQ: A systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haddow (1999)</td>
<td>3.00 (1.00, 8.00)</td>
<td>9.90</td>
</tr>
<tr>
<td>Smit (2000)</td>
<td>1.47 (0.15, 13.99)</td>
<td>4.55</td>
</tr>
<tr>
<td>Li (2010)</td>
<td>15.63 (4.70, 51.99)</td>
<td>8.95</td>
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<tr>
<td>Su (2011)</td>
<td>10.49 (1.01, 119.19)</td>
<td>4.21</td>
</tr>
<tr>
<td>Behrooz (2011)</td>
<td>1.15 (0.36, 3.66)</td>
<td>9.22</td>
</tr>
<tr>
<td>Williams (2012)</td>
<td>3.70 (1.80, 7.61)</td>
<td>11.85</td>
</tr>
<tr>
<td>Williams (2013)</td>
<td>1.28 (0.21, 7.90)</td>
<td>5.99</td>
</tr>
<tr>
<td>Chen (2015)</td>
<td>1.65 (0.52, 5.22)</td>
<td>9.24</td>
</tr>
<tr>
<td>Noten (2015)</td>
<td>0.72 (0.44, 1.17)</td>
<td>13.15</td>
</tr>
<tr>
<td>Murphy (2015)</td>
<td>2.53 (1.01, 6.34)</td>
<td>10.65</td>
</tr>
<tr>
<td>Pakkila (2015)</td>
<td>1.05 (0.55, 2.02)</td>
<td>12.27</td>
</tr>
<tr>
<td>Overall (I^2 = 72.2%, P = .000)</td>
<td>2.14 (1.20, 3.83)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random-effects analysis
Other reasons for doubt apart from paucity of high quality studies.....
Our usually reliable tests:
TSH, T4, Anti-TPO antibodies - moving targets during pregnancy
Issues in TFT measurements in pregnancy

- TSH assay
  - What is the normal range?
  - Are all TSH assays equal?

- FT4 assay
  - Can we rely on it?
Anti-thyroid antibodies in pregnancy

➢ What is the significance of anti-TPO antibodies when TSH is ‘normal’?

➢ What is the significance of the decline of anti-TPO antibodies as pregnancy progresses?
Maternal physiological changes in pregnancy: what’s different?

- Increased TBG production (estrogen effect)
- Prolonged TBG half life (estrogen effect)
- Rises in Total T4 & Total T3 (TBG effect)
- May cause lower Free T4 & Free T3 levels

- Reduced availability of iodine:
  - increased maternal renal clearance
  - fetal uptake of iodine
  - placental metabolism of iodine

- Maternal thyroid enlargement
  - (by 10-40% in volume)

Cignini P et al 2012: Journal of Prenatal Medicine, 6(4), 64–71
Glinoer D Endocrine Reviews 1997; 18 (3): 404-433
βhCG has weak TSH-like activity

β-subunits (hormone-specific) of βHCG and TSH have 85% homology in the first 110 amino acids

Glinoer et al JCEM 1990; 71 : 276
TSH distribution curve is affected by HCG levels

HCG <20,000 U/L does not have significant effect on TSH

Slide courtesy of Dr Zhong Lu, Head Chemical Pathology, Melbourne Pathology
Reliability of Free T4 assays in pregnancy?

Gold standard is equilibrium dialysis: measures ‘true’ free T4 levels

Common TFT Methods in Australia

Roche e602
Melbourne Pathology
Cabrini Pathology
Austin / Mercy Hosp
Box Hill Hospital
(66 labs in EQA)

Abbott Architect
• RMH
• Alfred Hospital
• SVH
(67 labs in EQA)

Siemens Centaur
• Dorevitch
• ACL
• Western Hosp.
(42 labs in EQA)

Beckman DxI
• Monash
(15 labs in EQA)


Slide courtesy of Dr Zhong Lu, Head Chemical Pathology, Melbourne Pathology
Methods are very different.

- **TSH**: Architect has the lowest values among all the methods
- **FT4**: Architect and Roche have similar values during pregnancy
Upper Reference Limit: Roche vs Abbott

Architect TSH is \(~0.7\) mU/L lower

Architect FT4 is \(~3-4\) pmol/L lower
TSH in pregnancy: what is normal?

- 2011 ATA Guidelines - Upper limit first trimester: 2.5 mU/L
- 2017 ATA Guidelines -
  - Substantial population differences in the TSH upper reference limit
  - Partly attributable to differences in
    - Iodine status
    - TSH assays used
    - BMI
    - Geography
    - Ethnicity
TSH in pregnancy: what is normal?

- 2017 ATA Guidelines:
  - A more liberal upper TSH reference range in healthy pregnant women with no thyroid disease
  - There appears to be a greater risk for adverse events in women who are TPOAb positive compared to those who are TPOAb negative, even when thyroid function is identical
  - As a consequence, it is difficult to precisely define a universal TSH cutoff above which LT4 therapy should be initiated for all pregnant women

Alexander EK et al. Thyroid 2017; 27 (3): 315-389
American Thyroid Association (ATA) Guidelines 2017

- TSH is the principal determinant of maternal thyroid status and should be used to guide treatment decisions and goals.
- Elevations in serum TSH concentrations during pregnancy should ideally be defined using pregnancy- and population specific reference ranges.

Alexander EK et al Thyroid 2017; 27 (3): 315-389
TSH Reference ranges in pregnancy

- Defined by a provider’s institute or laboratory in healthy TPOAb-negative pregnant women with optimal iodine intake and without thyroid illness.

- Should represent the typical population for whom care is provided.
If internal or transferable pregnancy-specific TSH reference ranges are not available, an upper reference limit of approx. 4.0 mU/L may be used.

For most assays, this limit represents a reduction in the nonpregnant TSH upper reference limit of approx. 0.5 mU/L.
Free T4 measurement in pregnancy

ATA 2017 Guidelines

- The accuracy of serum FT4 measurement by indirect analog immunoassays is influenced by pregnancy and also varies significantly by manufacturer.

- If measured in pregnant women, assay method-specific and trimester specific pregnancy reference ranges should be applied.

Alexander EK et al Thyroid 2017; 27 (3): 315-389
Anti thyroid antibodies

- Anti-TPO or anti-Tg thyroid autoantibodies are present in up to 18% of Australian unselected pregnant women\(^1\)

- More common in Caucasian and Asian women\(^2\)

\(^2\) La‘ulu SL Roberts WL Clin Chem. 2007; 53(9):1658-64
Anti-TPO antibodies fall during pregnancy

Ekinci et al Clin Endocrinol 2015; 82: 604-610
Take home messages so far

- Know how your local assays perform
- Upper limit normal TSH is not straightforward
- First trimester TSH interpretation depends whether early or late in first trimester
- FT4 drifts down as pregnancy progresses and may be unreliable
- Anti-TPO antibodies may become normal as pregnancy progresses
Elevated TSH in pregnancy

- High TSH & Low free T4: Overt hypothyroidism
- High TSH & Normal free T4: Subclinical hypothyroidism
Overt hypothyroidism in pregnancy

- No prospective, randomised trials of L-T4 intervention exist for:
  - obstetric outcomes
  - child development

- Numerous retrospective and case-control studies confirm the detrimental effects of overt hypothyroidism on both pregnancy and fetal health

Alexander EK et al Thyroid 2017; 27 (3): 315-389
Overt hypothyroidism

- **Standard advice for pre-existing hypothyroidism treated with L-thyroxine**

- As soon as pregnancy is confirmed: Increase usual L-T4 dose by 30% (an amount approx. equal to 2 extra daily doses/week)

- L-T4 dose may need to be increased by up to 50% extra per week, in women with a higher baseline TSH

- After 4 weeks, measure TSH—adjust dose accordingly

- Continue to measure TSH every 4 to 6 weeks in the first trimester—adjust dose accordingly

- Measure TSH at least once during the second and third trimester, or more frequently if there has been a dose change—adjust dose accordingly

- Aim for TSH 0.1 - 2.5 mU/L

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Alexander EK et al Thyroid 2017; 27 (3): 315-389
Therapeutic Guidelines Ltd Published 2013 (eTG March 2018 edition)
ATA Recommendations:
Subclinical hypothyroidism in pregnancy

- Pregnant women with TSH concentrations >2.5 mU/L should be evaluated for TPOAb status

Alexander EK et al Thyroid 2017; 27 (3): 315-389
ATA 2017 Recommendations: Subclinical hypothyroidism in pregnancy

- **If anti-TPO positive**, treat with L-thyroxine if TSH is:
  - Above trimester specific reference range, or
  - Above 4 mU/L (If trimester specific range is unavailable)
  - **May consider** therapy if TSH > 2.5 mU/L (weak recommendation; moderate quality evidence)

- **If anti-TPO negative**, treat with L-thyroxine if TSH is:
  - **Above** 10 mU/L (strong recommendation, low quality evidence)
  - **May consider therapy** if TSH is above trimester specific reference range (weak recommendation, low quality evidence)
  - Or, if trimester specific range is unavailable: TSH > 4 mU/L

Alexander EK et al Thyroid 2017; 27 (3): 315-389
ATA Recommendations: Subclinical hypothyroidism in pregnancy

- L-T4 not recommended if anti-TPO negative and TSH is within pregnancy reference range (or less than 4 mU/L if trimester specific range unavailable)

- Strong recommendation, high quality evidence

Alexander EK et al Thyroid 2017; 27 (3): 315-389
ATA 2017 Guidelines: thanks guys!

L-T4 can be started with a TSH of -
- 2.5 mU/L or
- Trimester specific upper limit or
- 4 mU/L or
- 10 mU/L

depending on TPO antibody status and the whim of the clinician
“I don’t dance on the head of a pin unless I’m really drunk.”
Does L-T4 therapy help cognitive development in subclinical hypothyroidism?
NUMBER OF PARTICIPANTS IN CLINICAL STUDIES

- HOPE: 9,541
- UKPDS: 5,102
- 4S: 4,444
- DCCT: 1,411
- IQ & L-T4 PREGNANCY TREATMENT (LAZARUS NEJM...): 794
- IQ & HIGH TSH OBSERVATIONAL STUDY (HADDOW...): 69
- PRETERM BIRTHS & SCH (LARGEST STUDY; CASEY...): 186
- PRETERM BIRTHS & SCH (SMALLEST STUDY; HAMM...): 404
- 15
Antenatal Thyroid Screening and Childhood Cognitive Function

Aldo Maina, M.D., Rhian Rees, M.Sc., Elisabetta Chiusano, M.Psy., Rhys John, Ph.D.,
Varvara Guaraldo, M.S.Chem., Lynne M. George, H.N.C., Marco Perona, M.S.Chem., Daniela Dall’Amico, M.D.,
Arthur B. Parkes, Ph.D., Mohammed Joomun, M.Sc., and Nicholas J. Wald, F.R.S.
Subclinical hypothyroidism & isolated hypothyroxinemia

Mean time to L-T4: 13.4 weeks gestation

Figure 1. Randomization and Follow-up of the Study Participants.

Lazarus J et al NEJM 2012
ITT analysis
IQ at age 3

On L-T4 analysis
IQ at age 3

Figure 2. Relative Risk of an IQ Score below Specified Cutoff Scores in the Screening Group as Compared with the Control Group, According to the Intention-to-Treat Analysis.

A total of 108 women (79%) were found to have complied with treatment (i.e., they had a decrease of at least 10% in the thyrotropin level and an increase of at least 10% in the free thyroxine level). Bars indicate 95% confidence intervals.
Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy

Subclinical hypothyroidism

Mean randomisation to L-T4 or placebo: 16.7 weeks gestation
| Outcome | Levothyroxine | | Placebo | | | Difference (95% CI) | | | P Value |
|---------|--------------|---|----------|---|---|-----------------|---|---|
| Primary outcome‡ | 323 | 97 (94 to 99) | 326 | 94 (92 to 96) | 0 (-3 to 2) | 0.71 |
| Bayley-III score§ | | | | At 12 mo | | | | | | |
| Cognitive | 311 | 100 (95 to 100) | 315 | 100 (95 to 100) | 0 (0 to 0) | 0.63 |
| Motor | 312 | 97 (97 to 97) | 314 | 97 (97 to 97) | 0 (0 to 3) | 0.83 |
| Language | 309 | 94 (94 to 97) | 312 | 94 (94 to 97) | 0 (0 to 3) | 0.48 |
| At 24 mo | | | | | | | | | | |
| Cognitive | 308 | 90 (90 to 90) | 302 | 90 (90 to 90) | 0 (0 to 0) | 0.59 |
| Motor | 304 | 97 (97 to 97) | 300 | 97 (97 to 100) | 0 (0 to 3) | 0.31 |
| Language | 300 | 89 (89 to 91) | 296 | 91 (89 to 94) | 0 (0 to 3) | 0.30 |
| Differential Ability Scales–II scores | | | | Overall at 36 mo | | | | | | |
| 304 | 90 (88 to 93) | 308 | 90 (87 to 93) | 0 (-2 to 3) | 0.90 |
| Recall of digits forward at 48 mo | 298 | 84 (76 to 91) | 299 | 84 (76 to 91) | 0 (-5 to 7) | 0.60 |
| Recognition of pictures at 48 mo | 298 | 74 (74 to 80) | 302 | 74 (74 to 80) | 0 (-6 to 0) | 0.52 |
| Child Behavior Checklist T score¶ | | | | At 36 mo | | | | | | |
| 306 | 46 (45 to 48) | 309 | 46 (45 to 48) | 0 (-2 to 2) | 0.99 |
| At 60 mo | 314 | 44 (43 to 46) | 313 | 44 (42 to 46) | 0 (-2 to 2) | 0.96 |
| Conners’ Rating Scales–Revised ADHD score at 48 mo | 306 | 48 (47 to 49) | 303 | 49 (47 to 51) | 0 (-1 to 2) | 0.37 |
| WPPSI-III at 60 mo | 311 | 97 (95 to 99) | 314 | 95 (93 to 97) | 0 (-3 to 2) | 0.89 |
Hypothyroidism & Obstetric Outcomes
### Obstetric outcomes: Pre-term birth & overt hypothyroidism

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypothyroidism</th>
<th>Euthyroid</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Andersen 2013</td>
<td>617</td>
<td>11186</td>
<td>70667</td>
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<tr>
<td>Hirsch 2013</td>
<td>3</td>
<td>101</td>
<td>3</td>
</tr>
<tr>
<td>Korevaar 2013</td>
<td>1</td>
<td>19</td>
<td>235</td>
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<tr>
<td>Léon 2015</td>
<td>5</td>
<td>104</td>
<td>80</td>
</tr>
<tr>
<td>Sahu 2010</td>
<td>1</td>
<td>27</td>
<td>22</td>
</tr>
<tr>
<td>Wikner 2008</td>
<td>453</td>
<td>8377</td>
<td>41505</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>19814</td>
<td>2447189</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>1080</td>
<td>112512</td>
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</tr>
</tbody>
</table>

**Heterogeneity:** Chi² = 6.12, df = 5 (P = 0.29); I² = 18%

**Test for overall effect:** Z = 5.45 (P < 0.00001)

Sheehan P et al JCEM 2015; 100: 4325-4331
Obstetric outcomes: Pre-term birth & subclinical hypothyroidism

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SCH Events</th>
<th>SCH Total</th>
<th>Euthyroid Events</th>
<th>Euthyroid Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI Year</th>
</tr>
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<tbody>
<tr>
<td>Casey 2005</td>
<td>27</td>
<td>404</td>
<td>891</td>
<td>15689</td>
<td>26.2%</td>
<td>1.19 [0.80, 1.77] 2005</td>
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<tr>
<td>Cleary-Goldman 2008</td>
<td>13</td>
<td>240</td>
<td>757</td>
<td>10021</td>
<td>21.0%</td>
<td>0.70 [0.40, 1.23] 2008</td>
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<tr>
<td>Hamm 2009</td>
<td>2</td>
<td>15</td>
<td>55</td>
<td>756</td>
<td>1.2%</td>
<td>1.96 [0.43, 8.91] 2009</td>
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<tr>
<td>Männistö 2009</td>
<td>11</td>
<td>224</td>
<td>262</td>
<td>4719</td>
<td>14.2%</td>
<td>0.88 [0.47, 1.63] 2009</td>
</tr>
<tr>
<td>Sahu 2010</td>
<td>3</td>
<td>31</td>
<td>22</td>
<td>468</td>
<td>1.5%</td>
<td>2.17 [0.61, 7.70] 2010</td>
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<tr>
<td>Su 2011</td>
<td>5</td>
<td>41</td>
<td>34</td>
<td>845</td>
<td>1.7%</td>
<td>3.31 [1.22, 8.97] 2011</td>
</tr>
<tr>
<td>Wang 2012</td>
<td>9</td>
<td>168</td>
<td>18</td>
<td>542</td>
<td>5.1%</td>
<td>1.65 [0.73, 3.74] 2012</td>
</tr>
<tr>
<td>Korevaar 2013</td>
<td>15</td>
<td>188</td>
<td>235</td>
<td>4970</td>
<td>9.9%</td>
<td>1.75 [1.01, 3.01] 2013</td>
</tr>
<tr>
<td>Chen 2014</td>
<td>13</td>
<td>371</td>
<td>268</td>
<td>6741</td>
<td>16.9%</td>
<td>0.88 [0.50, 1.55] 2014</td>
</tr>
<tr>
<td>Ong 2014</td>
<td>1</td>
<td>117</td>
<td>37</td>
<td>2134</td>
<td>2.4%</td>
<td>0.49 [0.07, 3.59] 2014</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1799</td>
<td>46885</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>1.11 [0.90, 1.37]</td>
</tr>
</tbody>
</table>

Total events: 99

Heterogeneity: Chi² = 14.33, df = 9 (P = 0.11); I² = 37%

Test for overall effect: Z = 1.00 (P = 0.32)

Sheehan P et al JCEM 2015; 100: 4325-4331
Obstetric outcomes: Pregnancy loss & subclinical hypothyroidism

A

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Untreated Events</th>
<th>Total</th>
<th>Euthyroid Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casey 2007</td>
<td>6</td>
<td>598</td>
<td>79</td>
<td>16011</td>
<td>5.4%</td>
<td>2.03 [0.89, 4.64]</td>
<td></td>
</tr>
<tr>
<td>Chen 2014</td>
<td>2</td>
<td>371</td>
<td>21</td>
<td>7641</td>
<td>1.8%</td>
<td>1.96 [0.46, 8.33]</td>
<td></td>
</tr>
<tr>
<td>Cleary-Goldman 2008</td>
<td>1</td>
<td>240</td>
<td>60</td>
<td>10021</td>
<td>1.0%</td>
<td>0.70 [0.10, 5.00]</td>
<td></td>
</tr>
<tr>
<td>Jacob 2012</td>
<td>33</td>
<td>263</td>
<td>25</td>
<td>533</td>
<td>14.9%</td>
<td>2.68 [1.63, 4.40]</td>
<td></td>
</tr>
<tr>
<td>Liu 2014</td>
<td>54</td>
<td>959</td>
<td>43</td>
<td>1961</td>
<td>24.0%</td>
<td>2.57 [1.73, 3.80]</td>
<td></td>
</tr>
<tr>
<td>Mannisto 2009</td>
<td>1</td>
<td>224</td>
<td>24</td>
<td>4719</td>
<td>0.9%</td>
<td>0.88 [0.12, 6.46]</td>
<td></td>
</tr>
<tr>
<td>Negro 2010</td>
<td>39</td>
<td>642</td>
<td>127</td>
<td>3481</td>
<td>30.5%</td>
<td>1.67 [1.17, 2.36]</td>
<td></td>
</tr>
<tr>
<td>Sahu 2010</td>
<td>1</td>
<td>41</td>
<td>7</td>
<td>552</td>
<td>0.9%</td>
<td>1.92 [0.24, 15.26]</td>
<td></td>
</tr>
<tr>
<td>Su 2011</td>
<td>2</td>
<td>41</td>
<td>19</td>
<td>845</td>
<td>1.8%</td>
<td>2.17 [0.52, 9.00]</td>
<td></td>
</tr>
<tr>
<td>Wang 2012</td>
<td>26</td>
<td>168</td>
<td>48</td>
<td>542</td>
<td>18.8%</td>
<td>1.75 [1.12, 2.73]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>3547</td>
<td>46306</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>2.01 [1.66, 2.44]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>165</td>
<td>453</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 6.05, df = 9 (P = 0.74); I² = 0%
Test for overall effect: Z = 7.12 (P < 0.000001)

Maraka S et al. Thyroid 2016; 26 (4): 580-590
### Table 3. Pooled Relative Risk with 95% Confidence Interval Comparing Pregnant Women with SCH to Pregnant Euthyroid Women for All Pregnancy Outcomes

<table>
<thead>
<tr>
<th>Pregnancy outcome</th>
<th>Pooled RR [95% CI]</th>
<th>$I^2$ (%)</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 [0.58–1.51]</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>(6–8,11–14,18–20,31,33–35)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>1.22 [0.84–1.78]</td>
<td>52</td>
<td>(11,12,14,18,20,21,32,33)</td>
</tr>
<tr>
<td>Preeclampsia</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>1.28 [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>1.43 [1.04–1.95]</td>
<td>9</td>
<td>(8,14,18,32,34,35)</td>
</tr>
<tr>
<td>Caesarean 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>Neonatal 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, intrauterine growth restriction.
Conclusions

The extant body of evidence supports an association of SCH during pregnancy with multiple adverse maternal and neonatal outcomes, but there is paucity of evidence for the value of levothyroxine therapy to mitigate this association.
Thyroid auto-immunity & adverse obstetric outcomes

- Thyroid antibodies may be a **marker** of a **generalised ‘autoimmune imbalance’**
- **Euthyroid women** positive for thyroid antibodies before pregnancy **may develop subclinical or overt hypothyroidism** during pregnancy
- **Thyroid auto-immunity is a risk factor for infertility**, women with antibodies are often older than those without, **so an older age, per se, may explain the increased rate of fetal loss**

Negro R et al JCEM 2006; 91(7) 2587-2591
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

TABLE 1. Characteristics of patients at 10, 20, and 30 wk gestation and delivery ( Continued )

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Age (yr)</th>
<th>10 wk</th>
<th>20 wk</th>
<th>30 wk</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPOAb$^+$ LT$_4$</td>
<td>57</td>
<td>30 ± 5</td>
<td>1.6 ± 0.5</td>
<td>1.1 ± 0.4</td>
<td>1.2 ± 0.4</td>
<td>1.9 ± 0.5</td>
</tr>
<tr>
<td>TPOAb$^+$</td>
<td>58</td>
<td>30 ± 6</td>
<td>1.7 ± 0.5</td>
<td>2.3 ± 0.5</td>
<td>2.5 ± 0.6</td>
<td>3.5 ± 0.7</td>
</tr>
<tr>
<td>TPOAb$^-$</td>
<td>869</td>
<td>28 ± 5</td>
<td>1.1 ± 0.4</td>
<td>1.2 ± 0.4</td>
<td>1.4 ± 0.4</td>
<td>2.1 ± 0.6</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.
Fig. 4. Percentage of miscarriages (top) and premature deliveries (bottom) in group A (TPOAb+ treated with LT4), group B (TPOAb-), and group C (TPOAb-). * P < 0.05; ** P < 0.01.
23/57 started L-T4 at week 10 or later. All miscarriages occurred before week 13 in TPO +ve women (both treated and untreated with L-T4). Causes of preterm delivery not reported (e.g. elective or emergency etc).
Potential for confounding

Women with thyroid disease have significant confounding factors for the most commonly quoted adverse obstetric associations

- Older
- More often multiparous
- More chronic conditions
- More likely to be overweight or obese
ATA Recommendations: Subclinical hypothyroidism in pregnancy

- **If anti-TPO positive,** treat with L-thyroxine if TSH is -
  - Above trimester specific reference range, or
  - Above 4 mU/L (If trimester specific range is unavailable)
  - **May consider** therapy if TSH > 2.5 mU/L (weak recommendation; moderate quality evidence)

- **If anti-TPO negative,** treat with L-thyroxine if TSH is:
  - **Above 10 mU/L** (strong recommendation, low quality evidence)
  - **May consider therapy** if TSH is above trimester specific reference range (weak recommendation, low quality evidence)
  - Or, if trimester specific range is unavailable: TSH > 4 mU/L

Alexander EK et al Thyroid 2017; 27 (3): 315-389
ATA Recommendations: Subclinical hypothyroidism in pregnancy

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  - **May consider** therapy if TSH > 2.5 mU/L (weak recommendation; moderate quality evidence)

- **If anti-TPO negative**, treat with L-thyroxine if TSH is:
  - Above 10 mU/L (strong recommendation, low quality evidence)
  - **May consider therapy** if TSH is above trimester specific reference range (weak recommendation, low quality evidence)
  - Or, if trimester specific range is unavailable: TSH > 4 mU/L

Alexander EK et al Thyroid 2017; 27 (3): 315-389
TSH > Trimester specific ULN
or TSH > 4 mU/L
(FT4 Normal)
Irrespective of TPO antibodies

No

Reassure

Yes

Start LT4
50 ug/day
Melbourne Public Hospitals Consensus

- Guidelines formally changed according to usual hospital processes
- Education of relevant triaging staff, midwives, obstetricians and endocrinologists
- Effective from October 2017 at Western Health
- Numbers attending Obstetric endocrinology clinics across Melbourne now 25% -50% previous levels
- No negative GP feedback to date
- One major hospital still to implement change (in principle agreement)
Take home messages (2)

- Poor quality data linking subclinical hypothyroidism to adverse outcomes
- Associations rather than proven cause & effect
- T4 intervention studies disappointing
- Larger studies of better design needed
- While waiting, makes sense to come to a consensus to avoid patient and clinician confusion
TSH tolerated in pregnancy: a bioassay for endocrinologist anxiety