Establishing Population- method- and gestational age- specific TFT reference intervals at Melbourne Pathology

2017 Melbourne Pathology Annual Endocrine Meeting

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1. Review why do we need pregnancy-related TSH reference intervals?
   - Are trimester-based intervals good enough?

2. How does Melbourne Pathology establish population- and gestational age-specific TFT intervals for our method?

3. Can we use the same TSH Reference interval for different methods?
1: Why do We Need pregnancy-specific reference intervals for TSH?

\[ \beta \text{-subunits (hormone-specific) of } \beta \text{HCG and TSH have 85% homology in the first 110 amino acids} \]

\[ \beta \text{hCG has weak TSH-like activity} \]

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

HCG $<20,000$ U/L does not have a significant effect on TSH
Are Trimester-specific TSH Reference Intervals Good Enough?

Further divide first trimester into early and late:
- Early T1: 4 to 6 weeks gestation
- Late T1: 7-13 weeks gestation

$\beta$HCG in T1:
- wide range
- peaks at ~10 wks
2. What is a Normal TSH in Pregnancy?

2017 ATA Guideline for establishing TSH reference range:

RECOMMENDATION 1

When possible, population-based trimester-specific reference ranges for serum TSH should be defined through assessment of local population data representative of a health care provider’s practice. Reference range determinations should only include pregnant women with no known thyroid disease, optimal iodine intake, and negative TPOAb status.

Strong recommendation, moderate-quality evidence.
Sonic IT System makes data mining possible

1. Doctors clinical notes are typed in to the Sonic LIS

2. Records gestational age

3. Can do keyword search and add codes

Other examples:

- E486 THXCA
- E488 THXHYPER
- S118 THXonT3
- E487 THXHYPO
- E712 THxCentral
- E711 HxMS
- MISCARRIAGE
- THYROXINE
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)

Stepwise Exclusion Criteria:

- Hx of thyroid disorder, n=26,035
- TSH clearly abnormal:
  - TSH >10, n = 75; Biochemically hyperthyroid, n = 36
- Thyroid antibodies (ATPO/ATG) positive, n=792
- Pregnancy related problems
  - Miscarriage, PV bleeding n=435; Twins, n = 85
  - GDM / Diabetes, n=335; Hyperemesis, n=21
  - Sick / medications that can affect TFT, N=26
- Gestational age unknown: n=20,660

All TFT tested in pregnant women, 2013 - 2017
Initial n=70,403. Final n after exclusion = 22,838
Roche method
Final No. in Each Gestational Week – MP data

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

Time for 1st T maternal serum screening

Time for OGTT
### Population-, method- and gestational age-specific TFT intervals: Roche Method

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>TSH (IU/L)</th>
<th>FT4 (pmol/L)</th>
<th>FT3 (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 – 97.5th</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-6 (early T1)</td>
<td>6,761</td>
<td>0.58 – 3.8</td>
<td>625</td>
</tr>
<tr>
<td>7-13 (late T1)</td>
<td>11,460</td>
<td>0.07 – 3.4</td>
<td>2065</td>
</tr>
<tr>
<td>14-27 (T2)</td>
<td>3,024</td>
<td>0.28 – 3.8</td>
<td>689</td>
</tr>
<tr>
<td>28-38 (T3)</td>
<td>1553</td>
<td>0.32 – 3.8</td>
<td>385</td>
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</table>
TSH cut-off used in first trimester

ATA 2011: < 2.5 mU/L
ATA 2017: < 4.0 mU/L

MelbPath: < 3.8 mU/L (Early T1)  
(Roche) < 3.4 mU/L (Late T1)

Do I have a thyroid problem?
• Recommend to use method and trimester-specific reference intervals for TSH.

• When these are not available, the following common RIs can be used:
  • T1: 0.1 – 2.5 mIU/L
  • T2: 0.2 – 3.0 mIU/L
  • T3: 0.3 – 3.0 mIU/L

Many studies have shown that TSH 2.5 as a cut-off for T1 is too low.
Flagging rate for high TSH - Roche

Melbourne Pathology data – Roche method: N=22,838 gestational age: 4-38 weeks

In early T1:
1 in 8 using TSH 2.5
1 in 40 using TSH 3.8
1 in 56 using TSH 4.0
1. Why do we need pregnancy-related TSH reference intervals?
   - Are trimester-based intervals good enough?

2. How Melbourne Pathology establish population- and gestational age-specific TFT intervals for our method?

3. Can we use the same TSH reference interval (or 4 mU/L) for different methods?
Methods are very different.

- TSH: Architect has the lowest values among all the methods
- FT4: Architect and Roche have similar values during pregnancy
Population-, method- and gestational age-specific TFT intervals: Abbott Architect method

Sydney Data – from DHM: TFT tested in pregnancy, 2014 -2016
- Initial extract n=91,960. Final n after exclusion 30,240

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<td>4-6 (early T1)</td>
<td>n = 9657</td>
<td>0.47 – 3.1</td>
<td>10.1 – 16.7</td>
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<tr>
<td>7-13 (late T1)</td>
<td>n = 11,556</td>
<td>0.10 – 2.7</td>
<td>10.2 – 17.6</td>
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<tr>
<td>14-27 (T2)</td>
<td>n = 6457</td>
<td>0.23 – 2.9</td>
<td>9.2 – 15.2</td>
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<td>28-38 (T3)</td>
<td>n = 2570</td>
<td>0.25 – 2.9</td>
<td>8.6 – 15.2</td>
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Upper reference limit: Roche vs Architect

Derived from local population data

**TSH**

- Roche: 3.4
- Architect: 2.7

**FT4**

- Roche: ~22.5 pmol/L
- Architect: ~17.6 pmol/L

Architect TSH is ~0.7 mU/L lower

Architect FT4 is ~3-4 pmol/L lower
2017 ATA Guideline

RECOMMENDATION 26
The pregnancy-specific TSH reference range should be defined as follows:

- When available, population- and trimester-specific reference ranges for serum TSH during pregnancy should be defined by a provider’s institute or laboratory and should represent the typical population for the region.
- When this goal is not feasible, pregnancy-specific TSH reference ranges obtained from similar patient populations and performed using similar TSH assays should be substituted (Table 4).

Strong recommendation, high-quality evidence.

- If internal or transferable pregnancy-specific TSH reference ranges are not available, an upper reference limit of ~4.0 mU/L may be used. For most assays, this limit represents a reduction in the nonpregnant TSH upper reference limit of ~0.5 mU/L.

Strong recommendation, moderate-quality evidence.

Roche: < 3.8 mU/L (Early T1)  
< 3.4 mU/L (Late T1)

Architect: < 3.1 mU/L (Early T1)  
< 2.7 mU/L (Late T1)

If the above not available,  
Upper limit of ~4.0 mU/L may be used

42% difference
Population- and gestational-specific reference

### Roche method (based on Melbourne Pathology data)

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### Architect method (based on Douglass Hanly Moir data)

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Roche method (based on Melbourne Pathology data)

Architect method (based on Douglass Hanly Moir data)