Thyroxine Deficiency in Pregnancy

Timothy Bilash MD MS OBG

Northern Inyo Hospital, Bishop, CA
October 20, 2006 1:30 PM
Clinical Significance

Target population

"clinical significance"
(requires knowing the patient)

A common-sense judgment is required to make inferences from the sampled to the target population.

"medical significance"
(requires additional medical knowledge and understanding)

Sampled population

Random sampling is required to make statistical inferences from the sample to the sampled population.

"statistical significance"
(requires no clinical knowledge)

Sample

--- > PATIENT

Figure 4–1. Target and sampled populations.

(from Dawson and Trapp Basic Clinical Statistics 2001 p 72)
Prenatal Ultrasound

Neuronal Migration to Superficial Cortex

Mice not exposed to prenatal US

Mice exposed to prenatal US

Ang, Rakic, et al. PNAS, 2006
Thyroxine Deficiency in Pregnancy

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Figure 1: The human thyroid (1)
Thyroid Physiology

Thyroid has influences on:

• Carbohydrate metabolism
• Growth

• …and just about everything else
Hypothalamic-Pituitary-Thyroid Axis

- Hypothalamus
- TRH
- Somatostatin
- TSH
- T4 → T3
- Pituitary (PIT)
- Thyroid
- T4
- T3

Hypothalamic-Pituitary-Thyroid Axis
Thyroid Axis Regulation

- TRH → TSH → T4 → T3 + rT3.
- TSH: alpha / beta (unique) units.
- Highest levels occur at night: mild diurnal rhythm.
- Classic endocrine feedback loop.
Thyroid modulators

PowerPoint Slide for Teaching

(Downloading may take up to 30 seconds. If the slide opens in your browser, select File -> Save As to save it.)
Thyroid Physiology in Pregnancy

Important Hormones

Mother

- $I_2$
- HCG
- TSH
- TBG
- FT4

Fetus

- $I_2$
- .
- .
- FT4 (20-40 weeks)

Serum Proteins

Serum Proteins
Thyroid hormone Structures

Thyronine Nucleus

"MIT"

"DIT"

3-Moniodotyrosine

3,5-Diiodotyrosine

Secrated Hormones

"T₄"

"T₃"

1-Thyroxine

3,5,3'-l-Triodothyronine

Figure 2: Structure of thyroxine and related compounds (4)
Thyroid Hormone in Pregnancy

2 Phases: **Production** + **Conversion/Modification**

**Central Production**
- (0-10 weeks) Thyroid, (HCG stim)
- (10-20 weeks) Thyroid, Liver

**Peripheral Conversion**
- (20-40 weeks) Liver, Placenta

**Bioactivity** ? modified in Pregnancy

assay *immunoreactivity* vs *biological activity*
Thyroid peroxidase

Thyroid peroxidase or Thyroperoxidase (TPO) is an enzyme mainly expressed in the thyroid that liberates iodine for addition onto tyrosine residues on thyroglobulin for the production of thyroxine (T4) or triiodothyronine (T3) (thyroid hormones). This process is termed the "organification of iodine".

It is inhibited by the thioamide drugs, such as propylthiouracil. It is a frequent epitope of autoantibodies in autoimmune thyroid disease, reducing T4 levels.

• From Wikipedia, the free encyclopedia
Thyroid Metabolism

Activating Enzymes

- **D1**, inner and outer ring Deiodinase converts $T4 \rightarrow T3 + I$ peripherally in liver, no change in pregnancy.

- **D2**, outer ring Deiodinase, intracellular conversion of $T4 \rightarrow T3 + I$, $rT3 \rightarrow T2 + I$ generates in cells locally (T3 determined by T4) important in pregnancy (esp 1st half) placenta (1st trimester), amnion/chorion membranes.
Thyroid Metabolism

**De-activating Enzymes**

- **D3**, Inner ring Deiodinase
- Inactivates $T_4 \rightarrow rT_3 + I$, $T_3 \rightarrow T_2 + I$
  and limits excess in tissues locally
- **Provides $I_2$ to Fetus** (crosses Placenta)
- **Limits Placental Transfer** of active thyroid hormone to Fetus
- Important **20-40 weeks**, placenta
The placenta contains high concentrations of the Type 3 or inner-ring iodothyronine deiodinase D3.

The inner-ring deiodination of T4 catalyzed by this enzyme is the source of high concentrations of reverse T3 present in the amniotic fluid. Reverse T3 levels parallel maternal serum T4 concentrations.

This enzyme may function to reduce the concentration of T3 and T4 in the fetal circulation (the latter being still contributed by 20-30% from thyroid hormones of maternal origin at the time of parturition), although fetal tissue T3 levels can reach adult levels due to the action of the Type 2 deiodinase D2.

The Type 3 deiodinase may also indirectly provide a source of iodide to the fetus via iodothyronine deiodination. In circumstances in which fetal T4 production is reduced or maternal free T4 markedly increased, transplacental passage occurs and fetal serum T4 levels are about one third of normal.
Thyroid Physiology

**IODINE requirements**

- **80 mcg/day** non-pregnant
- **120 mcg/day** pregnant (50% higher),
- **220 mcg/day pregnant** recommended

- **150 mcg/day** avg in US - iodine adequate
- **70 mcg/day** avg in Europe - iodine restricted

empties stores by 2 months of pregnancy
(10mcg/day loss, despite improved uptake)

Sources: Iodized salt, Fish, Multivitamins
Thyroid Physiology

IODINE

There has been a marked decline in Iodine excretion 1970 thru 1990
Thyroid Buffer System

1) **Binding Proteins** are made in the liver, carry/store the bulk of **inactive** hormone

2) **Free hormone** is **active**, a small percentage

3) Free hormone is **metabolized** and inactivated (T4 ->T3, T3->rT3, gluconated, sulfated)
Thyroid Physiology

**TBG** (Thyroid Binding Globulin)

- **E2** increases TBG (liver stim)
- 500-1000pg/ml threshold to increase TBG *
- Increase to **plateau at 20 weeks preg**
- **TBG lowers FreeT4** after 20 weeks
- **TBG lowers the T4/T3 ratio**
- Large **patient variation**
Low Thyroid Symptoms

Hypothyroid

• Fatigue
• Cold hands and feet (Cold Intolerance)
• Dry skin, Dry hair
• Constipation
• Weight Gain
• Depression / Memory Deficits
• Infertility, Irregular Menses
• Elevated Serum Cholesterol
• Anemia
Low Thyroid Symptoms

Hypothyroid - Pregnancy

- Hypertension, Preeclampsia, Fluid Retention
- Diabetes Mellitus/ Glucose Intolerance
- Placental Abruption
- Hydramnios
- Arrythmias
- Failure to progress
- Large birthweight (mild), Low birthweight (severe)
- TTN
High Thyroid Symptoms

Hyperthyroid

- Insomnia/ Hyperactivity
- Diarrhea
- Hot sweats
- Weight loss
- Tachycardia/ Palpitation
- Hypertension
- Seizures
- Irritability
**Fetal Effects**

*Subclinical Hypothyroidism and Pregnancy.* Two studies published in 1999 suggested that maternal hypothyroidism may impair fetal neuropsychological development. In one study, Pop and associates (1999) studied a group of women beginning at 12 weeks’ gestation. Children born to women with free T₄ levels below the 10th percentile were at increased risk for impaired psychomotor development. In the other study, Haddow and colleagues (1999) retrospectively evaluated children born to 48 untreated women whose serum thyrotropin values exceeded the 98th percentile. Some offspring of these women had diminished school performance, reading recognition, and IQ scores. Importantly, while described as “subclinically hypothyroid,” these women had significantly lower mean serum free thyroxine levels, and thus had overt hypothyroidism. Subsequently, Casey and co-workers (2003) identified subclinical hypothyroidism in 2.3 percent of 17,298 women screened before midpregnancy. These women had significantly higher incidences of preterm birth, placental abruption, and admission of infants to the intensive care nursery (Table 53–4).
## Thyroid Mean Values in Pregnancy

Mean Values in Pregnancy (Resnik and Creasy p985, Glinoer 97)

<table>
<thead>
<tr>
<th>Parameter</th>
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<td>1.1</td>
<td>1.3</td>
<td>2.1 (I2 deficient)</td>
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<td>B. - FT4 (0.8-2.0 ng/dL)</td>
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Figure 1. The pattern of serum TSH and hCG changes are shown as a function of gestation.
FT4 in Pregnancy

![Graph showing the relationship between hCG (IU/L x 10^3) and FREE T4 (ng/dl). The x-axis represents hCG levels, and the y-axis represents FREE T4 levels. The graph includes error bars for each data point, indicating variability. A dashed line trend shows an increase in FREE T4 with hCG levels.]
T4 in Pregnancy [3.9-11.0 mcg/dl]
(Resnik and Creasy p985)
### TSH in Pregnancy [0.2-4.0 mU/L]

(Resnik and Creasy p985)

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Free (unbound) T4 in Pregnancy [0.8-2.0ng/dl]

(Resnik and Creasy p985)

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TSH & Total T4 Values in Pregnancy
(Resnik and Creasy p985)
FreeT4/FreeT3 (unbound) Values in Pregnancy
(Resnik and Creasy p985)
THYROID SCREENING TESTS
Use of TSH as the Screening Test for Hypothyroidism

- TSH is the “bioassay” for thyroid hormone effects on the body
- This assumes that all tissues require the same amount of thyroid hormone as the pituitary gland
- There are no other accurate, sensitive ways to assess thyroid hormone effects on the body
- There are clinical situations where TSH is not an adequate marker for thyroid function
TSH Normal (Gaussian) Distribution

95% Limits

~0.45
1.0 to 1.5
~2.5
Current TSH Upper Reference Limits

Why is the TSH upper reference range skewed?

95% Limits

~0.45  1-1.5  ~2.5  ~4.0  10
The True “Normal” TSH Range

- The “normal” TSH range is skewed at the upper range by subjects with early autoimmune thyroid disease.
- In reference subjects ages 20-29 years, the normal TSH range is 0.40 – 3.56 mU/L (NHANES 2002).
- If TSH levels are normalized to a Gaussian distribution, the normal range is 0.40 – 2.5 mU/L.
American Thyroid Association
Figure 13. A proposed algorithm for the systematic screening of thyroid autoimmunity and hypothyroidism during pregnancy, based on the determination of thyroid antibodies (Ab), serum TSH and free T4 concentrations during the first half of pregnancy. GA = gestational age; NL = normal limits; PP = postpartum.

(Adapted, with modifications, and by permission of Glinoer; Trends in Endocrinology and Metabolism 9:403, 1998; Ref 134).
Thyroid Screening ACOG

Specifically, the American College of Obstetricians and Gynecologists (2002) concluded that observational data from the Haddow study were consistent with the possibility that subclinical hypothyroidism was associated with adverse neuropsychological development. The College thus recommended against implementation of screening until further studies were done to validate or refute these findings. One ma-

Williams Obstetrics 22ndEd p 1145
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24-hour TSH levels in a healthy subject
Progression of Mild Thyroid Failure

Euthyroid

Mild Thyroid Failure

Overt Hypothyroidism

- TSH

- NORMAL RANGE

- T4

- T3

Years

Adapted from Ayala AR, Wartofsky L. The Endocrinologist. 1997;7:44.
Table 1. Causes of FT4/TSH Discordance in the Absence of Serious Associated Illness

<table>
<thead>
<tr>
<th>Misleading Test</th>
<th>Result</th>
<th>Likely Causes</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TSH</td>
<td>FT4</td>
<td>1. Unre...</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>N</td>
<td>2. Treated—inadequate L-T4 dose or non-compliance</td>
</tr>
<tr>
<td>FT4</td>
<td>1</td>
<td>N</td>
<td>1. Mild (subclinical) hyperthyroidism</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>or ↓</td>
<td>2. Overtreatment with T3-containing preparation</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>↑</td>
<td>1. Common during L-T4 treatent</td>
</tr>
<tr>
<td></td>
<td>2. Abnormal binding proteins (i.e. FDH)</td>
<td>2 &amp; 3. Check FT4 by alternate method ideally one using physical separation i.e. equilibrium dialysis or ultrafiltration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Antibody interferences (T4 antibody, HAMA or rheumatoid factor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>↓</td>
<td>1. Binding-protein competitor drugs [see Section-3 B3(c)vi]</td>
</tr>
<tr>
<td></td>
<td>↑</td>
<td>N</td>
<td>1. Dysequilibrium (first 6-8 weeks of L-T4 Rx. for primary hypothyroidism)</td>
</tr>
<tr>
<td></td>
<td>2. HAMA &amp; other interferences</td>
<td>2. Check TSH (new specimen) by alternate method</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓</td>
<td>N</td>
<td>1. Dysequilibrium (first 2-3 months post Rx. for hyperthyroidism)</td>
</tr>
<tr>
<td></td>
<td>2. Medications, i.e. glucocorticoids, dopamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>N</td>
<td>or ↑</td>
<td>1. TSH-secreting pituitary adenoma</td>
</tr>
<tr>
<td></td>
<td>↑</td>
<td>T</td>
<td>2. TRH-stim or thyroid hormone suppression test</td>
</tr>
<tr>
<td></td>
<td>3. TSH alpha subunit</td>
<td>3. TSH alpha subunit</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Pituitary Imaging</td>
<td>4. Pituitary Imaging</td>
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</tr>
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<td></td>
<td>N</td>
<td>↓</td>
<td>1. Central hypothyroidism</td>
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<tr>
<td></td>
<td>2. Other signs of pituitary deficiency</td>
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<td></td>
</tr>
</tbody>
</table>

Source: Thyroid © 2003 Mary Ann Liebert, Inc.
<table>
<thead>
<tr>
<th></th>
<th>Euthyroid (n = 6)</th>
<th>Pregnant (n = 10)</th>
<th>Severely III (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TBG, mg/L</strong></td>
<td>Mean (7)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>T3 uptake</td>
<td>1.01 (0.07)</td>
<td>0.74 (0.03)</td>
<td>1.08 (0.09)</td>
</tr>
<tr>
<td>T4 uptake</td>
<td>0.87 (0.2)</td>
<td>1.7 (0.2)</td>
<td>0.6 (0.1)</td>
</tr>
<tr>
<td>Total T4, nmol/L</td>
<td>125 (30)</td>
<td>144 (20)</td>
<td>53 (38)</td>
</tr>
<tr>
<td>FTI</td>
<td>125 (23)</td>
<td>108 (18)</td>
<td>56 (36)</td>
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<td>Free T4, ng/L, Abbott</td>
<td>113 (13)</td>
<td>81 (40)</td>
<td>90 (42)</td>
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<td>Free T4, ng/L, Corning</td>
<td>19 (6)</td>
<td>12 (7)</td>
<td>56 (3)</td>
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<td>Free T4, ng/L, Amerlex</td>
<td>16 (2)</td>
<td>77 (1)</td>
<td>53 (4)</td>
</tr>
<tr>
<td>Total T3, nmol/L</td>
<td>2.1 (0.4)</td>
<td>3.0 (0.4)</td>
<td>0.85 (0.4)</td>
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<td>Free T3, pmol/L, Corning</td>
<td>6.4 (1.0)</td>
<td>4.3 (0.7)</td>
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<td>1 (1)</td>
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<td>2.9 (3)</td>
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TBG T3/T4

Fig. 1. Total specific T4 (●) and T3 (■) binding at increasing dilutions of sera in assay buffer, each dilution assayed in duplicate.
Case Presentation
Thyroid Levels Change in Pregnancy

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Thyroid Screening Pregnancy

**TSH** (0.1-5.0) +/- 0.6
(Thyroid Stimulating Hormone)

<table>
<thead>
<tr>
<th>TSH &lt; 2.0 mIU</th>
<th>TSH &lt; 2.5 mIU</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20weeks</td>
<td>&gt; 20weeks</td>
</tr>
<tr>
<td>0wk---------</td>
<td>20wk--------</td>
</tr>
</tbody>
</table>

- **HCG** suppresses TSH (Pituitary), stimulates T4 (Thyroid)
- TSH increase from 10-20weeks (mirrors HCG)
- TPO-AB(+) skews TSH distribution to higher TSH
- TWINS, PIH, GTP, HYPEREMESIS (hi HCG lowers TSH)
Current TSH Upper Reference Limits

Why is the TSH upper reference range skewed?
## Thyroid Screening Pregnancy 2

**FT4** *(0.6-1.6) +/- 0.1*

“Free Thyroxine Estimate Test”, FreeT4

| FT4 >20% ile | FT4 >10% ile |
| <20 weeks    | >20 weeks    |
| >0.8         | >0.7         |

[for 0.6-1.6 ng/ml] [for 0.6-1.6 ng/ml]

0wk-------------------20wk-------------------40wk

**HCG** *increases* (T4-Thyr), **Estradiol** *decreases* (TBG-Liv)

Higher in early pregnancy than non-pregnant, then falls with GA, but remains in normal range
Thyroid Screening in Pregnancy

**T4 Total Thyroxine**

- **+150%** increase for Pregnancy normal range (upper normal or elevated)
- 7-18.5 mcg/dl approximate nl range
- Haddow identified **7.9mcg/dl** (100nm/dl) as cutoff for hypothyroxinemia
Thyroid Screening in Pregnancy

- **Repeat q4-6 weeks** (non-pregnant and first trimester)
- **q8weeks** (2nd and 3rd trimester)
- as close to next dose as possible, late afternoon (diurnal, low at midnite)
Thyroid Screening

Non-Pregnancy

- **TSH**
  - $< 2.5$ $(+/- 0.6)$ (Consider AACE recs)

- **FreeT4**
  - $0.7-1.7$ (in normal range) $(+/- 0.1)$
Other Tests to consider Antibodies

- **Antithyroid Antibodies ATA (-):**
  - TPO-microsomal
  - ATG (antithyroglobin)
  - if FreeT4 <10%ile

- **Thyroid Stimulating Antibodies TSI (+)**
- **Thyroid Blocking Antibodies TBI (-)**

Causes Fetal effects (IgG)
Other Tests to consider
Iodine Deficiency

• **Urinary iodide**: <100mcg/24hr (normal 100-500)
• **FT3/FT4 molar ratio** >2.5 (FreeT3)  
  (if Iodine deficient or subclinical)
• **TSH**: increases between 20-40 weeks  
  (if Iodine deficient)
• **TG (Thyroglobin)**: elevation correlates with  
  degree of Iodine Deficiency
TREATMENT
Available Brands of L-T4

- Levothroid (Forrest)
- Levoxyl (King)
- Synthroid (Abbott)
- Unithroid (Watson)
Goals of Thyroxine Treatment

- **Replacement doses:** hypothyroid patients
  - Goal: Mid-normal TSH
  - Mean L-T4 dose = 1.7 ug/kg

- **Suppressive doses:** thyroid cancer patients
  - Goal: Low or suppressed TSH
  - Mean L-T4 dose = 1.9-2.4 ug/kg
THYROXINE DEFICIENCY

Treatment

• **L-thyroxine**, estimate **1.7mcg/kg/day** qhs (100-200mcg)
  - Pregnancy may require ~25% increase, more with increased GA
  - No food within 1 hour
  - Iron supplements inhibits absorption- take beyond 2 hours
  - Dose depends on brand
  - FreeT4 maintain upper normal vs clinical improvement?
  - TSH can be low in 10-20%, sub-normal in first trimester
  - ? Newer recommendations **1.9-2.4mcg/kg/day**

• Iodide, **200mcg/day** (if deficient)
Thyroxine Deficiency

Problems to consider

– FreeT4 assays are *not standardized* for pregnancy
– Serum values have *non-normal* distribution
– Serum values are *skewed* to low values
– Labs *vary* in pregnancy, gestational age, albumin