Ontogeny of Thyroid Function

Volumetric Analysis of the Germinal Matrix and Lateral Ventricles Performed Using MR Images of Postmortem Fetuses

Yoshimasa Kinoshita, Toshio Okudera, Eichi Tsuru, and Akira Yokota

American Journal of Neuroradiology February 2001, 22 (2) 382-388;
Association between maternal free T4 concentrations during early pregnancy and child IQ and cortical volume


Postnatal Thyroid Hormone Secretion
Consequences of maternal hypothyroidism

Pregnancy Outcome

Concerns about Maternal Hypothyroidism During Pregnancy

- Pregnancy Outcome
- Fetal Growth
- Child Neurodevelopment

Effects of Levothyroxine on pregnant women with subclinical hypothyroidism, negative for thyroid peroxidase antibodies
Sima Nazarpour Fahimeh Ramezani Tehrani Masoumeh Simbar Maryam Tohidi Sonia Minooe Maryam Rahmati Feridoun Azizi
The Journal of Clinical Endocrinology & Metabolism, jc.2017-01850 (in print)

Using the TSH cut-off 2.5 mIU/L, no significant difference in preterm delivery was observed between groups A and B (RR=0.86, 95% CI: 0.47-1.55, P=0.61).

Based on cut-point of 4.0 mIU/L, demonstrated a significantly lower rate of preterm delivery in LT4-treated women, compared with those who received no treatment (RR=0.38, 95% CI: 0.16-0.98, P=0.04).
Neurodevelopment


Neuropsychological Test Scores among the Children of Women with Hypothyroidism during Pregnancy as Compared with the Children of Matched Control Women, Stratified According to Whether the Hypothyroidism Was Being Treated

<table>
<thead>
<tr>
<th>Test</th>
<th>Children of Women with Hypothyroidism (N=40)</th>
<th>P Value</th>
<th>Children of Women with Hypothyroidism (N=40)</th>
<th>P Value</th>
<th>Control Children (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intelligence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WISC-III Full Scale IQ score</td>
<td>111</td>
<td>0.24</td>
<td>160</td>
<td>0.005</td>
<td>187</td>
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<tr>
<td>WISC-III Full Scale IQ score</td>
<td>9</td>
<td>0.99</td>
<td>9.2</td>
<td>0.497</td>
<td>5</td>
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<tr>
<td>Attention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WISC-III Freedom from Distractionality score</td>
<td>100</td>
<td>0.008</td>
<td>97</td>
<td>0.03</td>
<td>182</td>
</tr>
<tr>
<td>Continuous Performance Test</td>
<td>70</td>
<td>0.91</td>
<td>32</td>
<td>0.94</td>
<td>19</td>
</tr>
</tbody>
</table>


Maternal Thyroid Deficiency During Pregnancy Impact Greatest with TSH >18 mIU/L
Mean IQ score 100 (hypothyroid) vs. 107 (control) (p<0.05)


Universal Screening for thyroid during pregnancy
Screening and subsequent management for thyroid dysfunction pre-pregnancy and during pregnancy for improving maternal and infant health.

No clear benefit on neurodevelopment

Universal Screening Remains Unclear
Not enough evidence to recommend universal screening of thyroid function for all pregnant women.

Randomized Trial of Treatment of Subclinical Hypothyroidism and Hypothyroxinemia

2017

Treatment >17 weeks

NO DIFFERENCES

Human Brain Development: Was treatment period too late?

Subclinical Hypothyroidism: To Treat or Not?

Treatment may reduce miscarriage in TPO-Ab positive women.

Treatment may potentially benefit select subgroups of women during pregnancy.

Treat If TSH >2.5 mU/L, evaluate for TPO antibodies.

Treatment with LT4 is strongly recommended for antibody positive women with TSH greater than the pregnancy specific references.

Treatment with LT4 for antibody negative women with TSH levels higher than 10 mU/L.

Therapy may also be considered for others, depending on TSH levels.

Consequences of maternal hyperthyroidism

Pregnancy Complications Reported in Hyperthyroid Women

- **MATERNAL**
  - Preeclampsia
  - Pregnancy-induced hypertension
  - Preterm labor
  - CHF
  - Thyroid storm
  - Placental abruption

- **FETAL**
  - SGA
  - FGR (IUGR)
  - Prematurity
  - Stillbirth
  - Fetal/neonatal hyperthyroidism
  - Central congenital hypothyroidism

Prediction of Fetal/Neonatal Graves’

<table>
<thead>
<tr>
<th>TRAb</th>
<th>x upper NL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zakaria 1983</td>
<td>TSI 5x</td>
</tr>
<tr>
<td>Matsura 1988</td>
<td>TBII 3x</td>
</tr>
<tr>
<td>Mortimer 1990</td>
<td>TSI 3.5x</td>
</tr>
<tr>
<td>Mitsuda 1992</td>
<td>TBII 5x</td>
</tr>
<tr>
<td>Smith 2001</td>
<td>TBII 3.5x</td>
</tr>
<tr>
<td>Peleg 2002</td>
<td>TSI 5x</td>
</tr>
<tr>
<td>Nachum 2003</td>
<td>TSI 2x</td>
</tr>
<tr>
<td>Luton 2005</td>
<td>TRAK 3x</td>
</tr>
</tbody>
</table>

If TRAb+ or on ATD → Fetal US at 28-32 weeks to check for fetal goiter, HR.

Recent Evolution of Treatment Guidelines

CLINICAL PRACTICE GUIDELINE
Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline

2007 TASK FORCE RECOMMENDATIONS: PTU DURING PREGNANCY
Recommendations to Avoid PTU

BUT

Concerns with Methimazole

Is MMI Embryopathy Real?

- Teratology studies in mice
- Teratology studies in rats
- Teratology studies in Xenopus
- Human epidemiology studies
Evaluation of Developmental Toxicity of Propylthiouracil and Methimazole

**BACKGROUND:** Propylthiouracil (PTU) and methimazole (MMI) are antithyroid drugs used to treat hypothyroidism. Despite the widespread use of PTU and MMI during pregnancy, studies examining their safety in a pregnant population have been limited, and no data from a large epidemiological database have been analyzed. This study was conducted to evaluate the safety of PTU and MMI during pregnancy in a large database.

**RESULTS:** The study included 1,200,000 pregnancies in the United States. There were no observed defects with PTU or MMI.

**CONCLUSIONS:** PTU and MMI are safe during pregnancy, and no increased risk of congenital heart disease or urinary system disorders was observed.

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**Epidemiology Studies Rivkees group**

- **Database studies**
  - Westast: MarketScan database
  - Kaiser Permanente
  - 1,200,000 pregnancies

**Increased risk of congenital heart disease and urinary system disorders with PTU**

**Consequences of the MMI-teratogen notion**

- Increased pregnancy termination: 30%
  - PTU 8%
  - MMI 31%

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**Consequences of the Chernobyl cancer risk in Greece myth**

- Increased pregnancy termination: 30%
MMI and PTU Birth Defect Risk
2015
No difference vs. controls

Additional Epidemiology Studies

MMI and PTU Birth Defect Risk
~10% vs 6% in Controls

Avoid the risk by offering definitive treatment to
individual considering pregnancy

High Dose effects of MMI
Beyond birth defects....
What are effects of prenatal hyperthyroidism on the developing brain?

Neural Circuit Plasticity: Axon Branch Tip Changes

Axon Branch Tip

Synapse

Neuronal Body

Effects of Maternal Hypo- and Hyperthyroidism on Cortical Circuit Plasticity

- **Net change in branch tip length**
  - Hypothyroidism → Reduced plasticity
  - Hyperthyroidism → Increased plasticity

- Altered prenatal thyroid status leads to long-term abnormalities in cortical circuit plasticity

The Preterm Infant

Newborn Screening

Treatment of Graves’ Hyperthyroidism in Pregnancy

In 2010 guidelines, it was recommended switching women with hyperthyroidism on methimazole (MMI) to propylthiouracil (PTU) during the first trimester. Not clear if that is the best approach.

PTU also linked with birth defects
Preconception surgery or radioiodine ablation should be considered.
Newborn screening of the premature infant

- Screen at the end of first postnatal week
- Screen again at 4 to 6 weeks after birth
- Screen prior to discharge
- Screen every 2 to 4 weeks if iodine exposure

Relationships Between Neonatal Thyroid Hormone Levels and Neurodevelopmental Outcome

1 in 250 VLBW Infants Develop Elevated TSH

Free Thyroxine Levels During the First Weeks of Life and Neurodevelopmental Outcome Until the Age of 5 Years in Very Premature Infants

Free Thyroxine Levels After Very Preterm Birth and Neurodevelopmental Outcomes at Age 7 Years

Relationships Between Neonatal Thyroid Hormone Levels and Neurodevelopmental Outcome

NO CLEAR ASSOCIATION
Thyroxine Supplementation Trials

1997
No benefit

2009
No benefit

2014
No benefit

Overall
No benefit
Conclusions: Special Considerations for Preterm Infants

- Use age specific reference standards
- Follow newborn screening recommendations for preterm infants
- Not clear that hypothyroxinemia is associated with adverse neurodevelopmental outcome
- No proven benefit of thyroid supplementation

Thank You!!

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