Maternal Thyroid Function and Autoimmunity and Risk of Problem Behavior: The Generation R Study

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Disclosure

Nothing to disclose
At the conclusion of this presentation, the participant should be able to:

1. Name one consequence of thyroid autoimmunity during pregnancy on maternal health
2. Name two pregnancy complications related to thyroid autoimmunity in pregnancy
3. Name two adverse effects of maternal thyroid autoimmunity on children’s mental health
4. Answer whether euthyroid women with Thyroid Peroxidase Antibodies need any intervention during pregnancy?
5. Answer whether the children who are born to euthyroid mothers with Thyroid Peroxidase Antibodies need early monitoring for Attention Deficit/Hyperactivity Disorders
Background

Maternal hypothyroidism in pregnancy

Hypothyroxinemia in first trimester of pregnancy (low-for-gestational age free T4 with normal TSH)

Elevated TPO-Abs in mothers

Child’s cognitive deficits

• Animals: Alterations of brain cortical cytoarchitecture
• Humans: Cognitive deficits

• Miscarriage/preterm delivery
• Pre and postnatal depression
• Deficits in child’s cognitive function and motor development
Thyroid Hormones and Brain

Maternal thyroid hormones

Neurogenesis
Neural migration

Birth

Child thyroid hormones

Synapse formation
Myelination
Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum

- Overt hypothyroidism should be treated in pregnancy.

- TPOAb⁺ Women and subclinical hypothyroidism should be treated.

- There is insufficient evidence to recommend for or against universal treatment of TAb⁻ pregnant women with subclinical hypothyroidism.

- Isolated hypothyroxinemia should not be treated in pregnancy.
Background

Maternal thyroid function

- Dietary iodine
- Maternal TPO-Abs

Child thyroid function

- Autoimmune condition

Child cognition and behavior

PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Akhgar Ghassabian)
Aim

**Early pregnancy thyroid function and autoimmunity**

- Attention deficit/hyperactivity problems
- Language delay
- Autistic symptoms
The Generation R Study

- Prospective cohort study
- From fetal life onwards
- 9,778 mothers and their children
- Urban, multi-ethnic population in Rotterdam
The Generation R Study

- TSH
- Free T4
- Thyroid Peroxidase Antibodies

< 18 wks

Birth

N~5200
The Generation R Study

- Iodine and creatinine in urine samples

- TSH
- Free T4
- Thyroid Peroxidase Antibodies

N~1000

< 18 wks Birth

N~5200
The Generation R Study

- Birth
- 3 years: Attention Deficit/Hyperactivity Problems
- 6 years: Executive Function, Autistic symptoms

PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Akhgar Ghassabian)
The Generation R Study

Parental Psychopathology

- Parental education
- Apgar score
- Household income
- Sex
- Mode of Delivery
- Birth weight
- Parental smoking
- Ethnic background

PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Akhgar Ghassabian)
Externalizing problems & Attention Deficit Hyperactivity Problems

- Cannot concentrate, cannot pay attention for long
- Cannot sit still, restless, or hyperactive
- Destroys property belonging to others

Executive Function

- Inhibition: to stop his/her own behavior
- Working memory: to hold information in mind to complete a task

Autistic symptoms

- Avoids eye contact, or has unusual eye contact
- Has repetitive, odd behaviors such as hand flapping or rocking
**Maternal hypothyroxinemia and language development in children up to age 2.5 years**

Maternal thyroid function in early pregnancy and expressive language delay at 18 and 30 months

<table>
<thead>
<tr>
<th>Maternal thyroid function measure</th>
<th>One time point</th>
<th>Across ages</th>
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<tr>
<td></td>
<td>Expressive language delay at age 18 months&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>n</td>
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<td>TSH, per sd</td>
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<td>FT&lt;sub&gt;4&lt;/sub&gt;, per sd</td>
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*Adjusted for maternal and child factors*

Henrichs et al. JCEM 2010, 95 (9), 4227-4234
Maternal hypothyroxinemia and language development in children up to age 2.5 years

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Henrichs et al. JCEM 2010, 95 (9), 4227-4234
Maternal TSH levels and externalizing problems in children at age 3 years

Maternal TSH, mIU/l

Externalizing problems at 3 years

<0.88  0.88-0.93  0.93-1.24  1.24-1.44  >1.44

Maternal Thyroid Peroxidase Antibodies in early pregnancy and problem behavior in the children at age 3 years

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<tr>
<th>Maternal Thyroid Parameters</th>
<th>Problem Behavior at the age of 3 years</th>
<th>Maternal Rating</th>
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<td>Outcomes</td>
<td>OR (95% CI)</td>
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<tr>
<td>Attention Deficit/Hyperactivity Problems</td>
<td>1.60 (0.90-2.87)</td>
<td>1.89* (1.16-3.07)</td>
<td>1.77* (1.15-2.72)</td>
<td></td>
</tr>
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<td>Oppositional Deviant Problems</td>
<td>1.46 (0.91-2.34)</td>
<td>1.36 (0.73-2.52)</td>
<td>1.39 (0.95-2.03)</td>
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Adjusted for maternal and child factors

Ghassabian et al. Thyroid 2012, 22 (2), 178-186
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Ghassabian et al. Thyroid 2012, 22 (2), 178-186
Maternal hypothyroxinemia in early pregnancy and autistic symptoms in the children at age 6 years

Roman et al. Ann Neurol 2013
Low maternal urinary iodine and children’s scores on executive function at 4 years

<table>
<thead>
<tr>
<th></th>
<th>All women (n = 692)</th>
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<td>Adjusted&lt;sup&gt;2,4&lt;/sup&gt;</td>
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<td>Additionall adjusted&lt;sup&gt;2-4&lt;/sup&gt;</td>
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<tr>
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<td>$\beta$ (95% CI)</td>
<td>$P$ value</td>
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<tr>
<td>Inhibition</td>
<td>0.05 (0.01, 0.10)</td>
<td>0.03</td>
<td>0.04 (−0.00, 0.09)</td>
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<tr>
<td>Shifting</td>
<td>−0.01 (−0.05, 0.03)</td>
<td>0.64</td>
<td>−0.02 (−0.06, 0.02)</td>
</tr>
<tr>
<td>Emotional control</td>
<td>0.01 (−0.04, 0.06)</td>
<td>0.63</td>
<td>0.00 (−0.05, 0.05)</td>
</tr>
<tr>
<td>Working memory</td>
<td>0.07 (0.03, 0.12)</td>
<td>0.003</td>
<td>0.06 (0.01, 0.10)</td>
</tr>
<tr>
<td>Planning/organization</td>
<td>0.03 (−0.02, 0.08)</td>
<td>0.19</td>
<td>0.02 (−0.03, 0.07)</td>
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<td>Global executive composite</td>
<td>0.05 (0.00, 0.10)</td>
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Adjusted for maternal and child factors

Van Mil et al. J Nutr 2012, 142 (12), 2167-2174
**Low maternal urinary iodine and children’s scores on executive function at 4 years**

Adjusted for maternal and child factors

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<tr>
<th>Variable</th>
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Limitations

- Maternal thyroid parameters, but not child thyroid function
- Parental rating of behavior and cognition but not clinical diagnosis
Conclusion

Observational studies suggest the effect of maternal low thyroid function (within the normal range) and thyroid autoimmune disease on child outcomes.
Conclusion

Observational studies suggest the effect of maternal low thyroid function (within the normal range) and thyroid autoimmune disease on child outcomes.

So far Randomized Trails failed to show the effectiveness of thyroid screening and treatment at population level.
Future investigations...

- Brain imaging
  Structural and functional abnormalities (e.g. hippocampus and cerebellum) in humans

- Genetics (Mendelian randomization)
Acknowledgment

All the participating children and their parents

Department of Child and Adolescent Psychiatry
Department of Internal Medicine
Department of Immunology
Department of Obstetrics and Gynecology
Department of Epidemiology

European Community 7th Framework Programme (NUTRIMENTHE)