Mild thyroid dysfunction during pregnancy - consequences for pregnancy outcome and fetal development

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Erasmus MC Academic Center for Thyroid Diseases
HESI meeting,
Washington DC, May 9th 2019
Congenital hypothyroidism
T4: essential for brain development

WITH T4

WITHOUT T4

- Low maternal T4 during pregnancy:
  - lower IQ
  - increased risk of:
    - autism
    - ADHD
    - schizophrenia

Oppenheimer et al; Endocr rev, 1997

Chaker, .., Peeters; Lancet, 2017

Korevaar, .., Peeters; Nat Rev Endo, 2017
During pregnancy

- Increased requirement of Thyroid Hormone
  - Increase in serum TBG levels
  - Increase in GFR and urinary iodine excretion
  - Increase in placental transport and metabolism of TH
  - Fetal need for TH (fetal thyroid is not fully functional until week 18-20 of pregnancy)
- Stimulation of the maternal thyroid by hCG
Changes in thyroid physiology

Fetal dependency on maternal thyroxine

Fetal thyroid hormone production
Thyroid Disease and Pregnancy

• What are the consequences of
  - Hypothyroidism?
  - Subclinical Hypothyroidism?
  - Hypothyroxinemia?

• Should we treat it?
Thyroid Disease and Pregnancy

- What are the consequences of
  - Hypothyroidism?
  - Subclinical Hypothyroidism?
  - Hypothyroxinemia?

- Should we treat it?
Mrs B., 29 years old

- Tired, weight gain, cold intolerance, 11 weeks pregnant
- Fam: positive for thyroid disease
- PE: small goiter, pulse rate 60/min, no other specific features

Lab/ (at 10 weeks of pregnancy)

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>17.0 mU/l</td>
<td>(0.2 – 4.0)</td>
</tr>
<tr>
<td>FT4</td>
<td>5 pmol/L</td>
<td>(11 - 25)</td>
</tr>
</tbody>
</table>

If untreated, her child is at risk of:

a) Prematurity
b) Low birth weight
c) Still birth
d) Decreased IQ
e) All of the above
Hypothyroidism and pregnancy complications

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Reference)</th>
<th>Number of women with thyroid dysfunction in the study</th>
<th>Early fetal loss (spontaneous abortion)</th>
<th>Anemia</th>
<th>Gestational-induced hypertension and pre-eclampsia</th>
<th>Placental abruption</th>
<th>Congenital anomalies</th>
<th>Preterm Delivery and/or Low Birth Weight</th>
<th>Fetal distress in labour</th>
<th>Stillbirths/Perinatal Death</th>
<th>Postpartum Hemorrhage</th>
<th>Increased frequency of Cesarean section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones &amp; Maan</td>
<td>(1969) (242)</td>
<td>33 (OH)</td>
<td>☑</td>
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<tr>
<td>Niswander</td>
<td>(1972) (288)</td>
<td>244 (OH)</td>
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<td>Montoro</td>
<td>(1981) (243)</td>
<td>11 (OH)</td>
<td>☑</td>
<td>☑</td>
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<tr>
<td>Davis</td>
<td>(1988) (283)</td>
<td>28 (OH: 16; SCH: 12)</td>
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<td>☑</td>
<td>☑</td>
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<tr>
<td>Leung</td>
<td>(1993) (244)</td>
<td>68 (OH: 23; SCH: 45)</td>
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<td>☑</td>
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<td>Wasserstrum</td>
<td>(1995) (284)</td>
<td>42 (OH: 9; SCH: 33)</td>
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<tr>
<td>Blazer</td>
<td>(2003) (289)</td>
<td>259 (treated HO)</td>
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<td></td>
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<td>☑</td>
<td>☑</td>
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<tr>
<td>Pop</td>
<td>(2004) (287)</td>
<td>135 (hypo-T4)</td>
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<tr>
<td>Casey</td>
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<td>404 (SCH)</td>
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<td></td>
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<tr>
<td>Idris</td>
<td>(2005) (290)</td>
<td>40 (OH)</td>
<td>☑</td>
<td></td>
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<tr>
<td>Tan</td>
<td>(2006) (285)</td>
<td>419 (treated HO)</td>
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<td></td>
<td>☑</td>
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<td>☑</td>
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<tr>
<td>Matalon</td>
<td>(2006) (291)</td>
<td>1.102 (treated HO)</td>
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<td></td>
<td>☑</td>
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<tr>
<td>Casey</td>
<td>(2007) (261)</td>
<td>831 (SCH: 598; Hypo-T4: 233)</td>
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<td></td>
<td>☑</td>
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<tr>
<td>Mannisto</td>
<td>(2009) (207)</td>
<td>278 (OH: 54; SCH: 224)</td>
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<td>☑</td>
<td></td>
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<td>☑</td>
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<tr>
<td>Benhadi</td>
<td>(2009) (208)</td>
<td>11 (SCH)</td>
<td>☑</td>
<td></td>
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<td>☑</td>
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</tr>
</tbody>
</table>

= positive association with Hypo  

Krassas et al, Endocr Rev 2010
Maternal Hypothyroidism and child neurocognitive development

TSH distribution

62 Women with Hypothyroidism

- 47 women: TSH > 99.7%
- 15 women: 96% < TSH > 99.6%
  & FT4 < 99.7%

124 matched controls

Main outcome:
Neuropsychological tests at 7-9 yrs

Haddow et al., 1999, NEJM
## Neurodevelopment in children of hypothyroid women

<table>
<thead>
<tr>
<th>Test</th>
<th>Children of Untreated Women with Hypothyroidism ($N=48$)</th>
<th>Control Children ($N=124$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intelligence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WISC-III full-scale IQ score</td>
<td>100</td>
<td>107</td>
</tr>
<tr>
<td>WISC-III full-scale IQ score $\leq 85$ (%)</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Attention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WISC-III freedom-from-distractibility score</td>
<td>97</td>
<td>102</td>
</tr>
<tr>
<td>Continuous Performance Test score $&gt;8$ (%)</td>
<td>33</td>
<td>19</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test of Language Development score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word articulation</td>
<td>10.0</td>
<td>10.2</td>
</tr>
<tr>
<td>Word discrimination</td>
<td>10.3</td>
<td>11.4</td>
</tr>
<tr>
<td>WISC-III verbal IQ score</td>
<td>101</td>
<td>107</td>
</tr>
<tr>
<td>School performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIAT-R reading-recognition score</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td>PIAT-R reading-comprehension score</td>
<td>96</td>
<td>101</td>
</tr>
<tr>
<td>School difficulties and learning problems (%)</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td>Repeated a grade (%)</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Visual–motor performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score on Developmental Test of Visual–Motor Integration</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td>WISC-III performance IQ score</td>
<td>99</td>
<td>105</td>
</tr>
<tr>
<td>Pegboard-test score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant hand (%)</td>
<td>88</td>
<td>83</td>
</tr>
<tr>
<td>Nondominant hand (%)</td>
<td>96</td>
<td>89</td>
</tr>
</tbody>
</table>

*Haddow et al., 1999, NEJM*
Thyroid Disease and Pregnancy

- What are the consequences of
  - Hypothyroidism?
  - Subclinical Hypothyroidism?
  - Hypothyroxinemia?

- Should we treat it?

Pregnancy outcomes → Child outcomes
Premature delivery and subclinical hypothyroidism

- Largest direct cause of child mortality worldwide
- No known risk factor in ~50% of cases
- Overt maternal thyroid disease is a known risk factor
- Sparse and conflicting data on mild maternal thyroid dysfunction
  * Subclinical hypothyroidism
  * TPO-antibody positivity
Methods: the Generation R study

Serum TSH, FT4 and TPOAb levels determined during early pregnancy in 6264 women

Exclusion criteria:
- Twin pregnancies N=128
- Pre-existing thyroid disease N=85
- Use of interfering medication N=4
- Fertility treatment N=76

Study population N=5971
- Iodine sufficient (median excretion 223 μg/L)
- TPOAb positivity 5.6%
## Elevated TSH and prematurity

### All deliveries (N=5971)

<table>
<thead>
<tr>
<th></th>
<th>Prematurity</th>
<th>&lt;37 weeks</th>
<th>&lt;34 weeks</th>
</tr>
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<tbody>
<tr>
<td>% (N)</td>
<td>aOR (95%CI)</td>
<td>P</td>
<td>aOR (95%CI)</td>
</tr>
<tr>
<td>TSH &gt;97.5th percentiles (&gt;4.04 mU/l)</td>
<td>7.8 (17/217)</td>
<td>1.9 (1.1-3.1)</td>
<td>0.02&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>TPOAb+ women excluded</td>
<td>2.3 (3/128)</td>
<td>1.4 (0.7-2.9)</td>
<td>0.39</td>
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<tr>
<td>Non-elevated TSH (reference)</td>
<td>4.7 (235/5370)</td>
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<sup>a</sup> Analysis adjusted for gestational age at blood sampling, maternal age, smoking, SES, parity, ethnicity, maternal BMI, maternal height and child gender.

*Korevaar et al, JCEM 2013*
### Elevated TSH and prematurity

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### Elevated TSH and prematurity

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<td>4.7 (235/5370)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH &gt; 2.50 mU.I (old ATA guideline)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.4 (30/551)</td>
<td>1.2 (0.8-1.7)</td>
<td>0.50</td>
</tr>
<tr>
<td>TPOAb+ women excluded</td>
<td>4.1 (16/386)</td>
<td>0.9 (0.5-1.5)</td>
<td>0.60</td>
</tr>
<tr>
<td>Non-elevated TSH (reference)</td>
<td>5.0 (252/5036)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Analysis adjusted for gestational age at blood sampling, maternal age, smoking, SES, parity, ethnicity, maternal BMI, maternal height and child gender.

*Korevaar et al, JCEM 2013*
TPOAb positivity

- Is associated with higher risk of miscarriage and preterm delivery
- Even in euthyroid women
- Synergistically higher risk for TPOAbs and TSH

Liu et al, Thyroid, 2014
### TPOAb positivity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk of premature delivery (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH &gt; ref range</td>
<td>1.70 (1.08-2.67)</td>
</tr>
<tr>
<td>TSH &gt; 2.5 mU/L</td>
<td>1.15 (0.77-1.70)</td>
</tr>
<tr>
<td>TPOAb+</td>
<td>1.87 (1.11-3.14)</td>
</tr>
<tr>
<td>TPOAb+ &amp; TSH &gt; 2.5 mU/L</td>
<td>2.18 (1.17-3.44)</td>
</tr>
<tr>
<td>TPOAb+ &amp; TSH &gt; ref range</td>
<td>2.53 (1.34-3.67)</td>
</tr>
</tbody>
</table>

**Why is there a synergistic effect of TPOab’s in women with an elevated TSH?**

- ? Autoimmune process per se
- ? Mediated via thyroid function

-> Do TPOab’s reflect a decreased thyroid reserve?

*Korevaar et al, JCEM, 2013 (+unpublished data)*
Thyroid autoimmunity and thyroid function in early pregnancy

Medici et al, JCEM 2012

Thyroid function

$\text{hCG}$

$P = 4.2 \times 10^{-35}$

$P = 0.002$

Premature delivery
Thyroidal response to hCG

Generation R study

Korevaar et al, JCEM 2016
Thyroidal response to hCG

Generation R study

Korevaar et al, JCEM 2016
Thyroidal response to hCG

Generation R study

HAPPY study

Korevaar et al, JCEM 2016
Thyroidal response to hCG

Generation R study

Korevaar et al, JCEM 2016
Thyroidal response to hCG

Generation R study

Korevaar et al, JCEM 2016
Thyroidal response to hCG

**Generation R study**

**HAPPY study**

Korevaar et al, JCEM 2016
Conclusion

• Subclinical hypothyroidism and TPOAb positivity are associated with an increased risk of prematurity

• TPOAb positivity is associated with a decreased response to hCG, suggesting a decreased functional capacity

• Impaired thyroidal response may be the underlying mechanism for premature delivery
Thyroid Disease and Pregnancy

• What are the consequences of
  - Hypothyroidism?
  - Subclinical Hypothyroidism?
  - Hypothyroxinemia?

• Should we treat it?

Pregnancy outcomes
  Child outcomes
### Associations with neurodevelopmental outcome

- Henrichs et al, JCEM 2010 -> lower IQ and language delay
- Li et al, Clin Endo 2010 -> lower IQ and motor scores
- Suarez-Rodriguez, Dev Neuro 2012 -> lower IQ
- Van Mil et al, Reprod Science 2012 -> Smaller Head
- Roman et al, Ann Neurol 2013 -> Increased risk of autism
- Julvez et al, Epidemiology 2013 -> lower IQ
- Finken et al, JCEM 2013 -> lower reaction time
- Ghassabian et al, JCEM 2014 & Korevaar et al, Lancet D&E 2016 -> lower IQ
- Gyllenberg et al, Biol Psych 2015 -> more often schizophrenia
- Modesto et al, JAMA ped. 2015 -> more parent reported ADHD
Maternal thyroid state vs offspring cognitive function (non-verbal) at 30 months

<table>
<thead>
<tr>
<th>Maternal thyroid function measure</th>
<th>n</th>
<th>Nonverbal cognitive delay, $^a$ OR (95% CI), P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH, per sd</td>
<td>2588</td>
<td>0.98 (0.88–1.10), 0.759</td>
</tr>
<tr>
<td>FT$_4$, per sd</td>
<td>2606</td>
<td>0.85 (0.72–1.01), 0.057</td>
</tr>
<tr>
<td>Mild hypothyroxinemia$^b$</td>
<td>2086$^d$</td>
<td>1.37 (0.90–2.07), 0.139</td>
</tr>
<tr>
<td>Severe hypothyroxinemia$^c$</td>
<td>2086$^d$</td>
<td>2.03 (1.22–3.39), 0.007</td>
</tr>
</tbody>
</table>
Maternal thyroid state vs offspring autistic symptoms at 6 years

<table>
<thead>
<tr>
<th>Maternal Thyroid Parameters</th>
<th>Pervasive Developmental Problems at Age 6 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Borderline Problems n = 263</td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>TSH per SD</td>
<td>0.91 (0.77–1.07)</td>
</tr>
<tr>
<td>fT₄ per SD</td>
<td>0.93 (0.80–1.09)</td>
</tr>
<tr>
<td>Mild hypothyroxinemia</td>
<td>1.31 (0.84–2.04)</td>
</tr>
<tr>
<td>Only mild hypothyroxinemia</td>
<td>0.77 (0.38–1.55)</td>
</tr>
<tr>
<td>Severe hypothyroxinemia</td>
<td>2.02 (1.16–3.51)</td>
</tr>
<tr>
<td>TPO-Abs⁺‡</td>
<td>1.47 (0.85–2.55)</td>
</tr>
</tbody>
</table>
EUthyroid:

Maternal iodine and thyroid status during pregnancy and neuropsychological development of the offspring

Collaboration between three different population based cohorts with:

- Detailed data on neurocognitive function
- Samples available for iodine measurements during pregnancy
- Differences in population iodine status
First steps:

- Harmonisation and integration of data in a central database to perform an individual participant-based analysis

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Location</th>
<th>Assay</th>
<th>Week of gestation at assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>INMA</td>
<td>Spain</td>
<td>AutoDEL-FIA</td>
<td>13.1</td>
</tr>
<tr>
<td>Gen R</td>
<td>The Netherlands</td>
<td>Vitros ECI immunodiagnostic</td>
<td>13.4</td>
</tr>
<tr>
<td>ALSPAC</td>
<td>United Kingdom</td>
<td>Abbott Architect i2000</td>
<td>11.0</td>
</tr>
</tbody>
</table>

Neurodevelopment:
- IQ, autism, ADHD, behavior, language

- Start of brain development: week 5
- Fetal thyroid developed: week 18-20

The project receives funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 634453
### Maternal thyroid function and offspring neuropsychological development in the combined dataset

<table>
<thead>
<tr>
<th>Cognitive/psychomotor function</th>
<th>Cohort</th>
<th>Test</th>
<th>Age child at assessment (years)</th>
<th>Evaluator</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>General cognition</td>
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<tr>
<td>Gen R</td>
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<tr>
<td>ALSPAC</td>
<td>WISC III</td>
<td>8</td>
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MSCA: McCarthy Scales of Children's Abilities  
WISC: Weschler Intelligence Scale for Children  
MCDI: MacArthur Communicative Development Inventory  
SON-R: Snijders-Domen Niet-verbale intelligentie Test-Revisie  
MIDI: Minnesota Infant Development Inventory  
DDST: Denver Developmental Screening Test

The project receives funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 634453
### Low FT4 and cognitive function

#### General cognitive function

<table>
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<th>Cohort</th>
<th>Coef (95 CI)</th>
<th>P</th>
<th>I2 (%)</th>
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<td>Generation R</td>
<td>-3.90 (-6.92, -1.79)</td>
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<td>-3.19 (-6.70, 0.47)</td>
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#### Nonverbal cognitive function

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Levie and Korevaar, JCEM 2018
Conclusion

• Hypothyroxinemia is consistently associated with a decreased cognitive function across different cohorts with a different background in iodine status
Thyroid Disease and Pregnancy

- What are the consequences of
  - Hypothyroidism?
  - Subclinical Hypothyroidism?
  - Hypothyroxinemia?

- Should we treat it?
ATA guideline 2016 -> Hypothyroidism

RECOMMENDATION

Treatment of overt hypothyroidism is recommended during pregnancy

Strong recommendation, Moderate Quality Evidence

How about subclinical hypothyroidism?
ATA guideline 2016 -> Subclinical Hypothyroidism

RECOMMENDATION

Treatment cut-offs are based on level of TSH elevation and TPO-ab status.

-> Evidence based on studies regarding pregnancy outcomes, NOT on child neurocognitive function
Hypothyroxinemia

RECOMMENDATION 27

Isolated hypothyroxinemia should not be routinely treated in pregnancy.
Weak recommendation, Low Quality Evidence

Hypothyroxinemia and neurodevelopmental outcome
(Studies since 2011)

- Roman et al, Ann Neurol 2013 -> Increased risk of autism
- Van Mil et al, Reprod Science 2012 -> Smaller Head
- Julvez et al, Epidemiology 2013 -> lower IQ
- Finken et al, JCEM 2013 -> lower reaction time
- Ghassabian JCEM 2014 -> lower IQ
- Suarez-Rodriguez Int J Devl Neurosc 2012 -> lower IQ
Subclinical Hypothyroidism

• If we start treatment, what dose should be given?
Cerebellar development in D3-/- mice is affected

Peeters et al. 2013, Endocrinology
Thyroid function and neurocognitive development


Maternal FT4 (pmol/L)

Child IQ (6 years)

Child grey matter volume

P=0.003

P=0.0062

Maternal FT4 (pmol/L)
No beneficial effect of L-T4 therapy and child cognition

Lazarus et al, NEJM, 2012

Median start of Tx: 13/3 weeks of gestation

A relatively high dose was given (150mcgr)

Maternal FT4 (pmol/L)

Normal range

IQ Cutoff Score

Relative Risk
Conclusion

• Mild thyroid dysfunction (i.e. hypothyroxinemia) is negatively associated with offspring neurocognitive development, independent of iodine status

• High levels of FT4 seem equally detrimental as low levels
Take home message:

• **Overt hypothyroidism**
  -> negative consequences on pregnancy outcomes and child neurodevelopment beyond doubt
  -> general agreement that this should be treated

• **Subclinical hypothyroidism**
  -> Different cut-offs for treatment between TPOab positive and negative women, and dependent on level of TSH elevation

• **Hypothyroxinemia**
  -> No evidence that treatment is beneficial
  -> if treatment is started, a modest dose should be given
Current work: ATHENA project

- **Assays for the identification of Thyroid Hormone axis-disrupting chemicals: Elaborating Novel Assessment strategies**
  - Andreas Kortenkamp (Brunel University London) Coordination
  - Terje Svingen (DTU Food, Copenhagen)
  - Josef Koehrle (Charite, Berlin)
  - Barbara Demeneix (CNRS, Paris)
  - Timo Hamers (Vrije Uni Amsterdam)
  - Robin Peeters (Erasmus Medical Centre, Rotterdam)
  - Tom Zoeller, Ake Bergman (Orebro University, Orebro)
  - David du Pasquier (WATCHFROG, Paris)
  - Carl-Gustav Bornehag (Karlstad Uni, Karlstad)
  - Johan Lindberg (RISE)
Figure 1 – Overview of the task of workpackage 1 and the relationships with other workpackages

WP1
Study human data for thyroid disrupting effects of major EDCs subgroups

Replication in humans

Proof-of-principle selection of thyroid disruptors

Workpackages 2, 3, 4, 5, 6, 7
In vitro and in vivo thyroid disruptor effect

Test overall hypothesis using mediation analyses

Thyroid disruptor → Thyroid function → Fetal Neurodevelopment

WP9
Thyroid disrupter testing in a multifactorial setting of iodine deficiency and hormonal cross-talk

Available EDC subgroups
- Phthalates
- Bisphenols
- (Organophosphate) Pesticides
- Perfluorinated chemicals (PFCs)
- Polychlorinated biphenyls (PCBs)
- Polybrominated diphenyl ether (PBDEs)

Available thyroid-related
- TSH
- FT4, T4
- FT3, T3
- TPO and Tg antibodies
- hCG
- Urinary iodine and creatinine excretion

Available neurodevelopment outcomes
- IQ, developmental milestones
- Brain neuroimaging
  - Structural (T1)
  - White matter integrity (DTI)
  - Functional (resting state)
Study design

- thyroid function
- UIC
- EDC exposure

start of brain development
week 5

fetal thyroid developed
week 18-20

birth

- thyroid function
- IQ, autism, ADHD, behavior, language
- thyroid function

Neurodevelopment

Detailed data from two prospective birth cohorts:
- Generation R, Rotterdam, the Netherlands
- SELMA, KAU, Sweden
Collaborators of the Consortium on thyroid and Pregnancy:

§ ABCD (Netherlands): Tanja G. Vrijkotte
§ ALSPAC (UK): Peter Taylor
§ Bermejo et al. (Spain): Abel López-Bermejo
§ Bliddal et al. (Denmark): Sofie Bliddal
§ Boucai et al. (Chile): Laura Boucai
§ Chen et al. (China): Liangmiao Chen
§ EFSOCH(UK): Bijay Vaidya
§ Generation R (Netherlands): Tim I.M. Korevaar
§ Ghafoor et al. (Pakistan): Farkhanda Ghafoor
§ HAPPY (Netherlands): Victor J.M. Pop
§ Hisada et al. (Japan): Aya Hisada
§ INMA (Spain): Mònica Guxens, Isolina Riaño

§ NFBC (Finland): Tuija Männistö
§ PIP Study (UK): David M. Carty
§ Popova et al. (Russia): Polina V. Popova
§ Rhea (Greece): Leda Chatzi
§ Viva (US): Elizabeth N. Pearce
§ Western Australia: John P. Walsh

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