Children Born to Women with Hypothyroidism during Pregnancy Show Abnormal Corpus Callosum Development

Arash Samadi, Jovanka Skocic, Joanne Rovet
Disclosure

I have nothing to disclose
Maternal Thyroid Hormone Deficiency in Pregnancy

- Hypothyroxinemia (low T4)
- Subclinical hypothyroidism (high TSH)
- Clinical hypothyroidism (low T4/high TSH)
- Iodine deficiency
Maternal Thyroid Hormone Deficiency Effects on Offspring

- Reduced IQ
- Attention problems
- Memory weaknesses
- Visual & visuomotor difficulties
- Poor language, auditory, & literacy skills
- Behavior problems

Willoughby K et al, 2013, Thyroid, in press

ITA 2011

ATA 2011

ATA 2012
Thyroid hormone is essential for corpus callosum development

Thyroid hormone is essential for corpus callosum development

Thyroid hormone is essential for corpus callosum development

Corpus Callosum

- Largest white matter (WM) tract in brain
- Transfers information between hemispheres

Hofer & Frahm (2006)
NeuroImage 32:989-994
Corpus Callosum

- Largest white matter (WM) tract in brain
- Transfers information between hemispheres
- Needed for many functions (e.g., bimanual coordination, social communication, complex reasoning)
Corpus Callosum Abnormalities

Fetal alcohol syndrome

Turner syndrome

Autism

Corpus Callosum Development

- Exuberant axonal growth in first 2 trimesters
- Exuberant pruning in third trimester
- Myelination from birth to adulthood

**Corpus Callosum Development images**

12 wk

13 wk

14 wk

22 wk

30 wk

**maternal thyroid hormones**
Maternal Hypothyroidism (HYPO)

Congenital Hypothyroidism (CH)

from the mother

from the child

Birth (term)

Gestational age in months

0 1 2 3 4 5 6 7 8

Maternal thyroid hormones

Morreale de Escobar G et al, 2000
Abnormal Corpus Callosum Morphology in Congenital Hypothyroidism

Ibrahim F et al, ATA 2013
CH have smaller genus

Control

CH

$p<0.01$

Mean Area (mm$^2$)

Rostrum  Genu  Anterior midbody  Posterior midbody  Isthmus  Splenium

$p<0.01$
Is corpus callosum development abnormal in children born to women with thyroid hormone insufficiency during pregnancy?
Research Questions

1. Is the corpus callosum (CC) abnormal in size and/or shape in offspring of hypothyroid women (HYPO)?

2. Are CC abnormalities related to severity or duration of maternal hypothyroidism?

3. Do CC abnormalities predict outcome in HYPO?
Sample: HYPO

- N=20
- 9 to 12 yrs (mean=10.3 yrs)
- Born 1996-2001 to women with hypothyroidism diagnosed prior to (83%) or during pregnancy
- Inclusion criterion: mothers not given L-T4 dose increase in pregnancy
- Excluded if mothers had normal TSH levels in all trimesters
Sample: Controls

- 22 children, mostly from same birth cohort as HYPO
- Matched with HYPO for sex, age, socioeconomic status
- Mean age = 10.9 years
- All mothers claimed no hypothyroidism during pregnancy or since
Procedures

- Day 1: 4-hour neuropsychological evaluation
- Day 2: 1-hour MRI scan in 1.5 Tesla magnet
  - 7-min axial T1 FSPGR sequence ($TR/TE=10.3/4.2$ ms, inversion time=$400$ ms, flip angle = $20^\circ$, slice thickness = 1.5mm)
- Corpus callosum manually traced and measured using Analyze 9.0
Quantitative Approach

Quantitative Approach
Qualitative Approach

- Curvature ($\delta$)
- Droop ($\varepsilon$)
- Peak ($\alpha$)

Qualitative Approach

- Shape of genu (A/B) and splenium (C/D)
HYPO Have Smaller Genu/Larger Splenium

Group X Region Interactions
Raw areas: $F=4.49, p=0.05$
Proportions: $F=5.15, p=0.02$
No significant group differences in lengths or widths
Angles

- No significant group differences in curvature or orientation of genu or splenium
HYPO have shorter/wider genu than controls
HYPO have longer/narrow spleniums than controls
Correlations with Maternal Hypothyroidism

- Corpus callosum size/shape not correlated with any trimester maternal TSH/T4
- Size of anterior and posterior segments correlated with duration of maternal hypothyroidism in pregnancy
Structure/Function Correlations

- Larger anterior CC (posterior midbody) associated with better reading ability

- Larger genu with better cognitive flexibility
Smaller isthmus with better nonverbal memory

Smaller splenium with better verbal ability
In Summary

- HYPO relative to controls show:
  - Reduced size of genu and increased size of splenium
  - Abnormal splenium and genu shapes
  - Normal lengths & thickness of CC
  - Normal CC shape
In Summary

- No effect of maternal hypothyroidism severity
- More severe effects reflect duration of hypothyroidism
- Size of specific CC regions associated performance in different cognitive abilities in HYPO
Effects on axonal growth & pruning?

HYPO
- Normal shaped CC
- Smaller & wider genu
- Larger (longer, skinnier) splenium

CH
- Flatter CC
- Smaller & narrower genu
- Abnormally oriented but normal size splenium

Morreale de Escobar G et al, 2000
Conclusion

- Inadequately treated hypothyroidism in pregnancy disturbs corpus callosum development by disrupting the patterning of axonal growth and pruning.

- These effects are associated with reduced cognitive abilities.
Thank You