

Severe Maternal Hypothyroxinemia Is Associated with Probable Autism in Offspring

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Román GC, Ghassabian A, Bongers-Schokking JJ, Jaddoe VW, Hofman A, de Rijke YB, Verhulst FC, Tiemeier H. Association of gestational maternal hypothyroxinemia and increased autism risk. Ann Neurol. August 13, 2013 [Epub ahead of print].

SUMMARY • • • • • • • • • • • •

Background

Adequate thyroid hormone is required in pregnancy for normal neurodevelopment of the fetus. Previous studies have demonstrated that maternal hypothyroxinemia in early pregnancy is associated with adverse effects on child cognitive development (1). There are some histologic similarities between brain pathology in autism and animal models of maternal hypothyroxinemia (2). Hoshiko and colleagues have reported a possible association between neonatal hypothyroxinemia and autism (3). The aim of this study was to assess relationships between maternal thyroid function in early pregnancy and autism symptoms in offspring.

Methods

This was a prospective cohort study using data from the Generation R Study population-based birth cohort in the Netherlands. A total of 8,879 pregnant women were enrolled between 2002 and 2006. Free T₄ levels drawn prior to 18 weeks of gestation were available for 5100 of these women, of whom 4039 provided information about autism symptoms when their children were 6 years old. Parents reported autism symptoms using the Pervasive Developmental Problems (PDP) subscale of the Child Behavior Checklist for Toddlers and a short-form version of the Social Responsiveness Scale (SRS). Children with probable autism were defined as those with PDP scores greater than the 98th percentile and an SRS score in the top 5%. Maternal thyroid function was assessed at a mean of 13.4 weeks gestation: serum TSH, free T_4 , and TPO antibodies were measured.

Women were defined as having mild hypothyroxinemia if the free T₄ was below the 10th percentile with a normal TSH (0.03 to 2.5 mIU/L). Severe maternal hypothyroxinemia was defined as a free T₄ below the fifth percentile with a normal TSH. Logistic regression was used to assess the odds of having a child with probable autism in mothers with hypothyroxinemia versus mothers with normal free T₄ values. Multiple linear-regression models were also used to assess maternal thyroid function as a predictor of children's continuous PDP and SRS scores. Models were adjusted for the following covariates: child's sex, ethnicity, gestational age at delivery (assessed by prenatal ultrasound), birth weight, parental age, education, smoking, prenatal maternal psychopathology (assessed by the Brief Symptom Inventory, a validated self-report questionnaire), gestational age at maternal thyroid-function testing, and early pregnancy maternal folate and C-reactive protein levels. All models were subsequently also adjusted for child IQ (assessed by two subtests of the Snijders-Oomen Nonverbal Intelligence Test, Revised).

Results

Eighty children were defined as having probable autism. Severe maternal hypothyroxinemia was associated with an adjusted odds ratio of 3.89 (95% CI, 1.83 to 8.20) of having a child with probable autism. Mild maternal hypothyroxinemia was not associated with an increased risk for having a child with probable autism. Maternal TSH and TPO antibody positivity were not associated with an increased risk for probable autism. Results were similar in multivariate analyses treating PDP and SRS as con*continued on next page*

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tinuous outcomes. Effect estimates were smaller, but results remained significant after adjustment for child IQ. Results did not change when the data set was restricted to women whose thyroid function was assessed in the first trimester.

Conclusions

Severe maternal hypothyroxinemia in early pregnancy was consistently associated with autistic symptoms in children.

ANALYSIS AND COMMENTARY • • • • •

The incidence and prevalence of autism spectrum disorders (ASD) has increased over the past several decades; currently, 1 in every 88 U.S. children is considered to be on the autism spectrum (4). The pathogenesis of ASD remains poorly understood, and there is great interest in identifying potentially modifiable risk factors. The strengths of this study include its prospective design, large population-based sample, and wide range of covariates assessed. The causes of

maternal hypothyroxinemia in this study are unclear; thyroid autoimmunity was not associated with autism symptoms, and although urinary iodine concentrations are not reported in this paper, the Generation R cohort is known to be iodine-sufficient. Interventional studies are needed to determine whether screening for and treating isolated maternal hypothyroxinemia improves the developmental outcomes of children. In the absence of such interventional data, current ATA guidelines recommend against treatment for maternal hypothyroxinemia (5).

References

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