Hypothyroxinemia predicts a higher risk for verbal and nonverbal cognitive delay in early childhood

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SUMMARY

BACKGROUND

Thyroid hormones play a critical role in fetal neurodevelopment from early pregnancy onward. Still, population-based data on the association between maternal thyroid function in early pregnancy and a child's cognitive development are sparse. The objective of this study was to review the associations of maternal hypothyroxinemia, thyrotropin (TSH), and free thyroxine (FT_4) levels during early pregnancy across the entire range of cognitive functioning during early childhood.

SUBJECTS AND METHODS

This study was derived from the Generation R Study, a population-based cohort from fetal life onward in Rotterdam, The Netherlands that has been reported previously. The children in this study were born from April 2002 through January 2006. Data concerning thyroid function were complete in 4892 pregnant women. Excluded from the study were women being treated with levothyroxine (n = 36), leaving 4856 women for the study cohort. Of this group, 1147 mothers did not provide information on cognitive outcome in the children, and 50 children who were assessed outside the age range of the cognitive measures were excluded from the study, leaving 3659 children (75.3%) of the 4856 eligible subjects. Analysis of language functioning was performed at 18 months after birth on 2819 observations and on nonverbal cognitive functioning at 30 months on 2748 observations.

THYROID MEASUREMENTS

Maternal blood samples were collected in early pregnancy (mean [±SD], 13.3±1.7 wk). In 2295 neonates, cord blood was also obtained and promptly stored at −80°C for TSH and FT_4 concentrations. The normal range of FT_4 was 11 to 25 pmol/L during early pregnancy, and the normal range for maternal TSH was 0.3 to 2.5 μIU/ml. Maternal mild and severe hypothyroxinemia were defined as normal TSH levels and FT_4 concentrations in early pregnancy below the 10th percentile (FT_4, <11.76 pmol/L) and the 5th percentile (FT_4, <10.96 pmol/L), respectively. The following cutoffs were used to define high TSH levels (TSH, >1 SD) above the gestational age–specific mean, and low FT_4 concentrations (FT_4 <1SD) below the gestational age–specific mean at birth. Neonates were categorized as having hypothyroidism when they had high TSH and low FT_4 levels at birth. Maternal hypothyroidism (TSH >2.5 μIU/ml and FT_4 <11 pmol/L) and hyperthyroidism were not studied as determinants because of the small number of at-risk children (54 and 29, respectively).

The interassay coefficients of variation for maternal TSH and FT_4 were 2.5 to 4.1% and 4.7 to 5.4%, respectively, and the intraassay coefficients of variation for maternal TSH and FT_4 were 1.0 to 1.2% and 2.6 to 2.7%, respectively.

VERBAL AND NONVERBAL COGNITIVE DEVELOPMENT

At 18 and 30 months after birth, verbal and nonverbal cognitive development was assessed using three reports mailed by parents. Expressive vocabulary was assessed by the MacArthur Communicative Development Inventory (MCDI), consisting of 680 words. Expressive vocabulary sum scores were converted to age-and gender-specific scores as described in the MCDI manual. At 30 months, mothers completed the Language Development Survey (LDS) , which is a 310-word vocabulary

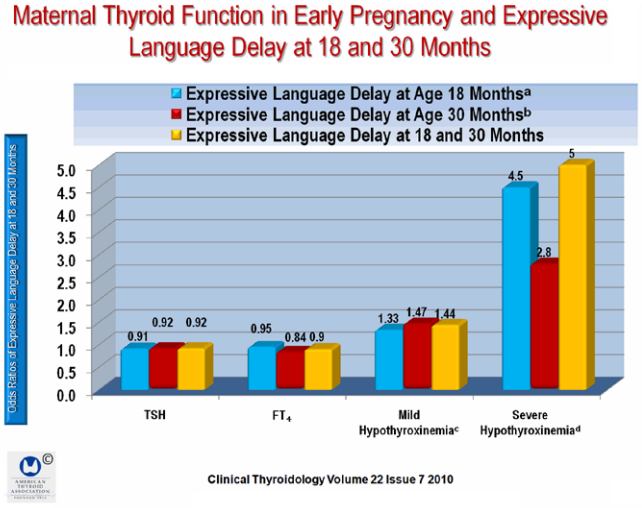

Figure 1. This figure shows maternal thyroid function in early pregnancy and expressive language delay at 18 and 30 months. Models were adjusted for maternal age, maternal educational level, maternal smoking during pregnancy, maternal prenatal distress, gestational age at blood sampling, birth weight, and child ethnicity. The sample size of the respective analysis is represented by a number. a Expressive language delay at 18 months was defined as an expressive vocabulary score below the 15th age-and gender-specific percentile. b Expressive language delay at 30 months was defined as an expressive vocabulary score below the 15th age and gender-specific percentile or no word combinations. c Mild maternal hypothyroxinemia was defined as normal TSH levels and FT_4 concentrations below the 10th percentile. d Severe maternal hypothyroxinemia was defined as normal TSH levels and FT_4 concentrations below the 5th percentile. Mothers with abnormal TSH levels during early pregnancy were excluded.

checklist. An expressive language delay at 30 months was categorized as LDS vocabulary scores below the 15th percentile or no word combinations. At 30 months, nonverbal cognitive development was assessed using the parent-administered and parent-report part of the Parent Report of Children's Abilities (PARCA) scores, which were calculated by summing the 22 parent-administered items and the 26 parent-report questions. Nonverbal cognitive delay was defined as nonverbal cognitive scores below the 15th age-and gender-specific percentile. Furthermore, with a population-based sample, PARCA and MCDI scores predicted language problems later in childhood.

General nonoptimal neurodevelopment was significantly correlated with word production scores at 18 and 30 months ($r = -0.11$; $P<0.010$), indicating that low cognitive scores as reported by parents are correlated with observed neuromotor problems.

RESULTS

Almost 66% of the children were Dutch, and 16% of the mothers had a primary education. On average, children were born at term (mean, 39.9±1.1 wk). Based on the criteria described, 1.5% of the mothers had hypothyroidism, 0.8% had hyperthyroidism, 8.5% had mild hypothyroxinemia, and 4.3% had severe hypothyroxinemia. A subgroup of 1815 children was tested to determine whether thyroid status differed among neonates of mothers with and without hypothyroxinemia. Neonates of mothers with severe hypothyroxinemia were not more likely to be hypothyroid (1.3 vs. 1.2%, $\chi 2 = 0.02$, $P = 0.964$) or to have higher FT_4 levels (mean, 12.9±12.6 vs. 12.0± 8.1 pmol/L; $P = 0.317$), but they were more likely to have lower FT_4 levels (mean, 19.9±3.39 vs. 21.0±3.39; $P= 0.017$) than neonates of mothers with normal prenatal thyroid function.

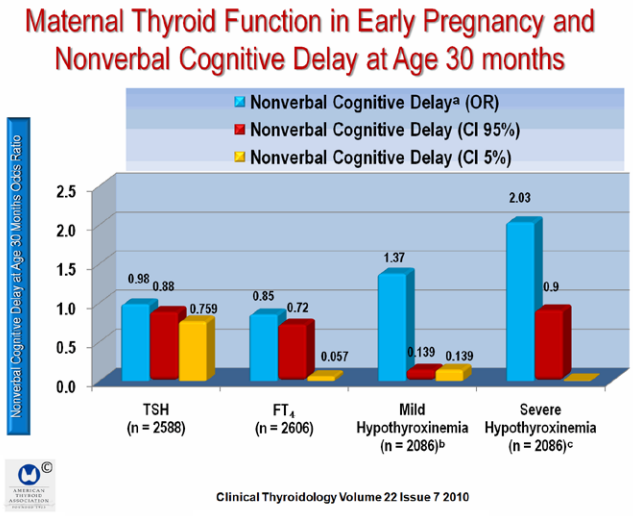

Figure 2. This figure shows maternal thyroid function in early pregnancy and nonverbal cognitive delay at 30 months.

A similar pattern of results was observed when comparing the status of neonates of mothers with or without mild hypothyroxinemia. *Figure 1* shows the adjusted associations of maternal thyroid function in early pregnancy with expressive language delay at 18 months, 30 months, and across ages. Maternal TSH and FT_4 levels were not related to different measures of language functioning, with one exception: higher FT_4 predicted a lower risk for expressive language delay at 30 months. In keeping with this pattern, mild hypothyroxinemia was associated with language delay at 18 and 30 months, although this was not statistically significant (odds ratio [OR], 1.33; 95% confidence interval [CI], 0.91 to 1.94; $P = 0.143$; and OR, 1.47; 95% CI, 1.00 to 2.17; $P = 0.051$, respectively). However, in an analysis across ages, mild hypothyroxinemia was significantly related to expressive language delay (OR, 1.44; 95% CI, 1.09 to 1.91; $P = 0.010$). Severe hypothyroxinemia predicted a higher likelihood of expressive language delay at both 18 and 30 months and across ages (OR, 1.80; 95% CI, 1.24 to 2.61; $P = 0.002$). The maternal thyroid function in early pregnancy and expressive language delay at 18 and 30 months is shown in *Figure 1*.

Once more, severe maternal hypothyroxinemia predicted a higher risk for nonverbal cognitive delay at 30 months (OR, 2.03; 95% CI, 1.22 to 3.39; $P = 0.007$). There also was a dose–response relationship in the lower range of the FT_4 distribution with verbal and nonverbal cognitive delay in early childhood. In addition, there was a dose–response relationship of maternal FT_4 categories with expressive language delay (OR per category, 1.30; 95% CI, 1.09 to 1.55; P for trend = 0.003). Thyroid function in early pregnancy and nonverbal cognitive delay at 30 months is shown in *Figure 2*. There were dose–response relations in the lower range of the FT_4 distribution with verbal and nonverbal cognitive delay in early childhood. There was a dose–response relationship of maternal FT_4 categories with expressive language delay (OR per category, 1.30, 95% CI, 1.09 to 1.55, P for trend = 0.003).

CONCLUSION

Models were adjusted for maternal age, maternal educational level, maternal smoking during pregnancy, maternal prenatal distress, gestational age at blood sampling, birth weight, and child ethnicity. The sample size of the respective analysis is represented by n. a Nonverbal cognitive delay was defined as a score below the 15th age- and gender-specific percentile Mild maternal hypothyroxinemia was defined as normal TSH levels and FT_4 concentrations below the 10th percentile. c Severe maternal hypothyroxinemia was defined as normal TSH levels and FT_4 concentrations below the 5th percentile. d Mothers with abnormal TSH levels during early pregnancy were excluded. The data for this figure are derived from Table 2 in Henrichs et.al Maternal hypothyroxinemia predicts a higher risk for verbal and nonverbal cognitive delay in early childhood. The results support the main hypothesis of this study that hypothyroxinemia is associated with poor cognitive function in early childhood,

COMMENTARY

This study demonstrates that maternal hypothyroxinemia predicts a higher risk for verbal and nonverbal cognitive delay in early childhood, whereas TSH levels across the entire range did not predict cognitive outcomes. TSH levels >98th percentile during pregnancy accompanied by low T_4 levels (maternal clinical hypothyroidism) resulted in neurodevelopmental deficits. Nonetheless, maternal gestational hypothyroidism should not be disregarded, as neuropsychological outcomes have been reported by Haddow et al. (1). Henrichs et al. suggest that the structure of cognitive abilities in early childhood is far from being clear. However, the study found that severe maternal hypothyroxinemia predicted a higher risk for both verbal and nonverbal cognitive delay, suggesting that maternal hypothyroxinemia below a certain threshold has a consistent effect on cognition. The authors suggest that low levels of FT_4 availability to early embryonic tissues may account for the study findings. A study by Morreale de Escobar et al. (2) suggested that the first trimester of pregnancy constitutes a critical period in which subtle FT_4 levels may affect brain development. Also, Henrichs et al. suggest that low FT_4 levels can indicate suboptimal placental function during early pregnancy (3). Another possibility, according to Henrichs et al. is that thyroid peroxidase antibodies and autoimmunity can cause hypothyroxinemia (4).

The authors point out that before 2 years of age, it is difficult to measure a child's cognitive development. However, a review of 23 studies that relate to parent-report measures with standard tester-administered assessments supports the validity of measurements by parents (5).

This is a large study that clearly shows how low FT_4 concentrations affect fetal brain development and put children at risk for subsequent neurodevelopmental deficits. The authors opine that T_4 screening and levothyroxine supplements early in pregnancy are needed in patients with hypothyroxinemia.

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