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Lower Cord Blood Total T_4 is Associated With Higher Child Neurodevelopmental Scores at Age 5.5 Years

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Williams FL, Watson J, Ogston SA, Visser TJ, Hume R, Willatts P. Maternal and Umbilical Cord Levels of T_4, FT_4, TSH, TPOAb, and TgAb in Term Infants and Neurodevelopmental Outcome at 5.5 Years. J Clin Endocrinol Metab 2013;98:829-38. Epub January 15, 2013.

SUMMARY

Background

Most (1-3), but not all (4) previous observational studies have noted associations between mild maternal thyroid hypofunction and decreased child intelligence. The goal of this study was to determine associations between maternal and cord-blood thyroid function and associations between maternal and neonatal thyroid function and the neurodevelopment of offspring.

Methods

This was a prospective observational cohort study that included 97 women and their full-term infants. Subjects were drawn from the larger Millennium Study, which enrolled 666 preterm and 135 full-term Scottish infants between 1998 and 2001. Women and infants with known thyroid disease were excluded. Cord blood T_4, FT_4, and thyroglobulin (Tg), Tg antibody, and thyroperoxidase (TPO) antibody levels were measured. Maternal serum TSH, T_4, FT_4, TPO antibody, and Tg antibody were measured at 10 weeks of gestation, at 34 weeks of gestation, and at delivery. Neurodevelopment was assessed in all children at 5.5 years of age using McCarthy scales, which include Verbal, Perceptual Performance, Quantitative, Memory, Motor, and General Cognitive Index scales. Unadjusted associations were assessed using Pearson correlation coefficients. Univariate general linear models were used to assess associations adjusted for maternal verbal IQ, age, and smoking history, maternal depression, child's birth order, duration of breast-feeding, infant sex, gestational age at delivery, multiple gestation, cord-blood antithyroid antibody positivity, and significant life events (moving, death of close family member).

Results

Fifteen percent of women were TPO-antibody–positive and 12% were Tg-antibody–positive. Four percent of women had serum TSH >2.5 mIU/L at 10 weeks of gestation and 14% of the women had serum TSH levels >3 mIU/L at delivery. There were no associations between maternal TSH and cord TSH or FT_4. Maternal and cord TSH, FT_4, and TPO antibodies were not associated with children's developmental scores. Positive maternal Tg antibodies were associated with decreased scores on child Perceptual Performance and Motor scales. Positive cord-blood Tg antibodies were associated with lower Perceptual Performance scores in unadjusted, but not adjusted, analyses. In unadjusted and adjusted analyses, children with cord blood FT_4 in the lowest decile had higher scores on the General Cognitive Index, Quantitative, Verbal, and Memory scales. Sensitivity analyses demonstrated that there was a U-shaped relationship between cord-blood total T_4 levels and Memory and Verbal developmental subscales.

Conclusions

This study demonstrates that lower cord-blood total T_4 levels were associated with higher scores on several child neurodevelopmental scales.

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ANALYSIS AND COMMENTARY

The results of this study are surprising, and diametrically opposite to the authors' original hypothesis. The data are discordant with previous studies, which found associations between mild maternal hypothyroidism or hypothyroxinemia and lower child IQ (1-3), but similar to the previous study by Oken and colleagues (4), which also demonstrated paradoxically higher developmental scores in children with low neonatal total T_4 . The reasons for the observed inverse association between neonatal total T_4 and neurodevelopmental measures are unclear. The number of infants with low T_4 concentrations was relatively small in both studies that have demonstrated this finding, and it may simply be an artifact due to small sample size. Although their analyses were adjusted for gestational age at delivery, Williams and colleagues speculate that this finding may be due to higher T_4 levels in infants born at 41 to 42 weeks of gestation than in those born at 37 to 40 weeks and that perhaps overly long gestation is related to poorer developmental outcomes. They suggest that further studies are needed to determine relationships between gestational age, neonatal T_4 levels, and the postnatal T_4 surge.

Strengths of this study include its prospective design and adjustments for many possible confounders. Limitations include the loss to follow-up of 35 of 135 full-term infants, the lack of measurements of maternal urinary iodine concentration, and the small sample size (only 10 newborns were in the low total T_4 group). Further research in larger cohorts is needed to better understand the complex relationships between maternal and neonatal thyroid function and subsequent child development.

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