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Neurodevelopment at 5.5 Years of Age Is Lower in Very Preterm Infants Born of Mothers with Mild TSH Elevation at Term, but Paradoxically, Lower Maternal FT_4 Was Associated with Better Neurodevelopment

Williams F, Watson J, Ogston S, Hume R, Willatts P, Visser T, Scottish Preterm Thyroid Group. Mild maternal thyroid dysfunction at delivery of infants born ≤34 weeks and neurodevelopmental outcome at 5.5 years. J Clin Endocrinol Metab. April 4, 2012 [Epub ahead of print]. doi:10.1210/jc.2011-2451.

SUMMARY

Background

Mild maternal thyroid dysfunction during early pregnancy is associated with poor neurodevelopment in affected offspring. Most studies are population-based or are smaller populations of term/late preterm infants. No studies were found that focused on earlier preterm infants. The objective of the authors was to describe the relationship between mild maternal thyroid dysfunction at delivery of infants born at 34 weeks and neurodevelopment at 5.5 years of age.

Methods

The Millennium study recruited women and infants between 1998 and 2001. Infants born at or before 34 weeks' gestation were recruited from all Scottish neonatal intensive care units; 662 women agreed to participate. The authors measured maternal and cord thyroid hormones, TSH, TgAb, TPOAb, and TBG levels at delivery; maternal TSH, FT_4, and T_4, and the association with McCarthy Scale scores adjusted for 26 confounders of neurodevelopment were available for 143 women and 166 children (122 singletons, 19 twins, and 2 triplets). The mean (±SD) gestation was 30.8±2.4 weeks. Neurodevelopment was assessed when children were 5.5 years old, using the McCarthy Scales, which provide six distinct measures: the general cognitive index (GCI), that is derived from verbal, perceptual performance, and quantitative subscales and separate memory and motor scales. Women with known thyroid disease were excluded from the analysis.

Results

The scores for memory and motor scales were both lower than the population norms (t = 2.27, P= 0.02, and t= 3.68, P = 0.0003, respectively). Following adjustment for 26 of the major confounding factors for neurodevelopment, each milliunit-per-liter increment of maternal TSH level at delivery was associated with a significant 3.2-point, 2.1-point, and 1.8-point decrement in general cognitive index, verbal subscale, and perceptual performance subscale, respectively. Higher maternal TSH levels were not associated with significant decrements in the other scales. Mild maternal hypothyroidism (TSH levels ≥3 mU/L) was evident in 27% of the women. McCarthy scores for children born to women with mild hypothyroidism were generally lower than those born to euthyroid women; the GCI, verbal, and perceptual performance scores were significantly lower by 13.5, 7.5, and 7.8 points, respectively. The results of the regression analyses using the data from only the singleton deliveries were similar to those using the full data set. BAPM (British Association of Perinatal Medicine) level 1, which is a proxy for severity of infant condition, was the confounding variable most frequently associated with large decrements in the McCarthy Scales.

Few women (8%, n = 11) were classified as having mild hypothyroxinemia (normal TSH levels), using FT_4 levels ≤11.6 pmol/L. After adjustment, significant associations were found for the general cognitive index, motor scale, and quantitative subscale; each picomole–per-liter decrease in FT_4 was associated with an increase of 1.5, 1.7, and 0.9 points, respectively. Maternal T_4 levels showed little relationship with neurodevelopment. None of the women in this analysis had overt hypothyroidism, but mild hypothyroidism was evident in 27% (n = 38) and there were high levels of TPOAb in 4%, whereas 28% had high TgAb levels.

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Conclusions

The authors found that higher levels of maternal TSH at delivery of infants born at ≤34 weeks' gestation are associated with significantly lower GCI and verbal and perceptual performance subscale scores, and that low maternal FT_4 levels are associated with higher scores on the GCI, quantitative subscale, and motor scale. The association of low maternal FT_4 levels and increased GCI and quantitative subscale (and possibly motor scale) scores is difficult to interpret. The robustness of these findings should be tested in another cohort of women who deliver preterm infants and for whom thyroid hormone data are available for each trimester of pregnancy.

ANALYSIS AND COMMENTARY

Abnormal obstetric and neonatal outcomes have been reported in the literature in the past decade in women with thyroid dysfunction and in euthyroid women affected by chronic thyroiditis. Not all reports agree with regard to the frequency and type of complications. In most of the reported studies, thyroid tests, including serum TSH, FT_4, and thyroid antibodies were measured at different weeks in the first trimester of pregnancy or early in the second trimester. Therefore, the incidence of complications was based on a single determination of thyroid function early in pregnancy. It is well recognized that in untreated euthyroid women suffering from autoimmune thyroid disease, serum TSH tends to increase with progression of pregnancy, with the potential development of hypothyroidism; also, there is a significant decline in antibodies titers starting in the second half of gestation (1, 2). Preterm delivery (PTD; at or before 37 weeks' gestation) and very preterm delivery (VPTD; at or before 34 weeks' gestation) are complications frequently reported in women with hypothyroidism and those with euthyroid chronic thyroiditis. PTD is the leading cause of perinatal morbidity and mortality in the United States. In a review of six published reports, an association between thyroid antibody elevations and preterm birth was found in only three of them (3). Adverse child neuropsychological outcomes due to maternal thyroid disease (dysfunction or presence of thyroid autoantibodies) have been reported (4, 5).

Williams et al.'s study of the effect of thyroid dysfunction and prematurity on children's neurodevelopment outcome differed from previous studies; they compared the neurodevelopmental outcome at age 5.5 years of infants born before 34 weeks' gestation in mothers with untreated mild thyroid dysfunction diagnosed at the time of delivery. No information is given about whether these mothers had hypothyroidism early in pregnancy or whether it developed with progression of gestation. Several aspects of the study are of interest; one of them is the lower percentage of women with positive TPOAb (4%) as compared with women with high TgAB titers (28%), while the prevalence in women delivering at term in their cohort was 10% and 9%, respectively. The authors did not speculate or comment about the potential significance of these findings but acknowledge that this deserves confirmation by future investigations. Another point of interest is the unusually high proportion, 21% of women in the Millennium cohort, with TSH levels at delivery of ≥3 mU/L (27% for the women reported in this analysis). The authors speculated "that these Scottish women are mildly iodine deficient, maintaining a euthyroid state for FT_4 and T_4 by slightly raised TSH levels," but they acknowledge that this interpretation is subject to challenge, since other studies have shown normal serum TSH levels and low FT_4 in areas of iodine deficiency.

An interesting observation by the authors is the potential "protective" effect of lower maternal levels

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of FT_4 on child neurodevelopment. Although they admitted that there is little information about whether levels of thyroid hormones differ between women who deliver prematurely or at term, they offered their own unpublished data showing that maternal serum FT_4 levels measured at 31 to 34 weeks' gestation are different in women who deliver at that point (15.4 pmol/L) as compared with women who go on to deliver at ≥37 weeks (11.7 pmol/L). The authors suggested that high maternal FT_4 levels at critical points of pregnancy may be detrimental to fetal/infant brain development. It could be helpful, as they pointed out, to use adjusted maternal thyroid hormone levels, in late pregnancy, according to gestational age, similar to interpretation of thyroid tests in newborns.

The authors' multiple observations need to be confirmed but offer the opportunity for applying different approaches in the evaluation of morbidities to an evolving and relatively new field of endocrine fetal–neonatal and child thyroid pathology.

— Jorge H. Mestman, MD

References

1. Glinoer D, Riahi M, Grün JP, Kinthaert J. Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. J Clin Endocrinol Metab 1994;79:197-204
2. Negro R, Formoso G, Mangieri, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab 2006;91:2587–91. Epub ahead of print April 18, 2006.
3. Haddow JE, Cleary-Goldman J, McClain MR, Palomaki GE, Neveux LM, Lambert-Messerlian G, Canick JA, Malone FD, Porter TF, Nyberg DA, et al. Thyroperoxidase and thyroglobulin antibodies in early pregnancy and preterm delivery. Obstet Gynecol 2010;116:58-62.
4. Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ, Hooijkaas H, de Muinck Keizer-Schrama SM, Hofman A, Jaddoe VV, et al. Maternal function during early pregnancy and cognitive functioning in early childhood: the generation R study. J Clin Endocrinol Metab 2010;95:4227-34. Epub June 9, 2010.
5. Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, Teng X, Guo R, Wang H, Li J, et al. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25–30 months. Clin Endocrinol (Oxf) 2010;72:825-9.