Neonatal Thyroxine, Maternal Thyroid Function, and Child Cognition

Emily Oken, Lewis E. Braverman, Deborah Platek, Marvin L. Mitchell, Stephanie L. Lee, and Elizabeth N. Pearce

Department of Ambulatory Care and Prevention (E.O.), Harvard Medical School and Harvard Pilgrim Health Care, Boston, Massachusetts 02215; Section of Endocrinology, Diabetes, and Nutrition (L.E.B., S.L.L., E.N.P.), Boston University Medical Center, Boston, Massachusetts 02118; Department of Obstetrics and Gynecology (D.P.), Harvard Vanguard Medical Associates, Boston, Massachusetts 02215-3904; and New England Newborn Screening Program (M.L.M.), University of Massachusetts Medical School, Boston, Massachusetts 01655

Context: Thyroid hormone is essential for normal brain development. Limited data are available regarding whether thyroid function in neonates influences later cognitive development.

Objective: Our objective was to study associations of newborn T4 levels with maternal thyroid function and childhood cognition.

Design and Setting: We studied participants in Project Viva, a cohort study in Massachusetts.

Participants: We studied a total of 500 children born 1999–2003 at 34 wk or more.

Main Outcome Measures: We determined cognitive test scores at ages 6 months and 3 yr.

Results: Mean newborn T4 at a mean age of 1.94 d was 17.6 (so 4.0) μg/dl, and levels were higher in girls (1.07 μg/dl; 95% confidence interval (CI) 0.38, 1.76) and infants born after longer gestation (0.42 μg/dl; 95% CI 0.17, 0.67 per wk). Newborn T4 levels were not associated with maternal T4, TSH, or thyroid peroxidase antibody levels. On multivariable linear regression analysis, adjusting for maternal and child characteristics, higher newborn T4 was unexpectedly associated with poorer scores on the visual recognition memory test among infants at age 6 months (0.5; 95% CI 0.9, 0.2), but not with scores at age 3 yr on either the Peabody Picture Vocabulary Test (0.2; 95% CI 0.1, 0.5) or the Wide Range Assessment of Visual Motor Abilities (0.1; 95% CI 0.2, 0.3). Maternal thyroid function test results were not associated with child cognitive test scores.

Conclusions: Newborn T4 concentrations within a normal physiological reference range are not associated with maternal thyroid function and do not predict cognitive outcome in a population living in an iodine-sufficient area. (J Clin Endocrinol Metab 94: 497–503, 2009)
tion. In the United States, severe iodine deficiency disorders such as goiter, cretinism, stillbirth, spontaneous abortion, and retarded offspring physical and intellectual development have been largely eliminated through the iodization of salt. However, even in the United States, many pregnant women consume insufficient iodine, and iodine consumption appears to be declining in recent years (6). Because maternal iodine intake is essential for both maternal and fetal thyroid hormone synthesis, even mild to moderate deficiency may result in lower T4 levels in both mother and child (1).

Limited data are available regarding whether moderate thyroid dysfunction in neonates, or even variation within the normal range of levels, can influence later development. In addition, little is known about how maternal thyroid function influences neonatal thyroid function. This is an important area for study because a substantial minority of young women may have undiagnosed or subclinical hypothyroidism (7–10). Although hypothyroxinemia in pregnancy is common and related to off-spring health, current obstetric guidelines do not recommend routine thyroid screening in pregnant women (11).

Another measure of risk for thyroid dysfunction, the presence of antibodies to thyroid peroxidase (TPO), may be even more common (10). The majority of women with TPO antibodies do not have clinical hypothyroidism, although they do tend to have higher serum TSH and lower free T4 at each trimester of pregnancy than women without detectable antibodies (12), and even those with normal baseline thyroid function may be at higher risk for the development of mild hypothyroidism during pregnancy than women who do not (13). Information about associations of maternal TPO antibody positivity with newborn thyroid function and child outcomes is limited but suggestive of an association (14).

In the current study, we examined associations of newborn infant T4 levels with maternal thyroid function and with later cognition in a prebirth cohort of mothers and children. We hypothesized that infants with lower T4 levels would have mothers with poorer thyroid function, manifest by higher TSH, lower T4, and/or detectable TPO antibodies, and that they would have lower scores on later cognitive testing. We also studied whether maternal dietary intake of foods likely to be high in iodine, and of iodine-containing vitamins, influenced maternal and child thyroid function.

**Subjects and Methods**

**Study population**

We studied children of mothers who enrolled in the Project Viva cohort between 1999 and 2002. We recruited women attending their initial prenatal visit at one of eight urban and suburban obstetrical offices in a multi-speciality group practice in eastern Massachusetts (15, 16). Eligibility criteria included fluency in English, gestational age less than 22 wk, singleton pregnancy, and plans to remain in the study area. All women provided informed consent, and all procedures were approved by a human studies committee and in accordance with ethical standards for human experimentation (17).

Of 2128 mothers who delivered a live infant, 988 had information on first trimester diet and infant cognitive testing at age 6 months, and were thus eligible for inclusion in the present study. Of these 988 women, 500 with term deliveries subsequently provided consent to us to obtain results of their infant’s T4 result, collected as part of routine statewide newborn screening for all newborns administered by the New England Newborn Screening Program (NENSP). Compared with those excluded, included children had higher fetal growth (0.28 vs. 0.15 U), longer gestation length (39.7 vs. 39.6 wk), and longer duration of breast-feeding (6.7 vs. 5.3 months). Their mothers were more likely to be white (83 vs. 62%) and to have graduate degrees (41 vs. 26%) but did not differ in history of thyroid disease, presence of detectable TPO antibodies, or prevalence of elevated TSH.

**Data collection and participant characteristics**

At the initial study visit, we collected information about parental demographics, health history, and health habits by interview and self-administered questionnaire. Salient variables included maternal age, race/ethnicity, education, household income, and history of thyroid disease. At the routine clinical blood draw (mean 10.2 wk gestation), we collected additional maternal blood in heparinized tubes. Samples were spun, and the plasma separated and stored within 24 h at −70°C.

At the same visit, participants were given a self-administered semi-quantitative food frequency questionnaire, which was modified for use during pregnancy from the extensively validated questionnaires used in the Nurses Health Study and other large cohort studies. The questionnaire quantified average frequency of consumption of over 140 specified foods and beverages “during this pregnancy” (i.e., since the last menstrual period), including questions regarding consumption of foods that tend to be high in iodine, such as fish, eggs, and dairy products (18, 19). In a separate questionnaire, we assessed intake of vitamins and supplements, including brand names. Using a reference database (20), we determined the amount of iodine in each supplement type. We obtained maternal thyroid hormone use, infant birth weight, and gestation length from medical records. We calculated birth weight for gestational age (fetal growth) z value using a U.S. national reference (21). Mothers reported on infant feeding on 6-month and 1-yr postpartum questionnaires. At 6 months postpartum, we assessed maternal depressive symptoms using the Edinburgh Postnatal Depression Scale, a validated 10-item questionnaire (22).

**Maternal and neonatal thyroid assays**

We assayed maternal plasma TSH, total T4, and TPO antibody levels by chemiluminescence assays (Centaur; Bayer, Fernwald, Germany) from the stored samples in batches of 25 over a 6-month period. The laboratory normal ranges were: TSH, 0.35–5.50 mU/liter; TPO antibody, 0–2.0 U/ml; and T4, 4.5–10.9 μg/dl. An expert panel recently recommended that the upper limit of normal for TSH during pregnancy should be 2.5 mU/liter (23). Therefore, we dichotomized TSH levels as more than or 2.5 mU/liter or less, and TPO as more than or 2.0 U/ml or less. We have previously reported upon predictors of maternal thyroid function test results in this study population (12). Mothers with elevated TPO concentrations had higher mean TSH (1.8 vs. 1.1 μU/ml; P < 0.001) but lower T4 levels (9.3 vs. 9.9 μg/dl; P = 0.03). Hospital clinicians collected newborn whole blood on filter paper before hospital discharge and sent samples to the NENSP (http://www.umassmed.edu/nbs/index.aspx) for 10 routine and 20 optional screening tests, including a T4 level. T4 assays were performed using AutoDELFI A kits (PerkinElmer Life and Analytical Sciences, Turku, Finland). The assay is a solid-phase time-resolved fluoroimmunoassay in which europium-labeled T4 competes against sample T4 for a limited number of binding sites on T4 specific monoclonal antibodies. Mean (SD) T4 concentrations in the NENSP are approximately 17.3 μg/dl (4.7).

**Child cognition at 6 months and 3 yr**

When infants reached approximately 6 months of age, we performed cognitive testing using the visual recognition memory (VRM) paradigm. All infants were first tested for visual acuity and had results within the normal range. The VRM test reflects the infant’s ability to encode a stimulus into memory, to recognize that stimulus, and to look preferen-
tially at a novel stimulus. The VRM score in infancy predicts intelligence in childhood and early adolescence as strongly as other standardized tests of infant development (e.g. the Bayley Scale of Infant Development) (24, 25). In a population of term infants, mean (sd) VRM score was 54.6 (5.9), and later full-scale intelligence quotient was 97.5 (11.8) (24).

When children reached age 3 yr, we assessed cognition using two tests. We tested receptive vocabulary using the Peabody Picture Vocabulary Test (PPVT). The PPVT generates raw scores that are converted to standardized scores for children aged 2½ yr and older, based on a nationally stratified sample of children and adolescents (26). Scores on the PPVT are strongly correlated (r = 0.90) with verbal and full-scale intelligence quotient on longer instruments such as the Weschler Intelligence Scale for Children III. Mothers also completed the PPVT, which we used as a covariate in analyses. We also tested children with the Wide Range Assessment of Visual Motor Ability (WRAVMA), which evaluates three domains, namely visual-spatial analysis (matching test), visual-motor ability (drawing test), and fine motor skills (pegboard test), which are used to generate a composite standard score. This test has norms for children ages 3 yr and older, has been extensively validated, and is sensitive to neurotoxins such as lead (27, 28). Both the PPVT and WRAVMA are standardized to have a mean score of 100 with a SD of 15.

In a subset of Project Viva participants, we have previously found that maternal second trimester fish intake was directly associated, and maternal mercury levels inversely associated, with child cognition assessed using these three tests (29, 30).

Statistical analysis

We examined associations of maternal and child characteristics with newborn T4 levels using linear regression. We adjusted all estimates for gestation length, age at heelstick testing, and child sex, factors that have established associations with thyroid function (31) and that were strong independent predictors of T4 levels in the study population.

We next studied associations of newborn T4 levels with child cognitive test results at ages 6 months and 3 yr using multivariable linear regression. We included as additional covariates expected independent predictors of T4 levels in the study population.

We next studied adjusted associations of newborn T4 levels with child cognitive test scores at ages 6 months and 3 yr using multivariable linear regression. We adjusted all estimates for gestation length, age at heelstick testing, and child sex, factors that have established associations with thyroid function (31) and that were strong independent predictors of T4 levels in the study population.

We next studied adjusted associations of newborn T4 and maternal thyroid function with child cognitive test scores (Table 2). Contrary to our hypothesis, higher newborn T4 was associated with slightly lower scores on the VRM test at 6 months (−0.5; 95% CI −0.9, −0.2). However, newborn T4 levels were not associated with scores on either the PPVT (0.2; 95% CI −0.1, 0.5) or WRAVMA (0.1; 95% CI −0.2, 0.3) at age 3 yr. Additional adjustment for maternal first trimester thyroid function, fish intake, intake of iodine-containing vitamins, thyroid medication use during pregnancy, or diagnosed thyroid disease did not substantially change effect estimates (data not shown).

In multivariate models adjusted for maternal and child characteristics, we saw no evidence that impaired maternal thyroid function was associated with lower child cognitive test scores (Table 2). In fact, higher maternal TPO antibodies as a continuous measure predicted slightly higher child PPVT scores (0.06; 95% CI 0.01, 0.10), although this association was not evident for the other two cognitive tests (data not shown), and was not present when we dichotomized TPO antibody status (Table 2). In adjusted and unadjusted analyses, the cognitive test scores of children of mothers in the highest and lowest T4 deciles did not differ. Maternal TSH levels more than or equal to 2.5 mU/liter (Table 2) or 5.5 mU/liter (data not shown) were not associated with child test scores. However, compared with women who had both TSH less than or equal to 2.5 mU/liter and TPO antibodies less than or equal to 2.0 U/ml, women with both high TSH and high TPO antibodies had children with somewhat higher scores on the VRM (4.1; 95% CI −1.0, 9.2) and PPVT (4.8; 95% CI 0.9, 8.7), but not on the WRAVMA (1.6; 95% CI −2.3, 5.4).

Mothers with a history of diagnosed thyroid disease had children with somewhat higher scores on the PPVT (7.1; 95% CI 1.7, 12.4) but no difference on the other cognitive tests (Table 2). Because we do not know whether these mothers were diagnosed with hypothyroidism, hyperthyroidism, or other conditions such as euthyroid goiter, it is difficult to interpret these results. After exclusion of the 17 women who took thyroid medication during pregnancy, history of thyroid disease was no longer associated with child PPVT scores (3.5; 95% CI −5.2, 12.3). Addition of

Results

Mean newborn T4 was 17.6 μg/dl (sd 4.0, range 6.4–35.7), or 226.5 nmol/liter. T4 levels were higher in girls [by 1.07 μg/dl; 95% confidence interval (CI) 0.38, 1.76] and infants born after longer gestation (by 0.42 μg/dl; 95% CI 0.17, 0.67 per wk). Mean (sd) infant birth weight was 3.56 (0.51) kg, gestation length was 39.7 (1.4) wk, and age at heelstick was 1.94 (0.68) d. Mean (sd) test scores were 62.9 (16.0) points for the VRM test in infants at 6 months, and 106.0 (13.2) points for the PPVT and 103.5 (11.5) points for the WRAVMA among children at age 3 yr.

Mean (sd) maternal age was 33.1 (4.4) yr. A total of 91 women (18.4%) had TPO antibodies above 2.0 U/ml, 15.8% had a TSH level at or above 2.5 mU/liter, and 2.9% had a TSH level above 5.5 mU/liter in their blood drawn at the end of the first trimester of pregnancy. Women with elevated TPO antibodies were substantially more likely to have TSH more than or equal to 2.5 mU/liter compared with women who had low TPO antibody levels (51% vs. 8%). We saw no evidence that maternal T4 levels, elevated TPO antibody, or elevated TSHs were associated with newborn T4 levels (Table 1). Newborn T4 levels also did not differ by maternal age, race/ethnicity, education, postpartum depression, or mode of delivery. Compared with never smokers, women who were former smokers had infants with lower T4, perhaps a chance finding because children of mothers with smoking during pregnancy did not have different T4 levels (Table 1).

We next studied adjusted associations of newborn T4 and maternal thyroid function with child cognitive test scores (Table 2).
TABLE 1. Participant characteristics and their associations with newborn T4 results among 500 mother-child pairs in Project Viva

<table>
<thead>
<tr>
<th>Maternal</th>
<th>No.</th>
<th>Mean ± sd</th>
<th>Association with newborn T4&lt;sub&gt;a&lt;/sub&gt;</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age (yr)</td>
<td>500</td>
<td>33.1 ± 4.4</td>
<td>-0.05 (−0.1, 0.03)</td>
<td></td>
</tr>
<tr>
<td>First trimester diet</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total dairy (svg/d)</td>
<td>500</td>
<td>2.77 ± 1.46</td>
<td>0.09 (−0.15, 0.33)</td>
<td></td>
</tr>
<tr>
<td>Fish (svg/wk)</td>
<td>500</td>
<td>1.70 ± 1.43</td>
<td>-0.07 (−0.31, 0.18)</td>
<td></td>
</tr>
<tr>
<td>Whole eggs (svg/wk)</td>
<td>500</td>
<td>1.89 ± 1.75</td>
<td>0.05 (−0.16, 0.26)</td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;4&lt;/sub&gt; (μg/dl)</td>
<td>496</td>
<td>9.98 ± 1.95</td>
<td>0.03 (−0.15, 0.21)</td>
<td></td>
</tr>
<tr>
<td>PPVT score</td>
<td>445</td>
<td>108.6 ± 14.3</td>
<td>0.01 (−0.02, 0.03)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No.</th>
<th>%</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Race/ethnicity

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>No.</th>
<th>%</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>27</td>
<td>5.4</td>
<td>-0.27 (−1.81, 1.27)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>24</td>
<td>4.8</td>
<td>0.81 (−0.84, 2.45)</td>
</tr>
<tr>
<td>Other</td>
<td>34</td>
<td>6.8</td>
<td>-0.36 (−1.72, 1.01)</td>
</tr>
<tr>
<td>White</td>
<td>415</td>
<td>83.0</td>
<td>Ref</td>
</tr>
</tbody>
</table>

Education

<table>
<thead>
<tr>
<th>Education</th>
<th>No.</th>
<th>%</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High school or less</td>
<td>20</td>
<td>4.0</td>
<td>0.10 (−1.67, 1.88)</td>
</tr>
<tr>
<td>Some college</td>
<td>77</td>
<td>15.4</td>
<td>-0.44 (−1.49, 0.61)</td>
</tr>
<tr>
<td>College graduate</td>
<td>196</td>
<td>39.2</td>
<td>-0.91 (−1.67, −0.14)</td>
</tr>
<tr>
<td>Graduate degree</td>
<td>207</td>
<td>41.4</td>
<td>Ref</td>
</tr>
</tbody>
</table>

Smoking

<table>
<thead>
<tr>
<th>Smoking</th>
<th>No.</th>
<th>%</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Former</td>
<td>98</td>
<td>19.8</td>
<td>-1.01 (−1.86, 0.15)</td>
</tr>
<tr>
<td>During pregnancy</td>
<td>43</td>
<td>8.7</td>
<td>0.52 (−0.71, 1.75)</td>
</tr>
<tr>
<td>Never</td>
<td>353</td>
<td>71.5</td>
<td>Ref</td>
</tr>
</tbody>
</table>

Postpartum depression

<table>
<thead>
<tr>
<th>Postpartum depression</th>
<th>No.</th>
<th>%</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>43</td>
<td>9.0</td>
<td>-0.57 (−1.8, 0.7)</td>
</tr>
<tr>
<td>No</td>
<td>435</td>
<td>91.0</td>
<td>Ref</td>
</tr>
</tbody>
</table>

History of thyroid problem

<table>
<thead>
<tr>
<th>History of thyroid problem</th>
<th>No.</th>
<th>%</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>23</td>
<td>4.6</td>
<td>-0.59 (−2.3, 1.11)</td>
</tr>
<tr>
<td>No</td>
<td>473</td>
<td>95.4</td>
<td>Ref</td>
</tr>
</tbody>
</table>

TPO antibody

<table>
<thead>
<tr>
<th>TPO antibody</th>
<th>No.</th>
<th>%</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2.0</td>
<td>405</td>
<td>81.7</td>
<td>Ref</td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>91</td>
<td>18.4</td>
<td>0.48 (−0.43, 1.38)</td>
</tr>
</tbody>
</table>

TSH

<table>
<thead>
<tr>
<th>TSH</th>
<th>No.</th>
<th>%</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.5</td>
<td>412</td>
<td>84.3</td>
<td>Ref</td>
</tr>
<tr>
<td>≥2.5</td>
<td>77</td>
<td>15.8</td>
<td>0.34 (−0.63, 1.31)</td>
</tr>
</tbody>
</table>

Iodine-containing vitamins

<table>
<thead>
<tr>
<th>Iodine-containing vitamins</th>
<th>No.</th>
<th>%</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>458</td>
<td>92.3</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>38</td>
<td>7.7</td>
<td>0.54 (−0.76, 1.84)</td>
</tr>
</tbody>
</table>

Paternal

<table>
<thead>
<tr>
<th>Paternal Education</th>
<th>No.</th>
<th>%</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing</td>
<td>20</td>
<td>4.0</td>
<td>-0.91 (−0.89, 2.71)</td>
</tr>
<tr>
<td>High school</td>
<td>40</td>
<td>8.0</td>
<td>0.25 (−1.12, 1.61)</td>
</tr>
<tr>
<td>Some college</td>
<td>74</td>
<td>14.8</td>
<td>-0.64 (−1.70, 0.43)</td>
</tr>
<tr>
<td>College graduate</td>
<td>192</td>
<td>38.4</td>
<td>-0.08 (−0.88, 0.73)</td>
</tr>
<tr>
<td>Graduate degree</td>
<td>174</td>
<td>34.8</td>
<td>Ref</td>
</tr>
</tbody>
</table>

Child

<table>
<thead>
<tr>
<th>Child Sex</th>
<th>No.</th>
<th>%</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boy</td>
<td>252</td>
<td>50.4</td>
<td>Ref</td>
</tr>
<tr>
<td>Girl</td>
<td>248</td>
<td>49.6</td>
<td>1.07 (0.38, 1.76)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cesarean delivery</th>
<th>No.</th>
<th>%</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>389</td>
<td>77.8</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>111</td>
<td>22.2</td>
<td>-0.50 (−1.44, 0.45)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Breast-feeding status at 6 months</th>
<th>No.</th>
<th>%</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula only</td>
<td>40</td>
<td>8.0</td>
<td>-0.72 (−2.1, 0.68)</td>
</tr>
<tr>
<td>Weaned</td>
<td>197</td>
<td>39.4</td>
<td>-0.41 (−1.28, 0.46)</td>
</tr>
<tr>
<td>Mixed</td>
<td>129</td>
<td>25.8</td>
<td>-0.20 (−1.15, 0.75)</td>
</tr>
<tr>
<td>Breast milk only</td>
<td>134</td>
<td>26.8</td>
<td>Ref</td>
</tr>
</tbody>
</table>

English as a second language

<table>
<thead>
<tr>
<th>English as a second language</th>
<th>No.</th>
<th>%</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>467</td>
<td>96.9</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>15</td>
<td>3.1</td>
<td>-0.61 (−2.68, 1.46)</td>
</tr>
</tbody>
</table>

(Continued)
TABLE 1. Continuous

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Mean</th>
<th>SD</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn T4 (µg/dl)</td>
<td>500</td>
<td>0.28</td>
<td>0.95</td>
<td>0.03 (−0.34, 0.41)</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>500</td>
<td>3.56</td>
<td>0.51</td>
<td>0.06 (−0.74, 0.87)</td>
</tr>
<tr>
<td>Gestation length (wk)</td>
<td>500</td>
<td>39.7</td>
<td>1.4</td>
<td>0.42 (0.17, 0.67)</td>
</tr>
<tr>
<td>Age at heelstick (d)</td>
<td>486</td>
<td>1.94</td>
<td>0.68</td>
<td>0.71 (−1.22, −0.20)</td>
</tr>
<tr>
<td>Breast-feeding (months)</td>
<td>494</td>
<td>6.72</td>
<td>4.56</td>
<td>0.01 (−0.07, 0.08)</td>
</tr>
<tr>
<td>VRM score</td>
<td>500</td>
<td>62.9</td>
<td>16.0</td>
<td>0.03 (−0.05, −0.01)</td>
</tr>
<tr>
<td>PPVT score</td>
<td>424</td>
<td>106.0</td>
<td>13.2</td>
<td>0.02 (−0.01, 0.05)</td>
</tr>
<tr>
<td>WRAVMA matching</td>
<td>424</td>
<td>109.3</td>
<td>13.7</td>
<td>0.01 (−0.02, 0.04)</td>
</tr>
<tr>
<td>WRAVMA pegboard</td>
<td>434</td>
<td>99.2</td>
<td>10.5</td>
<td>0.01 (−0.04, 0.03)</td>
</tr>
<tr>
<td>WRAVMA drawing</td>
<td>432</td>
<td>99.8</td>
<td>11.8</td>
<td>0.01 (−0.04, 0.03)</td>
</tr>
<tr>
<td>WRAVMA total</td>
<td>416</td>
<td>103.5</td>
<td>11.5</td>
<td>0.00 (−0.03, 0.04)</td>
</tr>
</tbody>
</table>

Ref, Reference; svg, serving.

a Newborn T4 reported in µg/dl (1 µg/dl = 12.87 nmol/liter). Estimates are adjusted for child sex, gestational age at delivery, and age at heelstick.

b Some numbers may not total 500 because of missing data.

diagnosed thyroid disease to models or exclusion of women taking thyroid medication during pregnancy did not alter the effect estimates for maternal first trimester thyroid function (data not shown). With the exception of a direct association of maternal fish consumption with VRM test scores, dietary intake of foods likely to be high in iodine was not associated with child cognition (Table 2).

Discussion

In this study of 500 children in Massachusetts born near term with normal thyroid function, we did not find evidence that newborn T4 concentrations were associated with maternal thyroid function or with later child cognitive development. Previous literature regarding associations of T4 among infants born at term with later developmental outcomes is limited. In one study of 52 cases, each matched with one to five controls, risk for attention deficit hyperactivity disorder was not associated with newborn T4 levels (32). All of the children in that study had T4 levels within normal limits. In another case-control study, neonatal T4 level was not associated with risk for a heterogeneous group of developmental diagnoses, including attention deficit disorder, autism spectrum disorder, behavioral disorder, cognitive disorder, developmental delay, emotional disorder, learning disability, and speech/language disorder (33).

Among preterm infants, transient hypothyroxinemia is common and associated with increased risk for cerebral palsy and poorer mental development (34). However, results from a large randomized trial of levothyroxine supplementation in preterm infants have been mixed, with improved neurocognitive function among supplemented infants born at younger gestational ages but worse outcomes in those born at more than 28 wk gestation (35).

We did not measure newborn TSH or other thyroid hormones other than T4, so we do not have information about the newborn’s thyroid regulatory system. It is not known whether low levels of T4 in a fetus exposed to maternal hypothyroidism result in a higher set point for T4 in later life, as is the case with con-

TABLE 2. Associations of newborn and maternal thyroid function with child cognition at ages 6 months and 3 yr

<table>
<thead>
<tr>
<th></th>
<th>VRM test</th>
<th>PPVT</th>
<th>WRAVMA As</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn heelstick blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4 (µg/dl)</td>
<td>−0.5 (−0.9, −0.2)</td>
<td>0.2 (−0.1, 0.5)</td>
<td>0.1 (−0.2, 0.3)</td>
</tr>
<tr>
<td>Maternal thyroid function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of diagnosed thyroid disease</td>
<td>2.4 (−4.8, 9.6)</td>
<td>7.1 (1.7, 12.4)</td>
<td>1.2 (−4.0, 6.4)</td>
</tr>
<tr>
<td>TPO antibody &gt;2.0 U/ml</td>
<td>2.1 (−1.7, 5.8)</td>
<td>2.6 (−0.4, 5.5)</td>
<td>1.8 (−1.0, 4.6)</td>
</tr>
<tr>
<td>TSH &gt;2.5 mU/liter</td>
<td>1.2 (−3.0, 5.3)</td>
<td>2.5 (−0.8, 5.7)</td>
<td>0.7 (−2.4, 3.8)</td>
</tr>
<tr>
<td>T4 (µg/dl)</td>
<td>−0.04 (−0.8, 0.7)</td>
<td>−0.1 (−0.7, 0.5)</td>
<td>0.004 (−0.6, 0.6)</td>
</tr>
<tr>
<td>Maternal first trimester diet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dairy (daily serving)</td>
<td>0.2 (−0.9, 1.2)</td>
<td>−0.4 (−1.2, 0.4)</td>
<td>−0.3 (−1.0, 0.4)</td>
</tr>
<tr>
<td>Fish (weekly serving)</td>
<td>1.2 (0.1, 2.3)</td>
<td>−0.4 (−1.0, 0.4)</td>
<td>−0.5 (−1.2, 0.3)</td>
</tr>
<tr>
<td>Eggs (weekly serving)</td>
<td>0.3 (−0.7, 1.2)</td>
<td>−0.2 (−0.9, 0.5)</td>
<td>−0.5 (−1.1, 0.2)</td>
</tr>
<tr>
<td>Iodine-containing vitamins (yes vs. no)</td>
<td>1.9 (−3.9, 7.6)</td>
<td>3.0 (−1.4, 7.5)</td>
<td>1.9 (−2.3, 6.1)</td>
</tr>
</tbody>
</table>

a Estimates for VRM test are adjusted for child sex, gestational age, fetal growth z score, breast-feeding status at 6 months (formula only, mixed formula and breast milk, weaned from breast milk to formula, and breast milk only) and age at testing, as well as and maternal race/ethnicity, education, and PPVT score. Estimates for PPVT and WRAVMAs are adjusted for child sex, gestational age, fetal growth z score, total duration of breast-feeding in months, age at testing, and primary language, as well as maternal race/ethnicity, education, and PPVT score.
We measured thyroid function at a single point in time. T4 measured soon after birth may not reflect thyroid function throughout gestation, or after birth. It is possible that newborn T4 might be associated with later child cognition in a population of women with iodine insufficiency or preexisting thyroid disease. Included infants differed from those excluded in sociodemographical and birth characteristics, and mothers enrolled in Project Viva overall tended to be well educated, and all had health insurance. Results may not be generalizable to other populations.

Contrary to expectation, we did not observe any association of maternal thyroid function with child cognitive outcomes. The administered cognitive tests were well validated and, within our population, sensitive to other expected predictors such as parity, breast-feeding duration, child sex, and mercury exposure (29, 30). However, because the absolute number of women with abnormal thyroid function was small, we may have had limited power to detect an association.

With the exception of maternal fish consumption, we saw no association of maternal dietary intake of foods likely to be high in iodine with child cognition. We have previously reported associations of greater maternal second trimester fish intake with improved child cognition, especially after adjustment for mercury levels (29, 30), which we anticipate largely results from the high concentration of n-3 polyunsaturated fatty acids found in seafood. We also saw no association of iodine-containing vitamin intake with outcomes. However, because we did not collect urine, we had no direct measure of maternal iodine status. Because the iodine content of foods tends to vary geographically, dietary questionnaires cannot accurately estimate dietary iodine intake. All Viva participants lived in New England. Intake of iodine-containing foods or vitamins may be more predictive of child development in other, less iodine replete, regions.

In conclusion, newborn T4 concentrations within a normal physiological reference range are not associated with maternal thyroid function and do not predict cognitive outcome in a population living in an iodine-sufficient area. We did not replicate previously established relationships of maternal early pregnancy thyroid dysfunction with poorer child development reported among larger study populations. However, we did find that a relatively large subset of women in this cohort had first trimester plasma TSH levels above 2.5 mU/liter and TPO antibodies above 2.0 U/ml.

Acknowledgments

We appreciate the invaluable assistance we received from Anne M. Comeau, Ph.D., of the New England Newborn Screening Program with obtaining the newborn T4 test results. We also appreciate the help with the maternal T4 assays we received from Erika Line-Nitu, from Joyce Tomson of the Boston Medical Center Clinical Laboratories, and from Jody Senter of the Channing Laboratory at Brigham and Women’s Hospital. We appreciate Patricia Elliott’s assistance with data management.

Address all correspondence and requests for reprints to: Emily Oken, M.D., M.P.H., 133 Brookline Avenue, Boston, Massachusetts 02215. E-mail: emily_oken@hphc.org.

This work was supported by grants from the Harvard Pilgrim Health Care Foundation and by the National Institutes of Health (HD44807, HD34568).

Disclosure Statement: The authors have nothing to disclose.

References


