Neonatal Thyroxine, Maternal Thyroid Function, and Child Cognition

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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 T_4 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 T_4 at a mean age of 1.94 d was 17.6 (SD 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 T_4 levels were not associated with maternal T_4, TSH, or thyroid peroxidase antibody levels. On multivariable linear regression analysis, adjusting for maternal and child characteristics, higher newborn T_4 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 T_4 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)**

Thyroid hormone is essential for normal brain development. Extremely low levels of thyroid hormone during gestation, *e.g.* from endemic iodine deficiency, result in mental retardation, although repletion soon after birth may prevent permanent brain damage in some cases. In early pregnancy the embryo depends entirely on maternal thyroid hormone that crosses the placenta, and by about 12–14 wk gestation, fetal thyroid function begins (1, 2). Even after the onset of fetal thyroid secretion, maternal transfer constitutes a fraction of circulating fetal T_4, and continues to have a protective role in fetal neurodevelopment until birth (2). Mothers with untreated hypothyroidism during the first trimester of pregnancy, and even those with low-normal T_4 levels or mild serum TSH elevations, have children with poorer neurocognitive function (3–5).

Thyroid hormone production requires iodine, and worldwide dietary iodine deficiency is a common cause of thyroid dysfunc-

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Abbreviations: CI, Confidence interval; NENSP, New England Newborn Screening Program; PPVT, Peabody Picture Vocabulary Test; TPO, thyroid peroxidase; VRM, visual recognition memory; WRAVMA, Wide Range Assessment of Visual Motor Ability.

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 T_4 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 offspring 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 T_4 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 T_4 levels with maternal thyroid function and with later cognition in a prebirth cohort of mothers and children. We hypothesized that infants with lower T_4 levels would have mothers with poorer thyroid function, manifest by higher TSH, lower T_4, 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-specialty 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 T_4 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 semiquantitative 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 T_4, 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 T_4, 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 mIU/ml; $P < 0.001$) but lower T_4 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 T_4 level. T_4 assays were performed using AutoDELFIA kits (PerkinElmer Life and Analytical Sciences, Turku, Finland). The assay is a solid-phase time-resolved fluoroimmunoassay in which europium-labeled T_4 competes against sample T_4 for a limited number of binding sites on T_4 specific monoclonal antibodies. Mean (SD) T_4 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 ($r \geq 0.90$) 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 T_4 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 T_4 levels in the study population.

We next studied associations of newborn T_4 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 the outcomes. For analyses using the 6-month VRM outcome, we included child sex, gestational age, fetal growth z score, breast-feeding status at 6 months (formula only, weaned from breast milk to formula, mixed formula and breast milk, and breast milk only), age at testing, and primary language, as well as maternal race/ethnicity, education, and maternal PPVT score. For analyses using the age 3-yr PPVT and WRAVMA outcomes, we included 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.

In secondary analyses we studied effect estimates for neonatal T_4 additionally adjusted for maternal self-reported history of thyroid problems diagnosed before pregnancy, first trimester thyroid hormone levels, fish consumption, and intake of iodine-containing vitamins.

We also studied associations of maternal first trimester thyroid hormone levels, TPO antibody status, history of thyroid problems, intake of iodine-containing multivitamins, and intake of foods likely to be high in iodine, with child cognitive test results at ages 6 months and 3 yr. We conducted all analyses using SAS version 9.1 (SAS Institute Inc., Cary, NC).

Results

Mean newborn T_4 was 17.6 μg/dl (SD 4.0, range 6.4–35.7), or 226.5 nmol/liter. T_4 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 T_4 levels, elevated TPO antibody, or elevated TSHs were associated with newborn T_4 levels (Table 1). Newborn T_4 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 T_4, perhaps a chance finding because children of mothers with smoking during pregnancy did not have different T_4 levels (Table 1).

We next studied adjusted associations of newborn T_4 and maternal thyroid function with child cognitive test scores (Table 2). Contrary to our hypothesis, higher newborn T_4 was associated with slightly lower scores on the VRM test at 6 months (−0.5; 95% CI −0.9, −0.2). However, newborn T_4 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 T_4 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

TABLE 1. Participant characteristics and their associations with newborn T_4 results among 500 mother-child pairs in Project Viva

				Association with newborn T_4[a]
	No.[b]	Mean	SD	Estimate (95% CI)
Maternal				
Age (yr)	500	33.1	4.4	−0.05 (−0.1, 0.03)
First trimester diet				
Total dairy (svg/d)	500	2.77	1.46	0.09 (−0.15, 0.33)
Fish (svg/wk)	500	1.70	1.43	−0.07 (−0.31, 0.18)
Whole eggs (svg/wk)	500	1.89	1.75	0.05 (−0.16, 0.26)
T_4 (μg/dl)	496	9.98	1.95	0.03 (−0.15, 0.21)
PPVT score	445	108.6	14.3	0.01 (−0.02, 0.03)
	No.	**%**		**Estimate (95% CI)**
Race/ethnicity				
Black	27	5.4		−0.27 (−1.81, 1.27)
Hispanic	24	4.8		0.81 (−0.84, 2.45)
Other	34	6.8		−0.36 (−1.72, 1.01)
White	415	83.0		Ref
Education				
High school or less	20	4.0		0.10 (−1.67, 1.88)
Some college	77	15.4		−0.44 (−1.49, 0.61)
College graduate	196	39.2		−0.91 (−1.67, −0.14)
Graduate degree	207	41.4		Ref
Smoking				
Former	98	19.8		−1.01 (−1.86, −0.15)
During pregnancy	43	8.7		0.52 (−0.71, 1.75)
Never	353	71.5		Ref
Postpartum depression				
Yes	43	9.0		−0.57 (−1.8, 0.7)
No	435	91.0		Ref
History of thyroid problem				
Yes	23	4.6		−0.59 (−2.30, 1.11)
No	473	95.4		Ref
TPO antibody				
≤2.0	405	81.7		Ref
>2.0	91	18.4		0.48 (−0.43, 1.38)
TSH				
<2.5	412	84.3		Ref
≥2.5	77	15.8		0.34 (−0.63, 1.31)
Iodine-containing vitamins				
No	458	92.3		Ref
Yes	38	7.7		0.54 (−0.76, 1.84)
Paternal				
Education				
Missing	20	4.0		−0.91 (−0.89, 2.71)
High school	40	8.0		0.25 (−1.12, 1.61)
Some college	74	14.8		−0.64 (−1.70, 0.43)
College graduate	192	38.4		−0.08 (−0.88, 0.73)
Graduate degree	174	34.8		Ref
Child				
Sex				
Boy	252	50.4		Ref
Girl	248	49.6		1.07 (0.38, 1.76)
Cesarean delivery				
No	389	77.8		Ref
Yes	111	22.2		−0.50 (−1.44, 0.45)
Breast-feeding status at 6 months				
Formula only	40	8.0		−0.72 (−2.11, 0.68)
Weaned	197	39.4		−0.41 (−1.28, 0.46)
Mixed	129	25.8		−0.20 (−1.15, 0.75)
Breast milk only	134	26.8		Ref
English as a second language				0.06 (−0.74, 0.87)
No	467	96.9		Ref
Yes	15	3.1		−0.61 (−2.68, 1.46)

(*Continued*)

TABLE 1. Continuous

	No.[b]	Mean	SD	Association with newborn T_4[a] Estimate (95% CI)
Fetal growth (z value)	500	0.28	0.95	0.03 (−0.34, 0.41)
Birth weight (kg)	500	3.56	0.51	0.06 (−0.74, 0.87)
Gestation length (wk)	500	39.7	1.4	0.42 (0.17, 0.67)
Age at heelstick (d)	486	1.94	0.68	−0.71 (−1.22, −0.20)
Breast-feeding (months)	494	6.72	4.56	0.01 (−0.07, 0.08)
VRM score	500	62.9	16.0	−0.03 (−0.05, −0.01)
PPVT score	424	106.0	13.2	0.02 (−0.01, 0.05)
WRAVMA matching	424	109.3	13.7	0.01 (−0.02, 0.04)
WRAVMA pegboard	434	99.2	10.5	−0.01 (−0.04, 0.03)
WRAVMA drawing	432	99.8	11.8	−0.01 (−0.04, 0.03)
WRAVMA total	416	103.5	11.5	0.00 (−0.03, 0.04)

Ref, Reference; svg, serving.

[a] Newborn T_4 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 T_4 concentrations were associated with maternal thyroid function or with later child cognitive development. Previous literature regarding associations of T_4 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 T_4 levels (32). All of the children in that study had T_4 levels within normal limits. In another case-control study, neonatal T_4 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 T_4, so we do not have information about the newborn's thyroid regulatory system. It is not known whether low levels of T_4 in a fetus exposed to maternal hypothyroidism result in a higher set point for T_4 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

	β-Coefficient[a] for change in test score (95% CI)		
	VRM test	PPVT	WRAVMAs
Newborn heelstick blood			
T_4 (μg/dl)	−0.5 (−0.9, −0.2)	0.2 (−0.1, 0.5)	0.1 (−0.2, 0.3)
Maternal thyroid function			
History of diagnosed thyroid disease	2.4 (−4.8, 9.6)	7.1 (1.7, 12.4)	1.2 (−4.0, 6.4)
TPO antibody >2.0 U/ml	2.1 (−1.7, 5.8)	2.6 (−0.4, 5.5)	1.8 (−1.0, 4.6)
TSH >2.5 mU/liter	1.2 (−3.0, 5.3)	2.5 (−0.8, 5.7)	0.7 (−2.4, 3.8)
T_4 (μg/dl)	−0.04 (−0.8, 0.7)	−0.1 (−0.7, 0.5)	0.004 (−0.6, 0.6)
Maternal first trimester diet			
Dairy (daily serving)	0.2 (−0.9, 1.2)	−0.4 (−1.2, 0.4)	−0.3 (−1.0, 0.4)
Fish (weekly serving)	1.2 (0.1, 2.3)	−0.4 (−1.0, 0.4)	−0.5 (−1.2, 0.3)
Eggs (weekly serving)	0.3 (−0.7, 1.2)	−0.2 (−0.9, 0.5)	−0.5 (−1.1, 0.2)
Iodine-containing vitamins (yes *vs.* no)	1.9 (−3.9, 7.6)	3.0 (−1.4, 7.5)	1.9 (−2.3, 6.1)

[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.

genital hypothyroidism. We measured child thyroid function at a single point in time. T_4 measured soon after birth may not reflect thyroid function throughout gestation, or after birth. It is possible that newborn T_4 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 T_4 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.

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References

1. **de Escobar GM, Obregon MJ, del Rey FE** 2007 Iodine deficiency and brain development in the first half of pregnancy. Public Health Nutr 10:1554–1570
2. **de Escobar GM, Obregon MJ, del Rey FE** 2004 Maternal thyroid hormones early in pregnancy and fetal brain development. Best Pract Res Clin Endocrinol Metab 18:225–248
3. **Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ** 1999 Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 341:549–555
4. **Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA, Vader HL** 1999 Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol (Oxf) 50:149–155
5. **Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ** 2003 Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol (Oxf) 59:282–288
6. **National Center for Health Statistics** Accessed October 28, 2004 Iodine Level, United States, 2000. Available at: http://www.cdc.gov/nchs/products/pubs/pubd/hestats/iodine.htm
7. **Canaris GJ, Manowitz NR, Mayor G, Ridgway EC** 2000 The Colorado thyroid disease prevalence study. Arch Intern Med 160:526–534
8. **Mitchell ML, Klein RZ** 2004 The sequelae of untreated maternal hypothyroidism. Eur J Endocrinol 151(Suppl 3):U45–U48
9. **Klein RZ, Haddow JE, Faix JD, Brown RS, Hermos RJ, Pulkkinen A, Mitchell ML** 1991 Prevalence of thyroid deficiency in pregnant women. Clin Endocrinol (Oxf) 35:41–46
10. **Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE** 2002 Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 87:489–499
11. **American College of Obstetrics and Gynecology** 2002 ACOG practice bulletin. Thyroid disease in pregnancy. Number 37, August 2002. American College of Obstetrics and Gynecology. Int J Gynaecol Obstet 79:171–180
12. **Pearce EN, Oken E, Gillman MW, Lee SL, Magnani B, Platek D, Braverman LE** 2008 Association of first-trimester thyroid function test values with thyroperoxidase antibody status, smoking, and multivitamin use. Endocr Pract 14:33–39
13. **Glinoer D, Riahi M, Grun JP, Kinthaert J** 1994 Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. J Clin Endocrinol Metab 79:197–204
14. **Pop VJ, de Vries E, van Baar AL, Waelkens JJ, de Rooy HA, Horsten M, Donkers MM, Komproe IH, van Son MM, Vader HL** 1995 Maternal thyroid peroxidase antibodies during pregnancy: a marker of impaired child development? J Clin Endocrinol Metab 80:3561–3566
15. **Gillman MW, Rich-Edwards JW, Rifas-Shiman SL, Lieberman ES, Kleinman KP, Lipshultz SE** 2004 Maternal age and other predictors of newborn blood pressure. J Pediatr 144:240–245
16. **Oken E, Kleinman KP, Olsen SF, Rich-Edwards JW, Gillman MW** 2004 Associations of seafood and elongated n-3 fatty acid intake with fetal growth and length of gestation: results from a US pregnancy cohort. Am J Epidemiol 160:774–783
17. 1997 World Medical Association declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. JAMA 277:925–926
18. **Rasmussen LB, Ovesen L, Bulow I, Jorgensen T, Knudsen N, Laurberg P, Perrild H** 2001 Evaluation of a semi-quantitative food frequency questionnaire to estimate iodine intake. Eur J Clin Nutr 55:287–292
19. **Pearce EN, Pino S, He X, Bazrafshan HR, Lee SL, Braverman LE** 2004 Sources of dietary iodine: bread, cows' milk, and infant formula in the Boston area. J Clin Endocrinol Metab 89:3421–3424
20. **Lee SL, Roper J** 2004 Inadequate supplementation in American multivitamins. Endocr Pract 10:46 (Abstract)
21. **Oken E, Kleinman KP, Rich-Edwards J, Gillman MW** 2003 A nearly continuous measure of birth weight for gestational age using a United States national reference. BMC Pediatr 3:6
22. **Cox JL, Holden JM, Sagovsky R** 1987 Detection of postnatal depression.

Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 150:782–786
23. **Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoer D, Mandel SJ, Stagnaro-Green A** 2007 Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 92(Suppl):S1–S47
24. **Rose SA, Feldman JF, Wallace IF** 1992 Infant information processing in relation to six-year cognitive outcomes. Child Dev 63:1126–1141
25. **Rose SA, Feldman JF** 1995 Prediction of IQ and specific cognitive abilities at 11 years from infancy measures. Dev Psychol 31:685–696
26. **Dunn LM, Dunn LM** 1997 Examiner's manual for the Peabody Picture Vocabulary Test. 3rd ed. Circle Pines, MN: American Guidance Service
27. **Bellinger DC, Hu H, Kalaniti K, Thomas N, Rajan P, Sambandam S, Ramaswamy P, Balakrishnan K** 2005 A pilot study of blood lead levels and neurobehavioral function in children living in Chennai, India. Int J Occup Environ Health 11:138–143
28. **Adams W, Sheslow D** 1995 Wide range assessment of visual motor abilities. Wilmington, DE: Wide Range, Inc
29. **Oken E, Wright RO, Kleinman KP, Bellinger D, Amarasiriwardena CJ, Hu H, Rich-Edwards JW, Gillman MW** 2005 Maternal fish consumption, hair mercury, and infant cognition in a U.S. Cohort. Environ Health Perspect 113: 1376–1380
30. **Oken E, Radesky JS, Wright RO, Bellinger DC, Amarasiriwardena CJ, Kleinman KP, Hu H, Gillman MW** 2008 Maternal fish intake during pregnancy, blood mercury, and child cognition at age 3 years in a US cohort. Am J Epidemiol 167:1171–1181
31. **Zurakowski D, Di Canzio J, Majzoub JA** 1999 Pediatric reference intervals for serum thyroxine, triiodothyronine, thyrotropin, and free thyroxine. Clin Chem 45:1087–1091
32. **Soldin OP, Nandedkar AK, Japal KM, Stein M, Mosee S, Magrab P, Lai S, Lamm SH** 2002 Newborn thyroxine levels and childhood ADHD. Clin Biochem 35:131–136
33. **Soldin OP, Lai S, Lamm SH, Mosee S** 2003 Lack of a relation between human neonatal thyroxine and pediatric neurobehavioral disorders. Thyroid 13:193–198
34. **Reuss ML, Paneth N, Pinto-Martin JA, Lorenz JM, Susser M** 1996 The relation of transient hypothyroxinemia in preterm infants to neurologic development at two years of age. N Engl J Med 334:821–827
35. **van Wassenaer AG, Westera J, Houtzager BA, Kok JH** 2005 Ten-year follow-up of children born at <30 wk' gestational age supplemented with thyroxine in the neonatal period in a randomized, controlled trial. Pediatrics 116:e613–e618