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ARTICLE

Neonatal Effects of Maternal Hypothyroxinemia During Early Pregnancy

Libbe Kooistra, PhD[a,b], Susan Crawford, MSc[b], Anneloes L. van Baar, PhD[c], Evelien P. Brouwers, PhD[d], Victor J. Pop, MD, PhD[d]

[a]Department of Pediatrics, University of Calgary, Calgary, Alberta, Canada; [b]Behavioral Research Unit, Alberta Children's Hospital, Calgary, Alberta, Canada; Departments of [c]Pediatric Psychology and [d]Clinical Health Psychology, University of Tilburg, Tilburg, Netherlands

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ABSTRACT

OBJECTIVE. We sought to examine the neurobehavioral profile of neonates who are born to women with hypothyroxinemia during early pregnancy.

METHODS. Examined were 108 neonates who were born to mothers with low maternal free thyroid hormone (fT4 concentrations; <10th percentile) at 12 weeks' gestation (case patients) and 96 neonates who were born to women whose fT4 values were between the 50th and 90th percentiles, matched for parity and gravidity (control subjects). Newborn development was assessed at 3 weeks of age using the Neonatal Behavioral Assessment Scale. Maternal thyroid function (fT4 and thyrotropin hormone) was assessed at 12, 24, and 32 weeks' gestation.

RESULTS. Infants of women with hypothyroxinemia at 12 weeks' gestation had significantly lower scores on the Neonatal Behavioral Assessment Scale orientation index compared with subjects. Regression analysis showed that first-trimester maternal fT4 but not maternal TSH or fT4 later in gestation was a significant predictor of orientation scores.

CONCLUSIONS. This study confirms that maternal hypothyroxinemia constitutes a serious risk factor for neurodevelopmental difficulties that can be identified in neonates as young as 3 weeks of age.

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Key Words
neonatal, outcome, thyroid disorders

Abbreviations
fT4—free thyroid hormone
TSH—thyrotropin hormone
NBAS—Neonatal Behavioral Assessment Scale
TPO-Ab—thyroid peroxidase antibodies
EPDS—Edinburgh Postnatal Depression Scale
RDC—Research Diagnostic Criteria
STAI—State-Trait Anxiety Inventory
ANOVA—analysis of variance
ADHD—attention-deficit/hyperactivity disorder

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Address correspondence to Libbe Kooistra, PhD, Alberta Children's Hospital, 1820 Richmond Rd (SW), Calgary, Alberta, Canada T2T 5C7. E-mail: libbe.kooistra@calgaryhealthregion.ca

Hypothyroxinemia is a common condition in pregnant women. It is characterized by low maternal free thyroid hormone (fT4) concentrations with thyrotropin hormone (TSH) concentrations in the normal range. This condition has long been regarded as being without consequences for mother and fetus. Recent findings by Pop et al[1,2] and very recently by Vermiglio et al[3] restimulated an earlier debate that originally was started by Man et al[4–6] regarding to what extent maternal hypothyroxinemia in early pregnancy constitutes a risk factor for impaired infant development. On the basis of the idea that hypothyroxinemia reflects a condition in which the mother may produce enough T4 for her own needs but cannot meet fetal T4 demands to preserve normal neurodevelopment, Pop et al[1] investigated the relationship between maternal plasma fT4 concentration during pregnancy and infant neurodevelopment in an iodine-sufficient area. They found that in otherwise normal pregnancies, maternal fT4 concentrations ≤10th percentile at 12 weeks' gestation but not at 32 weeks' gestation were associated with developmental delays at 10 months of age as measured with the Dutch version of the Bayley Scales of Infant Development.[7] Subsequently, a prospective 3-year follow-up study of children of mothers with fT4 concentrations at the lowest 10th percentile demonstrated cognitive and neuromotor delays at both 1 and 2 years of age[2] compared with children of mothers with gestational fT4 levels between the 50th and 90th percentiles. However, for minimizing the influence of the postnatal environment when determining the impact of gestational hypothyroxinemia, it would be desirable to evaluate children as close as possible to the time of birth.

The current report, therefore, used the Neonatal Behavioral Assessment Scale (NBAS),[8] administered at 3 weeks of age, to examine the neurobehavioral profile of neonates as a function of maternal fT4 status measured at 12, 24, and 32 weeks' gestation. It was hypothesized that low scores on the NBAS, indicating less mature behavior, would be associated with low maternal fT4 concentrations at 12 weeks' gestation but not at 24 or 32 weeks' gestation.

METHODS

Between January 1997 and April 1998, 1361 pregnant women from the Dutch city of Veldhoven and its immediate vicinity were screened for thyroid parameters (TSH, fT4, and thyroid peroxidase antibodies [TPO-Ab]) during their first antenatal visit to the midwife or gynecologist at 12 weeks' gestation. After the exclusion of 8 women with overt thyroid dysfunction, in the remaining 1353 women, the 10th, 50th, and 90th percentiles of fT4 were calculated. The 135 women with fT4 values <10th percentile (case patients) were matched for parity and gravidity with an equal number of women whose fT4 values were between the 50th and 90th percentiles (control subjects). All 270 women were invited to participate. Previously set exclusion criteria were verified (fertility problems, previous thyroid disease, rheumatism, diabetes, nonwhite and not fluent in Dutch [all anxiety and depression measures were in the Dutch language]), resulting in the exclusion of 19 women. An additional 12 women decided not to participate in the follow-up. During the study period, an additional 11 women were excluded because they delivered prematurely or had severe psychiatric problems during pregnancy. Finally, 1 mother of a newborn who died of congenital heart disease and 1 mother whose child received a diagnosis of trisomy 18 syndrome were excluded from the study.

Of the remaining 226 women who completed the study, thyroid parameters at 24 and/or 32 weeks were not obtained in 22 women. Therefore, data analysis refers to 204 mothers and their children (108 case patients and 96 control subjects), none of whom had serious complications during pregnancy or delivery. As shown in Table 1, no differences in descriptive characteristics, for both mothers and newborns, were observed between case patients and control subjects. Mothers and children were white, with the mothers ranging in age from 21 to 40 years (mean: 31.4 years; SD: 3.3). The sample did not differ from the eligible cohort of 1361 women on any of the characteristics listed in Table 1. The study was approved by the medical ethical committee of the St Joseph Hospital (Veldhoven, Netherlands).

TABLE 1 **Characteristics According to Group**

Variable	Case Patients ($N = 108$)	Control Subjects ($N = 96$)
Maternal education, %		
Low	13.5	9.8
Middle	47.1	50.0
High	39.4	40.2
Mean maternal age (SD), y	31.9 (3.1)	30.9 (3.5)
Proportion of mothers >35 y old, %	15.4	15.2
Lifestyle habits during pregnancy, %		
Smoking	15.8	18.0
Alcohol intake	10.9	11.2
Caffeine	73.3	68.5
Breastfeeding, %	63.8	70.8
Mean parity (SD)	1.12 (1.2)	1.03 (1.1)
Gender of the child		
Male	56	50
Female	52	46
Birth weight, g		
Mean (SD)	3470.6 (442.5)	3508.0 (563.7)
Range	2460–4530	2350–5100
Gestational age, wk		
Mean (SD)	40.3 (1.3)	40.2 (1.4)
Range	37–44	37–46
Mean Apgar score at 1 min (SD)	8.7 (1.2)	9.0 (0.7)
Mean Apgar score at 5 min (SD)	9.8 (0.5)	9.7 (0.5)

Measures

Neonatal Development

Newborn development was assessed at 3 weeks of age using the NBAS.[8] The NBAS allows the systematic assessment of different aspects of newborn behavior, such as motor performance, orientation, and state regulation, and has been applied successfully in the study of various groups of newborns at risk (eg, very low birth weight infants,[9] neonates with moderate hyperbilirubinemia,[10] children prenatally exposed to alcohol[11]). The NBAS attributes an active role to the infant in his or her interaction with the environment, thereby focusing on the newborn's capacity to control levels of stimulation by using states of consciousness when adapting to the environment.[12] The scale contains 28 behavioral items, 18 neurologic reflex items, and 7 supplementary items that measure the quality of responsiveness and the amount of input that the infant needs from the examiner to show his or her best performance. All of the items were scored in the correct states as defined in the NBAS guidelines.[8]

Scores on the NBAS were reduced to the following 7 clusters: (1) habituation: the ability to respond to and inhibit discrete stimuli while asleep; (2) orientation: includes the ability to attend to visual and auditory stimuli and the quality of overall alertness; (3) motor: measures motor performance and the quality of movement and tone; (4) range of state: a measure of infant arousal and state lability; (5) regulation of state: measures the infant's ability to regulate his or her state in the face of increasing levels of stimulation; (6) autonomic stability: records signs of stress related to homeostatic adjustments of the central nervous system; and (7) reflexes: the total number of nonoptimal responses (Table 2).

Missing values often occur when administering the NBAS, because the infants have to be in the appropriate state for specific items to be observed. For example, all items included in the orientation cluster were scored in the alert states, reflecting state 4 (alert with minimal motor activity) and state 5 (eyes open with considerable motor activity and sometimes fussiness), in accordance with the NBAS examination guidelines.[8] Therefore, all NBAS examinations took place midway between feedings, in a quiet, semidarkened environment. In the analyses, missing values for an item were replaced by the individual mean cluster score. When >3 of the items in a cluster were missing, the child's cluster score was considered to be missing and was not included in the analysis. All examinations were done by 1 researcher (E.P.B.), who was trained and certified in the NBAS.

TABLE 2 **NBAS Cluster Items**

Cluster	Item
Habituation	Light
	Rattle
	Bell
	Pin-prick
Orientation	Inanimate visual
	Inanimate auditory
	Inanimate visual-auditory
	Animate visual
	Animate auditory
	Animate visual-auditory
	Alertness
Motor	Tonus
	Maturity
	Pull-to-sit
	Defense
	Activity
Range of state	Peak of excitement
	Rapidity of build-up
	Irritability
	Lability of state
Regulation of state	Cuddliness
	Consolability
	Self-quieting
	Hand-to-mouth
Autonomic stability	Tremors
	Startles
	Skin color

Thyroid Parameters

TSH (reference range: 0.15–2.0 mIU/L) was measured using a solid-phase, 2-site chemiluminescent enzyme immunometric assay (Immulite Third Generation TSH; Diagnostic Products Corporation, Los Angeles, CA). The fT4 concentration (reference range: 8.7–19.6 pmol/L) was also measured with a solid-phase immunometric assay (Immulite Free T4). The Immulite Anti–TPO-Ab kit was used to determine antibodies against TPO. The anti-TPO assay is standardized in accordance with the International Reference Preparation for anti-TPO MRC 66/387. An antibody concentration of ≥35 IU/mL was regarded as elevated. A concentration of >100 IU/mL was regarded as clearly elevated. As part of the nationwide screening of congenital hypothyroidism, thyroid function (total T4) was assessed in all neonates between days 5 and 7 postpartum.

Maternal Depression and Anxiety

Information on maternal depression and anxiety was obtained to control statistically for their potential influence on infant development. Depressive symptoms were measured at 24 weeks' gestation using the Edinburgh Postnatal Depression Scale (EPDS). The EPDS is a 10-item self-report scale that measures the intensity of depressive symptoms but does not provide a syndromal diagnosis. The Dutch translation of the EPDS has been found to have good psychometric properties,[13] with a Cronbach's α of .82.

The diagnosis of an episode of major depression during early postpartum (3 weeks) was made using a semistructured interview applying the Research Diagnostic Criteria (RDC).[14] The RDC evaluates the occurrence of a

depressive disorder in the 2 weeks before the interview and discriminates between major and minor depression.

Anxiety at 24 weeks' gestation was measured by the general anxiety scale of the Symptom Check List-90,[15] Dutch version.[16] The internal consistency of the Dutch version was found to be high, with Cronbach's α of .91 for the anxiety subscale.[17]

Anxiety was also measured at 32 weeks' gestation by self-report using the Dutch State-Trait Anxiety Inventory (STAI).[18] The STAI[19] consists of 2 subscales, each containing 20 items. The state anxiety subscale measures anxiety at the moment of scoring; trait anxiety measures dispositional anxiety, or anxiety in general. Higher scores on the STAI indicate a higher intensity of anxiety.

Statistical Analyses

The statistical analyses were performed using the Statistical Package for the Social Sciences 12.0 (SPSS Inc, Chicago, IL). Initial data analyses involved comparing case patients and control subjects on various demographic and pregnancy-related factors, using analysis of variance (ANOVA) for continuous variables and χ^2 tests of association for categorical variables. Between-group comparisons on the NBAS cluster scores used a series of ANOVAs and analysis of covariance to control for potentially confounding factors. The final phase of the analysis involved an examination of predictors of scores on the orientation cluster of the NBAS, using both a multiple regression and a logistic-regression approach.

RESULTS

Maternal and Infant Thyroid Functioning

Between-group differences emerged for the prevalence of TPO antibodies >35 U/mL and TSH levels in the first trimester (Table 3). Both variables were significantly higher in case patients (TPO-Ab, $\chi^2[1, N = 204] = 8.25$, $P = .004$; and TSH first trimester, $F_{1,202} = 15.94$, $P < .0001$). It is to be noted that although higher in the case patients than in the control subjects, the TSH levels of both groups were clearly within the normal reference range. No significant group differences were found for TSH or fT4 levels in the second and third trimesters. There were also no significant differences between case patients and control subjects for the total T4 level in infant heel blood samples or in the SD of heel blood samples compared with all infants who were born that day in Holland.

There were no significant correlations between infant total T4 from heel blood samples and maternal fT4 in the first, second, or third trimester. Infant heel blood samples for total T4 were significantly inversely correlated with maternal TSH in the first trimester ($r = -0.171$; $P = .016$) but not with TPO-Ab, gender, birth weight, or gestational age.

TABLE 3 **Maternal and Infant Thyroid Functioning**

Variable	Case Patients ($N = 108$)	Control Subjects ($N = 96$)
Mean maternal fT4 first trimester (SD)	11.4 (1.0)	17.0 (0.9)[a,b]
Mean maternal TSH first trimester (SD)	1.6 (1.0)	1.1 (0.8)[a]
Prevalence of TPO-Ab >35 U/mL, %	16.7	4.2[c]
Mean maternal fT4 second trimester (SD)	12.1 (2.4)	11.9 (2.3)
Mean maternal TSH second trimester (SD)	1.3 (0.7)	1.2 (0.6)
Mean maternal fT4 third trimester (SD)	12.0 (2.2)	11.4 (2.2)
Mean maternal TSH third trimester (SD)	1.3 (0.7)	1.2 (0.5)
Mean T4 infant heel blood sample (SD)	178.3 (38.5)	179.2 (39.4)
SD of infant heel blood sample compared with all infants who were born that day in Holland (SD)	0.12 (0.9)	0.07 (0.9)

[a] $P < .001$.
[b] This difference is expected, given that case patients and control subjects were defined by this variable.
[c] $P < .01$.

NBAS Cluster Scores

NBAS cluster scores are reported in Table 4. A series of ANOVAs were used to compare case patients and control subjects on each of the cluster scores for the NBAS. A significant group difference emerged for only 1 cluster: the orientation cluster score ($F_{1,189} = 4.19$; $P = .042$). Control subjects scored significantly higher than case patients. The 2 groups did not differ significantly on the remaining cluster scores.

For the next set of analyses, maternal TSH levels in the first trimester were controlled for. The difference on the orientation cluster remained ($F_{1,191} = 3.84$; $P = .052$), whereas there were still no significant differences between case patients and control subjects on the habituation, motor maturity, range of state, regulation of state, autonomic stability, and total reflexes cluster scores.

Maternal Depression and Anxiety

There was no group difference in the prevalence of depression in the third week postpartum as measured by RDC criteria; none of the control subjects met criteria for major depression, although 4 (3.8%) case patients did. Because of those 4 case patients, the analysis was rerun controlling for depression, and the group difference on

TABLE 4 **NBAS Cluster Scores According to Group**

	Case Patients ($N = 108$), Mean Cluster Score (SD)	Control Subjects ($N = 96$), Mean Cluster Score (SD)
Habituation	6.99 (2.29)	7.31 (1.89)
Orientation	5.83 (1.33)	6.20 (1.04)[a]
Motor maturity	4.85 (0.85)	4.94 (0.74)
Range of state	3.16 (0.93)	3.35 (0.91)
Regulation of state	4.89 (1.43)	5.16 (1.36)
Autonomic stability	7.19 (0.80)	7.03 (0.90)
Total reflexes	1.03 (1.06)	0.84 (1.03)

[a] $P < .05$.

the orientation cluster remained significant ($F_{1,191}$ = 4.18; P = .042). Similar results were obtained when meeting criteria for major depression at 24 weeks' gestation (measured by the EPDS; P = .040) was used as a covariate. The control group still scored higher than case patients on the orientation cluster. The groups did not differ significantly in terms of maternal state or trait anxiety as measured at 24 weeks' gestation by the Symptom Check List-90 Anxiety subscale or at 32 weeks' gestation as measured by the STAI.

Predictors of Neonatal Orientation Scores

A multiple regression approach was used to predict the orientation cluster score from various factors related to pregnancy, thyroid functioning, maternal mood, and demographics (Table 5). The overall regression was significant (R^2 = 0.108; $F_{10,160}$ = 1.94; P = .043). Lower orientation cluster scores were associated with lower fT4 levels in the first trimester (P = .024), higher maternal anxiety (P = .028), and younger gestational ages (P = .003). Maternal fT4 levels in the second and third trimesters were not significant predictors of the orientation cluster score.

Because the NBAS has no normative data at present, it was decided to use a 1-SD cutoff generated from the overall sample to examine the proportion of case patients and control subjects who scored below this cutoff on the orientation cluster score. In total, 24 case patients and 7 control subjects scored below the cutoff of 4.8 on the orientation cluster. This difference was significant (χ^2[1, N = 194] = 8.77; P = .003).

A logistic-regression analysis was conducted to determine the best predictors of scores below the 1-SD cutoff on the orientation cluster. The same factors that were used in the multiple regression mentioned previously were used as predictors (Table 6). The overall regression was significant (χ^2[10, N = 171] = 26.50; P = .003). An fT4 concentration in the lowest 10th percentile (<10.4 pmol/L) at 12 weeks' gestation, younger gestational age, and maternal anxiety at 24 weeks' gestation all were related to a low score (below 1 SD of the mean) on the orientation cluster score. None of the other variables listed in Table 5 was related to low orientation cluster scores.

TABLE 5 **Multiple-Regression Results**

	Standardized Coefficients, β	P
Pregnancy-related factors		
Smoking during gestation	−.029	.698
Alcohol use during gestation	−.020	.789
fT4 of lowest 10th percentile at 12 wk gestation	.173	.024
fT4 of lowest 10th percentile at 32 wk gestation	.007	.929
Female child	−.035	.648
Gestational age	.231	.003
Maternal mood state		
Gestational depression at 24 wk	.092	.314
Postpartum major depression (3 wk)	.019	.803
Anxiety at 24 wk	−.202	.028
Demographic factors		
Low educational level for mothers	.004	.953

TABLE 6 **Logistic-Regression Results**

	Odds Ratio	95% Confidence Interval
Pregnancy-related factors		
Smoking during gestation	0.64	0.16–2.56
Alcohol use during gestation	0.59	0.12–3.01
fT4 of lowest 10th percentile at 12 wk gestation	0.17[a]	0.05–0.51
fT4 of lowest 10th percentile at 32 wk gestation	1.02	0.83–1.25
Female child	0.91	0.36–2.30
Gestational age	0.93[a]	0.88–0.98
Maternal mood state		
Gestational depression at 24 wk	0.76	0.11–5.38
Postpartum major depression (3 wk)	0.01	0.01–3.87
Anxiety at 24 wk	1.20[a]	1.02–1.42
Demographic factors		
Low educational level for mothers	1.15	0.29–4.60

[a] $P < .05$.

DISCUSSION

This study confirms continued concerns that low maternal fT4 concentrations in early gestation may pose a threat to fetal brain development. Infants who were born to women with first-trimester fT4 concentrations ≤10th percentile had significantly lower scores on the NBAS orientation index than children of mothers with higher fT4 values. Similarly, regression analysis showed that first-trimester maternal fT4 but not maternal TSH or fT4 later in gestation was a significant predictor of orientation scores. In addition to these statistically significant results, there were some supportive findings, albeit nonsignificant, that were in the expected direction: after controlling for first-trimester maternal TSH levels, case patients and control subjects differed for both the range of state and regulation of state cluster scores ($P < .10$).

These results are in accordance with recent findings by Pop et al[1,2] in which maternal hypothyroxinemia in the first trimester of pregnancy was adversely related to child development. However, the children in these reports were between 10 months and 2 years of age, whereas the present study focused on neonatal behavior at 3 weeks of age. Clearly, the value of having such a short interval between birth and assessment is that the possible impact of psychosocial factors that may interfere with infant development is kept to a minimum. Hence, the current findings of early neurodevelopmental delay, albeit subtle, could be more directly attributable to the neurologic consequences of maternal hypothyroxinemia per se.

The association between first-trimester maternal fT4 and neonatal development may have been mediated by other independent factors. Therefore, several pregnancy- and infant-related factors that are known to affect

infant outcome either were defined as exclusion criteria (eg, gestational age <37 weeks) or were statistically controlled for in the between-group analyses (eg, anxiety, depression). As a result, the between-group comparisons were clear in regard to the predominant impact of first-trimester maternal fT4. Admittedly, though, the regression analyses did show additional correlations between the NBAS orientation scores and both gestational age and anxiety at 24 weeks' gestation.

The association between gestational age and outcome was surprising given that all case patients who were <37 weeks' gestational age were excluded from the analyses. Finding an association between gestational age and early neonatal behavior, even with a time window ranging from 37 weeks' gestation to full term, not only illustrates the significance of abbreviated gestational age as a neonatal risk factor but also emphasizes the sensitivity of the NBAS as a neonatal assessment tool.

The association between anxiety and low scores on the NBAS orientation cluster as found in the current study should be considered in the light of an ongoing debate as to what extent maternal antenatal anxiety constitutes an independent risk factor for compromised neonatal outcome. The results of initial studies have supported the notion of a relationship between maternal antenatal anxiety and neonatal outcome in terms of low birth weight and preterm delivery. However, these studies were targeted mainly at specific risk groups (eg, teenage mothers, mothers of low socioeconomic status) using small sample sizes. Recently, 1 study of a large (n = 1465) population-based sample[20] found no evidence for such a relationship, as neonatal outcome did not deteriorate as a function of maternal antenatal anxiety.

More direct evidence supporting the causal relationships between early maternal hypothyroxinemia and neurodevelopmental outcome comes from Lavado et al.[21] Pregnant rat dams (an animal species that shows the closest similarity to humans with respect to placentation and hence the passage of maternal thyroid hormone to the fetus) were put on a low-iodine diet to produce maternal hypothyroxinemia throughout pregnancy. Neuronal migration into the neocortex was found to be affected in the pups that were born to the hypothyroxinemic dams, resulting in permanent alterations in the cytoarchitecture of the somatosensory cortex and the hippocampus. These findings were confirmed in a recent study by the same research group in which pregnant rats were treated with a goitrogen for 3 days at the start of the neocorticogenesis.[22] The resulting mild and transient hypothyroxinemia resulted in similar cytoarchitectural changes in the somatosensory cortex and the hippocampus as found by Lavado et al[21] but this time with a more strictly controlled protocol. As pointed out by Morreale de Escobar et al,[23] these results, when extrapolated to humans, define the first trimester of pregnancy as a critical window in which subtle insufficiency of fT4 may interfere with normal brain development, thereby constituting a potential danger for neurodevelopment.

An important issue worth commenting on concerns the type of assessment used in this study: the NBAS as a measure of early neonatal development. There no doubt is a price to be paid for such an early neonatal follow-up, as results often have limited predictive value for future developmental outcome. This is because early neonatal behavior is inherently unstable and thus difficult to assess in a consistent manner. However, the NBAS, as shown in several studies, has considerable predictive power, especially with regard to its ability to predict neurobehavioral outcome within the first year of life.[9] Although the literature is less clear about the long-term predictive power of the NBAS,[8,24] the fact that the current results at 3 weeks of age are in accordance with the findings of Pop et al[1,2] obtained at 1 and 2 years of age do suggest the start of unfavorable developmental pathways in infants who are born to hypothyroxinemic mothers. Clearly, what is important to assess is whether the neurodevelopmental problems noted in the first 2 years of life persist into childhood and adolescence. So far, there has been only 1 long-term prospective follow-up study[3]: children who were born to healthy mothers from a moderately iodine-deficient area were compared with control children who were born to healthy mothers from an iodine-sufficient area. By the time children had reached the age of 10 years, 11 (68.7%) of 16 children from the iodine-deficient area had developed attention-deficit/hyperactivity disorder (ADHD) versus none of the children who were born in the iodine-sufficient area. Most interesting for the purpose of the present study, however, was the finding that the overall prevalence of ADHD in the iodine-deficient area was significantly higher ($P < .01$) in children who were born to mothers who had developed hypothyroxinemia with normal TSH, presumably related to iodine deficiency early in gestation. These results, although awaiting confirmation from larger cohort studies, are intriguing as they signal, to our knowledge for the second time in the literature, an association between thyroid deficiency during pregnancy and ADHD. The first time this relationship was reported involved a study by Hauser et al[25] in which 70% of children who had a diagnosis of generalized resistance to thyroid hormone were found to have ADHD. Which mechanisms both (iodine-induced) maternal hypothyroxinemia and generalized resistance to thyroid hormone share that could explain the postnatal development of ADHD in both disorders, however, remains a matter of speculation and constitutes an important question for additional research. An additional reason that the connection between first-trimester maternal hypothyroxinemia and childhood ADHD is intriguing relates to the fact that the current finding of low scores on the orientation cluster of the NBAS could be interpreted as an early marker of

attention difficulties. For answering this question, the population as seen in the current study should be reassessed for attention difficulties and ADHD symptoms at school age.

CONCLUSIONS

The current study is one in a sequence of recent outcome studies[1,2,26] reporting on the relationship between maternal hypothyroxinemia in early pregnancy and subsequent child development. The net result of this work has been conclusive as repeatedly confirming that low first-trimester fT4 concentrations in seemingly healthy pregnant women put children at risk for future neurodevelopmental difficulties. Given these findings, the field thus is confronted with the question of whether the magnitude of the problems would justify the implementation of maternal fT4-screening programs.

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