The New England Journal of Medicine

VOLUME 341 AUGUST 19, 1999 NUMBER 8

MATERNAL THYROID DEFICIENCY DURING PREGNANCY AND SUBSEQUENT NEUROPSYCHOLOGICAL DEVELOPMENT OF THE CHILD

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ABSTRACT

Background When thyroid deficiency occurs simultaneously in a pregnant woman and her fetus, the child's neuropsychological development is adversely affected. Whether developmental problems occur when only the mother has hypothyroidism during pregnancy is not known.

Methods In 1996 and 1997, we measured thyrotropin in stored serum samples collected from 25,216 pregnant women between January 1987 and March 1990. We then located 47 women with serum thyrotropin concentrations at or above the 99.7th percentile of the values for all the pregnant women, 15 women with values between the 98th and 99.6th percentiles, inclusive, in combination with low thyroxine levels, and 124 matched women with normal values. Their seven-to-nine-year-old children, none of whom had hypothyroidism as newborns, underwent 15 tests relating to intelligence, attention, language, reading ability, school performance, and visual–motor performance.

Results The children of the 62 women with high serum thyrotropin concentrations performed slightly less well on all 15 tests. Their full-scale IQ scores on the Wechsler Intelligence Scale for Children, third edition, averaged 4 points lower than those of the children of the 124 matched control women ($P=0.06$); 15 percent had scores of 85 or less, as compared with 5 percent of the matched control children. Of the 62 women with thyroid deficiency, 48 were not treated for the condition during the pregnancy under study. The full-scale IQ scores of their children averaged 7 points lower than those of the 124 matched control children ($P=0.005$); 19 percent had scores of 85 or less. Eleven years after the pregnancy under study, 64 percent of the untreated women and 4 percent of the matched control women had confirmed hypothyroidism.

Conclusions Undiagnosed hypothyroidism in pregnant women may adversely affect their fetuses; therefore, screening for thyroid deficiency during pregnancy may be warranted. (N Engl J Med 1999;341:549-55.)

THE link between hypothyroidism caused by iodine deficiency during pregnancy and mental retardation in the offspring has been recognized for nearly 100 years.[1] Iodine deficiency is associated with thyroid deficiency in both mother and fetus,[2] a situation that makes it impossible to determine whether the mental retardation of the fetus is due to maternal hypothyroidism or both maternal and fetal hypothyroidism. In developed countries, chronic autoimmune thyroiditis is the most common cause of hypothyroidism among women in their childbearing years. Antibodies responsible for compromising maternal thyroid function can cross the placenta and, in some instances, compromise fetal and neonatal thyroid function.[3-8] One such antibody, the thyrotropin-receptor–blocking antibody, has been implicated in cases of transient congenital hypothyroidism that were identified by screening programs for newborns.[9]

In 1969, Man and Jones suggested that mild maternal hypothyroidism alone was associated with lower IQ levels in the offspring; their study involved a cohort of 1349 children, and measurements of serum butanol extractable iodine were used to distinguish between euthyroidism and hypothyroidism in women.[8] A study by Matsuura and Konishi in 1990 documented that fetal brain development is adversely affected when both the mother and fetus have hypothyroidism caused by chronic autoimmune thyroiditis.[10] In such cases, transient neonatal hypothyroidism is present.

In an earlier, population-based survey of 2000

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pregnancies, we measured serum thyrotropin concentrations during the second trimester.[11] The concentrations were high (above 6 mU per liter) in 49 of the women, of whom 6 (3 per 1000) had low serum free thyroxine concentrations. If a lowering of the IQ levels of the offspring were to occur sufficiently often in association with this degree and frequency of maternal thyroid deficiency, then systematically determining the thyroid status of all women before or very early in pregnancy might be justified. The aim of the current study was to determine whether undetected or inadequately treated maternal thyroid deficiency during pregnancy is associated with lower IQ scores in the offspring in the absence of neonatal hypothyroidism.

METHODS

The Foundation for Blood Research administers a statewide, second-trimester prenatal serum screening program for open neural-tube defects and Down's syndrome in Maine.[12,13] Aliquots of serum that remain after screening are routinely coded and stored at −20°C. Outcome information is available through a contract with the state's Bureau of Vital Records. The current study cohort was limited to women with viable singleton pregnancies, who were screened between January 1987 and March 1990, and their infants whose birth weight was at least 1500 g. The serum from the mothers was shipped to the New England Newborn Screening Program in Boston, where serum thyrotropin was measured. Samples from 25,216 women were analyzed in five batches over a two-year period.

Selection of Women with Hypothyroidism and Control Subjects

We recruited women with hypothyroidism during pregnancy, as determined by a high serum thyrotropin concentration, without regard to treatment status, and we tested their children between March 1996 and December 1997. We contacted 55 of the 75 pregnant women with serum thyrotropin concentrations at or above the 99.7th percentile of the values for all the pregnant women; 47 (85 percent) agreed to participate. In 2 of the 75 pregnancies, the women were enrolled through a previous pregnancy. Of the 18 women not contacted, 3 had moved to another state, 1 had died, and for 1, the child was a ward of the state. The remaining 13 were not contacted because of limited funds. At the urging of a grant review panel, we recruited 18 more women to represent a range of milder cases, defined by a serum thyrotropin concentration between the 98th and 99.6th percentiles, inclusive, and a serum thyroxine concentration below 7.75 μg per deciliter (99.7 nmol per liter). To identify this second subgroup, we measured serum thyroxine concentrations in 247 pregnant women with serum thyrotropin concentrations between the 98th and 99.7th percentiles. Fifteen of the 18 women identified (83 percent) agreed to participate. After recruitment, we measured thyroxine, free thyroxine, and antithyroid peroxidase antibodies in the original serum samples from all women in the study.

For each woman with hypothyroidism, we identified potential control subjects who had serum thyrotropin concentrations below the 98th percentile and who were matched according to the following criteria: mother's age at delivery (within one year), number of years of education of the mother (within one year), gestational age at the time of sampling (same completed week), duration of storage of serum sample (within one month), and sex of the child. From this group, two women were randomly selected and recruited for each woman with hypothyroidism. Additional matched control women were available from the same list, if one initially declined participation.

The protocols for the additional assays and the follow-up study were approved by the institutional review board at the Foundation for Blood Research. Enrollment began with a telephone call to the woman and a letter describing the study. Then an appointment was arranged, at which informed consent was requested and, if consent was granted, testing was performed on the child. The neuropsychological test results were provided to the family within one month after the child's testing was completed.

At the end of the study, we contacted the women with hypothyroidism and the matched control women again to determine whether hypothyroidism had been clinically diagnosed since the pregnancy in those who had not received a diagnosis of hypothyroidism at the time of pregnancy. The contact was initially by a letter, which also included information about the thyrotropin concentrations in the stored serum samples. The letter was followed by a telephone call, during which a questionnaire was administered and a blood test for measuring thyrotropin was offered. For those who agreed to be tested, blood spots were collected on filter paper by a finger prick.

Study Procedures

We collected standardized information about socioeconomic status and medical history from all women enrolled in the study, using the Four Factor Index of Social Status (the Hollingshead score).[14] Each woman and her husband or partner were assigned an education code ranging from 1 (corresponding to less than seven years of schooling) to 7 (corresponding to graduate or professional training) and an occupation code ranging from 1 (e.g., "farm worker") to 9 (e.g., "higher executive"). Each couple's individual education scores were multiplied by 3, the occupation scores were multiplied by 5, and the two values were then added together. The final score was the average of the scores of the woman and her partner. When one partner was not employed, the final score was taken to be the score of the employed partner. The woman was also asked whether her child had repeated a grade and about her child's school performance, including whether the child had had learning problems or other difficulties in school.

Neuropsychological testing of the women's children included assessment of intelligence, attention, language, reading ability, school performance, and visual–motor performance. One of two certified psychologists performed the testing, and the project's consulting psychologist supervised the testing and rescored the tests. The staff involved in the neuropsychological testing did not know whether the children's mothers were women with hypothyroidism or control women. Intelligence was measured with use of the Wechsler Intelligence Scale for Children, third edition,[15] the most widely used intelligence test. This test provides a full-scale IQ score and subscale scores (range, 40 to 160) for verbal skills, performance, and freedom from distractibility. To measure hearing deficits in the children, the staff administered subtests on word discrimination and word articulation from the Test of Language Development, second edition[16] (range of scores, 1 to 20). We used the norms for children 8 years 11 months of age, because the version for older children did not have scales for word discrimination or articulation. The Peabody Individual Achievement Test, revised (PIAT-R),[17] was used to measure reading recognition and reading comprehension (range of scores, 55 to 145).

The staff administered the Conners' Continuous Performance Test to measure sustained vigilance and attention,[18] using a computer program that employs a go–no go paradigm (range of overall index score, 1 to 30). The Developmental Test of Visual-Motor Integration[19] was administered to provide a standard measure of visual perception and fine motor skills (range, 55 to 145). The grooved pegboard test[20] was administered to assess visual–motor coordination and dexterity by measuring the time required to insert pegs with both the preferred and nonpreferred hand (for this test, it is recommended that normative data be derived from control children in the study).

Assay Methods

We measured serum thyrotropin using a coated-tube radioimmunoassay (Diagnostic Products, Los Angeles). Thyrotropin was measured on dried blood spots with a time-resolved immunofluorometric assay (Wallac Oy, Turku, Finland). Serum thyroxine was measured with a solid-phase radioimmunoassay[21] or a time-resolved immunofluorometric assay (Wallac Oy); serum free thyroxine was measured with a time-resolved immunofluorometric assay. We measured serum antithyroid peroxidase antibodies using the Kalibre enzyme-linked immunosorbent assay (Kronus, San Clemente, Calif.) (normal concentration, ≤2 U per milliliter).

Statistical Analysis

The serum thyrotropin, thyroxine, and free thyroxine concentrations were logarithmically transformed before analysis. We used geometric means and logarithmic standard deviations to summarize the results (after censoring seven measurements that were more than 3 SD above or below the group mean). We compared categorical variables using an exact test of significance or odds ratios, and we compared continuous variables using the Student's t-test. When necessary, the t-test was modified to allow for unequal variances. The primary analysis was of all 62 women with hypothyroidism and all 124 control women; we preserved matching by comparing the result from the child of a woman with hypothyroidism with the average result from the two matched control children. No adjustment was made for multiple comparisons. All statistical tests were two-sided.

RESULTS

According to records from the New England Newborn Screening Program, none of the children of the 62 women with high serum thyrotropin concentrations while pregnant were identified as having transient or permanent congenital hypothyroidism. The distribution of serum thyrotropin concentrations in the 62 women with hypothyroidism and the 124 matched control women is shown in Figure 1. Fifteen of the 62 women with hypothyroidism reported that they had received a diagnosis of hypothyroidism before the pregnancy, and 14 of these 15 women were treated for hypothyroidism during that pregnancy. Two of the control women reported that they had had hypothyroidism in the distant past but were never treated.

Demographic and pregnancy-related information about the women with hypothyroidism and the control women and the remainder of the cohort from which the women were selected is shown in Table 1. There were no significant differences between the women with hypothyroidism and the control women for any of the variables. Four of the variables were used for matching: number of years of education of the mother, mother's age at delivery, gestational week when the serum sample was obtained, and sex of the child. The use of the number of years of education as a matching variable was intended to control for socioeconomic status. To assess the effectiveness of this matching, we used the Hollingshead score as an additional measure. This score took into account the mother's educational level and occupation and also the father's educational level and occupation. The mean Hollingshead score in the women with hypothyroidism was one point lower than that in the control women ($P=0.43$). The study children were similar in most respects to the remainder of the cohort, but more were girls, their mothers were older, a higher percentage of their mothers were married, and more of their mothers were multiparous.

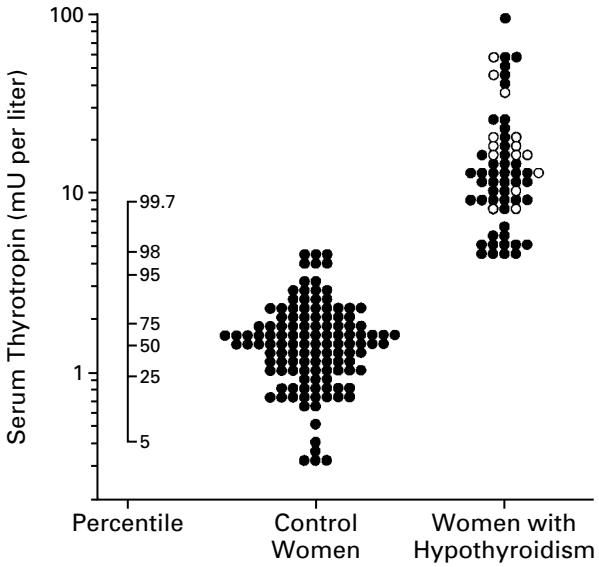

Figure 1. Distribution of Serum Thyrotropin Concentrations during Pregnancy in the 62 Women with Hypothyroidism and the 124 Matched Control Women.

Open circles indicate the 14 women who were treated for hypothyroidism during the pregnancy under study. Selected percentiles are shown for the entire cohort of 25,216 pregnant women.

The results of the measurements of thyroid function in the women with hypothyroidism and the control women during pregnancy are shown in Table 2. As expected, according to the selection process, the women with hypothyroidism had higher serum thyrotropin and lower serum thyroxine concentrations.

The children's neuropsychological test scores are shown in Table 3. All the children were between seven and nine years of age when tested, and the child of a woman with hypothyroidism and his or her matched control children were tested at the same age. The analysis preserved matching for each of the tests by expressing the relative performance between case and control children as a mean difference (the value in the case child minus the average of the values in the two control children). The case children performed less well on all the tests; 2 of the 15 differences reached statistical significance ($P<0.05$).

The results in the children were then grouped according to whether the mother's hypothyroidism was treated during the pregnancy (Table 4). The larger deficits in performance were found among the children of the untreated women; their scores for all 15

TABLE 1. CHARACTERISTICS OF THE STUDY WOMEN, THE REMAINDER OF THE COHORT, AND THEIR CHILDREN.*

CHARACTERISTIC	WOMEN WITH HYPOTHYROIDISM (N=62)	CONTROL WOMEN (N=124)	REMAINDER OF THE COHORT (N=25,030)
Women			
No. of years of education	13.3±1.8	13.3±1.8	13.0±2.0
Hollingshead score			
Mean	45±10	46±8	Not available
Range†	26–63	27–62	Not available
Age at delivery (yr)	28±4	28±4	26±5
Weight at second trimester (lb)‡	154±29	145±28	148±30
Smoked cigarettes during pregnancy (%)	15	17	21
Married at the time of delivery (%)	89	92	83
Gestational month of first prenatal visit	2.5±0.8	2.3±0.8	2.4±0.9
Multiparous (%)	73	65	51
Gestational week when serum obtained	17±1	17±1	17±1
Children			
Male:female ratio	1:1.4	1:1.4	1:0.9
Birth weight (g)			
Mean	3601±493	3532±471	3495±504
Range	2590–4763	1870–5075	1503±6039
Gestational week at delivery	40±2	40±2	40±2
Five-minute Apgar score	9±1	9±1	9±1
Median no. of days in hospital after birth	2.1	2.7	Not available
Age at testing (yr)	8±1	8±1	Not applicable

*Plus–minus values are means ±SD.

†One outlying value of 19 in a woman with hypothyroidism is not shown, but data for this woman are included in the other analyses.

‡To convert values for weight to kilograms, multiply by 0.45.

TABLE 2. MEASUREMENTS OF THYROID FUNCTION IN THE STUDY WOMEN DURING PREGNANCY.*

VARIABLE	WOMEN WITH HYPOTHYROIDISM (N=62)	CONTROL WOMEN (N=124)
Serum thyrotropin concentration (mU/liter)	13.2±0.3†	1.4±0.2
Serum thyroxine concentration (μg/dl)	7.4±0.1†	10.6±0.1
Serum free thyroxine concentration (ng/dl)	0.71±0.1†	0.97±0.07
High serum concentrations of antithyroid peroxidase antibodies (%)‡	77†	14

*Plus–minus values are geometric means ± the logarithmic SD. To convert values for serum thyroxine and free thyroxine to nanomoles per liter and picomoles per liter, respectively, multiply by 12.87.

†$P<0.001$ for the comparison with the control women.

‡Concentrations of more than 2 U per milliliter were considered high.

tests were worse than those of the control children (their scores for 9 tests were significantly worse). Their average full-scale IQ score on the Wechsler Intelligence Scale for Children, third edition, was 7 points lower, and 19 percent of the children of women with hypothyroidism had an IQ score of 85 or lower, as compared with 5 percent of the control children. The test scores of the children whose mothers were being treated (albeit inadequately) during pregnancy were similar to those of the control children in most categories, even though the serum thyrotropin concentrations were at or above the 99.7th percentile in 12 of the 14 women. The serum thyroxine and free thyroxine concentrations in the 14 treated women were very similar to the concentrations in the 48 women with undiagnosed hypothyroidism.

The mean Hollingshead scores for the women who received treatment (48) and those who were not treated (44, or 45 if one low outlier was removed) were similar, and these scores were similar to those of the control women (46). A linear regression analysis of the full-scale intelligence score of the control children against the Hollingshead score of the control women indicated that there was an increase in intelligence of 0.4 point (95 percent confidence interval, 0.2 to 0.7) for each 1-point increase in the Hollingshead score ($P=0.002$). Thus, the 2-point-higher mean Hollingshead score of the treated women as compared with that of the control women could account for a 0.8-point-higher IQ score of their children as compared with the control children, and the 2-point-lower mean Hollingshead score of the untreated women could account for a 0.8-point-lower IQ score. Therefore, differences in maternal intelli-

TABLE 3. NEUROPSYCHOLOGICAL TEST SCORES AMONG THE CHILDREN OF WOMEN WITH HYPOTHYROIDISM DURING PREGNANCY AS COMPARED WITH THE CHILDREN OF MATCHED CONTROL WOMEN.*

TEST	CHILDREN OF WOMEN WITH HYPOTHYROIDISM (N=62)	CONTROL CHILDREN (N=124)	MEAN DIFFERENCE†	P VALUE
Intelligence				
WISC-III full-scale IQ score	103±15	107±12	−4.1±2.1	0.06
WISC-III full-scale IQ score ≤85 (%)	15	5	3 (1–8)	0.08
Attention				
WISC-III freedom-from-distractibility score	98±13	102±13	−3±2	0.08
Continuous Performance Test score >8 (%)‡	37	19	3 (1–5)	0.01
Language				
Test of Language Development score				
Word articulation	10.1±2.5	10.2±2.4	−0.2±0.4	0.80
Word discrimination	10.5±2.9	11.4±2.4	−0.9±0.4	0.04
WISC-III verbal IQ score	103±16	107±16	−4.2±2.2	0.06
Reading ability and school performance				
PIAT-R reading-recognition score	96±14	100±16	−3.8±2.5	0.14
PIAT-R reading-comprehension score	98±17	101±17	−3.0±2.6	0.20
School difficulties and learning problems (%)‡	23	11	2 (1–6)	0.06
Repeated a grade (%)‡	8	4	2 (0.6–7)	0.40
Visual–motor performance				
Score on Developmental Test of Visual–Motor Integration	96±13	97±11	−1±2	0.40
WISC-III performance IQ score	101±16	105±13	−4±2	0.08
Pegboard-test score				
Dominant hand‡	86±16	83±15	3±2	0.10
Nondominant hand‡	94±22	89±16	5±3	0.10

*Plus–minus values are means ±SD, except as indicated. WISC-III denotes Wechsler Intelligence Scale for Children, third edition, and PIAT-R Peabody Individual Achievement Test, revised.

†The difference is the value in the case child minus the average of the values in the two control children. The values shown are the means (±SE) of the individual differences in each matched set. For categorical variables, this column provides the odds ratio for the children of the women with hypothyroidism as compared with the control children and (in parentheses) the 95 percent confidence interval.

‡A higher score or percentage indicates more problems.

gence or socioeconomic status might account for only a small fraction of the differences shown in Table 4.

At the end of the study, we telephoned the women who were not known to have hypothyroidism during pregnancy to determine whether hypothyroidism had been clinically diagnosed subsequently; 120 of the 124 control women and 45 of the 48 case women responded. Of those who responded, 5 (4 percent) of the control women and 26 (58 percent) of the women with undiagnosed hypothyroidism during pregnancy were now known to have hypothyroidism (odds ratio, 31; 95 percent confidence interval, 10 to 108). The median interval between pregnancy and clinical diagnosis was 5 years (range, 1 to 10). A total of 99 of the 115 control women who identified themselves as having normal thyroid function agreed to undergo follow-up testing; all the thyrotropin concentrations in the blood spots were below 10 mU per liter. Fifteen of the 19 women with hypothyroidism during pregnancy who identified themselves as having normal thyroid function agreed to be tested; 3 had high thyrotropin concentrations (14, 89, and 243 mU per liter). Altogether, 4 percent of the control women and 64 percent of the women with undiagnosed hypothyroidism during pregnancy had confirmed hypothyroidism at the time of follow-up about 11 years later.

DISCUSSION

The current study shows that hypothyroidism in pregnant women can adversely affect their children's subsequent performance on neuropsychological tests. Decreases in performance can occur even when the pregnant woman's hypothyroidism is mild and probably asymptomatic. The presence of high serum concentrations of antithyroid peroxidase antibodies in 77 percent of the women with hypothyroidism indicates that chronic autoimmune thyroiditis was the most frequent cause of hypothyroidism in these women. Treating maternal hypothyroidism during pregnancy appears to be beneficial for the child, even when treatment is inadequate as determined by measurements of thyrotropin.

If our findings were to be confirmed, and routine screening for hypothyroidism during pregnancy were

TABLE 4. NEUROPSYCHOLOGICAL TEST SCORES AMONG THE CHILDREN OF WOMEN WITH HYPOTHYROIDISM DURING PREGNANCY AS COMPARED WITH THE CHILDREN OF MATCHED CONTROL WOMEN, STRATIFIED ACCORDING TO WHETHER THE HYPOTHYROIDISM WAS BEING TREATED.*

TEST	CHILDREN OF TREATED WOMEN WITH HYPOTHYROIDISM (N=14)	P VALUE†	CHILDREN OF UNTREATED WOMEN WITH HYPOTHYROIDISM‡ (N=48)	P VALUE§	CONTROL CHILDREN (N=124)
Intelligence					
WISC-III full-scale IQ score	111	0.20	100	0.005	107
WISC-III full-scale IQ score ≤85 (%)	0	0.90	19	0.007	5
Attention					
WISC-III freedom-from-distractibility score	103	0.80	97	0.03	102
Continuous Performance Test score >8 (%)¶	50	0.01	33	0.04	19
Language					
Test of Language Development score					
Word articulation	10.5	0.60	10.0	0.6	10.2
Word discrimination	11.4	0.90	10.3	0.02	11.4
WISC-III verbal IQ score	111	0.30	101	0.006	107
School performance					
PIAT-R reading-recognition score	101	0.80	95	0.05	100
PIAT-R reading-comprehension score	105	0.40	96	0.09	101
School difficulties and learning problems (%)¶	29	0.08	21	0.09	11
Repeated a grade (%)¶	7	0.50	8	0.3	4
Visual–motor performance					
Score on Developmental Test of Visual–Motor Integration	102	0.30	94	0.1	97
WISC-III performance IQ score	109	0.30	99	0.01	105
Pegboard-test score					
Dominant hand¶	79	0.40	88	0.06	83
Nondominant hand¶	87	0.70	96	0.04	89

*WISC-III denotes Wechsler Intelligence Scale for Children, third edition, and PIAT-R Peabody Individual Achievement Test, revised.

†The P values are for the comparison of the children of the treated women with the children of the untreated women.

‡One woman received treatment before, but not during, the pregnancy under study.

§The P values are for the comparison of the children of the untreated women with the children of the control women.

¶A higher score or percentage indicates more problems.

to be instituted, what might the benefits be? The main benefit — an increase of approximately 4 points in IQ scores — would occur in the children of women with serum thyrotropin concentrations at or above the 98th percentile. A secondary benefit would be reduced morbidity for women who were systematically identified and treated. The present study shows that a large percentage of pregnant women with high serum thyrotropin concentrations subsequently have clinically apparent hypothyroidism. Because the symptoms associated with hypothyroidism are nonspecific, the condition can be difficult to diagnose, as reflected by the five-year median time to diagnosis in the women.

Before about 12 weeks' gestation, when the fetal thyroid gland becomes active, the mother is the sole source of thyroid hormones. Maternal thyroid sufficiency might therefore be most important in the first trimester. This theory is supported by a recent study in a small cohort of 220 healthy infants in which lower maternal serum free thyroxine concentrations at 12 weeks' gestation were associated with impaired psychomotor development at 10 months of age.[22] However, the later stages of fetal brain development involve neuronal migration and organization. Since these processes are responsible for functions measured by the neuropsychological tests used in the present study, thyroid insufficiency beyond the first trimester is also likely to have adverse effects.[23] In rats, triiodothyronine receptors are first detected in the brain in the second trimester, and the induction by triiodothyronine of enzymes that are important in

nervous-system development begins late in fetal development.[24] The current study documents a relatively long average interval between early biochemical evidence of hypothyroidism and clinical diagnosis, a finding that suggests that ongoing maternal health problems might hinder the child's development after birth. In the absence of objective data, the most prudent policy would be to identify and treat maternal hypothyroidism as early in pregnancy as possible, keeping in mind that the need for thyroxine increases during pregnancy.[25]

We conclude that systematic screening for hypothyroidism early in pregnancy may be worthwhile, even when the degree of deficiency is mild and does not cause immediate clinical manifestations in the woman. If routine screening were to be introduced, the most conservative policy would be to perform testing at the first prenatal visit, preferably in the first trimester. Follow-up of women with positive screening results would need to be prompt, so that treatment could begin quickly.

Supported by grants from the Thrasher Research Fund (02810-7), Knoll Pharmaceutical Company (SYN-0398-09), and the National Institute of Child Health and Human Development (supplement to RO1-HD31183).

We are indebted to Professor Nicholas J. Wald of the Wolfson Institute of Preventive Medicine, University of London, for statistical advice and consultation; to Ms. Sonia Nelson for helping to locate study participants; and to Ms. Penny Guerin for her assistance in scheduling and data entry.

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CORRECTION

Maternal Thyroid Deficiency during Pregnancy and Subsequent Neuropsychological Development of the Child

To the Editor: Haddow et al. (Aug. 19 issue)[1] suggest that screening pregnant women for hypothyroidism by measuring serum thyrotropin may be worthwhile and that treating women with serum thyrotropin concentrations at or above the 98th percentile could lead to ``an increase of approximately 4 points in IQ scores'' in their children. However, the results of their study should be interpreted with caution. The difference in full-scale IQ scores between children whose mothers had hypothyroidism during pregnancy and the children of matched control women is not statistically significant (103 vs. 107, P=0.06), and the results of only 2 of the 13 neuropsychological tests were significantly worse in the children of the women with hypothyroidism during pregnancy.

Many factors have a role in the neuropsychological development of children, apart from maternal thyroid function. We are not given details of the women's marital status after delivery, even though parental separation and divorce or serial monogamy on the part of one parent can impair a child's development.[2,3] The effect of siblings, though variable, should also be considered[2,4]; 73 percent of the women who had hypothyroidism during pregnancy were multiparous, as compared with 65 percent of the control women and 51 percent of the remaining cohort of pregnant women. Maternal thyroid status may be important in the development of a healthy child, but on the basis of the data presented by Haddow et al., it is not clear that widespread screening is justified.

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To the Editor: The paper by Haddow et al. has drawn attention to an often disregarded and possibly preventable cause of poor neuropsychological development in children — namely, hypothyroidism in pregnant women. Is the principal underlying factor in this poorer development maternal hypothyroidism, as defined by a high serum thyrotropin concentration, or maternal hypothyroxinemia itself, whether or not serum thyrotropin concentrations are high? In the study by Haddow et al., the children were selected according to the mothers' serum thyrotropin concentrations in the second trimester. The control children may therefore have included children whose mothers had hypothyroxinemia, which might have decreased the magnitude of the differences in neuropsychological development in the two groups, which was smaller than that reported in other studies.[1,2,3]

In those studies, low maternal serum thyroxine or free thyroxine concentrations in the first or second trimester were correlated with poor postnatal neuropsychological development. During the first trimester, maternal thyroxine is the only source of thyroid hormone for the fetus. Normal maternal serum triiodothyronine concentrations, which mitigate hypothyroidism in pregnant women, do not prevent poorer cognitive development in their infants.[2] In preterm infants, who are prematurely deprived of maternal thyroxine and iodine, poor cognitive development and an increased risk of cerebral palsy are also correlated with the presence of perinatal hypothyroxinemia, not with high serum thyrotropin concentrations,[4] indicating the continuing importance of thyroxine for later stages of brain development.

As Utiger noted in the accompanying editorial,[5] an inadequate iodine intake may be a crucial factor contributing to the frequency of hypothyroidism during pregnancy, and it is also a crucial determinant of relative hypothyroxinemia. In Brussels, Belgium (with a median urinary iodine excretion of 56 μg per liter), 30 percent of pregnant women had low serum free thyroxine values in the first trimester and 2.3 percent had high serum thyrotropin values.[6] Even in Madrid, an area where mild iodine deficiency is prevalent (median urinary iodine excretion, 90 μg per liter), 20 percent of pregnant women had first-trimester serum free thyroxine values below the 10th percentile of values for women with adequate iodine intake. These data support Utiger's recommendation that measures be taken to ensure that pregnant women have an adequate intake of iodine (>200 μg per day). Thyroxine therapy should be limited to pregnant women who have persistent hypothyroxinemia.

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To the Editor: Haddow et al. suggest that screening for thyroid deficiency during pregnancy may be warranted. We would like to report the results of screening for thyroid disease among pregnant women in Sapporo, Japan.

Sapporo has a population of 1.8 million, and 16,000 infants are born every year. Our screening program for thyroid function in early pregnancy was initiated in June 1986 and consists of measurements of serum thyrotropin, free thyroxine, and antithyroid peroxidase and antithyroglobulin antibodies in blood specimens collected on filter paper. By the end of March 1997, 70,632 pregnant women had been screened. At first, only 11 percent of pregnant women agreed to testing, but the percentage has been in the range of 45 to 55 percent since 1991. The mean (±SD) age of the women was 28±5 years, and the specimens were collected at 12±5 weeks of gestation.

The overall rate of reexamination because of abnormal results was 2.0 percent (1409 of 70,632 women), and 671 women (1.0 percent) were referred for further medical evaluation. Among these 671 women, 171 (25.5 percent) had hyperthyroidism (162 had Graves' disease, and 9 had other causes of hyperthyroidism) and 102 (15.2 percent) had hypothyroidism (67 had chronic autoimmune thyroiditis, and 35 had other causes of hypothyroidism). The overall incidence of the disorders was 1 in 413 and 1 in 692, respectively. In addition, 220 women (32.8 percent) had transient hyperthyroxinemia, and 121 women (18.0 percent) had low serum thyrotropin concentrations. None of the pregnant women with thyroid disease had symptoms or signs of thyroid dysfunction.

We subsequently obtained the results of neonatal screening for congenital hypothyroidism in the infants whose mothers had been referred for medical evaluation during pregnancy. We found six cases of transient hypothyroidism (incidence, 1 in 11,772), eight cases of transient hypothyroxinemia (incidence, 1 in 8829), three cases of neonatal Graves' disease, and one case of transient subclinical hypothyroidism. Thyroid function was not controlled during pregnancy in the mothers of these infants, and all the infants whose mothers' thyroid disorder was well controlled during pregnancy were normal. (The overall incidence of congenital hypothyroidism as detected by neonatal screening is about 1 in 3000 in Sapporo.)

The frequency of thyroid disease among pregnant women may be lower in Japan than elsewhere.[1] Nonetheless, we believe that our voluntary program of screening for thyroid disease in early pregnancy is useful because women who have thyroid dysfunction are so often asymptomatic.

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1. Utiger RD. Maternal hypothyroidism and fetal development. N Engl J Med 1999;341:601-602.

To the Editor: Haddow et al. provide evidence of an important link between hypothyroidism in early pregnancy and a delay in neuropsychological development among children at the ages of seven to nine years. In the accompanying editorial, Utiger discussed the importance of thyroid hormones for fetal and infant development and pointed out that thyroid deficiency in most pregnant women is presumed to be due to autoimmune thyroid disease. He noted that hypothyroidism can also be caused by iodine deficiency, a preventable condition, and recommended that the dietary intake of iodine be increased in this country through vitamin supplements, by increasing the amount of iodine in salt, and by adding iodine to other foods. We are concerned that our study of iodine nutrition in the United States,[1] which revealed a significant decrease in the urinary concentration of iodine between the period from 1971 to 1974 and the period from 1988 to 1994, was the basis for that recommendation. The median urinary iodine concentration in the period from 1988 to 1994 was 145 μg per liter, which reflects an intake that exceeds the recommended daily allowance.[2] We could not, therefore, conclude from our study that iodine intake in the United States was inadequate. Rather, we concluded that iodine intake had fallen over a 20-year period and should be monitored care-

fully. As important as it is to ensure that iodine intake is adequate, it is equally important to avoid excessive intake of iodine. Excessive iodine intake can increase the risk of hypothyroidism through several mechanisms, including the development of autoimmune thyroid disease.[3] Given this risk, we do not believe that a general recommendation to increase iodine intake in this country in order to ensure that pregnant women have an adequate intake is prudent.

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The authors reply:

To the Editor: In our study, the seven-to-nine-year-old children of 62 women who had hypothyroidism during pregnancy performed less well on all the administered neuropsychological tests than did the control children. It is highly unlikely that this consistently poorer performance would be due to chance, even though most of the differences in individual test scores were not statistically significant. Performance problems were limited to the 48 children of women whose hypothyroidism was not treated during pregnancy. In this group, the average full-scale IQ score was 7 points lower than that of the control children, 19 percent of the scores were 85 or less (as compared with 5 percent in the control children), and the scores for the majority of tests were significantly poorer. It is this group that deserves the most attention. Herzmann and Torrens suggest several other variables that might influence neuropsychological performance. Table 1 of our study includes an extensive comparison of the women with hypothyroidism and the control women, including an assessment of their socioeconomic status at the time of testing. Given the similarities between the two groups, additional variables are not likely to explain our findings.

Morreale de Escobar and Escobar del Rey raise the point that maternal serum thyroxine concentrations appear to be an important factor in fetal neural development, even in pregnant women with normal serum thyrotropin concentrations. To address their comment, we performed a regression analysis to determine the relation between full-scale IQ scores in the 124 control children and serum free thyroxine values in their mothers. The correlation coefficient was 0.14, with a 10-point gain in IQ predicted from the low end to the high end of the range of serum free thyroxine values (P=0.13). A larger data set would be needed to determine whether this is a chance finding, but the trend in values supports their point.

We thank Fukushi and colleagues for providing the data on prenatal screening for thyroid disease in Sapporo. We agree with Hollowell and colleagues that excessive iodine intake during gestation can have adverse effects on thyroid function.

There was an error in Table 4 of our paper: the first column of P values is for the comparison of the children of the treated women with the children of the control women, not the children of the untreated women.

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Dr. Utiger replies:

The decrease in median urinary iodine excretion of more than 50 percent in the United States between the period from 1971 to 1974 and the period from 1988 to 1994 that was reported by Hollowell et al.[1] was indeed the basis for my recommendation that dietary iodine intake be increased. In their population-based study, not only did 15 percent of women of childbearing age studied in the period from 1988 to 1994 have urinary iodine values of less than 50 µg per liter, but also the median value in these women was 127 µg per liter, and the median value in men of all ages was 160 µg per liter. Urinary iodine values slightly underestimate iodine intake, but given that adults should have an iodine intake of 150 µg daily and pregnant women should have an intake of 200 µg daily,[2] it is clear that many people have an inadequate dietary iodine intake.

I agree that ``excessive´´ iodine intake can cause hypothyroidism in patients with certain thyroid diseases, notably chronic autoimmune thyroiditis, but I know of no evidence that an increase in dietary iodine intake of, for example, 300 µg daily can do so.

Given that urinary iodine excretion has fallen substantially in the past 15 to 20 years to values indicative of at least marginally low iodine intake in both women and men, I stand by my conclusion that an increase in iodine intake would benefit everyone, not just pregnant women and their offspring.

Robert D. Utiger, M.D.

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