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

JAMES E. HADDOW, M.D., GLENN E. PALOMAKI, B.S., WALTER C. ALLAN, M.D., JOSEPHINE R. WILLIAMS, GEORGE J. KNIGHT, PH.D., JUNE GAGNON, M.A., CHERYL E. O'HEIR, M.ED., ED.S., MARVIN L. MITCHELL, M.D., ROSALIE J. HERMOS, M.P.H., SUSAN E. WAISBREN, PH.D., JAMES D. FAIX, M.D., AND ROBERT Z. KLEIN, M.D.

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

From the Foundation for Blood Research, Scarborough, Me. (J.E.H., G.E.P., W.C.A., J.R.W., G.J.K., J.G., C.E.O.); the New England Newborn Screening Program, Jamaica Plain, Mass. (M.L.M., R.J.H.); Children's Hospital, Boston (S.E.W.); Beth Israel Deaconess Medical Center, Boston (J.D.F.); and Dartmouth Medical School, Hanover, N.H. (R.Z.K.). Address reprint requests to Dr. Haddow at the Foundation for Blood Research, 69 U.S. Rte. 1, Scarborough, ME 04074.

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.

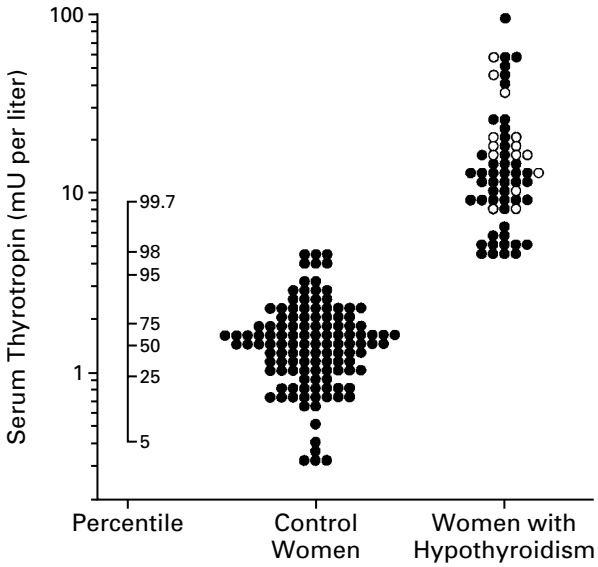

Figure 1. Distribution of Serum Thyrotropin Concentrations during Pregnancy in the 62 Women with Hypothyroidism and the 124 Matched Control Women.

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.

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