

THE RELATION OF TRANSIENT HYPOTHYROXINEMIA IN PRETERM INFANTS TO NEUROLOGIC DEVELOPMENT AT TWO YEARS OF AGE

MARY LYNNE REUSS, M.D., M.P.H., NIGEL PANETH, M.D., M.P.H., JENNIFER A. PINTO-MARTIN, PH.D., JOHN M. LORENZ, M.D., AND MERVYN SUSSER, M.B., B.CH., D.P.H.

Abstract Background. Transient hypothyroxinemia, a common finding in premature infants, is not thought to have long-term sequelae or to require treatment. We investigated whether hypothyroxinemia in premature infants is a cause of subsequent motor and cognitive abnormalities.

Methods. In this historical cohort study, we retrieved blood thyroxine values, obtained on routine screening in the first week of life, from state screening records of children who weighed 2000 g or less at birth, who were born at 33 weeks' gestation or earlier, and who were enrolled in a population-based study of the late sequelae of neonatal brain hemorrhage. We investigated the relation of these values to the odds for disabling cerebral palsy among 463 subjects for whom data were available and to the mental-development score on the Bayley Scales of Infant Development or the Stanford-Binet Intelligence Scales for Children at the age of two years in 400 subjects. The effects of severe hypothyroxinemia, defined as a blood thyroxine value more than 2.6 SD below the mean for New Jersey newborns, were assessed before and after adjustment for gestational age and potentially confounding variables.

TRANSIENT hypothyroxinemia is common among preterm infants and has been variously viewed as a benign developmental phenomenon, an expression of temporary hypothalamic-pituitary immaturity, or a manifestation of nonthyroidal illness.¹⁻¹¹ Until recently, it was not thought to have sequelae or to require thyroid-hormone replacement.^{3,4,12} Recently, however, studies have linked hypothyroxinemia in the neonatal period to subsequent problems in motor and cognitive development.¹³⁻¹⁵ Neither study, however, controlled for the presence of ultrasonographically detected lesions in the white matter, which is the most powerful known predictor of subsequent cerebral palsy in preterm infants.¹⁶⁻¹⁸

In this historical cohort study, we tested the hypothesis that hypothyroxinemia is an independent cause of cerebral palsy and cognitive deficits in preterm infants. We obtained the results of thyroxine screening of newborns with a gestational age of 33 weeks or less who were enrolled in the Central New Jersey Neonatal Brain Hemorrhage Study.¹⁹ In this study, data on the presence or absence of brain lesions during the first seven days after birth were collected prospectively, as were other prenatal and perinatal characteristics, and neurologic and developmental assessments were performed when the children were two years of age. We investigated the relation of disabling cerebral palsy and mental-develop-

Results. In analyses adjusted for gestational age, infants with severe hypothyroxinemia had a risk of disabling cerebral palsy that was nearly 11 times that of infants without hypothyroxinemia (odds ratio, 10.8; 95 percent confidence interval, 3.0 to 39.3) and a mean mental-development score at the age of two that was 15.4 points lower (95 percent confidence interval, 8.1 to 22.6 points) than the mean score of children with normal neonatal blood thyroxine concentrations. After adjustment for gestational age and multiple prenatal, perinatal, and early and late neonatal variables, severe hypothyroxinemia was still associated with an increased risk of disabling cerebral palsy (odds ratio, 4.4; 95 percent confidence interval, 1.0 to 18.6) and a reduction of nearly 7 points (95 percent confidence interval, 0.3 to 13.2 points) in the mental-development score.

Conclusions. Severe hypothyroxinemia in preterm infants may be an important cause of problems in neurologic and mental development detected at the age of two years. (N Engl J Med 1996;334:821-7.)

©1996, Massachusetts Medical Society.

ment scores at the age of two to blood thyroxine values in the first week of life.

METHODS

Study Population

The Central New Jersey Neonatal Brain Hemorrhage Study, a population-based study of the antecedents and correlates of neonatal brain hemorrhage in low-birth-weight infants, enrolled all newborns weighing 501 to 2000 g who were born from September 1, 1984, through June 30, 1987, and were cared for in the three newborn intensive care units that serve three counties in central New Jersey (Fig. 1). In this study, we restricted our attention to the 882 newborns who were born at 33 weeks of gestation or earlier, since severe hypothyroxinemia is rare at higher gestational ages. Of the 882 infants, 186 (21 percent) died before reaching the age of two years. The results of neonatal thyroxine screening were obtained for 665 (96 percent) of the 696 survivors. Because we sought to investigate the correlates of hypothyroxinemia in the first week of life, we included in these analyses only the 536 infants who were tested in the first seven days (75 percent of whom were tested on day 3). The 129 infants tested after 1 week of age (and therefore excluded from the analyses) had a shorter average gestation than the children tested earlier (210 days vs. 213 days, $P=0.03$), had lower blood thyroxine values on the first test (1.9 SD vs. 1.6 SD below the mean for New Jersey newborns, $P=0.02$), more often required mechanical ventilation on day 10 (30 percent vs. 16 percent, $P<0.001$), and were hospitalized longer (63 days vs. 47 days, $P<0.001$).

The presence or absence of cerebral palsy at two years of age was ascertained for 463 of the 536 infants (86 percent); 400 were evaluated in person and 63 by chart review or telephone interview with the child's mother; 73 were lost to follow up. Mental-development scores were available for 400 (75 percent) of the 536 children at two years of age. Four of the 63 infants in whom mental development was not assessed were classified as having disabling cerebral palsy.

Perinatal Data

Mothers were interviewed after delivery about the date of their last menstrual periods and any complications of pregnancy. Information on the antepartum course, complications of pregnancy, and labor and

From the Sergievsky Center (M.L.R., M.S.) and the Department of Obstetrics and Gynecology (M.L.R.), Columbia University, New York; the Program in Epidemiology (N.P.) and the Department of Pediatrics and Human Genetics (N.P., J.M.L.), the College of Human Medicine, Michigan State University, East Lansing; and the School of Nursing, University of Pennsylvania, Philadelphia (J.A.P.-M.). Address reprint requests to Dr. Reuss at 2 Beach Ct., Saratoga Springs, NY 12866.

Supported by grants (NS-20713 and HD-30278) from the National Institutes of Health.

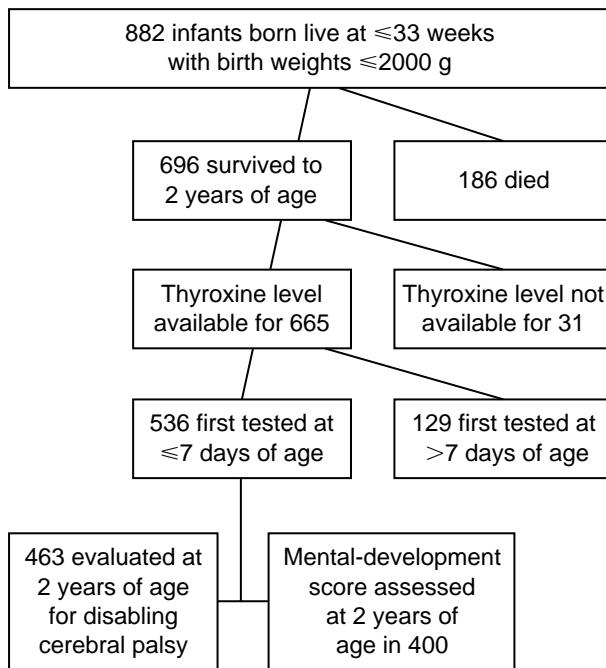


Figure 1. Enrollment and Assessment of the Study Subjects.

Our study enrolled 882 infants born at or before 33 weeks of gestation who were therefore at risk for hypothyroxinemia. The infants were drawn from the 1105 newborns with birth weights of 2000 g or less who were enrolled in the population-based Central New Jersey Neonatal Brain Hemorrhage Study.

delivery was abstracted from the prenatal and hospital records. Data on neonatal events were abstracted from the medical records at intervals corresponding to the timing of cranial ultrasonography prescribed by the study protocol (4 hours, 24 hours, and 7 days after birth). Data covering the first two ultrasonographic intervals (by definition the first 24 hours of life, but in practice ranging up to 48 hours) were combined, and this interval was designated the early neonatal period. The time from the second ultrasonographic examination until discharge was designated the late neonatal period. Data obtained from this period included the results of the third and any later cranial ultrasound examinations, the clinical diagnoses of patent ductus arteriosus and bronchopulmonary dysplasia, if present, and also the number of days of mechanical ventilation, oxygen supplementation, and hospitalization.

Gestational age was determined by means of a hierarchical algorithm that incorporated the results of prenatal ultrasonography performed before 22 weeks, if available, but excluded postnatal physical assessments. The fetal growth ratio was calculated as the ratio of the measured birth weight to the median birth weight for infants with the same number of completed weeks of gestational age in a reference population.²⁰

The presence or absence of brain injury was assessed by ultrasonographic scanning of the brain.¹⁹ The infants were classified according to the results of scanning into three nonoverlapping groups, according to the most severe lesion present: no lesion; isolated germinal-matrix or intraventricular hemorrhage; and ventriculomegaly or parenchymal lesions with or without germinal-matrix or intraventricular hemorrhage.

The study protocols were approved by the institutional review committees of all the institutions involved, and a parent or guardian provided written informed consent for each infant's participation.

Measurements of Blood Thyroxine

Results of the measurement of thyroxine and thyrotropin in the newborns' blood as part of routine screening were obtained from the Inborn Errors of Metabolism Laboratory of the New Jersey State Department of Health and were matched to the study subjects according

to hospital, date of birth, birth weight, and name by personnel unaware of the neurologic and developmental status of the study subjects.

To correct for variation among assays, we followed the procedure of the state laboratory and standardized the blood thyroxine concentration as follows: (measured thyroxine value) - (mean thyroxine value for the assay) ÷ standard deviation of the assay. Each assay included about 240 specimens (dried blood spots) from unselected New Jersey newborns, predominantly those born at term. For these analyses, we defined categories of thyroxine values that reflected those used at the laboratory. Severe hypothyroxinemia was defined as a thyroxine concentration more than 2.6 SD below the mean for the assay; mild hypothyroxinemia as a thyroxine concentration 1.3 to 2.6 SD below the mean; and a normal thyroxine concentration as one more than 1.3 SD below the mean. No subject was known to have congenital hypothyroidism.

Neurologic and Developmental Outcomes at Two Years of Age

The standardized examination for major developmental handicaps has been described in detail elsewhere.¹⁸ Cerebral palsy was classified as disabling when, in addition to specific neurologic findings, at least one of the following conditions was met: the inability to walk five steps unaided by the age of two years; a score on the Bayley Psychomotor Developmental Index that was more than 1 SD below the mental-development score on the Bayley Scales of Infant Development or the Stanford-Binet Intelligence Scales for Children; motor disability requiring physical therapy; motor disorder requiring surgical intervention; or the use of braces or other physical-assistance devices. Of the 463 children evaluated, 38 (8 percent) were classified as having disabling cerebral palsy. All but one child with disabling cerebral palsy had scores on the Psychomotor Developmental Index that were below 50 (mean [±SD] for normal children, 100±16); that child had a score of 96 and required a leg brace.

The mental-development score reported here is the score on the Bayley Mental Developmental Index²¹ for children tested at less than 30 months of corrected age (the age the child would have been if born at term) and the Stanford-Binet intelligence quotient (IQ)²² for children tested at 30 months of age or later (median, 33 months; range, 30 to 62). Both tests assess sensory-perceptual acuity, problem-solving ability, language, and memory. For both tests the mean (±SD) values in normal children are 100±16 points.^{21,22} For 22 children in whom severe cognitive deficits precluded testing, a score of 49 was assigned. Of the 400 children assessed with these tests, 31 (8 percent) were classified as mentally retarded (defined as having a mental-development score <68, or more than 2 SD below the mean); 39 (10 percent) were of borderline intelligence (defined as having a mental-development score ≥68 and <84, or 1 to 2 SD below the mean). Among the 38 children with disabling cerebral palsy, 22 had mental retardation, 5 had borderline intelligence, 7 had scores in the normal range, and 4 were not tested.

Statistical Analysis

Using logistic-regression analysis when disabling cerebral palsy was the outcome and linear regression analysis when the mental-development score was the outcome (with SPSSPC+ software, SPSS, Inc., Chicago), we estimated the effects of mild and severe hypothyroxinemia on each of the neurologic and developmental outcomes in four models with the following different levels of adjustment for potentially confounding variables: the analyses were unadjusted; adjusted only for gestational age; adjusted for gestational age and prenatal, perinatal, and early neonatal variables; or adjusted for these variables and late neonatal variables. For the last two models, measures of effect were estimated by including all variables that had statistically significant independent associations with the outcomes. The addition of variables without significant independent associations with neurologic and developmental outcomes did not alter the effect of severe hypothyroxinemia on neurologic development. These various models are presented because the mechanisms of the associations among hypothyroxinemia, cerebral palsy, and neurologic and developmental outcome are unknown; the models reflect the range of possible effects, given different hypothetical causal pathways. The unadjusted model may overestimate the effect of hypothyroxinemia by failing to control adequately for confounding factors; the adjusted models may under-

Table 1. Blood Thyroxine Values According to Gestational Age in 536 Surviving Premature Infants Who Underwent Thyroxine Testing in the First Week of Life.*

GESTATIONAL AGE (WK)	NO. OF INFANTS	MILD HYPOTHYROXINEMIA		SEVERE HYPOTHYROXINEMIA		
		NO. (%)	THYROXINE $\mu\text{g/dl}$	NO. (%)	THYROXINE $\mu\text{g/dl}$	
≤ 24	11	6.5 \pm 3.8	5 (45)	6.7 \pm 1.7	3 (27)	2.0 \pm 1.5
25	18	7.1 \pm 3.8	8 (44)	7.3 \pm 1.4	8 (44)	4.8 \pm 1.8
26	27	7.0 \pm 3.5	15 (56)	5.6 \pm 1.2	5 (19)	4.3 \pm 1.9
27	32	7.1 \pm 3.0	12 (38)	7.5 \pm 1.5	13 (41)	4.4 \pm 1.4
28	45	7.2 \pm 2.4	26 (58)	7.7 \pm 1.8	12 (27)	4.5 \pm 1.2
29	57	7.1 \pm 3.2	33 (58)	6.8 \pm 2.4	13 (23)	4.4 \pm 1.9
30	76	8.1 \pm 3.9	38 (50)	6.6 \pm 1.9	12 (16)	4.2 \pm 1.4
31	99	8.7 \pm 3.4	60 (61)	7.3 \pm 1.9	6 (6)	4.5 \pm 0.7
32	94	9.5 \pm 3.8	45 (48)	7.4 \pm 1.8	7 (7)	5.0 \pm 2.0
33	77	10.1 \pm 3.6	32 (42)	7.4 \pm 1.7	3 (4)	5.2 \pm 3.3
Total	536	8.4 \pm 3.5	274 (51)	7.1 \pm 1.9	82 (15)	4.4 \pm 1.7

*Plus-minus values are means \pm SD. Mild hypothyroxinemia was defined as a standardized thyroxine concentration 1.3 to 2.6 SD below the mean, and severe hypothyroxinemia as a standardized thyroxine concentration more than 2.6 SD below the mean. To convert thyroxine values to nanomoles per liter, multiply by 12.9.

estimate the effect because of overcontrol of intervening variables in the causal pathway from hypothyroxinemia to the neurologic and developmental outcomes.

In adjusting for gestational age, we used the continuous measure of number of days of gestation at birth. For other continuous variables, categorical representations conveyed at least as much information as the continuous measure. All statistical tests were two-tailed.

RESULTS

Blood Thyroxine Values According to Week of Gestation

Among the 190 infants born at 29 weeks of gestation or earlier, gestational age was not related to the blood thyroxine concentration ($r=0.02$, $P=0.80$) (Table 1). For those born after 29 weeks, the concentrations increased by 0.2 SD per week ($r=0.2$, $P<0.001$). Gestational age explained 9 percent of the variation in blood thyroxine values.

Risk Factors for Disabling Cerebral Palsy and Low Mental-Development Scores

In each of four gestational-age groups, disabling cerebral palsy was roughly two to six times more common among infants with severe hypothyroxinemia than among those without it (Table 2). Similarly, in these four gestational-age groups, the mean mental-development score was from 8 to 18 points lower among the infants with severe hypothyroxinemia.

The percentages of infants with various characteristics and the associations of these variables with severe hypothyroxinemia, disabling cerebral palsy, and mental-development scores, after adjustment for gestational age, are shown in Table 3. Of 22 variables examined, 17 had significant associations with one of the two outcomes ($P\leq 0.05$). Variables significantly associated with the odds of both severe hypothyroxinemia and disabling cerebral palsy were the mother's level of education, the location of the intensive care unit (i.e., which of the three hospitals), the need for mechanical ventilation, the fraction of inspired oxygen at 24 hours, and

abnormalities on cranial ultrasonography. Variables significantly associated with both the odds of severe hypothyroxinemia and significant differences in the mean mental-development score were maternal education, the location of the intensive care unit, systolic blood pressure, whether mechanical ventilation was required, the fraction of inspired oxygen, and whether there were abnormalities on cranial ultrasonography. Hypertension in the infant's mother, the infant's year of birth and sex, the length of time from the rupture of membranes to delivery, and the presence or absence of hypoglycemia and sepsis were not associated with severe hypothyroxinemia or with either outcome.

Association of Disabling Cerebral Palsy and Hypothyroxinemia

Infants with severe hypothyroxinemia had a risk of disabling cerebral palsy that was 4.4 to 17.6 times that of the infants with normal thyroxine concentrations (Table 4), depending on the extent of adjustment for covariates. After adjustment for gestational age, infants with severe hypothyroxinemia had an odds ratio of 10.8 for disabling cerebral palsy (95 percent confidence interval, 3.0 to 39.3), as compared with infants with normal thyroxine concentrations. In the model with adjustment for the most variables, severe hypothyroxinemia was associated with a quadrupling of the risk of disabling cerebral palsy (odds ratio, 4.4; 95 percent confidence interval, 1.0 to 18.6). After adjustment for gestational age, mild hypothyroxinemia did not significantly increase the risk of disabling cerebral palsy.

Association of Mental-Development Scores and Hypothyroxinemia

Infants with severe hypothyroxinemia had mental-development scores at the age of two that were roughly 7 to 18 points lower than those of infants with normal thyroxine concentrations (Table 5). Once again, the magnitude of the reduction in the score depended on the extent of adjustment for covariates. After adjustment for gestational age, infants with severe hypothyroxinemia had mental-development scores that were a mean of 15 points lower than those of infants with nor-

Table 2. Frequency of Disabling Cerebral Palsy among 463 Infants and Mental-Development Scores in 400 Infants at Two Years of Age, According to Gestational-Age Group and the Presence or Absence of Severe Hypothyroxinemia.*

GESTATIONAL AGE (WK)	SEVERE HYPOTHYROXINEMIA	DISABLING CEREBRAL PALSY		MENTAL-DEVELOPMENT INDEX	
		NO. OF INFANTS	% WITH CEREBRAL PALSY	NO. OF INFANTS	MEAN SCORE \pm SD
22-27	No	48	17	45	98 \pm 26
	Yes	26	31	25	90 \pm 25
28-29	No	68	4	55	102 \pm 20
	Yes	23	26	19	88 \pm 28
30-31	No	138	4	119	106 \pm 21
	Yes	17	24	12	88 \pm 25
32-33	No	135	2	118	106 \pm 22
	Yes	8	12	7	96 \pm 25

*Severe hypothyroxinemia was defined as a standardized thyroxine concentration more than 2.6 SD below the mean.

Table 3. Frequency of Selected Prenatal, Perinatal, and Early Neonatal Characteristics and Their Relation to Severe Hypothyroxinemia, Disabling Cerebral Palsy, and Lower Mental-Development Scores among Infants Born at 33 Weeks of Gestation or Earlier.*

CHARACTERISTIC	% OF INFANTS	SEVERE HYPOTHYROXINEMIA ODDS RATIO (95% CI)	DISABLING CEREBRAL PALSY ODDS RATIO (95% CI)	MENTAL-DEVELOPMENT SCORE — DIFFERENCE IN MEANS (95% CI)
No. of infants		536	463	400
Prenatal				
Mother's age (yr)				
≤19	14	1.4 (0.6 to 2.9)	0.9 (0.5 to 1.9)	-11.7 (-18.3 to -5.2)†
20-34‡	76	1.0	1.0	—
≥35	10	0.6 (0.2 to 1.9)	0.9 (0.7 to 1.2)	2.2 (-0.2 to 4.5)
Mother's education (yr)§				
<12	12	0.8 (0.4 to 1.9)	0.8 (0.4 to 2.6)	-9.5 (-17.3 to -1.7)†
12‡	30	1.0	1.0	—
>12	33	0.5 (0.2 to 0.8)†	0.4 (0.2 to 0.8)†	7.3 (1.9 to 12.7)†
Mother's race or ethnic group				
White‡	67	1.0	1.0	—
Black	27	0.9 (0.5 to 1.6)	0.5 (0.3 to 1.3)	-13.6 (-18.6 to -8.6)†
Other or unknown	6	1.2 (0.3 to 3.9)	1.8 (0.6 to 5.6)	-18.9 (-28.6 to -9.2)†
Multiple gestation	25	1.5 (0.9 to 2.7)	2.0 (0.9 to 3.5)	-5.8 (-10.9 to -0.8)†
Weight >10% below median for gestational age	36	1.2 (0.7 to 2.0)	1.4 (0.6 to 3.1)	-5.8 (-10.9 to -0.7)†
Maternal smoking	30	0.8 (0.5 to 1.4)	1.8 (0.9 to 3.7)	-7.5 (-12.3 to -2.6)†
Perinatal				
Labor and delivery§				
Vaginal‡	42	1.0	1.0	—
Cesarean section after labor	32	2.0 (1.1 to 3.6)†	1.5 (0.7 to 3.3)	-0.4 (-5.8 to 4.9)
Cesarean section, no labor	21	1.8 (0.9 to 3.6)	0.4 (0.1 to 1.5)	-0.4 (-6.5 to 5.6)
Apgar scores				
≤5 at 1 minute	38	1.4 (0.8 to 2.4)	2.0 (0.9 to 4.2)	-6.2 (-11.2 to -1.3)†
≤5 at 5 minutes	8	0.7 (0.3 to 1.7)	1.1 (0.4 to 3.3)	-4.7 (-13.2 to 3.8)
Location of intensive care nursery				
Hospital A	25	2.0 (1.1 to 3.7)†	2.0 (1.0 to 4.5)†	-2.6 (-8.0 to 2.9)
Hospital B	25	1.8 (1.0 to 3.3)†	0.5 (0.2 to 1.6)	6.8 (1.2 to 12.3)†
Hospital C‡	49	1.0	1.0	—
Early neonatal				
Arterial blood gases¶				
PO ₂ <40 mm Hg	27	2.3 (1.3 to 3.8)†	1.6 (0.8 to 3.3)	-0.6 (-5.6 to 4.5)
PCO ₂ <25 mm Hg	9	1.5 (0.8 to 2.8)	1.9 (0.9 to 4.3)	-3.3 (-9.7 to 3.1)
PCO ₂ >65 mm Hg	13	0.9 (0.4 to 2.3)	0.5 (0.2 to 1.8)	2.3 (-4.6 to 9.1)
pH <7.20	15	1.3 (0.8 to 2.1)	2.7 (1.2 to 5.7)†	-5.0 (-10.8 to 1.7)
pH >7.50	11	0.7 (0.4 to 1.7)	1.0 (0.4 to 2.4)	5.0 (-13.7 to 12.4)
Age >3 days at thyroxine test	18	2.2 (1.2 to 4.1)†	0.7 (0.2 to 2.0)	-3.0 (-9.2 to 3.2)
Lowest systolic blood pressure (mm Hg)§				
≥50‡	23	1.0	1.0	—
38-49	49	2.0 (0.8 to 4.7)	1.2 (0.4 to 3.9)	-1.7 (-7.6 to 4.2)
<38	21	4.2 (1.7 to 10.4)†	2.9 (0.9 to 9.5)	-7.8 (-15.2 to -0.4)†
Lowest diastolic blood pressure (mm Hg)§				
≥29‡	23	1.0	1.0	—
20-28	49	1.5 (0.7 to 3.4)	1.8 (0.6 to 5.5)	-3.8 (-9.6 to 2.0)
<20	18	4.3 (1.9 to 9.9)†	2.4 (0.7 to 8.2)	-6.2 (-13.7 to 1.3)
Mechanical ventilation	58	8.1 (3.3 to 19.6)†	19.3 (2.6 to 146.0)†	-7.0 (-12.2 to -1.8)†
Fraction of inspired oxygen at end of first 24 hr				
Room air	38	1.0	1.0	—
0.21-0.40	37	2.0 (0.9 to 4.5)	2.3 (0.7 to 7.5)	-3.6 (-9.0 to 1.8)
>0.40	26	7.5 (3.6 to 15.7)†	5.8 (1.9 to 17.9)†	-9.3 (-15.3 to -3.3)†
Hypocalcemia (<6.5 mg/dl)	5	0.6 (0.2 to 2.0)	3.7 (1.3 to 10.5)†	-6.8 (-16.5 to 2.9)
Brain lesions detected on early ultrasound examination				
No lesion‡	78	1.0	1.0	—
Germinal-matrix or intraventricular hemorrhage	18	1.8 (1.0 to 3.2)†	6.8 (2.9 to 16.0)†	-9.3 (-15.2 to -3.4)†
Parenchymal lesions or ventriculomegaly	4	3.1 (1.2 to 7.9)†	32.7 (11.2 to 96.0)†	-27.0 (-37.0 to -17.1)†

*Odds ratios and differences in mean scores have been adjusted for gestational age. CI denotes confidence interval.

†P≤0.05 (range of exact values, P=0.05 to P<0.001).

‡Reference category.

§Percentages total less than 100 because of missing values for some subjects.

¶PO₂ denotes partial pressure of oxygen, and PCO₂ partial pressure of carbon dioxide.

||To convert to millimoles per liter, multiply by 0.25.

mal thyroxine concentrations (95 percent confidence interval for the decrease, 8.1 to 22.6 points). In the model with the most extensive adjustment, severe hypothyroxinemia was associated with a 7-point reduction in the mean mental-development score (95 percent confi-

dence interval, 0.3 to 13.2 points). After adjustment for gestational age, mild hypothyroxinemia was not significantly associated with reductions in the mental-development score.

Because the mental-development scales we used may

Table 4. Odds Ratios for Disabling Cerebral Palsy at Two Years of Age Associated with Mild or Severe Hypothyroxinemia among 463 Infants Born at 33 Weeks of Gestation or Earlier, in Unadjusted and Adjusted Models.*

MODEL	MILD	SEVERE
	HYPOTHYROXINEMIA	HYPOTHYROXINEMIA
<i>odds ratio (95% CI)</i>		
Unadjusted	3.7 (1.1–13.1)	17.6 (5.0–61.7)
Adjusted for gestational age	3.1 (0.9–11.0)	10.8 (3.0–39.3)
Adjusted for gestational age, prenatal, perinatal, and early neonatal variables	1.1 (0.3–4.2)	3.5 (0.9–13.6)
Adjusted for gestational age, prenatal, perinatal, and early and late neonatal variables	1.6 (0.4–6.5)	4.4 (1.0–18.6)

*Prenatal, perinatal, and early neonatal variables assessed in multivariate models were maternal age, education, race or ethnic group, single or multiple gestation, sex, growth retardation, maternal hypertension, maternal smoking, year of birth, prolonged rupture of membranes, type of labor and delivery, Apgar scores, location of intensive care nursery, lowest and highest arterial-blood gas values in the first 24 hours, age at thyroxine test, lowest systolic and diastolic blood pressure, mechanical ventilation (yes or no), fraction of inspired oxygen at the end of the first 24 hours, hypoglycemia, hypocalcemia, brain lesions in the first two days, and clinical or confirmed sepsis in the first week. Additional late neonatal variables assessed in multivariate models were the number of days of mechanical ventilation, number of days receiving supplemental oxygen, number of days in the hospital, late brain lesions, patent ductus arteriosus, and bronchopulmonary dysplasia. CI denotes confidence interval.

not provide a valid assessment in the presence of motor impairment, we also assessed the association of severe hypothyroxinemia with the mental-development score in the children without disabling cerebral palsy. After adjustment for gestational age, severe hypothyroxinemia was associated with an 8-point decrease in the mean mental-development score (95 percent confidence interval, 0.5 to 15.3 points) as compared with the scores of children who had normal thyroxine concentrations.

DISCUSSION

The importance of thyroid hormones to perinatal neural development is well established,²³⁻²⁶ but their relation to the developmental sequelae of preterm birth is uncertain. Infants born prematurely tend to have hypothyroxinemia and are also at risk for neurologic and developmental problems^{16,18,27} similar to those caused by other types of perinatal thyroid abnormalities, such as periconceptional iodine deficiency^{25,28,29} and congenital hypothyroidism.³⁰⁻³² In this population-based study, preterm infants who had blood thyroxine concentrations in the first week of life that were more than 2.6 SD below the mean had an increased risk of disabling cerebral palsy and lower mental-development scores, even after adjustment for other potentially confounding variables, including ultrasonographic evidence of white-matter damage.

All the study infants had normal blood thyrotropin concentrations, and those with severe hypothyroxinemia were usually retested until their thyroxine concentrations were in the normal range; thus, transient hypothyroxinemia of prematurity, and not congenital hypothyroidism, was the cause of the hypothyroxinemia in these children. The lack of a regular schedule for retesting precluded our documenting with certainty the duration of hypothyroxinemia in these infants. Nonetheless, the infants with very low initial blood thyroxine concentrations tended to have more severe and pro-

longed hypothyroxinemia than those with higher initial thyroxine concentrations. Our findings support the hypothesis that prolonged severe hypothyroxinemia, even if it is transient, may cause motor and cognitive sequelae in infants born before term.

Our findings are consistent with those of recent studies¹³⁻¹⁵ in which preterm infants with very low thyroid hormone concentrations had significantly poorer motor and cognitive outcomes than other infants. In a study of 280 infants weighing less than 1850 g at birth, those with blood triiodothyronine concentrations below 195 ng per deciliter (3.0 nmol per liter) in the first weeks of life had a score on the Bayley Mental Developmental Index that was 8 points lower and a Bayley motor-development score that was 7 points lower at 18 months of age than those with higher concentrations, but there was no association between thyroid concentrations and cerebral palsy.¹³ Although the authors of that study did not report on thyroxine concentrations, other studies have shown that triiodothyronine and thyroxine concentrations are directly correlated in preterm infants.^{8-11,33} In another study, in which fine-motor development and coordination, passive language, and gross-motor skills, but not cerebral palsy, were assessed at the age of two years, blood thyroxine concentrations more than 3 SD below the mean shortly after birth were associated with a risk of failing to achieve one or more developmental milestones that was 3.5 times the normal risk.¹⁴ The 479 subjects in that study were premature infants with gestational ages of less than 32 weeks or birth weights below 1500 g. The cohort was reevaluated at five and nine years of age¹⁵; each decrease of 1 SD in the thyroxine concentration in the first weeks of life was associated with a 30 percent increase in the risk of handicap and neurologic dysfunction at five years of age and a 30 percent increase in the likelihood that the child would need special education or repeat a grade in school by the age of nine.

These studies, in contrast to ours, did not find an association between hypothyroxinemia and disabling

Table 5. Reductions in Mental-Development Scores at Two Years of Age Associated with Mild or Severe Hypothyroxinemia among 400 Infants Born at 33 Weeks of Gestation or Earlier, in Unadjusted and Adjusted Models.*

MODEL	MILD	SEVERE
	HYPOTHYROXINEMIA	HYPOTHYROXINEMIA
<i>mean difference (95% CI)</i>		
Unadjusted	-5.0 (-9.9 to -0.1)	-17.5 (-24.3 to -10.7)
Adjusted for gestational age	-4.3 (-9.3 to 0.7)	-15.4 (-22.6 to -8.1)
Adjusted for gestational age, prenatal, perinatal, and early neonatal variables	-2.3 (-7.0 to 2.5)	-9.9 (-16.9 to -3.0)
Adjusted for gestational age, prenatal, perinatal, and early and late neonatal variables	-1.5 (-6.1 to 3.0)	-6.8 (-13.2 to -0.3)

*The variables assessed in multivariate models are listed in the footnote to Table 4. CI denotes confidence interval. Negative numbers indicate lower mean scores among the infants with hypothyroxinemia than among those without it.

cerebral palsy. However, the congenital diplegia associated with endemic cretinism has long been considered a form of cerebral palsy.²⁸ In addition, maternal thyroid dysfunction and treatment of the mother with thyroid hormone during pregnancy were both found to be associated with an increased risk of cerebral palsy in the National Collaborative Perinatal Project.³⁴

Although we adjusted for many variables, residual confounding could conceivably have produced a spurious association between thyroxine concentrations and neurologic development if the thyroxine concentration is a marker for unsuspected or unmeasured factors in the chain of events causing cerebral palsy or neurologic deficit. Such an unidentified confounder would have to have a larger effect in preterm newborns than the effect we measured for severe hypothyroxinemia. The number of variables we tested and the magnitude of the association make that unlikely. Indeed, in this study the odds ratios for adverse neurologic outcomes after adjustment for a number of variables could well underestimate the strength of a true causal association because of over-control for variables in the causal pathway.

A therapeutic trial directed at increasing neonatal thyroxine concentrations, perhaps by postnatal thyroxine therapy (with or without the administration of thyrotropin-releasing hormone to the mothers before delivery), might resolve the issue of causality and determine whether such therapy could prevent or modify the adverse neurologic and developmental outcomes associated with prematurity. Crucial to an estimation of the risks of thyroxine administration is a better understanding of the causes of severe hypothyroxinemia. It may be that the low thyroxine concentrations typically seen in preterm infants (along with the low triiodothyronine concentrations) are the result of nonthyroidal illness.^{2-4,7,9,35} If such illness is present, thyroid hormone production falls and protein catabolism and oxygen consumption may be reduced — a potentially beneficial adaptive response to illness. If hypothyroxinemia is caused by nonthyroidal illness and if the change is protective,³⁶ the administration of thyroid hormones might not be appropriate.

Thyroid hormones have been given to small numbers of preterm infants with either beneficial effects^{5,37-41} or no apparent effects.^{42,43} The studies in which this has been done have not provided rigorous proof of the safety or efficacy of such treatment. Taken together, however, they do not appear to contraindicate further study of thyroid hormone therapy in infants born prematurely.

We are indebted to Mrs. Katherine Coons and Ms. Max Kuroda for research assistance, to Dr. Melissa Begg and Mr. Roger Vaughan for assistance with the statistical analyses, to Dr. Alan Leviton for helpful suggestions during the preparation of the manuscript, and to Ms. Carol Southard, of the Inborn Errors of Metabolism Laboratory of the New Jersey State Department of Health, who made it possible for us to obtain the results of thyroid screening in the study subjects.

REFERENCES

1. Cuestas RA, Engel RR. Thyroid function in preterm infants with respiratory distress syndrome. *J Pediatr* 1979;94:643-6.

2. Klein AH, Foley B, Kenny FM, Fisher DA. Thyroid hormone and thyrotropin responses to parturition in premature infants with and without the respiratory distress syndrome. *Pediatrics* 1979;63:380-5.
3. Fisher DA, Klein AH, Hadeed A. Normal and abnormal thyroid function in premature infants: the low T₃ syndrome. In: Hesch R-D, ed. The "Low T₃ syndrome." Vol. 40 of Proceedings of the Sero Symposium. London: Academic Press, 1981:225-31.
4. Hadeed AJ, Asay LD, Klein AH, Fisher DA. Significance of transient postnatal hypothyroxinemia in premature infants with and without respiratory distress syndrome. *Pediatrics* 1981;68:494-8.
5. Eggermont E, Vanderschueren-Lodeweyckx M, De Nayer PH, et al. The thyroid-system function in preterm infants of postmenstrual ages of 31 weeks or less: evidence for a "transient lazy thyroid system." *Helv Paediatr Acta* 1984;39:209-22.
6. Etling N, Padovani E, Gehin-Fouque F, Tato L. Serum and urine thyroid hormone levels in healthy preterm and small for date infants on the first and fifth day of life. *Helv Paediatr Acta* 1984;39:223-30.
7. Franklin RC, Purdie GL, O'Grady CM. Neonatal thyroid function: prematurity, prenatal steroids, and respiratory distress syndrome. *Arch Dis Child* 1986;61:589-92.
8. John R, Bamforth FJ. Serum free thyroxine and free triiodothyronine concentrations in healthy fullterm, preterm and sick preterm neonates. *Ann Clin Biochem* 1987;24:461-5.
9. Mercado M, Yu VYH, Francis I, Szymonowicz W, Gold H. Thyroid function in very preterm infants. *Early Hum Dev* 1988;16:131-41.
10. Fuse Y, Shimizu M, Uga N, Fujii T, Irie M. Maturation of feedback control of thyrotropin in premature infants. *J Dev Physiol* 1990;14:17-22.
11. Harkavy KL, Enecio CE. Free thyroxine levels in hospitalized newborns: depressed levels in critical, nonthyroidal illness. *J Perinatol* 1991;11:117-21.
12. Karna P. Developmental follow-up of very low birthweight premature infants with low free thyroxine. *Am J Perinatol* 1991;8:288-91.
13. Lucas A, Rennie J, Baker BA, Morley R. Low plasma triiodothyronine concentrations and outcome in preterm infants. *Arch Dis Child* 1988;63:1201-6.
14. Meijer WJ, Verloove-Vanhorick SP, Brand R, van den Brande JL. Transient hypothyroxinaemia associated with developmental delay in very preterm infants. *Arch Dis Child* 1992;67:944-7.
15. den Ouden AL, Kok JH, Verkerk PH, Brand R, Verloove-Vanhorick SP. The relation between neonatal thyroxine levels and neurodevelopmental outcome at age 5 and 9 years in a national cohort of very preterm and/or very low birth weight infants. *Pediatr Res* 1996;39:142-5.
16. Hack M, Taylor G, Klein N, Eiben R, Schatschneider C, Mercuri-Minich N. School-age outcomes in children with birth weights under 750 g. *N Engl J Med* 1994;331:753-9.
17. Leviton A, Paneth N. White matter damage in preterm newborns — an epidemiologic perspective. *Early Hum Dev* 1990;24:1-22.
18. Pinto-Martin JA, Riolo S, Cnaan A, Holzman C, Susser MW, Paneth N. Cranial ultrasound prediction of disabling and nondisabling cerebral palsy at age two in a low birth weight population. *Pediatrics* 1995;95:249-54.
19. Pinto-Martin J, Paneth N, Witomski T, et al. The Central New Jersey Neonatal Brain Haemorrhage Study: design of the study and reliability of ultrasound diagnosis. *Paediatr Perinat Epidemiol* 1992;6:273-84.
20. Yudkin PL, Aboualfa M, Eyre JA, Redman CWG, Wilkinson AR. New birthweight and head circumference centiles for gestational ages 24 to 42 weeks. *Early Hum Dev* 1987;15:45-52.
21. Bayley N. Manual for the Bayley Scales of Infant Development. New York: Psychological Corporation, 1969.
22. Terman LM, Merrill MA. Stanford-Binet Intelligence Scales. 3rd rev. Stanford, Calif.: Stanford University Press, 1972.
23. Morreale de Escobar G, Obregon MJ, del Rey FE. Fetal and maternal thyroid hormones. *Horm Res* 1987;26:12-27.
24. Stein SA, Adams PM, Shanklin DR, Mihailoff GA, Palnitkar MB. Thyroid hormone control of brain and motor development: molecular, neuroanatomical, and behavioral studies. In: Bercu BB, Shulman DI, eds. Advances in perinatal thyroidology. New York: Plenum Press, 1991:47-105.
25. DeLong GR. Effects of nutrition on brain development in humans. *Am J Clin Nutr* 1993;57:Suppl:286S-290S.
26. Porterfield SP, Hendrich CE. The role of thyroid hormones in prenatal and neonatal neurological development — current perspectives. *Endocr Rev* 1993;14:94-106.
27. Robertson CMT, Hrynchynshyn GJ, Etches PC, Pain KS. Population-based study of the incidence, complexity, and severity of neurologic disability among survivors weighing 500 through 1250 grams at birth: a comparison of two birth cohorts. *Pediatrics* 1992;90:750-5.
28. Hetzel BS, Mano MT. A review of experimental studies of iodine deficiency during fetal development. *J Nutr* 1989;119:145-51.
29. Pharoah P, Connolly K, Hetzel B, Ekins R. Maternal thyroid function and motor competence in the child. *Dev Med Child Neurol* 1981;23:76-82.
30. Rovet J, Ehrlich R, Sorbara D. Intellectual outcome in children with fetal hypothyroidism. *J Pediatr* 1987;110:700-4.

31. Kooistra L, Laane C, Vulsma T, Schellekens JMH, van der Meere JJ, Kalverboer AF. Motor and cognitive development in children with congenital hypothyroidism: a long-term evaluation of the effects of neonatal treatment. *J Pediatr* 1994;124:903-9.
32. Tillotson SL, Fuggle PW, Smith I, Ades AE, Grant DB. Relation between biochemical severity and intelligence in early treated congenital hypothyroidism: a threshold effect. *BMJ* 1994;309:440-5.
33. Burrow GN, Fisher DA, Larsen PR. Maternal and fetal thyroid function. *N Engl J Med* 1994;331:1072-8.
34. Nelson KB, Ellenberg JH. Antecedents of cerebral palsy: multivariate analysis of risk. *N Engl J Med* 1986;315:81-6.
35. Fisher DA. Euthyroid low thyroxine (T_4) and triiodothyronine (T_3) states in prematures and sick neonates. *Pediatr Clin North Am* 1990;37:1297-312.
36. Hennemann G, Docter R, Krenning EP. Causes and effects of the low T_3 syndrome during caloric deprivation and non-thyroidal illness: an overview. *Acta Med Austriaca* 1988;15:Suppl 1:42-5.
37. Schonberger W, Grimm W, Emmrich P, Gempp W. Reduction of mortality rate in premature infants by substitution of thyroid hormones. *Eur J Pediatr* 1981;135:245-53.
38. Mercado M, Szymonowicz W, Yu VYH, Gold H. Symptomatic hypothyroxinemia with normal TSH levels in preterm infants. *Clin Pediatr* 1987;26:343-6.
39. Fabris N, Mocchegiani E, Mariotti S, et al. Thymlin deficiency and low 3,5,3'-triiodothyronine syndrome in infants with low birth weight syndromes. *J Clin Endocrinol Metab* 1987;65:247-52.
40. Amato M, Guggisberg C, Schneider H. Postnatal triiodothyronine replacement and respiratory distress syndrome of the preterm infant. *Horm Res* 1989;32:213-7.
41. Kok JH, van Wassenaer AG, de Vijlder JJM. Randomized placebo-controlled trial of thyroxine administration to infants <30 weeks in relation to mortality and morbidity. *Pediatr Res* 1995;37:Suppl:218A. abstract.
42. van Wassenaer AG, Kok JH, Ender E, Vulsma T, de Vijlder JJM. Thyroxine administration to infants of less than 30 weeks' gestational age does not increase plasma triiodothyronine concentrations. *Acta Endocrinol (Copenh)* 1993;129:139-46.
43. Chowdhry P, Scanlon JW, Auerbach R, Abbassi V. Results of controlled double-blind study of thyroid replacement in very low-birth-weight premature infants with hypothyroxinemia. *Pediatrics* 1984;73:301-5.