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van Wassenaer, A.G.; Kok, J.H.; de Vijlder, J.J.M.; Briët, J.M.; Smit, B.J.; Tamminga, P.; van Baar, A.L.; Dekker, F.W.; Vulsma, T.

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EFFECTS OF THYROXINE SUPPLEMENTATION ON NEUROLOGIC DEVELOPMENT IN INFANTS BORN AT LESS THAN 30 WEEKS' GESTATION

ALEID G. VAN WASSENAER, M.D., PH.D., JOKE H. KOK, M.D., PH.D., JAN J.M. DE VIJLDER, PH.D., JUDY M. BRIËT, M.A., BERT J. SMIT, M.D., PIETER TAMMINGA, M.D., ANNELOES VAN BAAR, PH.D., FRIEDO W. DEKKER, M.D., PH.D., AND THOMAS VULSMA, M.D., PH.D.

ABSTRACT

Background Premature infants who have transient hypothyroxinemia in the first weeks of life may have developmental delay and neurologic dysfunction. Whether thyroxine treatment during this period results in improved developmental outcomes is not known.

Methods We carried out a randomized, placebo-controlled, double-blind trial of thyroxine supplementation in 200 infants born at less than 30 weeks' gestation. Thyroxine (8 μg per kilogram of birth weight) or placebo was administered daily, starting 12 to 24 hours after birth, for six weeks. Plasma free thyroxine concentrations were measured weekly for the first eight weeks after birth. Scores on the Bayley Mental and Psychomotor Development Indexes and neurologic function were assessed at 6, 12, and 24 months of age (corrected for prematurity).

Results Mortality and morbidity up to the time of discharge from the hospital were similar in the study groups. At 24 months of age, 157 infants were evaluated. Overall, neither mental nor psychomotor scores differed significantly between the study groups at any time, nor was the frequency of abnormal neurologic outcome significantly different. In thyroxine-treated infants born at gestational ages of less than 27 weeks, the score on the Bayley Mental Development Index at 24 months of age was 18 points higher than the score for the infants with similar gestational ages at birth in the placebo group ($P=0.01$); for thyroxine-treated infants born at 27 weeks or later, the mental-development score was 10 points lower than that of their counterparts in the placebo group ($P=0.03$). There was no relation between the initial plasma free thyroxine concentration and the effect of treatment.

Conclusions In infants born before 30 weeks' gestation, thyroxine supplementation does not improve the developmental outcome at 24 months. (N Engl J Med 1997;336:21-6.)

TRANSIENT hypothyroxinemia after birth is common in premature infants.[1-7] The degree of hypothyroxinemia is related to gestational age and the severity of neonatal disease.[1,3,5-7] It has been assumed that low plasma thyroxine concentrations in premature infants do not require treatment.[6] Thyroid hormone is essential for the normal growth and maturation of the central nervous system,[8] however, and developmental delay and an increased risk of cerebral palsy have been found in premature infants with low plasma concentrations of thyroxine[9,10] or triiodothyronine[11] during the neonatal period. So far, the effect of thyroxine administration on the development of the nervous system has been studied in only eight infants, and the results indicated no effect of thyroxine treatment.[12]

We conducted a randomized, placebo-controlled, double-blind trial of thyroxine supplementation in infants born at less than 30 weeks' gestation. The principal outcome measure was the score on the Bayley Mental Development Index at 24 months of age (corrected for prematurity). Because developmental problems, hypothyroxinemia, and gestational age are interrelated,[1,7,13] we also investigated whether the effect of thyroxine, if any, was related to the degree of prematurity of the infants and their initial plasma free thyroxine values.

METHODS

Eligibility and Randomization

This study was approved by the Committee of Medical Ethics of the Academic Medical Center in Amsterdam. Infants admitted to our neonatal intensive care unit within 24 hours after birth between January 1991 and July 1993 were eligible for the trial. The inclusion criteria were a gestational age of 25 to 30 weeks and the absence of severe congenital malformations, maternal endocrine disease, and illicit-drug use by the mother. After informed consent had been obtained from at least one parent, the infants were randomly assigned to receive either thyroxine or placebo; study-group assignments were made in blocks of 10, with use of a computerized randomization program. All investigators, medical staff, and parents remained unaware of the infants' study-group assignments throughout the study.

Administration of Thyroxine or Placebo

For each infant who entered the study, a numbered set of 50 ampules containing 25 μg of thyroxine per milliliter or placebo was prepared. Thyroxine (in a fixed dose of 8 μg per kilogram of birth weight) or placebo was given once daily, starting 12 to 24 hours after birth. In a preliminary study, we found that with this dose the plasma free thyroxine concentration did not decrease below the mean free thyroxine concentration in the cord blood of

From the Departments of Neonatology (A.G.W., J.H.K., J.M.B., B.J.S., P.T., A.B.), Pediatric Endocrinology (J.J.M.V., T.V.), and Clinical Epidemiology and Biostatistics (F.W.D.), Academic Medical Center, University of Amsterdam and Emma Children's Hospital, Amsterdam. Address reprint requests to Dr. van Wassenaer at the Department of Neonatology, H3N, Academic Medical Center, University of Amsterdam, P.O. Box 22700, 1100 DE Amsterdam, the Netherlands.

infants born at less than 30 weeks' gestation and that the concentration remained below the upper limit of the plasma free thyroxine range for infants born at term.[14] The assigned medication was given by intravenous injection as long as intravenous nutrition was required (mean, 14 days) and orally thereafter. The treatment period lasted six weeks.

Assays

A 1-ml sample of blood was drawn before the administration of thyroxine or placebo began and again on day 3, each week during treatment, and two weeks after the discontinuation of treatment. Plasma free thyroxine was measured in each of these specimens by a two-step radioimmunoassay (SPAC-fT4 Fraktion, Byk-Sangtec Diagnostica, Dietzenbach, Germany) (detection limit, 0.08 ng per deciliter [1.0 pmol per liter]); the intraassay and interassay coefficients of variation were 2.8 percent and 5.7 percent, respectively.

Clinical Data

Gestational age was determined on the basis of the mother's menstrual history. When this information was inconclusive, the results of early ultrasonography or the Dubowitz score[15] was used. Clinical data were collected until discharge from the hospital. The outcome measures assessed were death; the need for supplemental oxygen at 36 weeks after the mother's last menstrual period (36 weeks of postmenstrual age); the incidence of cerebral hemorrhage, ischemic lesions, ventriculomegaly, retinopathy of prematurity, or patent ductus arteriosus (i.e., clinical symptoms confirmed by cardiac ultrasonography); and the number of episodes of proved septicemia. Cranial ultrasonography was performed with use of a 7.5-MHz transducer before treatment and on days 5, 14, 28, and 42, or more often if clinically indicated. Hemorrhage was classified as described by Volpe.[16] Cysts appearing after hemorrhagic venous infarction were classified as parenchymal hemorrhages. Ischemic lesions were classified according to the system of de Vries et al.,[17] and ventriculomegaly according to the definition of Levene.[18]

Follow-up with Respect to Neurologic Development

Neurologic outcome and scores on the Bayley Mental and Psychomotor Development Indexes were assessed by the same pediatrician and developmental psychologist at 6, 12, and 24 months of corrected age (defined as the number of months after term). Neurologic development was assessed according to the method of Touwen[19] at 6 and 12 months and according to the method of Hempel[20] at 24 months. The results of the tests of neurologic development were classified as normal, suspect, or abnormal. Abnormality was defined as severe abnormality of tone, posture, and movement leading to functional impairment or delay in motor development. A "suspect" outcome was defined as moderate functional impairment or developmental delay. The scores on the Bayley Mental and Psychomotor Development Indexes were determined in relation to Dutch norms (mean, 100; standard deviation, 16).[21]

Statistical Analysis

Confidence intervals for risk ratios and differences in risk were calculated according to the recommendations of Gardner and Altman.[22] For subgroup analyses, each treatment group was divided into four groups according to gestational age (25 or 26 weeks, 27 weeks, 28 weeks, and 29 weeks) to permit us to study the effect of treatment in relation to gestational age. To study the effect of treatment in relation to the initial plasma free thyroxine concentration (measured 12 to 24 hours after birth), each study group was divided according to quartiles of plasma free thyroxine.

Differences between the mean plasma free thyroxine concentrations in the thyroxine and placebo groups were tested by analysis of variance for repeated measures (BMDP software, program 5V), in which the hormone concentration was examined as a function of time, thyroxine supplementation, and a term for the interaction between time and thyroxine supplementation. The distribution of residuals was checked for skewness. When a significant interaction term was found, the difference between the values of the two study groups at corresponding times was determined by calculating the P value for the difference in the estimated mean values.

The effect of treatment on the longitudinal course of the Bayley mental-development and psychomotor-development scores was tested by analysis of variance for repeated measures (BMDP software, program 5V), in which the score was examined as a function of thyroxine supplementation, time, and a term for the interaction between thyroxine supplementation and time. To establish the difference between the treatment groups in mental- and psychomotor-development scores at the age of 24 months (the end of the trial), multivariate linear regression analysis was performed (BMDP software, program 1R). The covariates in this model were gestational age, sex, whether intubation was necessary at birth, maternal educational level, ethnic origin, presence or absence of growth retardation, and use or nonuse of surfactant. To evaluate the effect of thyroxine on the scores for mental and psychomotor development in the four gestational-age groups, we used linear regression analysis and the same model. Neurologic outcome was analyzed separately at 6, 12, and 24 months with use of the chi-square test for two-by-three tables (BMDP software, program 4F). For data obtained at 24 months, we used logistic-regression analysis (BMDP software, program LR) with the model described above.

RESULTS

Patients

Of the infants admitted to the neonatal intensive care unit, 264 were eligible for the study on the basis of gestational age. Sixty-four of these were not enrolled for a variety of reasons. Twenty-two died within 24 hours after birth, four had severe congenital malformations, two had mothers with endocrine disease, and four had mothers who used illicit drugs. The parents of 13 infants were not asked for informed consent because of various social problems (such as an age of less than 18 years for both parents, planned departure from the country, or a language barrier), and the parents of 19 infants refused consent. One hundred infants were enrolled in each of the two study groups. The characteristics of the infants in the two study groups were similar (Table 1); however, the number of infants with a gestational age below 27 weeks was higher in the placebo group, and there were more infants who were very small for gestational age and more with intrauterine infection in the thyroxine group.

Plasma Free Thyroxine Concentration

The infants' mean plasma free thyroxine concentrations are shown in Figure 1. In the placebo group, the values increased slightly and then decreased to a nadir on day 7, after which there was an increase. The values were significantly higher in the thyroxine group ($P<0.001$) at most times.

Clinical Course

The data on infant mortality and morbidity up to the time of discharge from the hospital are shown in

Table 2. There were 14 deaths in the thyroxine group and 21 in the placebo group. The incidence of chronic lung disease, patent ductus arteriosus, and cerebral bleeding and ischemia was similar in the two groups. Retinopathy of prematurity was diagnosed in only one infant in each group. The postmenstrual age at discharge was similar in both groups (39⅐ weeks in the thyroxine group vs. 38⅘ weeks in the placebo group). During the six-week treatment period, a total of seven infants were withdrawn from the study, four because severe congenital malformations were diagnosed after entry into the study (agenesis of the septum pellucidum, congenital hypothyroidism, the Crouzon syndrome, and severe heart malformation) and three because of parental discomfort with the study. Consequently, after the period of hospitalization, 158 infants remained for follow-up, 82 in the thyroxine group and 76 in the placebo group.

Assessment of Neurologic Development

The mean gestational age of the infants evaluated at follow-up was 28⅐ weeks in both groups. The social (educational and professional) status of the parents and the racial background of the infants did not differ significantly between the two groups, and they were similar with respect to other antenatal, perinatal, and postnatal characteristics. One infant's family moved abroad, and she was lost to follow-up. At the age of six months, another six infants could not be tested, because their residence was unknown (two infants), because they were temporarily abroad (three infants), or because of the sudden death of the infant's father (one infant). Another two infants underwent neurologic assessment, but the Bayley test was not performed because of the unexpected absence of the developmental psychologist. When the infants were 12 months old, the address of one family (accounting for two infants) was unknown. At 24 months all 157 infants remaining in the study were assessed neurologically. However, five infants did not cooperate with the administration of the Bayley Psychomotor Development Index (all were neurologically normal), and one did not cooperate with the administration of the Mental Development Index.

The infants' mental and psychomotor scores at the corrected ages of 6, 12, and 24 months are shown in Figure 2. The scores on both the Mental and Psychomotor Development Indexes were similar in the groups at all times ($P = 0.62$ and $P = 0.39$, respectively). At 24 months, the mental-development score was 3.5 points lower in the thyroxine group than in the placebo group (95 percent confidence interval, 11.4 points lower to 3.9 points higher). After adjustment for various covariates, no effect of thyroxine on the mental-development score at 24 months was evident. The number of infants with normal mental and motor development at 24 months (i.e., mental-

TABLE 1. CHARACTERISTICS OF THE PREMATURE INFANTS IN THE THYROXINE AND PLACEBO GROUPS.*

CHARACTERISTIC	THYROXINE (N = 100)	PLACEBO (N = 100)
Sex (M/F)	53/47	47/53
Birth weight (g)	1078±218	1077±239
Gestational age (days)	197±8	196±9
Gestational age <27 wk (no.)	19	27
Very small for gestational age (no.)†	5	2
Twins or triplets (no.)	36	42
Premature rupture of membranes (no.)‡	34	33
Antenatal glucocorticoid therapy (no.)§	68	65
Delivery by cesarean section (no.)	24	22
Apgar score at 5 min	8.3±1.8	8.1±1.8
Intubation at birth (no.)	37	40
Respiratory distress syndrome (no.)	54	53
Surfactant therapy (no.)	39	38
Intrauterine infection (no.)¶	10	5
Grade 3 or 4 cerebral hemorrhage (no.)	5	3

*Plus–minus values are means ±SD. Other values are numbers of infants. No statistically significant differences were found between the study groups.

†Infants classified as very small for gestational age had birth weights below the 3rd percentile of the Dutch growth charts.

‡Premature rupture was defined as rupture more than 24 hours before birth.

§Two doses of 12 mg of betamethasone each were given to mothers 24 hours apart in cases of imminent premature delivery.

¶Only infections confirmed by positive bacterial culture are included.

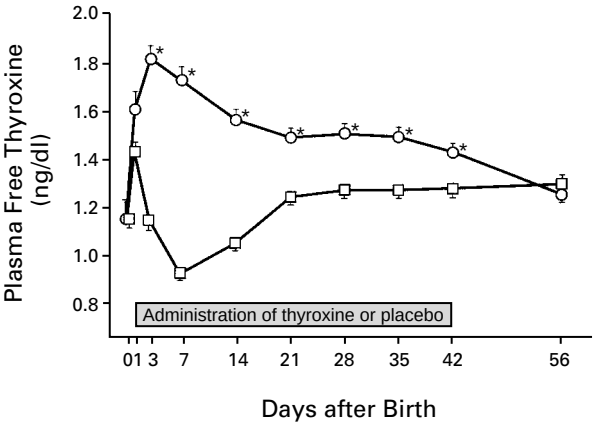

Figure 1. Mean (±SE) Plasma Free Thyroxine Concentrations in the Thyroxine (○) and Placebo (□) Groups during the First Eight Weeks after Birth.

The asterisks indicate $P<0.005$. To convert plasma free thyroxine values to picomoles per liter, multiply by 12.9.

TABLE 2. CLINICAL DATA ON THE PREMATURE INFANTS IN THE THYROXINE AND PLACEBO GROUPS UP TO THE TIME OF DISCHARGE FROM THE HOSPITAL.

VARIABLE*	THYROXINE (N = 100)	PLACEBO (N = 100)
Duration of hospitalization (days)†	80±44	80±29
	no. (%)	
Death	14 (14)	21 (21)
Supplemental oxygen at 36 wk‡	17 (19)	17 (21)
Patent ductus arteriosus	21 (21)	29 (29)
Septicemia	19 (19)	20 (20)
Cerebral hemorrhage		
Total	45 (45)	37 (37)
Grade 3 or 4§	12 (12)	11 (11)
Cerebral ischemia†		
Total	12 (14)	10 (13)
Grade 2 or 3	2 (2)	1 (1)
Grade 2 ventriculomegaly	3 (3)	4 (4)

*There were no significant differences in these variables between the two groups; in all instances the 95 percent confidence intervals for the ratio of the risk (frequency) of the variable in the thyroxine group to the risk in the placebo group overlapped 1.0.

†Only infants who survived to discharge are included. Plus–minus values are means ±SD.

‡These infants required supplemental oxygen at 36 weeks' postmenstrual age; the percentages shown are of the infants who were alive at the time of diagnosis.

§A grade 3 or 4 hemorrhage was found in 13 infants who died, 6 of 12 in the thyroxine group and 7 of 11 in the placebo group. Included in this category was one infant with a cerebral abscess.

and psychomotor-development scores higher than 1 SD below the test mean of 100) was 40 in the thyroxine group and 36 in the placebo group (absolute reduction in the risk of a score ≥1 SD below the mean, 4 percent; 95 percent confidence interval, 18 percent reduction to 10 percent increase).

The neurologic outcomes at 6, 12, and 24 months of age are shown in Table 3. There was no significant difference between the groups in neurologic outcome at any time.

Subgroup Analyses

The mental-development scores at 24 months of corrected age varied among the gestational-age groups. For the 13 infants born at 25 or 26 weeks' gestation in the thyroxine group, the mean (±SD) mental-development score was 18 points higher than that of the 18 infants of the same gestational age in the placebo group (93±26 vs. 75±23, P = 0.01). Among infants born at 27, 28, and 29 weeks' gestation, there was a trend toward a lower score in the thyroxine group than in the placebo group. Among all the infants born at 27 weeks of gestation or later combined, the mental-development score was 10 points lower for the 67 infants in the thyroxine group than for the 58 infants in the placebo group (93±24 vs. 103±24, P = 0.03). At the ages of 6 and 12 months, no relation between gestational age and the effect of treatment was found. The psychomotor-development scores and the neurologic outcome during follow-up did not differ among the four gestational-age groups. The relation of the mental-development scores to the initial plasma free thyroxine concentration (in quartiles) was similar in the study groups at the age of 24 months (data not shown).

DISCUSSION

Transient hypothyroxinemia is common in premature infants in the first weeks after birth and is more severe in infants with lower gestational ages.[1,3,5-7] It is thought to be caused by the immaturity of the hypothalamic–pituitary–thyroid axis,[2,6] nonthyroidal illness,[5] or premature withdrawal of the maternal contribution to the fetal thyroxine pool.[14] Thyroid hormone is essential for normal brain development.[8] Therefore, low plasma thyroxine concentrations could well be a preventable factor contributing to the developmental delay that often occurs in premature infants.[13,23] Recently, severe hypothyroxinemia was found to be associated with school failure at nine years of age[9] and with a quadrupled risk of disabling cerebral palsy and a seven-point reduction in mental-development scores at two years of age.[10] In this study, we found that the administration of thyroxine to infants born at less than 30 weeks' gestation did not improve mental, motor, or neurologic development.

The association between hypothyroxinemia and neurologic and developmental problems may have been overestimated in cohort studies because the duration of hypothyroxinemia was not taken into account.[9,10] In addition, these studies measured serum total thyroxine concentrations. Some of the variations in serum total thyroxine values could have been due to changes in serum concentrations of thyroxine-binding globulin, which are decreased in infants with respiratory disease.[24] We enrolled infants according to their gestational age, not the severity of hypothyroxinemia, because in all infants born at less than 30 weeks of gestational age, serum thyroxine concentrations after birth fall below the cord-blood concentration.[1,7,14,25] We may therefore have included infants who had only mild hypothyroxinemia, thus diluting the possible beneficial effect of thyroxine. Post hoc subgroup analyses were performed to address this possibility.

The initial plasma free thyroxine concentrations were not related to the effect of treatment. This lack of association may have been due to the time the blood sample was obtained, since blood was collected during the surge of thyroxine that occurs soon after birth, not during the period of hypothyroxinemia. It is possible that a delay of several days in initiating

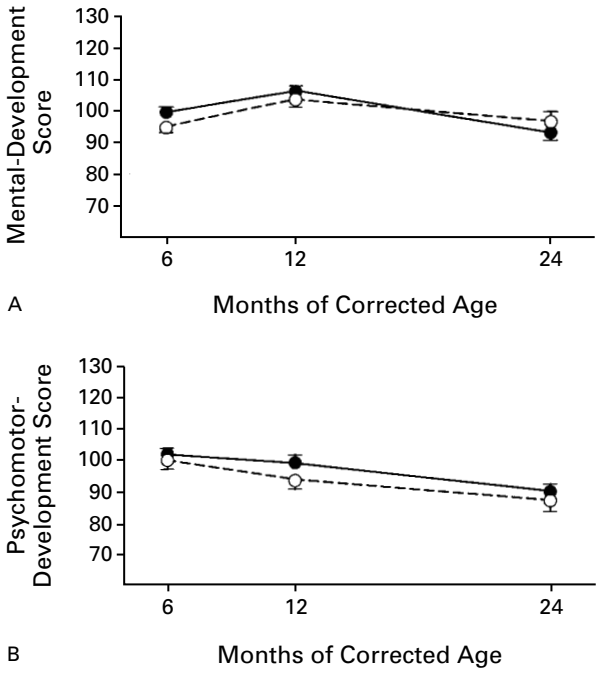

Figure 2. Mean (±SE) Scores on the Bayley Mental Development Index (Panel A) and Psychomotor Development Index (Panel B) in the Thyroxine (●) and Placebo (○) Groups at 6, 12, and 24 Months of Corrected Age.

There were no statistically significant differences between the groups for either score at any time.

TABLE 3. NEUROLOGIC OUTCOME AT THE CORRECTED AGES OF 6, 12, AND 24 MONTHS IN PREMATURE INFANTS GIVEN THYROXINE OR PLACEBO.

AGE AND OUTCOME*	THYROXINE	PLACEBO
6 Months		
No. of infants	77	74
Outcome — no. (%)		
Normal	48 (62)	46 (62)
Suspect	23 (30)	19 (26)
Abnormal	6 (8)	9 (12)
P value	0.57	
12 Months		
No. of infants	81	74
Outcome — no. (%)		
Normal	64 (79)	50 (68)
Suspect	11 (14)	15 (20)
Abnormal	6 (7)	9 (12)
P value	0.27	
24 Months		
No. of infants	82	75
Outcome — no. (%)		
Normal	63 (77)	54 (72)
Suspect	14 (17)	12 (16)
Abnormal†	5 (6)	9 (12)
P value	0.40	

*P values are for the differences in the distribution of outcomes between the study groups.

†P=0.20 for the significance of abnormal results (vs. normal and suspect) by logistic-regression analysis.

treatment could make it possible to identify a cutoff value for the plasma free thyroxine concentration below which thyroxine treatment is beneficial.

We did identify a relation between gestational age and the effect of treatment. In thyroxine-treated infants born at less than 27 weeks of gestation, the mental-development score at two years was 18 points higher than in the infants of similar gestational age who were given placebo. Among infants born at 27 weeks or later, in contrast, the mental-development score in the thyroxine group was 10 points lower than that in the placebo group. These findings may indicate that in infants born at less than 27 weeks' gestation, plasma free thyroxine concentrations are indeed too low to ensure adequate cerebral triiodothyronine concentrations, thus causing damage to the brain. The protective mechanisms that ensure a sufficient supply of triiodothyronine for brain cells in times of shortage of substrate (thyroxine) may not be functioning adequately at that time.[26,27] On the other hand, hyperthyroidism can also be harmful to brain development[28]; the dose of thyroxine used in our trial could have been appropriate for infants of 25 and 26 weeks' gestation but too high for infants of 27 or more weeks' gestation.

We conclude that the administration of thyroxine to all infants born at less than 30 weeks' gestation cannot be advised on the basis of our results. Infants with a gestational age of less than 27 weeks might benefit from this treatment, however.

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