Chapter 6

Neonatal thyroxine supplementation in very preterm children: developmental outcome evaluated at early school age

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ABSTRACT

Objective: Transient hypothyroxinemia in very premature infants is associated with developmental problems. A randomized, placebo-controlled trial of thyroxine (T4) 26 weeks' gestation only. The effect of T4 supplementation beyond 2 years of age is unknown. We present the effects of neonatal T4 supplementation on outcome at early school age.

Methods: Standardized measurements were used to assess cognitive, behavioral and motor outcome as well as a qualitative assessment of neurologic functioning. Survivors of the T4 trial were assessed at the age of 5.7 years.

Results: Ninety-nine percent of the 157 survivors participated. Outcome on all domains was comparable between the T4 group and Placebo group. Gestation groups: In children <27 weeks' gestation, a 10 IQ point difference was found in favor of the T4 group, while in children of 29 weeks' gestation, a difference of 15 IQ points was found in favor of the Placebo group. Teachers' reports showed less behavioral problems in the T4-treated children of 25/26 weeks' gestation, but more behavioral problems in the T4-treated children of 27 weeks' gestation. Differences in motor outcome and neurological outcome were in favor of the T4-treated children <29 weeks' gestation, but not of the T4-treated children of 29 weeks' gestation.

Conclusions: We found benefits of T4 supplementation for children <29 weeks' gestation, and especially in children of 25/26 weeks' gestation. However, in children of 29 weeks' gestation T4 supplementation is associated with more developmental problems.

INTRODUCTION

Thyroxine (T4) supplementation is necessary to ensure normal brain development in conditions where thyroid hormone supply is insufficient, such as in congenital hypothyroidism. It has recently been suggested that thyroxine should be administered to women with low normal plasma thyroid hormone levels during the first trimester of pregnancy, as an association with a delay in child development was found.[1] Another situation of concern is the case of the very preterm infant attributable to the immaturity of the infants' thyroid hormone regulation system. A period of at least 6 to 8 weeks of hypothyroxinemia occurs in these preterm infants, which is more severe with shorter gestational age.[2-4] Associations between low thyroid hormone levels and developmental problems have been reported[5-7], especially cognitive problems at school age.[5 6] T4 supplementation prevents neonatal hypothyroxinemia[8] and might therefore prevent the associated developmental problems. Follow-up of T4 supplementation in very preterm children has only been described until the age of 2 years. Apart from our own study[9], which included 200 infants <30 weeks' gestation, only 2 other studies[10 11] with smaller groups of children have been conducted. In accordance with these studies we found no improvement in developmental outcome for the total group of children. However, we did find a positive effect in mental outcome at 2 years of age for infants <27 weeks' gestation.[9]

After the age of 2 years a tremendous differentiation in skills and development continues to take place. More importantly, performance at early school age provides a more reliable picture of school-age functioning and has better predictive value for later functioning than outcome at 2 years of age. [12 13]

Therefore, we studied the effects of neonatal T4 supplementation in very preterm-born children on outcome at early school age. We focussed on effects in gestational age subgroups because of the gestational age-related results found at 2 years of age.

METHODS

Participants

Children, enrolled in our randomized, placebo controlled, clinical trial of T4 administration (8 mg/kg per day for 6 weeks)[9], were invited at the corrected age of 5 years and 8 months to participate in a follow-up study. Inclusion criteria of the original study were gestational age <30 weeks, absence of severe congenital abnormalities, no maternal endocrine disease, and no maternal drug use. Plasma free T4 (FT4) levels, determined weekly for 8 weeks, were available for all children.[9] After the neonatal period, 158 children remained in the trial: 35 children died (14 in the T4 group and 21 in the placebo group) and 7 children were withdrawn from the study.[9] In the first year, 1 child moved abroad and was lost for follow-up.

Informed consent was obtained from the parents for different parts of the follow-up study.

All investigators as well as all parents of the children remained blind for trial assignment until the last developmental assessment was completed.

This study was approved by the Committee of Medical Ethics of the Academic Medical Center in Amsterdam.

Developmental measurements at the corrected age of 5 years and 8 months

All children were examined by the same psychologist (JMB) and pediatrician (AGvW).

Cognitive functioning

The short version of the Revised Amsterdam Children's Intelligence Test for 4 to 11 years was used for assessment of cognitive functioning.[14] Subtests of the Revised Amsterdam Children's Intelligence Test refer to logical reasoning, word knowledge, word fluency, visual-motor integration, memory, and visual synthesis. The norm score (IQ score) of the test is 100 ± 15.

Behavioral assessment

To assess behavioral outcome, the Child Behavior Checklist for ages 4 to 18 (CBCL)[15] and the Teacher Report Form (TRF)[16] were used. The behavior questionnaires were mailed to the parents and the teachers 1 month before the follow-up assessment would take place. The completed questionnaires were returned by mail or received when the family attended the hospital.

Both behavior questionnaires comprise 113 descriptions of behavioral problems. Each behavior description on the questionnaire is scored: 0, when the description does not fit the child's behavior; 1, when it is occasionally correct; and 2, when it is frequently correct.

A total problem score is obtained by summing all items, with higher scores indicating more behavioral problems. Raw scores are used for the analyses as well as standardized borderline and clinical cutoff points that correspond with the norm scores of respectively 60 and 63.[15,16]

Motor outcome

The Movement Assessment Battery for Children[17] was used to assess motor skills such as manual dexterity, ball skills and balance. Scores ranged from 0 to 5: a score of 0 is given when the child passes the task and a score of 5 when it fails the task. A total motor impairment score (ranging from 0 - 40) is computed by summing the scores on all motor tasks, with

higher scores indicating more motor problems. Cutoff scores for mild and severe motor problems are represented by the 15th and 5th percentile of the reference population, respectively, corresponding with a total impairment score ≥10.5 and ≥17.

Neurological outcome

Neurologic development was qualitatively assessed according to the method of Touwen.[18] A 3-point classification was made: normal, minor neurologic dysfunction (MND) and cerebral palsy (CP). MND was diagnosed when 1 or more abnormalities occurred in posture and muscle tone, muscle power, reflexes, coordination, balance and involuntary movements. CP was classified according to Hagberg.[19]

Statistics

Univariate as well as multivariate analyses were carried out for the total group of children. The Student's *t*-test was used to compare continuous variables and the X^2-test for analyzing categorical data. The effect of T4 supplementation on outcome was tested with multivariate linear or logistic regression analysis. Predefined factors occurring before trial randomization that independently might affect developmental outcome were used as covariates: sex, educational level of the mother, ethnic background, gestation age, growth retardation at birth, intubation at birth, and use of surfactant. Treatment with antenatal steroids was not used as a covariate because results from a randomized double blind trial showed no evidence for long-term side effects of antenatal steroids in infants born between 28 and 33 weeks.[20,21] Four subgroups were formed according to weeks of gestation: 25/26 weeks, 27 weeks, 28 weeks and 29 weeks. An interaction term between T4 supplementation and gestational age subgroups was added to the model to study whether the treatment effect was equal for all gestational age subgroups. Explorative analyses were done within all subgroups, for T4 and Placebo group separately, to study if a linear effect existed between plasma FT4 levels and developmental outcome. All statistical tests (SPSS version 9.0, SPSS, Inc, Chicago, IL) were 2-sided, with $p < .05$ for statistical significance.

RESULTS

The parents of 156 children (99%) consented to participate in the follow-up study, although for 5 children permission to approach their teachers was refused. The children in the T4 group did not differ from those in the Placebo group with respect to prenatal and clinical characteristics or background variables (Table 1). Ninety-four percent of the children were

Table 1: Characteristics of the two follow up groups before and during T4 administration*

	Thyroxine Group (n=81)	Placebo Group (n=75)
Before T4 administration		
Male	40 (49%)	33 (44%)
Ethnic origin: white	67 (83%)	65 (87%)
Educational level of mother:†		
low	29 (36%)	25 (33%)
middle	39 (48%)	34 (46%)
high	12 (15%)	15 (20%)
missing	1 (1%)	1 (1%)
Gestational age (d)	198 (± 8)	197 (± 9)
Birth weight (g)	1085 (± 225)	1106 (± 237)
VSGA ‡	3 (4%)	1 (1%)
Intubation at birth	22 (27%)	25 (33%)
Surfactant	26 (32 %)	22 (29%)
Antenatal steroids	43 (53%)	42 (56%)
During T4 administration		
Broncho pulmonary dysplasia	31 (38%)	32 (43%)
O_2 at 36 weeks §	13 (16%)	16 (21%)
Cerebral hemorrhage: gr. 3 + gr. 4‖	6 (7%)	4 (5%)
Cerebral ischaemia: gr. 2 + gr. 3¶	2 (3%)	1 (1%)
Ventricular dilatation gr. 2**	2 (3%)	3 (4%)
Severely abnormal ultrasound††	9 (11%)	6 (8%)

Continuous variables are summarized as mean (SD). Categorical variables are summarized as number in group (%). VSGA indicates very small for gestational age

* No statistically significant differences were found between both groups

† Low: lower vocational education/lower general secondary education; middle: intermediate vocational education/ higher general secondary education/ pre-university education; high: high vocational education/ university

‡ VSGA < P 2.3

§ Oxygen requirement at 36 weeks' postmenstrual age

‖ Grade 3 + grade 4: cerebral hemorrhage was classified by Volpe [24]

¶ Grade 2 + grade 3: cerebral ischemia lesions were classified according to De Vries et al. [25]

** Grade 2: ventricular dilatation was performed according to Levene [26]

†† Severely abnormal ultrasound: a grade 3 or 4 hemorrhage and/or a grade 2 or 3 ischemia and/or a grade 2 ventricular dilatation

tested in the age range 5.6 yrs. to 5.8 yrs., mean age of the children at assessment was 5.7 yrs in both groups (age range in the T4 group was 5.4 yrs.- 6.8 yrs. and in the Placebo group 5.5 yrs.- 6.5 yrs.). Four children had been tested with the same assessment tool for cognitive functioning within a period of three months before our examination. These test results were obtained and used for data analysis. Six children were tested at the age of 6 years because they were hard to trace (n=2) and because the assessment was delayed due to circumstances in the home situation at the intended time (n=4, two pairs of twins).

Behavior questionnaires were scored by parents and teachers of, respectively, 144

(92%) and 147 children (94%). The CBCL was not completed for 12 children (n=6 in the T4 group and n=6 in the Placebo group) because of language problems (n=6), inapplicability for severe physically and mentally handicapped children (n=3), and for no apparent reason (n=3). The TRF was not completed for 9 children (5 in the T4 group

Table 2: Total study group: neurodevelopmental outcome at early school age*

	Thyroxine Group	Placebo Group
Cognitive Outcome (RAKIT)	n = 81	n = 75
IQ score †	93.6 (± 16.2)	95.7 (± 20.4)
≥70 - < 85	18 (22%)	15 (20%)
< 70	5 (6%)	7 (9%)
Child Behavior Checklist (CBCL)	n = 75	n = 69
Total problem score ‡	28.5 (± 22.0)	26.0 (± 21.9)
Borderline range	4 (5%)	4 (6%)
Clinical range	14 (19%)	11 (16%)
Teacher Report Form (TRF)	n = 76	n = 71
Total problem score ‡	31.5 (± 25.0)	26.8 (± 25.6)
Borderline range	7 (9%)	3 (4%)
Clinical range	15 (20%)	13 (18%)
Motor outcome (Movement ABC)	n = 81	n = 75
Motor impairment score ‡	7.2 (± 8.4)	9.9 (± 11.0)
>5th% - ≤15th%	9 (11%)	7 (9%)
≤ 5th%	9 (11%)	15 (20%)
Neurological Outcome (Touwen)	n = 81	n = 75
Normal	46 (57%)	40 (53%)
MND§	28 (35%)	26 (35%)
Cerebral palsy	7 (8%)	9 (12%)

Continuous variables are summarized as mean (SD). Categorical variables are summarized as number in group (%). RAKIT indicates Revised Amsterdam Children's Intelligence Test, Movement ABC, Movement Assessment Battery for Children

* No significant differences were found between both study groups

† High scores mean better outcome

‡ High scores mean worse outcome

§ MND: minor neurologic dysfunction

and 4 in the Placebo group); in 1 case there was no apparent reason. Compared with the respondent groups, nonrespondents on CBCL and TRF consisted of more children of nonwhite background and of more children who had suffered from chronic lung disease or ischemic brain lesions.

Outcome in the total study group

In Table 2, the different outcome measures of both study groups of children are presented.

Univariate analyses as well as multivariate analyses (adjusted for sex, educational level of the mother, ethnic background, gestational age, growth retardation, intubation at birth, and use of surfactant) showed no differences between both study groups in IQ scores, in behavioral questionnaires completed by parents and teachers, in motor outcome or neurologic outcome, nor in percentages of children receiving deviant scores on any of the developmental assessments. No effects of T4 supplementation were found on length, weight and head circumference.

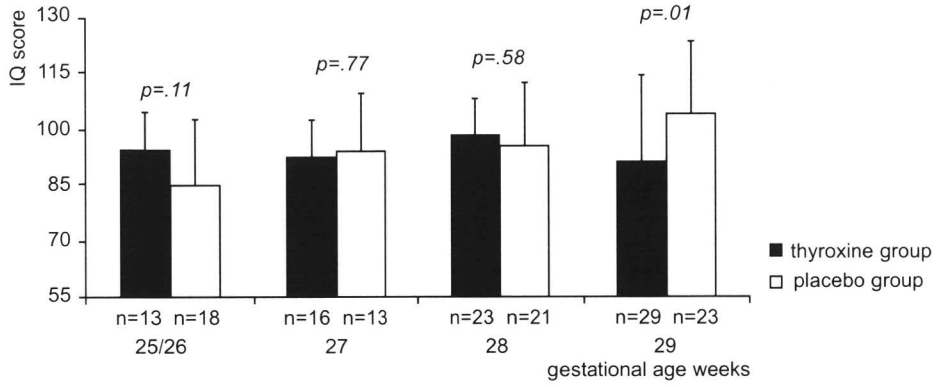

FIGURE 1: Cognitive outcome per gestational age week*
* high scores represent better outcome

Significant interactions between T4 supplementation and gestational age were found on cognitive (p=.006) and motor outcome (p=.023), indicating that the effect of T4 supplementation differed for gestational age subgroups.

Effect of T4 administration on outcome by gestational age subgroups

Distribution of clinical characteristics, such as bronchopulmonary dysplasia and intraventricular hemorrhage, has also been studied in the gestation subgroups. No differences in clinical outcome were found. We refer to an earlier report on the description of clinical characteristics in the different subgroups. [22]

Cognitive outcome

Mean IQ scores increased with gestational age within the placebo subgroups, which is not seen within the T4 subgroups (fig 1). In the subgroup of 25/26 weeks, the mean IQ score of the T4-treated children (94.2 ± 10.7) was higher than that of the placebo children (84.7 ± 18.6), but the 9.5 point difference was not statistically significant. Mean IQ scores of T4 children and placebo children were comparable in the subgroups of 27 and 28 weeks.

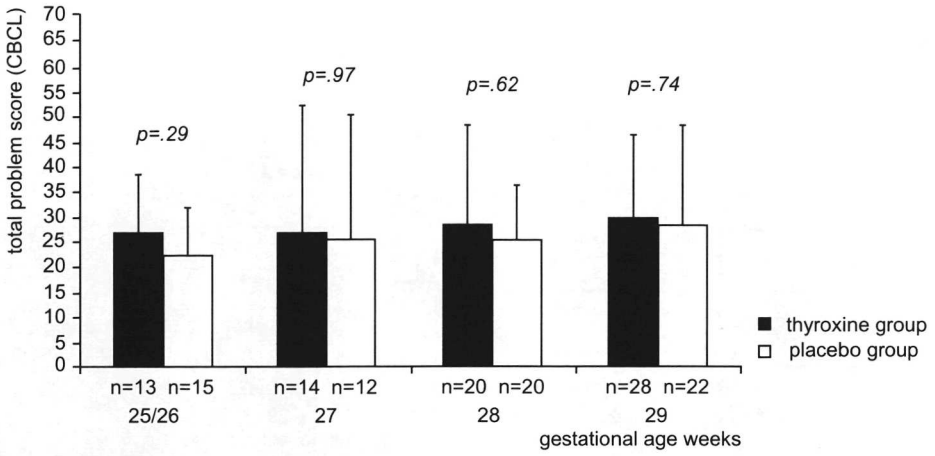

FIGURE 2: Behavioral outcome based on parental questionnaires (CBCL), per gestational age week*
* High scores represent worse outcome; no gestational age related differences were found between the study groups

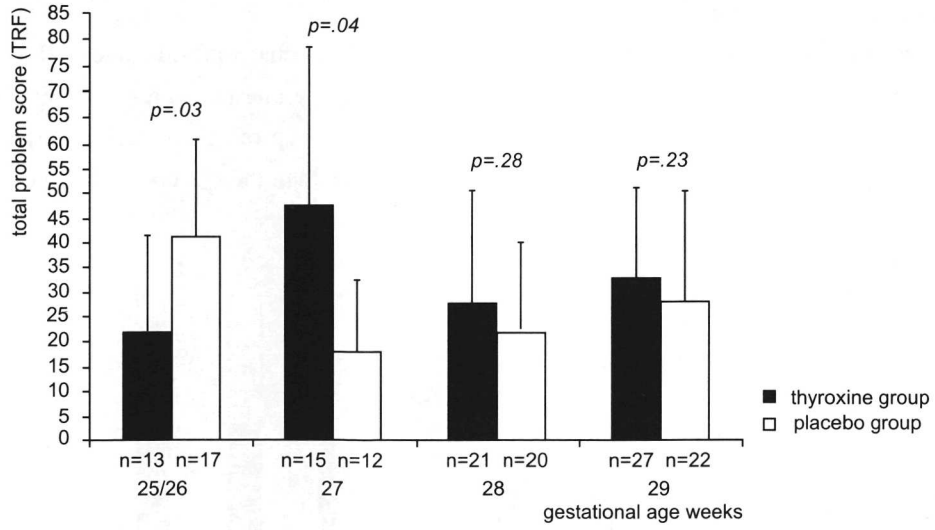

FIGURE 3: Behavioral outcome based on teachers' questionnaires (TRF), per gestational age week*
* High scores represent worse outcome

Within the gestation subgroup of 29 weeks, children in the placebo group obtained a significantly higher mean IQ score of 14.6 points compared to the children in the T4 group: 90.6 ± 19.6 vs. 105.2 ± 19. In all 4 subgroups, mean scores on subtest level showed that there were no cognitive functions specifically affected by T4 supplementation (data not shown).

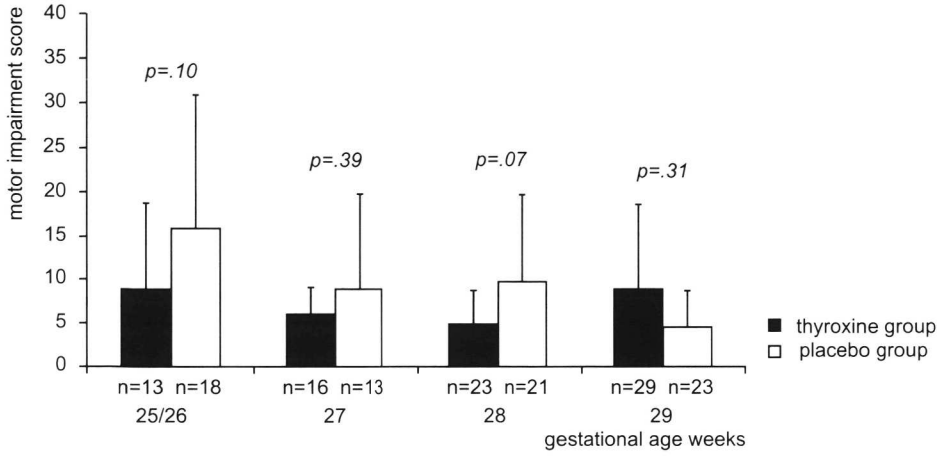

FIGURE 4: Motor outcome per gestational age week
* High scores represent worse outcome, no gestational age related differences were found between the study groups

Behavioral outcome

Based on questionnaires answered by parents (CBCL), behavioral outcome in T4 and placebo subgroups was comparable (fig 2). According to the questionnaires completed by teachers (TRF) (figure 3) T4-treated children in the subgroup of 25/26 weeks' gestation seemed to have less behavioral problems in the classroom than the placebo children of the

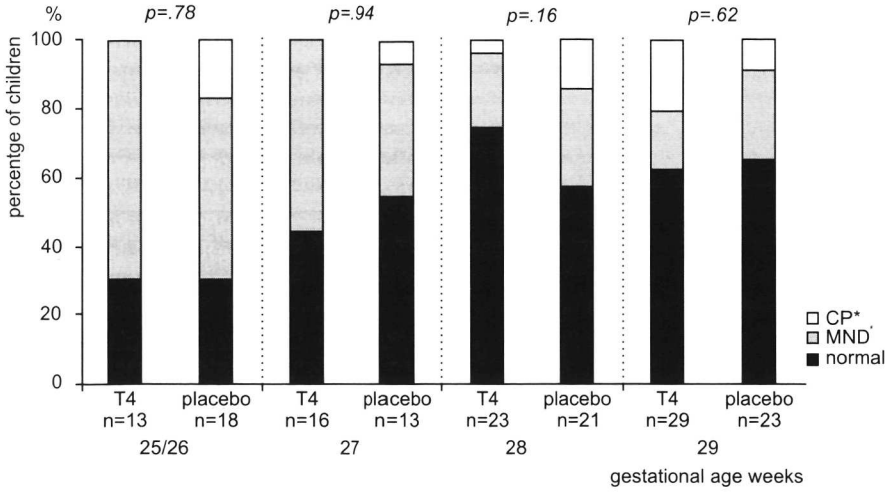

FIGURE 5: Neurological outcome per gestational age week†
† No gestational age related differences were found between the study groups
*CP: cerebral palsy
#MND: minor neurological dysfunction

same gestational age: 22.3 ± 14.5 vs. 41.2 ± 29.2. In the subgroup of 27 weeks' gestation, T4 children were described as more problematic than the placebo children 46.9 ± 29.1 vs. 16.7 ± 16.8. In the subgroups of 28 weeks' gestation and 29 weeks' gestation no differences were found.

Motor outcome

Figure 4 shows data on motor outcome. Lower motor impairment scores were found in T4-treated children of 25/26 weeks', 27 weeks' and 28 weeks' gestation, but higher motor impairment scores were found in T4-treated children of 29 weeks' gestation compared with the comparable placebo children. These differences were not statistically significant. Also on subtest level, no motor functions were found in the 4 subgroups that could have been specifically affected by T4 supplementation (data not shown).

Neurologic outcome

In the gestational age subgroups of 25/26 weeks, 27 weeks and 28 weeks CP was diagnosed in fewer T4-treated children, whereas in the subgroup of 29 weeks CP was diagnosed in more T4-treated children (figure 5). None of these differences was significant.

Relation between plasma FT4 levels and developmental outcome

No systematic pattern or relationship was found between plasma FT4 levels in the gestational age subgroups of the T4 group and the Placebo group separately for IQ scores, total behavior problem scores, motor impairment scores and neurological outcome (data not shown).

DISCUSSION

This study shows that T4 supplementation in the neonatal period does not improve developmental outcome at early school age in all children born at less than 30 weeks' gestation. However, we did find that effects of T4 supplementation on outcome differ between children of different gestational ages. In children of the youngest gestational age the effects seem positive whereas in children of the oldest gestational age these seem negative.

This is the first study on effects of neonatal T4 supplementation at early school age and therefore comparisons with similar studies cannot be made. In our study, sample sizes in the different subgroups are too small to draw definite conclusions, while dividing our study group into 4 gestational age subgroups increased the risk of finding results by chance. Bias

could also have occurred, for example, mortality was lower (although not significantly) in the T4-treated subgroup of 27 weeks' gestation (10% versus 18% in the placebo subgroup) and of 29 weeks' gestation (6% versus 14% in the placebo subgroup). The findings of our study are, nevertheless, clear enough to develop strategies for additional research in this field. The gestational age-related effects of T4 supplementation suggest a decreasing need for T4 supplementation between 25 and 30 weeks' gestation. The positive effects of T4 supplementation in infants of 25/26 weeks' gestation, although not all statistically significant, support the initiation of new trials specifically in this gestational age subgroup. Indeed, untreated infants of this gestational age have the lowest FT4 levels, as well as the highest risk of impaired developmental outcome. On the other hand, the negative effect of T4 supplementation in infants of 29 weeks' gestational age does not support supplementation of these infants with thyroid hormone. The fixed treatment dose and period could have been inappropriate for children of 29 weeks' gestation who only had low FT4 levels for a short period of time. Although neonatal plasma FT4 levels in the treated children of this subgroup were higher than those in treated children of 25/26 weeks' gestation, they were comparable to those in treated children of 27 and 28 weeks' gestation.[22] In addition, no significant relationships were found between plasma FT4 levels and developmental outcome in T4-treated children of 29 weeks' gestation. Thus, no direct evidence was found that higher neonatal plasma FT4 levels were harmful. Developmental outcome in placebo children of 29 weeks' gestation was superior to all (T4 and placebo) subgroups and, in view of the normal cognitive outcome, it might be unnecessary to supplement infants of 29 weeks' gestational age with T4.

Developmental changes in type II deiodinase expression might have played a role in the various effects we have observed in the gestational age subgroups. This enzyme converts plasma T4 to triiodothyronine for intracellular use.[23] However, little is known about the developmental pattern of type II deiodinase expression in the human brain. Our results may indicate different levels of expression of this enzyme between 25 and 30 weeks' gestation. And, if they are not attributable to chance, our findings would seem to suggest lower type II deiodinase concentrations before 29 weeks' gestation and higher levels thereafter. Only postmortem studies can support this hypothesis.

Our protocol was designed to prevent the FT4 nadir, which generally occurs 7 days after birth, and T4 supplementation was therefore started shortly after birth. Treatment protocols with a more individualized dose, for example based on a cutoff value for plasma FT4, might be more effective. However, data on cutoff values are presently not available. A problem for such a strategy is that after birth FT4 levels change from a postnatal surge above cord blood

level on day 1 to a FT4 nadir below cord blood level on day 7[9], and, therefore, separate cutoff values must be identified for different postnatal days. Before any treatment recommendations for clinical practice can be made, additional evidence from randomized trials is needed whether or not T4 supplementation can improve developmental outcome. This study shows the importance of extending follow-up until early school age as an outcome parameter of a neonatal intervention. At 1 year old, a gestational age dependent effect of T4 was not seen, whereas it was visible at the age of 2 years. It is still present at the age of 5 years, although better differentiation in relation to the developmental domain can be made. As outcome at early school age predicts school performance more reliably than assessment outcomes at earlier ages,[12,13] it also evaluates the value of early treatment for later life.

Conclusion

T4 supplementation during the first 6 weeks of life in infants <30 weeks' gestation results in a differentiated outcome pattern at early school age in relation to weeks of gestational age. New trials are required to establish whether or not thyroid supplementation improves developmental outcome, especially in children <27 weeks' gestational age.

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