Pulmonary Effects of Triiodothyronine (T₃) and Hydrocortisone (HC) Supplementation in Preterm Infants less than 30 Weeks Gestation: Results of the THORN Trial—Thyroid Hormone Replacement in Neonates

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ABSTRACT

The THORN trial was a multicenter, randomized, double-blind, placebo-controlled clinical trial to test the hypothesis that administration of triiodothyronine (T₃) and hydrocortisone would decrease mortality and respiratory morbidity in preterm infants of less than 30 wk gestation. Two hundred fifty-three infants were randomized to receive either $6~\mu g \cdot kg^{-1} \cdot d^{-1}$ of T₃ with $1~mg \cdot kg^{-1} \cdot d^{-1}$ of hydrocortisone or 5% dextrose (placebo) as a continuous i.v. infusion for 7 d. The dose was halved on d 5. Our first primary outcome was death or ventilator dependence at 1 wk, and the second was death or oxygen dependence at 2 wk. The overall mortality rate for both groups was 11.4%. Relative risk of death or ventilator dependence at 1 wk, treated *versus* placebo, was 0.87, $p = 0.2$, and death or oxygen dependence at 2 wk, 1.00, $p = 0.9$. We examined the relationship between free T₃ (FT₃) and free thyroxine (FT₄) levels in the first 7 d and the primary outcome death or ventilator dependence at 1 wk in all 253 babies. We found significant positive correlations of $p = 0.05$ for FT₃ and $p = 0.002$ for FT₄. Thus the higher the FT₃ and FT₄ levels, the better the outcome. No beneficial effects of T₃ and hydrocortisone were shown. In this study, although FT₃ levels were doubled by the treatment infusion, FT₄ levels were significantly suppressed. The lack of any beneficial effect of T₃ in our study may be explained by suppression of FT₄ in the treatment group. (*Pediatr Res* **53: 48–56, 2003**)

Abbreviations

T₃, triiodothyronine
T₄, thyroxine
HC, hydrocortisone
FT₃, free T₃
FT₄, free T₄
PROM, prolonged rupture of membranes
TT₃, total T₃
TT₄, total T₄
ENaC, epithelial sodium channel

A number of studies have demonstrated that premature babies have low levels of T₃ and T₄ (1–5) and that hypothyroxinemia has been associated with developmental problems (6–8) and increased respiratory morbidity (9, 10). Consequently, several studies have examined thyroid hormone substitution in preterm infants, but most of these have involved small numbers of subjects. One large study of T₄ given to babies of less than 30 wk gestation assessed neurodevelopmental outcome and found no overall beneficial effect (11). However mental outcome in a subgroup of T₄-treated infants less than 27 wk gestation was significantly better than in the placebo infants when tested at 2 y of age. Two studies examining respiratory factors as end points, one giving T₄ (12) and another T₃ (13), have not shown any clear-cut benefit.

In spite of improvements in neonatal care during the past few decades (14), most tertiary level neonatal units have seen an increase in the incidence (15) of bronchopulmonary dysplasia (chronic lung disease) defined as an oxygen requirement at the age of 4 wk or beyond 36 wk conceptual age. Much of the increase can be attributed to the increasing survival of very premature babies born before 30 wk gestational age, which in turn raises the question of why these infants develop chronic lung disease when pulmonary surfactants are readily available. The lungs of babies born between 23 and 28 wk gestation are

far from ready to undertake gas exchange for many reasons including immature structural maturity of the lung, inadequate pulmonary surfactant formation and secretion, and immature epithelial ion transport. The effects of high oxygen tensions (compared with fetal environment) and barotrauma from mechanical ventilation on the friable tissue have been implicated also (16). The pathophysiology underlying "new bronchopulmonary dysplasia" indicates an interference with septation (leading to fewer and larger alveoli) and abnormal vascular development (17). Proinflammatory cytokines and chronic chorioamnionitis have been suggested as causal factors (17).

The hypothesis underlying this study is that the lungs of very premature babies cannot make the transition sufficiently quickly from being a fetal organ that secretes liquid to the normal postnatal organ that absorbs liquid constantly. Throughout fetal life, lung liquid is secreted at 4 to 5 $mL\cdot kg^{-1}\cdot h^{-1}$, which at term is a volume of 300 to 500 mL passing up the trachea every day to contribute to amniotic fluid volume turnover (18, 19). Resting lung liquid volumes are maintained at approximately functional residual capacity, *i.e.* 30 mL/kg, and this volume of liquid and its secretion rate are important for lung growth (20). During labor, liquid secretion ceases and a rapid absorption of lung luminal liquid can occur at rates in excess of 40 mL/h, a change that is produced by the endogenous release by the fetus of epinephrine (21) and perhaps other mediators such as AVP (22), released as a result of the stress of labor. Epinephrine has been shown to activate sodium channels (ENaC) in the pulmonary epithelium, which allows the rapid removal of sodium ions and thus of water by osmotic forces (23). The functional appearance of the sodium channels during fetal development is under the synergistic control of thyroid hormone and of HC (24–26). The central role of ENaC in the transition at birth has been demonstrated in ENaC knockout mice: deletion of the gene coding for the α subunit of ENaC leads to early and universal death of homozygous "null" newborn animals, associated with absent clearance of lung liquid (27).

We propose that babies born very prematurely cannot clear their lung liquid adequately as a result of insufficient expression or activation of ENaC because their lungs have not been exposed to thyroid hormone and HC in adequate concentrations or for a sufficient period of time. In addition, it is possible that these babies may continue to secrete lung liquid after birth for, as a group, they have very low levels of thyroid hormone especially during the first few weeks of life (1–5). This in turn could lead to respiratory compromise and continued dependence on ventilatory support with its damaging effects on the lung.

We undertook a clinical study in which we infused T_3 and HC into preterm infants born before 30 wk gestation to ascertain whether we could alter clinical outcome as measured by death and respiratory morbidity. We used T_3, the active thyroid hormone, rather than T_4 for two reasons: *1*) this was used in the animal studies and had been proven to be effective, and *2*) postnatally most T_3 is produced by peripheral monodeiodination of T_4 and this process is immature in very preterm infants. We combined T_3 with HC because of their synergistic effect seen in the animal studies. Cortisol blood levels may be

adequate in premature babies, but there is considerable variation of blood concentrations in normal preterm (see below) and we wished to ensure that sufficient HC was present in each case.

METHODS

Four large neonatal intensive care units in London, namely Chelsea and Westminster Hospital, St. Georges' Hospital, University College Hospital, and the Whittington Hospital were involved in this trial. Ethical committee approval was obtained from each center.

Patients were recruited between January 1996 and April 1998. Our inclusion criteria were infants *1*) less than 30 wk gestation—up to 29 wk and 6 d, *2*) mechanically ventilated, *3*) less than 5 h of age, and *4*) with informed written parental consent. Any baby with a major morphologic abnormality was excluded from the trial. All babies were recruited after birth and randomized after consent was obtained.

T_3 and HC—Pilot Study

A pilot study was performed to select the dose of T_3 that would produce plasma levels of FT_3 closer to that seen in term infants at 24 h of age (1200 pg/100 mL or 18 pmol/L) (28).

The entry criteria and the timing of the infusion (the start and duration) in the pilot study were identical to that in the main randomized trial (see below). From the animal studies we extrapolated a starting dose of 3 $\mu g\cdot kg^{-1}\cdot d^{-1}$ of T_3. This, however, did not elevate plasma FT_3 levels significantly. We found that 6 $\mu g\cdot kg^{-1}\cdot d^{-1}$ of T_3 given as a continuous i.v. infusion produced plasma levels of $FT_3 > 10$ pmol/L in the first 24 h. Although this was lower than that seen in term infants, it was significantly higher than that measured in our control patients. We did not increase the dose further because of the risk of inducing adverse effects, particularly suppression of FT_4, which theoretically could affect neurodevelopment. In our control patients HC levels varied greatly and some babies had levels < 200 nmol/L. HC was given as a continuous infusion at 1 $mg\cdot kg^{-1}\cdot d^{-1}$. This produced HC levels > 400 nmol/L. Outcome was not assessed in the pilot study.

Dosage and Administration

Once the doses had been determined, liothyronine sodium (T_3; Goldsheilds Pharmaceuticals Ltd., Croydon, U.K.) and hydrocortisone sodium succinate (HC; Pharmacia & Upjohn, Milton Keynes, U.K.) were added to a solution of 5% dextrose so that a rate of 0.5 mls/kg.hour of solution was equivalent to a dose of 6 $\mu g\cdot kg^{-1}\cdot d^{-1}$ T_3 and 1 $mg\cdot kg^{-1}\cdot d^{-1}$ HC. Stabilization studies indicated that this solution was stable for up to one month. The treatment and placebo syringes were prepared by the Pharmacy Department at Charing Cross Hospital, London. The placebo was 5% dextrose alone. The "trial infusion" was started within 5 h of birth and given continuously at 0.5 $mL\cdot kg^{-1}\cdot h^{-1}$ for 7 d, the dose being halved to 0.25 $mL\cdot kg^{-1}\cdot h^{-1}$ on d 5. Although the choice of duration of treatment was arbitrary, we believed the babies should be exposed to the hormones until their own endocrine and respi-

ratory systems had time to mature, hence 7 d. The dose was halved after 5 d for 2 d to allow a period of weaning to prevent a sudden drop in hormone levels. A continuous infusion rather than intermittent daily administration was used for two reasons: *1*) the half-life of T_3 was found, from the pilot study, to be only a few hours, and *2*) we wished to obtain a relatively constant concentration of hormones in the blood because the hormone effects in the fetal animal studies were reversible within 24 h.

Hormone Analysis

Blood was collected at less than 5 h (before start of infusion), 24, 48, and 72 h of age and again on d 7, 10, and 14. The amount taken was 1 mL from babies > 1000 g and 0.5 mL from babies < 1000 g. Plasma was separated and frozen.

As the quantity of plasma obtained from each sample was relatively small, an order of priority for hormone analysis was selected. We thought that FT_3 and FT_4 were the most important as these were the active hormones. Next plasma was analyzed for TT_3 in the first 126 babies recruited and TT_4 in the next 127 babies. Any plasma left over was then analyzed for TSH and HC. All the hormones were assayed at the endocrine department at Charing Cross Hospital, London. Commercial kit (Amerlex-MAB* kit specific for each hormone, Ortho-Clinical Diagnostics, Amersham, UK) using a radioimmunoassay technique was used for hormone assay.

Recruitment and Data Collection

All babies were recruited by one of three researchers. Exclusively these three people collected all data. A software program called TELEFORM (29) was used to create our data collection forms and database. Hand-written information was then entered directly into the database (ACCESS) by means of a scanner. The program allowed us to check and verify the information before this was stored in the database.

Clinical Data

Babies were ventilated according to the practice at the hospital of recruitment. At one hospital this involved prophylactic use of high-frequency oscillatory ventilation. Two of the four centers used high-frequency oscillatory ventilation for both prophylaxis and rescue, with the decision being made by the attending clinician. In the fourth hospital only conventional ventilation was used. In all four centers surfactant was given prophylactically, the first dose within 4 h of birth and the second 12 h later. Three of the centers used the natural surfactant Curosurf (Chiesi Farmaceutical Spa, Italy) and one the synthetic surfactant Exosurf (Glaxo-Wellcome, Brentford, UK). The dosage used was that recommended by the manufacturers.

In all four centers, babies were extubated onto continuous positive airway pressure when thought to be ready by the attending clinician.

Primary Outcomes

Our first primary outcome was death or ventilator dependence at 7 d and the second was death or oxygen dependence at 2 wk. Our secondary outcomes included mean duration of ventilation, mean duration of oxygen supplementation, and oxygen dependency at 36 wk postconceptual age. Other outcomes that were noted included mean duration of hospitalization, rate of intraventricular hemorrhage, presence of patent ductus arteriosus, and sepsis.

Statistical Methods

Randomization. The Perinatal Trials Unit at Oxford conducted the randomization, with stratification for center and sex. Our pharmacist held the randomization code. Syringes containing either T_3 and HC or placebo were prepared and numbered according to the randomization code. This number became the trial number of the baby recruited. Babies were randomized after consent.

Power calculations suggested a sample size of 262 babies to have an 80% chance of detecting a 25% reduction in our primary outcomes.

Comparison of outcomes between the two groups. This was obtained by the χ^2 test. The relative risk of each outcome and confidence interval was also calculated.

Comparison of hormone levels between the two groups. To use the data as efficiently as possible hormone levels taken at time 0 (before start of infusion) and d 1, 2, 3, and 7 were converted into a single index using the "area under the curve." Measurements up to d 7 were used as this represented the period of treatment. The area under the curve was calculated using the trapezium method. There were many missing values. These were estimated from the mean of the whole sample at that time. The effect of this would be to make the two groups more similar than they should be, so any bias introduced would make the difference between treatment groups smaller rather than larger. Thus the procedure was statistically conservative. Any subjects for whom there were three or more observations missing were omitted. Areas were estimated for FT_3, FT_4, and HC. In each case the area under the curve had a positive skew distribution, so a logarithmic transformation was used. The difference between the means for the two groups was compared using the two-sample *t* test, which gave us a *p* value and 95% confidence interval. Differences were converted to their antilogarithms to give the ratio of treated to control. The results were adjusted for the following prognostic variables: gestational age, sex, birth weight, center, antenatal steroids, chorioamnionitis, presence of preeclampsia, and PROM. Analysis was performed using Stata 5.0, (Stata Corp, College Station, TX, U.S.A.).

FT_3, FT_4, and HC as predictors of outcome. For this analysis the area under the curve data for FT_3, FT_4, and HC were ranked and then divided into quintiles or fifths and tabulated against three outcomes: death or ventilator dependence at 7 d, oxygen dependence at 36 wk (using χ^2 test), and total number of days on oxygen (using Kruskal-Wallis test). The results were adjusted for the following prognostic variables: gestational age, sex, birth weight, center, antenatal steroids, chorioamnionitis, presence of preeclampsia, and PROM.

Interim analysis. A data-monitoring committee comprising a statistician, endocrinologist, obstetrician, and neonatologist examined the primary outcomes after 100 babies had been recruited and did not find a reason not to continue the trial.

They looked at the following outcomes: death by 7 d, death by 14 d, ventilation by 7 d, and oxygen supplementation at 14 d.

RESULTS

Patient characteristics. A total of 367 babies less than 30 wk gestation were identified as possible recruits. Thirty-five were excluded because mechanical ventilation was not needed. Out of the remaining 332 eligible cases, 125 babies were recruited into the treatment group and 128 into the placebo group. The two groups did not differ significantly in their baseline characteristics such as gestational age, birth weight, type of delivery, race, sex, antenatal steroids, maternal factors, PROM, type of ventilation, or surfactant given (Table 1). In 66 cases consent was refused, and in 12 cases the research team was not informed of the birth in time to recruit the infants. One infant was not recruited because of a major congenital malformation. All infants received their assigned treatment, and treatment was not discontinued in any cases.

Outcome. Our overall mortality rate was 11%. Table 2*A* summarizes the relative risk of the major outcomes. There were no significant differences in the primary outcomes between the treatment and placebo groups. There was also no difference between the groups in the rate of chronic lung disease at 36 wk postconceptual age (Table 2*B*).

Table 1. *Baseline population characteristics and mode of ventilation and surfactant therapy*

	Treatment group	Placebo group
No randomized	125	128
Mean age at trial entry (hr)	3.8 (range 1.45–9.14)	3.9 (range 0.49–8)
Normal delivery, n (%)	48 (38)	52 (40.6)
Instrumental delivery, n (%)	7 (5.7)	8 (6.3)
Emergency caesarean section, n (%)	61 (49.5)	57 (44.5)
Elective caesarean section, n (%)	8 (6.5)	10 (6)
Maternal diabetes, n (%)	1 (0.8)	2 (1.6)
Maternal hypothyroidism, n (%)	1 (0.8)	0
Pre-eclampsia, n (%)	19 (15.2)	23 (17.9)
Essential hypertension, n (%)	10 (8)	14 (10.9)
PROM > 24 hr, n (%)	37 (29.6)	38 (29.6)
Chorioamnionitis, n (%)	20 (16)	18 (14)
No received Antenatal steroids, n (%)	101 (80.8)	108 (84)
Female, n (%)	62 (49.6)	64 (50)
Race: Afro—Caribbean, n (%)	19 (15.2)	14 (10.9)
Race: Asian, n (%)	14 (11.2)	17 (13.2)
Race: Black African, n (%)	8 (6.4)	11 (8.5)
Race: White European, n (%)	76 (60.8)	81 (63.2)
Mean birth weight, g (SEM)	867 (77.5)	870 (76.9)
Mean gestational age, (wk)	26	26
No. < 27 wk gestation, n (%)	64 (51)	72 (56)
Conventional ventilation, n (%)	79 (63)	78 (61)
Oscillation, n (%)	41 (33)	43 (34)
Nasal CPAP, n (%)	3 (2)	3 (2.3)
Self ventilating, n (%)	2 (2)	4 (3.1)
Received surfactant, n (%)	114 (92)	120 (94)
Curosurf, n (%)	90 (72)	95 (74)
Exosurf, n (%)	24 (19)	25 (20)
Other surfactant, n (%)	0 (0)	0 (0)
Mean age of surfactant Administration, mins	87	90

No = Number, hrs = Hours, n = Number, (%) = Percentage, PROM = Prolonged Rupture of Membranes, g = Grams, SEM = Standard error of the mean, wks = Weeks, mins = minutes, CPAP = Continuous positive airway pressure

There were no significant differences between the two groups.

The rate of pneumothorax, pulmonary hemorrhage, intraventricular hemorrhage, periventricular leukomalacia, incidence of patent ductus arteriosus, and sepsis was similar in the two groups (Table 3). Blood pressure and heart rate were measured every 2 h for the first 48 h, and no statistical differences were noted between the treatment and placebo groups.

Mean hormone levels in the first 2 wk of life. The changes in mean plasma hormone levels for both the treatment and placebo groups are shown in Tables 4 and 5, and a graphical representation can be found on our Web site (30). In the treatment group, FT_3 levels increased from 4.9 pmol/L at less than 5 h of age to 11.5 pmol/L at 24 h and then remained at approximately this level. T_3 infusion rate was halved on d 5 and stopped on d 7. FT_3 levels thereafter declined and were similar to those in the placebo group by d 10 and 14.

In the treatment group, FT_4 levels in the first 48 h were similar to those in the placebo group, but then declined dramatically to a nadir of 4.0 pmol/L on d 7. FT_4 levels subsequently recovered to 10.7 pmol/L by d 14.

TT_3 levels in the treated group increased after the start of the T_3 infusion as expected and reached a peak level of 4.2 nmol/L at 48 h of age. This peak occurred a day later than that of FT_3.

TT_4 levels in the placebo group decreased during the first 3 d, falling from 97.2 nmol/L to 66.8 nmol/L on d 3. In the treatment group, the decrease in TT_4 levels was more precipitous, falling from 91.9 nmol/L to a lowest level of 34.0 nmol/L on d 7 but recovering to 79.3 nmol/L by d 14.

TSH levels in both treatment and placebo groups were highest at birth, 8.4 and 9.2 mU/L, respectively, and then decreased to their lowest level at 48 h of age in the placebo group and 72 h of age in the treatment group. This fall was again more dramatic in the treatment group. TSH levels at d 14 were similar in both groups. Cortisol levels in the treated group were higher than in the placebo during the period of HC infusion.

Comparison of hormone levels between treatment and placebo groups for FT_3, FT_4, and HC levels (area under the curve) during the 7-d treatment period were compared between the two groups (statistical method described earlier). There were significant differences between the treatment and placebo groups for all three hormones. FT_3 levels were twice as high (ratio of treatment to placebo, 2.1: 1; 95% confidence interval, 2.0–2.3; $p < 0.0001$, $df = 221$) and FT_4 levels significantly lower (ratio of treatment to placebo, 0.79; 95% confidence interval, 0.79–0.84; $p < 0.0001$, $df = 218$) in the treatment group. Cortisol levels were also significantly higher (ratio treatment to placebo, 1.27; 95% confidence interval, 1.07–1.51; $p = 0.006$, $df = 99$) in the treatment group.

Correlation between FT_3, FT_4, and HC. The correlations are presented for "area under the curve" for FT_3 and FT_4 in the treatment and placebo groups in Figure 1. Within each group, FT_3 and FT_4 are significantly positively correlated with each other, with moderate correlation coefficients (0.41, $p < 0.001$ for the treatment group; 0.6, $p < 0.001$ for the control group). For the pooled data, there is a slight negative correlation, because T_3 treatment depressed FT_4 (−0.13, $p = 0.06$). Cortisol is weakly correlated with FT_3 for all patients (0.28, $p = 0.003$) because the treatment group received both T_3 and HC

Table 2A. *Summary table of primary outcomes*

	n babies Treatment/control	Relative risk Treatment/control	95% confidence interval	*p* value (χ^2 squared)
Primary outcome 1				
Death or ventilator dependence 7 days	62/74	0.87	0.69–1.10	0.2
Primary outcome 2				
Death or oxygen dependence 14 days	107/124	1.00	0.89–1.11	0.9
Death by 7 days	13/15	0.90	0.46–1.76	0.7
Death by 14 days	16/17	0.97	0.52–1.79	0.9
Ventilated at 7 days	49/59	0.87	0.65–1.16	0.3
Ventilated at 14 days	40/40	1.05	0.73–1.51	0.8
Death or ventilator dependence at 14 days	56/57	1.02	0.78–1.35	0.9

There were no significant differences in outcome between the two groups.

Table 2B. *Summary table of secondary outcomes*

Secondary outcomes	Treatment group	Placebo group
Mean duration of ventilation, d (SD)	13 (13)	12 (12)
Of survivors, babies still in O_2 at 28 days, *n* (%)	86 (69)	88 (69)
Of survivors, babies still in O_2 at 36 weeks post conceptual age, *n* (%)	59 (47)	56 (51)
Mean duration of nasal CPAP, d (SD)	27 (32)	31 (32)
Mean duration of O_2 supplementation, d (SD)	32 (23)	33 (27)
Mean duration of hospitalization, d (SD)	99 (52)	107 (65)
Discharged home on O_2, *n* (%)	15 (12)	19 (15)

d = Days, (SD) = Standard deviation, *n* = number, (%) = Percentage.
There were no significant differences between the two groups.

Table 3. *Adverse effects*

	Treatment group	Placebo group
Pneumothorax, *n* (%)	16 (13)	13 (10)
Pulmonary Hemorrhage, *n* (%)	15 (12)	9 (7)
PIE, *n* (%)	24 (19)	32 (25)
IVH grade 3, *n* (%)	4 (3)	11 (9)
IVH grade 4, *n* (%)	11 (9)	8 (7)
PVL, *n* (%)	4 (3)	2 (2)
Pore encephalic cyst, *n* (%)	5 (4)	0 (0)
Hydrocephalus needing shunt, *n* (%)	3 (2)	1 (1)
PDA, *n* (%)	41 (32)	60 (48)
PDA requiring Indomethacin, *n* (%)	21 (16)	34 (19)
PDA requiring surgical ligation, *n* (%)	4 (3)	1 (1)
Sepsis (1st episode) presumed or blood culture positive, *n* (%)	63 (50)	64 (50)
Sepsis (2nd episode) presumed or blood culture positive, *n* (%)	36 (29)	36 (28)
Sepsis (3rd episode) presumed or blood culture positive, *n* (%)	9 (7)	10 (8)
NEC, *n* (%)	16 (13)	15 (12)

n = Number, PIE = pulmonary insterstitial emphysema, IVH grade 3 = Intraventricular haemorrhage filling more than half of the ventricle, IVH grade 4 = Intraventricular hemorrhage extending into the brain parenchyma, PVL = periventricular leucomalacia, PDA = patient ductus arteriosus, NEC = necrotizing enterocolitis.

There were no significant differences in adverse outcome between the two groups.

and so had raised HC, but there is no evidence of such a relationship within either treatment group.

FT₃, FT₄, and HC as predictors of outcome. FT_3, FT_4, and HC levels (area under the curve) during the 7-d treatment period were tabulated against the outcomes death or ventilator dependence at 1 wk, oxygen dependence at 36 wk postnatal age, and the median number of days in oxygen. The statistical method has been described earlier. As there was no significant difference between treatment and placebo groups, analysis of outcome was calculated for the pooled data of the two groups (that is, 253 babies). The results are presented graphically in Figure 2. The higher the FT_3 and FT_4, the smaller the percentage of babies dead or ventilated at 1 wk and the shorter the total number of days in oxygen. Although the proportion of babies on oxygen at 36 wk gestation fell with increasing FT_3 and FT_4, this was not statistically significant. Cortisol levels were associated with a U-shaped curve, *i.e.* both low and high cortisol levels were associated with a poorer outcome.

DISCUSSION

Direct comparison of the treatment and placebo groups for outcome did not show any significant beneficial affect of T_3 and HC treatment on mortality or chronic lung disease (oxygen dependency at 36 wk). Comparison of hormone levels between the two groups showed that T_3 treatment did in fact influence plasma FT_3 and FT_4 levels by significantly increasing FT_3 levels and suppressing FT_4, most likely through suppression of TSH. After cessation of T_3 treatment, TSH and FT_4 levels recovered and were not significantly different from those in the placebo group at d 14. We found that FT_3 and FT_4 levels were positively related to outcome, that is the higher the plasma FT_3 or FT_4 the more likely a baby was to survive or have less severe lung disease and spend less time in oxygen. This analysis took into account confounding variables such as gestational age, sex, birth weight, center, antenatal steroids, chorioamnionitis, presence of preeclampsia, and PROM. We found a bimodal association between HC and outcome, suggesting too high or too low levels are associated with an adverse outcome. It may be that the sickest babies are those with the highest HC levels and will have a bad outcome. Additionally, babies who for whatever reason (immaturity, severe illness) cannot mount a sufficient HC response will also have a poor outcome. These results cannot be explained by gestational age or birth weight as the data were adjusted for these variables.

One of the technical difficulties of this trial was obtaining all hormonal measurements on each blood sample because the amount of plasma was sometimes too small. It should be stressed that missing hormonal measurements are not preferentially from babies of lower gestational age and birth weight. For each hormone, at every time point, the mean gestational

Table 4. *Mean plasma hormone levels in the first 2 weeks of life: Treatment group*

	FT3 (SEM) pmol/L	FT4 (SEM) pmol/L	TT3 (SEM) nmol/L	TT4 (SEM) nmol/L	Cort (SEM) nmol/L	TSH (SEM) mU/L
<5 h of age	4.9 (0.2)	14.0 (0.6)	0.8 (0.08)	91.9 (4.8)	653.9 (135.4)	8.4 (0.8)
	n = 109	*n* = 105	*n* = 51	*n* = 62	*n* = 53	*n* = 62
24 h of age	11.5 (0.3)	12.3 (0.5)	2.9 (0.17)	81 (3.9)	1003.6 (185.4)	1.3 (0.3)
	n = 114	*n* = 112	*n* = 55	*n* = 74	*n* = 59	*n* = 75
48 h of age	11.0 (0.3)	10.5 (0.4)	4.2 (1.14)	73.6 (3.8)	670.7 (62.0)	0.5 (0.2)
	n = 112	*n* = 108	*n* = 53	*n* = 67	*n* = 53	*n* = 58
72 h of age	10.5 (0.3)	8.2 (0.3)	2.8 (0.21)	62.2 (3.1)	621.2 (51.4)	0.3 (0.2)
	n = 107	*n* = 101	*n* = 52	*n* = 60	*n* = 53	*n* = 52
Day 7	4.6 (0.3)	4.0 (0.3)	1.8 (0.17)	34.0 (1.6)	440.1 (53.1)	0.5 (0.2)
	n = 95	*n* = 91	*n* = 45	*n* = 54	*n* = 51	*n* = 51
Day 10	3.6 (0.1)	7.9 (0.6)	0.7 (0.06)	60.1 (4.5)	297.9 (28.6)	4.7 (0.7)
	n = 93	*n* = 88	*n* = 42	*n* = 56	*n* = 51	*n* = 55
Day 14	4.1 (0.1)	10.7 (0.4)	0.8 (0.06)	79.3 (3.8)	258.9 (19.5)	3.5 (0.41)
	n = 91	*n* = 89	*n* = 36	*n* = 62	*n* = 54	*n* = 57

FT3 = Free T3, FT4 = Free T4, TT3 = Total T3, TT4 = Total T4, Cort = Cortisol, TSH = thyroid stimulating hormone. Figures in brackets are the standard error of the means (SEM), *n* is the number of babies. FT3 and FT4 were considered the most important and thus the majority of babies have results for these two hormones.

**Table 5.** *Mean plasma hormone levels in the first 2 weeks of life: Placebo group*

	FT3 (SEM) pmol/L	FT4 (SEM) pmol/L	TT3 (SEM) nmol/L	TT4 (SEM) nmol/L	Cort (SEM) nmol/L	TSH (SEM) mU/L
<5 h of age	4.9 (0.17)	15.0 (0.5)	0.8 (0.06)	97.2 (5.3)	481.7 (62.6)	9.2 (1.1)
	n = 108	*n* = 105	*n* = 50	*n* = 57	*n* = 53	*n* = 53
24 h of age	4.0 (0.12)	12.6 (0.4)	0.6 (0.07)	83.5 (4.9)	623.8 (82.3)	2.6 (0.3)
	n = 117	*n* = 112	*n* = 55	*n* = 68	*n* = 63	*n* = 67
48 h of age	4.1 (0.18)	12.0 (0.4)	0.5 (0.02)	81.5 (4.6)	458.2 (48.0)	1.8 (0.2)
	n = 115	*n* = 112	*n* = 54	*n* = 66	*n* = 56	*n* = 65
72 h of age	3.6 (0.09)	10.1 (0.4)	0.5 (0.02)	66.8 (3.8)	507.6 (51.7)	2.0 (0.4)
	n = 107	*n* = 101	*n* = 48	*n* = 59	*n* = 50	*n* = 62
Day 7	4.0 (0.15)	9.7 (0.5)	0.6 (0.05)	68.2 (4.1)	378.1 (41.1)	4.3 (0.6)
	n = 101	*n* = 96	*n* = 43	*n* = 57	*n* = 53	*n* = 58
Day 10	4.1 (0.19)	10.0 (0.4)	0.6 (0.05)	68.1 (4.1)	305.9 (28.8)	4.3 (0.5)
	n = 90	*n* = 88	*n* = 40	*n* = 56	*n* = 52	*n* = 61
Day 14	4.3 (0.12)	11.0 (0.4)	0.8 (0.07)	74.8 (4.2)	294.4 (31.1)	3.3 (0.4)
	n = 92	*n* = 89	*n* = 39	*n* = 55	*n* = 52	*n* = 58

FT3 = Free T3, FT4 = Free T4, TT3 = Total T3, TT4 = Total T4, Cort = Cortisol, TSH = thyroid stimulating hormone. Figures in brackets are the standard error of the means (SEM), *n* is the number of babies. FT3 and FT4 were considered the most important and thus the majority of babies have results for these two hormones.

age and the mean birth weight of the babies from whom a measurement was obtained was 26 wk and 861g, respectively.

One of the entry criteria of the study was that all babies had to be on a mechanical ventilator. [This excluded a small number of babies (approximately 35) who did not require ventilation.] Our study population thus comprised the sickest individuals, but because the study was randomized at entry any beneficial effect of intervention should have been observed.

Previous trials of thyroid hormones in preterm infants have shown no significant improvement in mortality, respiratory morbidity, and neurodevelopmental outcome when either T_4 or T_3 have been administered alone (13, 31–33). In a large, multicenter, randomized, placebo-controlled trial of T_4 in preterm infants less than 30 wk gestation, Van Wassenaer *et al.* (34, 35) showed that supplementation of T_4 suppressed TSH and TT_3 levels while elevating TT_4 and FT_4. This study comprised 200 infants, and T_4 was given daily for 6 wk. Neurodevelopmental assessment at 2 y (8, 36) and early school age (37) showed no benefit of T_4 in the whole study group, but in a subgroup of babies less than 27 wk gestation, T_4 supple-
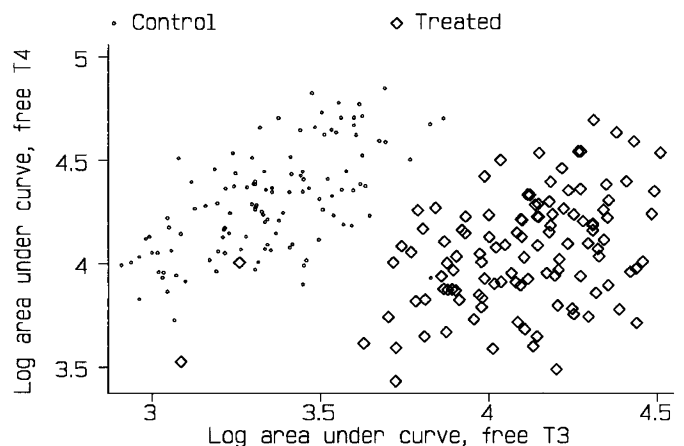
Figure 1. Correlation between FT_3 and FT_4. FT_3 and FT_4 are positively correlated with each other in both the control and treatment groups.

mentation seemed to have a positive effect on neurodevelopment whereas in the subgroup of 29 wk, T_4 supplementation seemed to have a negative effect. The sample sizes in the
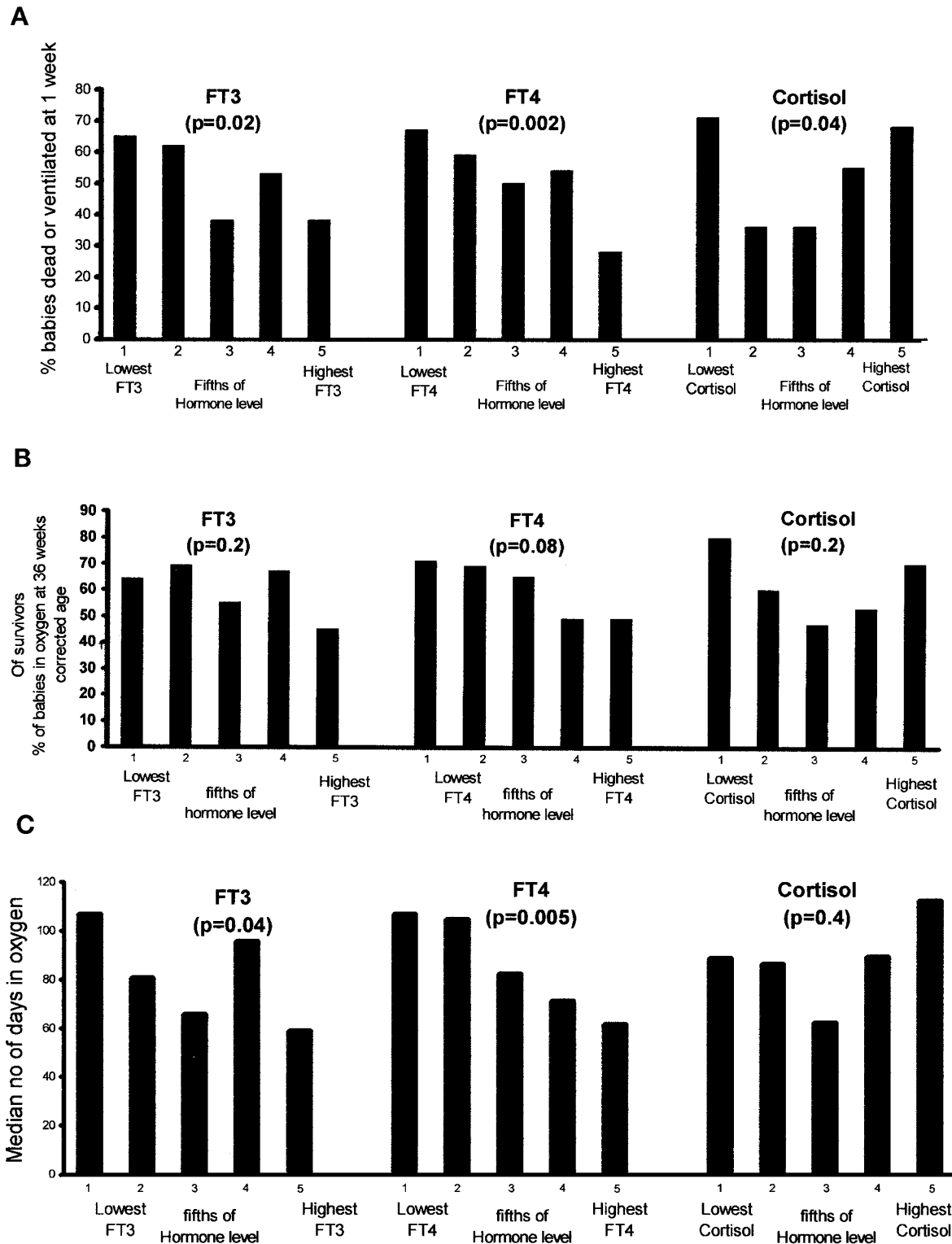
Figure 2. Outcomes by fifths of hormone levels area under the curve. Hormone levels were ranked and divided by quintiles into fifths. Hormone levels increased from 1 (lowest fifth) to 5 (highest fifth).

subgroups are too small to draw definite conclusions. The only trial to have shown any overall benefit is one in which both T_4 and T_3 were given together (38). In this trial the mortality was reduced from 29% to 6.6%, but the results must be interpreted with caution because the study population included any baby less than 37 wk gestation and only 11% of the treated group and 16% of the untreated group were < 31 wk. The majority of babies in that trial were therefore more mature and larger than the babies in our trial. Also the number of babies recruited were much smaller, 45 in the treated group, 55 in the non-

treated group. Furthermore, this trial was conducted in the presurfactant era. Nevertheless, this trial suggests that both T_3 and T_4 may be necessary for a beneficial clinical effect. One other study that should be mentioned is that by Watterberg *et al.* (39), who gave continuous low-dose HC (1 mg·kg^{-1}·d^{-1}) for 12 d to preterm infants to prevent chronic lung disease. These investigators showed significantly higher survival without oxygen at 36 wk postconceptual age in the group of infants receiving HC. This was not found in our group of infants. The numbers of infants in the study by Watterberg *et al.* (39) was much smaller (40 in total) with a high rate of chorioamnionitis (70% in the treatment group and 45% in the placebo, compared with 16% in our study). The difference in the result between their study and ours is perhaps related to a smaller number of subjects or to a different pathophysiologic process.

There is considerable interest in the effects of thyroid hormones on neurodevelopmental outcome in premature babies (37, 40, 41). Our study is not yet sufficiently advanced for these data to be collected. Indications that outcome differs after thyroid hormone replacement before and after 27 wk gestation (8, 36, 37) were not known when this trial was planned and initiated. It would be statistically improper to perform *post hoc* subgroup analysis comparing babies before and after this gestation because our study was not designed with this in mind (42–44). However, based on work by Van Wassenaer *et al.* (36, 37), we investigated the possibility that treatment effect was different at different gestational ages. An interaction between treatment and gestation was sought in a logistic regression predicting ventilation or death at 7 d. The interaction was not significant ($p = 0.6$). This was also the case for ventilation and death at 14 d ($p = 0.6$) and for ventilation, oxygen, and death at 14 d ($p = 0.1$).

CONCLUSION

In our trial we significantly raised FT_3 and TT_3 levels by T_3 supplementation but in doing so, suppressed FT_4, TT_4, and TSH levels. If high levels of both FT_3 and FT_4 are required for a good outcome, this may be a reason why no net beneficial treatment effect was seen in our trial. We cannot conclude from our results or previous trials that low levels of FT_4 and FT_3 are causally related to disease severity. Low levels of FT_3 and FT_4 may be just a marker of disease severity. To clarify these arguments a randomized multicenter trial needs to be undertaken supplementing both T_3 and T_4.

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