A Randomized, Masked Study of Triiodothyronine Plus Thyroxine Administration in Preterm Infants Less Than 28 Weeks of Gestational Age: Hormonal and Clinical Effects

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ABSTRACT

A randomized, placebo-controlled, masked study was conducted of the responses of thyroid parameters, cortisol, and the cardiovascular system to a single dose of triiodothyronine (T_3) 24 h after birth, followed by a daily dose of thyroxine (T_4) during 6 wk to infants <28 wk gestational age. Thirty-one infants were assigned to three groups: 1) group A: T_3 24 h after birth plus daily T_4 during 6 wk; 2) group B: placebo T_3 and T_4 during 6 wk; and 3) group C: placebo T_3 and placebo T_4 . T_4 , free T_4 , T_3 , free T_3 , reverse T_3 , thyroid-stimulating hormone, and cortisol were measured in cord blood and on days 1, 3, 7, 14, 21, 42, and 56. Data on pulse rate, blood pressure, and cumulative dose of inotropic agents were collected. T_3 (0.5 $\mu\text{g/kg}$) resulted in a plasma increase until day 3. Thereafter, plasma T_3 levels were comparable between the groups. T_4 , free T_4 , and reverse T_3 were increased in groups A and B during the period of T_4 administration. Thyroid-stimulating hormone suppression was of shorter duration in group A. T_3 and T_4 administration did not have any

effect on cortisol levels. We did not find any effects of T_3 or of T_4 administration on the cardiovascular system. A single injection of T_3 (0.5 $\mu\text{g/kg}$) given 22–26 h after birth only leads to a 2-d increase of T_3 levels and does not have effects on the cardiovascular system. This study does not support the use of T_3 according to our regimen in preterm infants. (*Pediatr Res* 55: 248–253, 2004)

Abbreviations

T_3 , triiodothyronine
 T_4 , thyroxine
TSH, thyroid-stimulating hormone
GA, gestational age
r T_3 , reverse T_3
FT $_4$, free T_4
FT $_3$, free T_3

Thyroid hormones play an important role in normal growth and development of the CNS (1, 2). In term infants, thyroxine (T_4) and triiodothyronine (T_3) increases shortly after birth. In premature infants, transient hypothyroxinemia after birth is a common finding (3–7). This hypothyroxinemia is characterized by low levels of T_4 and T_3 , which do not cause elevations in thyroid-stimulating hormone (TSH) above 20 mU/L. The degree of hypothyroxinemia is related to gestational age (GA) and the severity of neonatal disease. Low T_3 and T_4 levels in premature infants have been found to be associated with poor neurologic and developmental outcome (8–11).

Transient hypothyroxinemia is a multicausal phenomenon in which immaturity of thyroid hormone metabolism with high activity of deiodinase type 3 together with factors such as

immaturity of the hypothalamo-pituitary-thyroid axis and the sudden interruption of the maternal contribution to fetal thyroid hormone pools are involved. Thyroid hormone supplementation in preterm infants has been the subject of several clinical studies with clinical and neurodevelopmental parameters as primary outcome (12–14). To date, no clear effect of supplemental T_4 treatment on neurodevelopmental outcome has been demonstrated. In an earlier study, however, we observed that a subgroup of T_4 -treated infants of <29 wk GA tended to have a better developmental outcome than infants of similar GA in the placebo group (13, 15).

T_4 administration to preterm infants of <30 wk GA did not result in increased plasma T_3 levels; in fact, it resulted in decreased plasma T_3 levels and increased plasma reverse T_3 (r T_3) levels (16). It was suggested that this T_3 decrease was caused by lower endogenous thyroidal T_3 production as a result of TSH suppression and that, because of low thyroidal and hepatic type 1 deiodinase activity and high deiodinase type 3 activity, an increase in plasma T_4 did not result in an increase in plasma T_3 .

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Although the T₃ decrease after T₄ administration did not result in worse clinical outcome, a T₃ increase shortly after birth could very well improve clinical outcome. We hypothesized that a single dose of T₃ is able to switch on deiodinating enzymes and thus simulate the rapid postnatal increase of T₃ levels as is especially seen in more mature infants. This increase in T₃ levels is thought to be necessary for metabolic adaptation after birth.

In an earlier study using historical controls, we described that a single dose of T₃ 12 h after birth resulted in a sustained increase of plasma T₃ both if given as a single treatment and in combination with 6 wk of T₄ supplementation. Because this study was done with a historical control group, these results need to be reproduced in a randomized trial (17).

The aim of the current study was to investigate the hormonal effects of three supplementation schemes (T₄ plus T₃, T₄ plus placebo, and placebo) in a randomized, masked way in infants <28 wk GA. In addition, we measured plasma cortisol levels concurrently with thyroid hormone levels. This was done because, to our knowledge, until now, there are no reports on the influence of transient hypothyroxinemia in preterm infants on adrenal cortex function, whereas glucocorticoid hormones and thyroid hormones are known to be functionally interrelated with respect both to maturational effects and to influencing each other's regulatory pathways (18, 19).

In several pediatric studies, it has been suggested that T₃ administration improves myocardial function, especially after cardiac surgery (20–22). In an earlier study, we found higher heart rates in children who received only T₄ (23). For studying the effects of T₃ plus T₄ administration on the cardiovascular system, intra-arterial blood pressure, heart rates, and cumulative doses of inotropic agents were measured in all infants included in the current study.

METHODS

Eligibility and randomization. This study was approved by the Committee of Medical Ethics of the Academic Medical Center in Amsterdam (The Netherlands) and by the National Committee on Human Research. Infants who were admitted to our neonatal intensive care unit and were born between September 2000 and September 2001 with a GA <28 wk were eligible for the study. Infants were excluded when they had a severe congenital anomaly or when there was maternal endocrine disease. When informed consent had been obtained from at least one of the parents within 24 h after birth, the infant was included in the study.

After inclusion, the infants were randomized to receive T₃ plus T₄ (group A), placebo-T₃ plus T₄ (group B), or placebo-T₃ plus placebo-T₄ (group C). Randomization took place with the use of a computerized randomization program in blocks of five. Randomization was stratified according to GA (27 wk and <27 wk). All investigators, medical staff, and parents remained unaware of the infants' study-group assignment throughout the study.

Intervention. For each infant who entered the study, a numbered set of 1 ampoule containing T₃ or placebo and 50 ampoules containing T₄ or placebo was prepared. T₃ was given

in a single i.v. dose of 0.5 µg/kg 22–26 h after birth. T₄ was given in a daily i.v. dose of 8 µg/kg during 42 d starting immediately after the single dose of T₃. As in previous studies of our group (13, 17), T₄ was given by enteral route when all feeding was given enterally.

Thyroid hormone and cortisol determinations. The primary outcome was thyroid function measured as plasma levels of T₄, free T₄ (FT₄), T₃, free T₃ (FT₃), rT₃, TSH, and plasma cortisol levels. Blood samples (1 mL) were taken from cord blood 24 h after birth (just before T₃ administration) and again on days 3, 7, 14, 21, 42, and 56. Furthermore, 0.3-mL blood samples were taken 30, 120, and 360 min after T₃ administration for determination of T₃ levels.

T₄, T₃, and rT₃ were measured by in-house RIA methods. FT₃, FT₄, and TSH were measured by time-resolved fluoroimmunoassay (Delfia FT₄, respectively, Delfia FT₃ and Delfia hTSH Ultra; Wallac Oy, Turku, Finland). Cortisol was measured by luminescence enzyme immunoassay (Immulite; Diagnostic Products Corporation, Los Angeles, CA, U.S.A.)

Detection limits were as follows: T₄, 5 nmol/L; T₃, 0.3 nmol/L; rT₃, 0.03 nmol/L; FT₃, 1 pmol/L; FT₄, 2 pmol/L; TSH, 0.01 mU/L; and cortisol, 30 nmol/L. Intra-assay variations were as follows: T₄, 2–4%; T₃, 3–4%; rT₃, 4–5%; FT₃, ±6%; FT₄, 4–6%; TSH, 1–2%; cortisol, 3.6–6.4%. Interassay variations were as follows: T₄, 3–6%; T₃, 7–8%; rT₃, 5–9%; FT₃, ±9%; FT₄, 5–8%; TSH, 3–4%; cortisol, 4.7–9.0%.

Cardiovascular measurements. Secondary outcomes were daily mean heart rate, daily mean intra-arterial blood pressure during the first week of life, and cumulative dose of inotropic agents. These data all were collected prospectively. Daily mean heart rate and intra-arterial blood pressure were calculated as the mean of four values at predefined time points (0400, 1000, 1600, and 2200 h). Cumulative doses of inotropic agents were calculated over the total study period and each of the first 4 d after T₃ administration separately.

Statistical analysis. Data analysis was done using SPSS version 10.0.7 (SPSS Inc., Chicago, IL, U.S.A.). The one-way ANOVA with Bonferroni *post hoc* analysis was used to compare continuous variables in the three study groups. For analysis of categorical data, the χ^2 -test (3 × 2 tables) was used. Statistical significance was set at $p = 0.05$.

RESULTS

Patients. Between September 1, 2000, and September 1, 2001, 42 infants were eligible for the study. Five infants died before consent could be asked. For three infants, consent was not given. Two infants were excluded because of severe congenital malformations and one because of thyroid illness of the mother.

Population characteristics of the remaining 31 infants enrolled in the study are shown in Table 1. In group A, mean birth weight was lowest and percentage of small-for-gestational-age infants was highest (NS). Clinical characteristics of the infants who were enrolled in the study are shown in Table 2. Infants in group A seemed to be sicker because they had a significantly higher incidence of intraventricular hemorrhage grades 3 and 4. They also needed higher cumulative doses of inotropic

Table 1. Baseline characteristics of the infants in the three study groups

	Group A (T ₃ ⁺ T ₄ ⁺) (n = 11)	Group B (T ₃ ⁻ T ₄ ⁺) (n = 10)	Group C (T ₃ ⁻ T ₄ ⁻) (n = 10)
Birth weight (g)	889 ± 60	982 ± 67	1067 ± 35
Gestational age (d)	189 ± 1.25	190 ± 1.36	188 ± 1.07
Birth weight <10th percentile*	3 (27)	1 (10)	0 (0)
Male/female	8/3	5/5	7/3
Premature rupture of membranes*	3 (27)	1 (10)	3 (30)
Antenatal steroids*	9 (82)	10 (100)	8 (80)
Apgar score at 5 min			
Median	8	8	8
Interquartile range	3–10	4–9	4–9
Intubation at birth*	9 (82)	8 (80)	8 (80)

Plus-minus values are means ± SEM. Other values are number of infants. There were no statistically significant differences among the three groups.

* Number of infants and (percentage of total study group).

Table 2. Clinical characteristics of the infants in the three study groups

	Group A (T ₃ ⁺ T ₄ ⁺) (n = 11)	Group B (T ₃ ⁻ T ₄ ⁺) (n = 10)	Group C (T ₃ ⁻ T ₄ ⁻) (n = 10)
Surfactant therapy*	7 (64)	7 (70)	6 (60)
Time on mechanical ventilation (d)†	11.4 ± 2.9	10.9 ± 1.1	11.6 ± 4.9
Time on parenteral nutrition (d)†	19.7 ± 4.1	19.7 ± 4.7	20.2 ± 3.6
Oxygen dependency at 28 d postnatal age*‡	4 (57)	6 (86)	7 (88)
Dexamethasone therapy*§	1 (9)	2 (20)	1 (10)
Cumulative dose of inotropic agents (mg/kg)	110.5 ± 63.0	45.9 ± 22.4	30.6 ± 16.2
Intraventricular hemorrhage grades 3 and 4*	4 (36)	1 (10)	1 (10)
Cystic periventricular leukomalacia*	0 (0)	1 (10)	0 (0)
Septicemia*‡	6 (55)	1 (10)	4 (40)
Death*	4 (36)	3 (30)	2 (20)

Plus-minus values are means ± SEM.

* Number of infants and (percentage of total study group).

† Analysis of surviving infants only.

‡ Number of children with at least one period of septicemia, confirmed by positive bacterial culture.

§ Dexamethasone therapy was indicated when an infant could not be weaned from the ventilator after 2 wk of mechanical ventilation. Dexamethasone was given in a course of 3 wk in a daily dose of 0.5 mg/kg tapered to 0.1 mg/kg.

|| $p = 0.047$; there were no statistically significant differences in the other clinical characteristics among the three groups.

agents and had more septicemia than infants in groups B and C, but these differences were not significant. All 31 children included received the intervention as described above until day 42 or, if earlier, until death.

Hormonal outcome. Figure 1 shows the time course of the mean plasma concentrations of T₃, FT₃, T₄, FT₄, TSH, rT₃, and cortisol. Mean T₃ levels in group C (placebo group) remained low at approximately 0.7 nmol/L until approximately day 7; thereafter, mean T₃ levels rose gradually to approximately 3.0 nmol/L on day 56.

In group B, T₃ levels were similar to the placebo group until approximately day 3. From day 7 onward, however, T₃ levels remained lower compared with the placebo group without reaching statistical significance.

In group A, after T₃ administration, there was a 200% increase compared with groups B and C with a maximum at 30 min after injection. At 5.5 h after this maximum, T₃ levels were already decreased by 30%. On day 3, T₃ levels were comparable to levels in group B. In group A, T₃ concentrations were somewhat higher on day 21 and day 42 compared with group B but not significantly.

Mean FT₃ levels remained comparable among the three groups until day 21. On day 42, the mean FT₃ level in group B was lower but not significantly lower than the mean FT₃ levels

in groups A and C. On day 56, mean FT₃ levels were comparable among the groups.

Mean FT₄ levels in group C remained between 10.3 and 12.9 pmol/L during the first 14 d and increased slowly to approximately 15 pmol/L on day 56. In groups A and B, mean FT₄ levels showed a clear elevation in the first 21 d of T₄ administration. Thereafter, the differences with the placebo group gradually disappeared. Two weeks after discontinuation of T₄ administration, FT₄ levels were similar in the three groups. T₃ administration did not have any effect on mean FT₄ levels.

Mean T₄ levels showed the same pattern as the mean FT₄ levels, but significance was not reached. Mean TSH levels in all groups initially showed the highest values (approximately 7 mU/L) in cord blood. In group C, the mean TSH levels dropped to approximately 3 mU/L at 24 h after birth and showed an increase at approximately day 14. Thereafter, mean TSH levels gradually decreased again to approximately 3 mU/L.

In groups A and B, mean TSH levels fell deeper to <1 mU/L on day 3. Mean TSH levels were equally suppressed in groups A and B during the first 21 d. After day 21, mean TSH levels in group A seemed to be less suppressed than in group B, and on day 42, mean TSH levels were decreased only in the children who received only T₄. After cessation of T₄ administration, TSH levels were comparable in all three groups.

Figure 1. Hormonal outcome. Plasma concentrations of T₃ (A), FT₃ (B), FT₄ (C), T₄ (D), TSH (E), rT₃ (F), and cortisol (G). Values presented are means $\pm$ SEM. ■, group A; ▲, group B; □, group C. The x axis represents time after birth. The x axis of A consists of three parts with different scales (birth to 24 h after birth, 30–360 min after T₃ administration, and day 3 to day 56 after birth). The moment of T₃ administration and the period of T₄ administration are indicated. Statistical significance ($p < 0.05$) is indicated with * for significance compared with group C and with # compared with group B. In C, the * on day 7 indicates statistical significance of group A compared with group C.

Mean rT_3 levels in all groups were highest in cord blood (group A, 5.4 ± 0.8 nmol/L; group B, 3.0 ± 0.5 nmol/L; group C, 3.9 ± 0.4 nmol/L). During the whole period of T_4 administration, mean rT_3 levels were higher in groups A and B compared with those in group C, although significance was not reached at all points. T_3 administration did not influence the time course of mean rT_3 levels.

Mean cortisol levels showed a peak at 24 h after birth (before T_3 and T_4 administration was started) and a lower peak 14 d after birth in all groups and stayed comparable between the groups. T_3 and T_4 administration did not influence the time course of cortisol levels.

Cardiovascular outcome. The cumulative doses of inotropic agents in the three groups are shown in Table 2. Mean heart rates, mean arterial blood pressure, and cumulative dose of inotropic agents showed no statistically significant differences among the three study groups, although the cumulative dose of inotropic agents was somewhat higher in group A compared with groups B and C. Even during the period of higher T_3 levels (days 1–3) in group A, there were no significant differences in mean heart rate, mean daily blood pressure, or daily use of inotropic agents.

DISCUSSION

In this randomized, placebo-controlled trial, we have studied the effect of T_3 plus T_4 administration in comparison with T_4 supplementation alone and with a placebo-treated control group on thyroid hormone and cortisol levels and on the cardiovascular condition in preterm infants. We found a significant, short-lasting increase in T_3 levels after the T_3 bolus without any effect of T_3 administration on concentrations of T_4 , FT_4 , and rT_3 . TSH levels in the group that received combined T_3 and T_4 were less suppressed on day 42 than in the group that received T_4 alone.

In an earlier study from our group (17), we described a longitudinal T_3 increase after a single T_3 dose, given 12 h after birth, in comparison with historical controls. We hypothesized that this T_3 increase was caused by a T_3 -mediated induction of type 1 deiodinase expression (24), most probably of thyroidal origin, causing increased levels of T_3 as a result of increased conversion of T_4 to T_3 . In this study, our findings are less strong.

T_3 is known to be decreased as a result of T_4 administration (16). Indeed, also in this study, T_3 concentrations were in the lowest range in the T_4 group. In the T_4 plus T_3 group, T_3 concentrations were somewhat higher on day 21 and day 42 compared with the T_4 group, but not significantly.

TSH seemed to be less suppressed in the T_4 plus T_3 group, compared with the T_4 group on day 42. A possible explanation for this higher TSH concentration could be the more severe illness in this group with a more pronounced rebound in TSH secretion when nonthyroid illness resolved.

In an earlier study, we found a clear nadir in the mean FT_4 concentration at approximately day 7 in a placebo group of preterm infants (25). It was also found that disease decreased FT_4 concentrations, especially during the first week of life. In a recent and larger study from the United Kingdom (26), an

FT_4 nadir was also found in infants of comparable GAs. In the present study, we did not find this nadir in the mean FT_4 concentrations in the placebo group, although our lowest FT_4 concentrations between day 3 and day 14 were well comparable with those from our earlier study (25). Although we cannot readily explain the different course in time in the placebo group, it could be due to the somewhat better clinical condition in this small study group.

Cortisol levels in all three study groups showed a longitudinal pattern similar to that described by others in preterm infants (27, 28). Although glucocorticoid hormones and thyroid hormones are known to influence each other's regulation in animal studies (18), we could not demonstrate any effect of T_3 and/or T_4 supplementation on cortisol levels. This is an important observation, as hypocortisolism is often suspected in sick preterm infants, and the need for cortisol supplementation in these infants is under ongoing debate (29). As cortisol levels did not differ among the study groups at time points on which low thyroid hormone levels were measured in one or two study groups, our study suggests that hypothyroxinemia is not involved in the development of hypocortisolism. In a recent study published by Biswas *et al.* (26), no effect of simultaneous administration of T_3 and hydrocortisone on pulmonary outcome was found, whereas in agreement with our results, no relationship between free thyroid hormone concentrations and plasma cortisol levels was found within the study group.

Several studies have suggested that T_3 and T_4 administration influences the cardiovascular system (20–23). We did not find any effect of T_3 or T_4 administration on the cardiovascular parameters measured. A possible explanation for this negative finding is the worse clinical condition of the infants in the group that received T_3 plus T_4 requiring relatively more inotropic agents for low blood pressure. It could also be that only a regimen of daily T_3 administration results in measurable cardiovascular effects.

Indeed, that our group A had a lower mean birth weight and a less favorable clinical course is a limitation in the interpretation of the results of this study. In this group, there were more deaths (NS) and significantly more infants with grades 3 and 4 intracranial bleeding. We do not believe that there is a causal relationship between T_3 plus T_4 administration and the clinical course, because of the unchanged cardiovascular parameters and the far too low power of this study to pick up such an effect, but of course, we cannot rule it out either.

The lack of both positive clinical findings and pronounced changes in thyroid hormone levels, especially T_3 levels, does not support the use of T_3 in preterm infants according to our regimen. For future studies in this field this could indicate that other treatment regimens, for example, with a daily or higher dose of T_3 , might be more successful in improvement of both hormonal and clinical outcome.

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REFERENCES

- Bernal J, Nunez J 1995 Thyroid hormones and brain development. *Eur J Endocrinol* 133:390–398
- Timiras PS, Nzekwe EU 1989 Thyroid hormones and nervous system development. *Biol Neonate* 55:376–385
- Adams LM, Emery JR, Clark SJ, Carlton EI, Nelson JC 1995 Reference ranges for newer thyroid function tests in premature infants. *J Pediatr* 126:122–127
- Cuevas RA 1978 Thyroid function in healthy premature infants. *J Pediatr* 92:963–967
- Hadeed AJ, Asay LD, Klein AH, Fisher DA 1981 Significance of transient postnatal hypothyroxinemia in premature infants with and without respiratory distress syndrome. *Pediatrics* 68:494–498
- Harkavy KL, Encio CE 1991 Free thyroxine levels in hospitalized newborns: depressed levels in critical, nonthyroidal illness. *J Perinatol* 11:117–121
- Uhrmann S, Marks KH, Maisels MJ, Kulin HE, Kaplan M, Utiger R 1981 Frequency of transient hypothyroxinaemia in low birthweight infants. Potential pitfall for neonatal screening programmes. *Arch Dis Child* 56:214–217
- Den Ouden AL, Kok JH, Verkerk PH, Brand R, Verloove-Vanhorick SP 1996 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* 39:142–145
- Lucas A, Morley R, Fewtrell MS 1996 Low triiodothyronine concentration in preterm infants and subsequent intelligence quotient (IQ) at 8 year follow up. *BMJ* 312:1132–1134
- Reuss ML, Paneth N, Pinto-Martin JA, Lorenz JM, Susser M 1996 The relation of transient hypothyroxinemia in preterm infants to neurologic development at two years of age. *N Engl J Med* 334:821–827
- van Wassenae AG, Briet JM, van Baar A, Smit BJ, Tamminga P, De Vijlder JJM, Kok JH 2002 Free thyroxine levels during the first weeks of life and neurodevelopmental outcome until the age of 5 years in very preterm infants. *Pediatrics* 110:534–539
- Chowdhry P, Scanlon JW, Auerbach R, Abbassi V 1984 Results of controlled double-blind study of thyroid replacement in very low-birth-weight premature infants with hypothyroxinemia. *Pediatrics* 73:301–305
- van Wassenae AG, Kok JH, de Vijlder JJ, Briet JM, Smit BJ, Tamminga P, van Baar A, Dekker FW, Vulsma T 1997 Effects of thyroxine supplementation on neurologic development in infants born at less than 30 weeks' gestation. *N Engl J Med* 336:21–26
- Vanhoe C, Aerssens P, Naulaers G, Casneuf A, Devlieger H, Van den BG, de Zegher F 1997 L-thyroxine treatment of preterm newborns: clinical and endocrine effects. *Pediatr Res* 42:87–92
- Briet JM, van Wassenae AG, Dekker FW, de Vijlder JJ, van Baar A, Kok JH 2001 Neonatal thyroxine supplementation in very preterm children: developmental outcome evaluated at early school age. *Pediatrics* 107:712–718
- van Wassenae AG, Kok JH, Dekker FW, Ender E, de Vijlder JJ 1998 Thyroxine administration to infants of less than 30 weeks gestational age decreases plasma tri-iodothyronine concentrations. *Eur J Endocrinol* 139:508–515
- Cools F, van Wassenae AG, Kok JH, de Vijlder JJ 2000 Changes in plasma thyroid hormone levels after a single dose of triiodothyronine in premature infants of less than 30 weeks gestational age. *Eur J Endocrinol* 143:733–740
- Darras VM, Kotanen SP, Geris KL, Berghman LR, Kuhn ER 1996 Plasma thyroid hormone levels and iodothyronine deiodinase activity following an acute glucocorticoid challenge in embryonic compared with posthatch chickens. *Gen Comp Endocrinol* 104:203–212
- Tohei A, Watanabe G, Taya K 1998 Hypersecretion of corticotrophin-releasing hormone and arginine vasopressin in hypothyroid male rats as estimated with push-pull perfusion. *J Endocrinol* 156:395–400
- Bettendorf M, Schmidt KG, Grulich-Henn J, Ulmer HE, Heinrich UE 2000 Tri-iodothyronine treatment in children after cardiac surgery: a double-blind, randomised, placebo-controlled study. *Lancet* 356:529–534
- Broderick TJ, Wechsler AS 1997 Triiodothyronine in cardiac surgery. *Thyroid* 7:133–137
- Portman MA, Fearneyhough C, Ning X-H, Duncan BW, Rosenthal GL, Lupinetti FM 2000 Triiodothyronine repletion in infants during cardiopulmonary bypass for congenital heart disease. *J Thorac Cardiovasc Surg* 120:604–608
- van Wassenae AG, Kok JH, Briet JM, Pijning AM, de Vijlder JJ 1999 Thyroid function in very preterm newborns: possible implications. *Thyroid* 9:85–91
- Maia AL, Kieffer JD, Harney JW, Larsen PR 1995 Effect of 3,5,3'-Triiodothyronine (T₃) administration on *diol* gene expression and T₃ metabolism in normal and type 1 deiodinase-deficient mice. *Endocrinology* 136:4842–4849
- van Wassenae AG, Kok JH, Dekker FW, De Vijlder JJM 1997 Thyroid function in very preterm infants: influences of gestational age and disease. *Pediatr Res* 42:604–609
- Biswas S, Buffery J, Enoch H, Bland M, Markiewicz M, Walters D 2003 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. *Pediatr Res* 53:48–56
- Midgley PC, Holownia P, Smith J, Moore M, Russell K, Oates N, Shaw JCL, Honour JW 2001 Plasma cortisol, cortisone and urinary glucocorticoid metabolites in preterm infants. *Biol Neonate* 79:79–86
- Scott SM, Watterberg KL 1995 Effect of gestational age, postnatal age, and illness on plasma cortisol concentrations in premature infants. *Pediatr Res* 37:112–116
- Watterberg KL, Gerdes JS, Cook KL 2001 Impaired glucocorticoid synthesis in premature infants developing chronic lung disease. *Pediatr Res* 50:190–195