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Serum Thyroid Hormones in Preterm Infants: Associations with Postnatal Illnesses and Drug Usage

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Context: Transient hypothyroxinemia is common in infants less than 30 wk gestation and is associated with neurodevelopmental deficits. Reductions in T_4 and T_3 levels with TSH unchanged are the key features of severe illness using surrogate indices of overall severity of illness, but these do not inform the impact of individual disease conditions or drug use.

Objective: Our objective was to investigate the contribution of postnatal factors to the variations in serum levels of iodothyronines, thyroid-binding globulin, and TSH.

Design: We recruited a cohort of infants (23–34 wk gestation; n = 780) between January 1998 and September 2001.

Setting and Patients: The study involved 11 level III Scottish neonatal intensive care units and included cohorts of infants delivered at 23–34 wk gestation.

Main Outcome: We assessed serum levels of iodothyronines, thyroid-binding globulin, and TSH at 7, 14, and 28 d adjusted for the potentially significant postnatal influences (n = 31).

Results: Serum levels of TSH, free T_4, T_3, and T_4 are variably but significantly associated with bacteremia, endotracheal bacterial cultures, persistent ductus arteriosus, necrotizing enterocolitis, cerebral ultrasonography changes, oxygen dependence at 28 d, and the use of aminophylline, caffeine, dexamethasone, diamorphine, and dopamine.

Conclusions: There are many more associations of postnatal factors with transient hypothyroxinemia than had previously been considered in preterm infants. Alternative strategies should be considered for correction of hypothyroxinemia rather than sole reliance on the direct therapy of hormone replacement. A more oblique preventative approach may be necessary through reduction in the incidence or severity of individual illness(es). Similarly, alternatives to those drugs that interfere with the hypothalamic-pituitary-thyroid axis should be evaluated (*e.g.* other inotropics instead of dopamine). **(*J Clin Endocrinol Metab* 90: 5954–5963, 2005)**

TRANSIENT HYPOTHYROXINEMIA IS the commonest thyroid dysfunction in preterm infants and is characterized by a temporary postnatal reduction from cord values in serum levels of T_4 and free T_4 (FT_4) but with normal TSH levels (1, 2). Transient hypothyroxinemia is present in the majority of infants less than 30 wk gestation and is associated with neurodevelopmental deficits, characteristically reductions in intelligence quotient scores (3–6) but also an increased risk of cerebral palsy (5). T_4 supplementation in infants less than 30 wk has shown no overall benefit in neurodevelopmental outcome but may improve outcome in infants less than 27 wk gestation (7). The etiology of transient hypothyroxinemia is not clear and may have contributions from the withdrawal of maternal-placental T_4 transfer (8–10), hypothalamic-pituitary-thyroid immaturity (11, 12), developmental constraints on the synthesis (13–15) and peripheral metabolism of iodothyronines (16–18), iodine deficiency (19, 20), and nonthyroidal illness (16, 21–23).

Respiratory distress syndrome is an acute nonthyroidal illness and the most frequently studied condition over the past 30 yr to determine whether illness alters serum thyroid hormone levels in preterm infants (22, 24–31). Respiratory distress syndrome is characteristically most severe in the few days after birth, and the majority of studies of thyroid hormone status in preterm infants have been limited to the first week of life (24, 25, 27, 29–31); but the nadir of transient hypothyroxinemia may extend beyond this early period (*e.g.* Ref. 2). In addition to respiratory distress syndrome, preterm infants can also suffer from a spectrum of illness within, and outside of, this early phase of postnatal life.

To determine the relationship between critical illness in preterm infants and thyroid hormone status, we recently analyzed data from a cohort of preterm infants (23). A range of serum thyroid hormones was measured over the first 28 d, and levels were then correlated with severity of illness on the day blood was sampled using a routinely applied scoring system as a surrogate marker of illness severity. The scoring system used was that of The British Association of Perinatal Medicine (BAPM), which was initially devised to quantify resources required by UK neonatal intensive care units such as nursing staffing numbers, expertise, and equipment, with severity of illness being related to the amount of resource required (32). The application of the BAPM scoring system allows systematic categorization of a large sample of preterm infants by a uniform set of parameters describing illness severity. The key outcomes of our study were that serum

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Abbreviations: FiO_2, Fractional inspired oxygen; FT_4, free T_4; TBG, thyroid-binding globulin; T_4S, T_4 sulfate.

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TSH was unchanged with BAPM score, but there were reductions in serum T_4 and T_3 in those infants requiring the maximal level of intensive care (23). However, this approach categorizes only overall severity of illness but not the impact of individual disease conditions on iodothyronine levels.

To reveal the relationship between specific illnesses, drug use, and nutrition on postnatal thyroid hormone status, we have analyzed data from a cohort of preterm infants born from 23–34 wk gestation.

Subjects and Methods

Data were collected between January 1998 and September 2001.

This study recruited a cohort of mothers and infants delivered at 23–34 wk gestation and who were part of a multicenter study of transient hypothyroxinemia in 11 level III Scottish neonatal intensive care units. Gestational age of infants was calculated from menstrual history and, in most instances, was confirmed by ultrasound examination in the first trimester. Exclusion criteria from the study were known viral hepatitis or HIV positivity (or at high risk), major congenital abnormality, or if mothers were unable to provide informed consent. The study was approved, as appropriate, by the Multicenter Research Ethics Committee (Edinburgh) and the Tayside Committee on Medical Research Ethics; in all cases, written informed consent was obtained.

All infants had intensive care support as required, including intermittent positive pressure ventilation and, where appropriate, correction of fluid, electrolyte, blood glucose, and acid-base abnormalities. Blood pressure was supported with inotropes, plasma, or crystalloids as required. Infants with significant persistence of the ductus arteriosus were treated with diuretics and indomethacin or surgical ligation if appropriate. Parenteral nutrition regimens, if required, were based on a solution of electrolytes, dextrose 10%, amino acids (Vaminolact; Fresenius Kabi, Cheshire, UK), a phosphate supplement (Addiphos; Fresenius Kabi), water-soluble vitamins (Solvito N; Fresenius Kabi), and trace elements (Peditrace; Fresenius Kabi) to levels recommended by the manufacturer. In tandem, a fat emulsion (Intralipid 20%; Fresenius Kabi) with added fat-soluble vitamins (Vitlipid; Fresenius Kabi) was used. Enteral feeds were started when the condition of the infant was stable, preferably expressed breast milk from the infant's mother or Cow and Gate Nutriprem I Low Birthweight Formula (Cow & Gate, Wiltshire, UK). Thereafter, enteral feed volumes were gradually increased as determined by the infants' clinical condition, with reciprocal reductions in the volume of parenteral nutrition infused. Total caloric intakes and the relative contributions from parenteral and enteral nutrition were calculated at 1, 7, 14, and 28 d.

Blood was collected at postnatal d 7 (n = 591), 14 (n = 514), and 28 (n = 375) from infants of 23–34 wk. The blood samples were allowed to separate for at least 15 min and then centrifuged at 4000 rpm for 5 min. If collected outside of normal laboratory hours, the blood was stored at 4 C (maximum, 12 h) before processing. The serum was removed, stored, and transported at a maximum of −20 C for assays in one laboratory (T.J.V.).

Provided sufficient serum was available, T_4, FT_4, TSH, T_3, rT_3, T_4 sulfate (T_4S), and thyroid-binding globulin (TBG) levels were determined. Serum T_4, T_3, and rT_3 were measured by in-house RIA; FT_4 by Vitros ECI technology (Ortho-Clinical Diagnostics; Amersham, Little Chalfont, UK); TSH by Dynotest immunoradiometric assay; and TBG by Dynotest RIA (Brahms, Berlin, Germany). T_4S was prepared by the method of Eelkman-Rooda *et al.* (33). The measurements of T_4S in serum were done by a specific antibody, as described previously (34). Within-assay coefficients of variation were calculated as 2–8% for T_4 (50–147 nmol/liter), 3–7% for FT_4 (7.4–27.7 pmol/liter), 2–6% for T_3 (0.72–4.24 nmol/liter), 3–4% for rT_3 (0.19–0.59 nmol/liter), 6–17% for T_4S (46–514 pmol/liter), 2–5% for TSH (0.2–16.6 mU/liter), and 2–4% for TBG (5.9–38.4 mg/liter). Between-assay coefficients of variation were 5–10% for T_4 (49–154 nmol/liter), 5–10% for FT_4 (9.0–28.8 pmol/liter), 8% for T_3 (0.86–4.54 nmol/liter), 9–16% for rT_3 (0.21–0.58 nmol/liter), 4–19% for T_4S (48–501 pmol/liter), 2–14% for TSH (0.1–16.9 mU/liter), and 2–3% for TBG (6.7–30.1 mg/liter).

Infants were subdivided into gestational age groups (23–27, 28–30, and 31–34 wk) to maintain consistency with previous publications using this data set.

Infant disorders were recorded as follows: respiratory distress syndrome [requiring oxygen with or without ventilatory support, with severity of illness as mean of first 48 hourly fractional inspired oxygen (FiO_2) measurements]; oxygen dependency at d 28 (28 d was the maximum length any one infant was included in our study and is an indicator of evolving chronic lung disease that is likely to have been present earlier in the neonatal period); cerebral pathology [the sonographic presence and grade of intraventricular hemorrhage (35) and periventricular leukomalacia]; persistent ductus arteriosus (requiring treatment with fluid restriction and diuretics with or without indomethacin or surgery); and necrotizing enterocolitis (requiring treatment with total parenteral nutrition and antibiotics). Birthweight ratios were calculated for each infant using reference values obtained from the Scottish Morbidity Record SMR2 as supplied by the Information and Statistics Division of the Common Services Agency, Edinburgh. Birthweight ratio is the infant's birthweight divided by the mean birthweight of all Scottish infants born between 1987 and 1998, matched for sex and gestational age.

For each infant, the postnatal day of onset, organism, and site(s) of positive culture was recorded for each episode of late-onset infection (≥3 postnatal days). Infections were included if one or more cultures were positive and if the infant was treated with an antibiotic course. Data were not recorded about infants who on clinical suspicion were treated with an antibiotic course as if infected but culture negative; it is likely that the number of such infants was small.

A pragmatic hierarchy of positive culture sites was established to allow grouping of culture-positive, antibiotic-treated infants: 1) blood (one infant with a positive cerebrospinal fluid as well as a positive blood culture with the same organism was included in this group), 2) endotracheal tube secretions, 3) vascular access catheter tips, 4) surface including oropharyngeal and rectal swab cultures, and 5) urine. Infants with more than one site culture positive were assigned to the higher site. The infants classified within each site of infection were then stratified according to the range of days of onset of infection (3–8, 10–16, and 24–29 d) and so linked to the thyroid hormone serum sampling days of 7, 14, and 28 postnatal days, respectively. The range of days of onset of infections was limited to a constant period before each day when blood was sampled for iodothyronine, TSH, and TBG levels and based on the assumption that with the onset of infection in these periods the attendant inflammatory response would have the most effect on their levels. If an infant was infected simultaneously with two or more organisms, then all were recorded in the data set and analyzed; the combinations of organisms (with number of episodes in parentheses) were as follows: in blood, bacteria and fungi (three) and bacteria and bacteria (two); in endotracheal tube secretions, bacteria and fungi or ureaplasma (three).

For the following drugs (selected on the basis of established or potential hormonal or metabolic effects on thyroid hormone metabolism or inflammatory responses), the postnatal days of prescription of various drugs was recorded: dexamethasone, phenobarbitone, diamorphine, morphine, insulin, glucagon, aminophylline, caffeine, dopamine, phenytoin, and indomethacin. Diamorphine and morphine were recorded separately but subsumed for the analysis; we refer to them hereafter as diamorphine.

The main analysis of the data was performed using univariate general linear modeling, in three steps. First, we assessed, singly, the impact of the 31 postnatal factors upon the levels of iodothyronine, TSH, and TBG on d 7, 14, and 28, as described in the previous paragraphs. Second, the factors that were significantly associated singly were then entered together into a model to determine their adjusted impact. If respiratory distress syndrome and mean FiO_2 were both significantly associated in step one, then only mean FiO_2 was entered into the second step. Third, a final model used only the significant factors (because this minimizes the loss of data caused by missing information). The iodothyronines, TSH, and TBG were log transformed for this analysis because the data were not normally distributed. Linear modeling was performed for each day of sera sampling. Respiratory distress, oxygen dependence at d 28, cranial ultrasound change, persistent ductus arteriosus, and necrotizing enterocolitis were recorded as present or absent and were not time specific and were entered into the first step of each regression analysis, *i.e.* on d 7, 14, and 28. Drug use was entered as present (or absent) on d 7, 14, and 28 as appropriate to the model.

The regression analysis was used to determine the predicted mean for

each iodothyronine, TBG, or TSH level, at each day of sampling, adjusted for other factors in the model; the difference was calculated, for each factor, between the groups geometric mean gestation (irrespective of gestational group) and predicted mean.

Results

Data were collected on cord blood (as reported previously) (36) and on postnatal d 7, 14, and 28. Seven hundred eighty infants were included in this data set and subdivided into the gestational age groups: 23–27, 28–30, and 31–34 wk (Table 1). The most common disorder noted was respiratory distress syndrome, particularly in the lower gestational groups, where the other disorders were also more frequent (Table 1).

On postnatal d 7, 14, and 28, data were available for 551, 488, and 355 infants, respectively. The number of descriptors of clinical disorders available for regression modeling varied on each day of sampling because not all infants had their full quota of three postnatal sera samples taken (Table 2).

Drug use coinciding with the day of the sera testing was variable (Table 2). Dexamethasone was used very infrequently. Dopamine and indomethacin use was moderate and more frequently administered at d 7 and in the infants born at a younger gestational age. Diamorphine, aminophylline, and caffeine were relatively frequently administered with a bias toward the lower gestational age groups. Total nutritional intakes were significantly lower in the 23- to 27-wk group compared with other groups at 7 and 14 d (Table 2), and this pattern was the same for enteral nutrition. Mean FiO_2 was significantly lower in the 31- to 34-wk gestational group compared with the other groups (Table 2). Birthweight ratio was significantly lower in the 28- to 30- and 31- to 34-wk groups compared with the 23- to 27-wk group at d 7 and more variably at d 14 and 28 (Table 2).

Infection was most common in the 23- to 27-wk group and most frequent with onset at d 3–8. Blood was the most common site of infection. Gram-positive cocci, especially coagulase-negative staphylococci, were the most common organism in all gestational groups (Table 3).

Data in parentheses in the following paragraphs refer to the difference between the predicted mean and the group mean.

T_4 levels on d 7 were positively associated with gestation (+11.3 nmol/liter per week of gestation) and aminophylline use on d 7 (+10.86 nmol/liter) and negatively associated with infection in blood or endotracheal tube (−10.40 nmol/liter), persistent ductus arteriosus (−14.07 nmol/liter), and necrotizing enterocolitis (−12.10 nmol/liter). Together, these factors contribute appreciably (56%) to the variation in T_4 levels (Table 4). Three factors associated with T_4 levels on d 7 were also significant at d 14: gestation (+6.59 nmol/liter), persistent ductus arteriosus (−21.87 nmol/liter), and infection in blood or endotracheal tube (−13.08 nmol/liter) (Table 5). Three other factors became significant by d 14: oxygen dependence at d 28 (−11.36 nmol/liter), diamorphine use on d 14 (−20.33 nmol/liter), and dopamine use on d 14 (−39.12 nmol/liter) (Table 5). By d 28, only diamorphine use (−45.74 nmol/liter) and gestation (+6.73 nmol/liter per week) were associated with levels of T_4 (Table 6).

TABLE 1. Burden of disease (number and percentage) in the study population

	Gestation age grouping		
	23–27 wk [n (%)]	28–30 wk [n (%)]	31–34 wk [n (%)]
Respiratory distress syndrome	138 (93)	223 (85)	184 (50)
Oxygen dependence at 28 d	100 (67)	72 (28)	11 (3)
Cranial ultrasound change	73 (49)	54 (21)	11 (3)
Persistent ductus arteriosus	68 (46)	36 (14)	8 (2)
Necrotizing enterocolitis	26 (18)	27 (10)	9 (2)
Total numbers per group	149	261	370

FT_4 levels on d 7 were positively associated with gestation (+1.85 pmol/liter per week) and cranial ultrasound changes (+2.73 pmol/liter) (Table 4). By d 14, gestation was still associated with levels of FT_4 (+1.26 pmol/liter per week) and also dexamethasone (−6.25 pmol/liter) (Table 5). At d 28, gestation FT_4 was still positively associated (+0.77 pmol/liter per week), but diamorphine was associated negatively (−3.89 pmol/liter) (Table 6).

TSH levels on d 7, 14, and 28 were negatively associated with birthweight ratio (−1.43, −1.84, and −1.15 mU/liter, respectively) (Tables 4–6). Caffeine was negatively associated with TSH at d 7 (−0.61 mU/liter) but positively associated at d 14 (+1.38 mU/liter).

T_3 levels at d 7 were positively associated with gestation (+0.16 nmol/liter), total nutrition (+0.51 nmol/liter), and aminophylline use (+0.21 nmol/liter); infection in blood or endotracheal tube on d 3–8 was negatively associated (−0.19 nmol/liter) (Table 4). At d 14, gestation remained positively associated (+0.14 nmol/liter); diamorphine was negatively associated with T_3 (−0.21 nmol/liter) as were dopamine (−0.57 nmol/liter), dexamethasone (−0.82 nmol/liter), infection in blood or endotracheal tube (−0.34 nmol/liter), persistent ductus arteriosus (−0.24 nmol/liter), cranial ultrasound changes (−0.18 nmol/liter), and oxygen dependence at 28 d (−0.20 nmol/liter) (Table 5). At d 28, gestation (+0.09 nmol/liter), total nutrition (+0.46 nmol/liter), dopamine (−0.83 nmol/liter), and diamorphine (-0.96 nmol/liter) were associated with T_3 levels (Table 6).

rT_3 levels at d 7 were positively associated with gestation (+0.07 nmol/liter) and negatively associated with birthweight ratio (−0.42 nmol/liter) and caffeine use (−0.20 nmol/liter) (Table 4). By d 14, gestation (+0.04 nmol/liter), FiO_2 (+0.01 nmol/liter), infection in blood on d 10–15 (+0.25 nmol/liter), indomethacin use on d 14 (+0.32 nmol/liter), and male gender (−0.09 nmol/liter) were associated with rT_3 levels (Table 5). At d 28, necrotizing enterocolitis (+0.19 nmol/liter) and total nutrition (−0.27 nmol/liter) were associated with rT_3 levels (Table 6).

TBG levels at d 7 were positively associated with gestation (+1.07 mg/liter) and negatively with infection in blood or endotracheal tube (−1.64 mg/liter) (Table 4). At d 14, gestation (+0.54 mg/liter), dopamine (−5.60 mg/liter), and diamorphine (−2.02 mg/liter) were associated with TBG (Table 5). At d 28, birthweight ratio (+7.49 mg/liter) and diamorphine (−4.10 mg/liter) were associated with TBG levels (Table 6).

At d 7, T_4S levels were associated with gestation (−134 pmol/liter), oxygen dependence at 28 d (−258 pmol/liter), FiO_2 (+9 pmol/liter), and male gender (+444 pmol/liter) (Table 4). At d 14, gestation (−86 pmol/liter), FiO_2 (+6

TABLE 2. Descriptors entered in final regression model by day of sampling and gestational age group

Maximum no. in group	23–27 wk gestation			28–30 wk gestation			31–34 wk gestation		
	d 7 (n = 101)	d 14 (n = 101)	d 28 (n = 97)	d 7 (n = 198)	d 14 (n = 190)	d 28 (n = 155)	d 7 (n = 252)	d 14 (n = 197)	d 28 (n = 103)
Respiratory distress syndrome[a]	100	100	94	169	164	132	109	87	49
Oxygen dependence at 28 d[a]	72	79	80	57	56	53	7	8	9
Cranial ultrasound change[a]	56	50	48	43	39	35	10	9	5
Persistent ductus arteriosus[a]	52	51	45	31	28	30	7	8	4
Necrotizing enterocolitis[a]	20	19	20	23	23	18	8	8	7
Male:female[a]	54:47	52:49	47:49	94:102	89:99	66:88	150:98	124:69	57:43
Mean, SD, and n for continuous variables									
FiO_2, mean 0–48 h ± SD[a] (n)	30.4 ± 10.4 (101)	30.3 ± 10.4 (101)	31.5 ± 11.2 (97)	29.0 ± 10.4 (198)	28.9 ± 10.6 (190)	29.8 ± 11.4 (155)	23.7 ± 9.5 (252)[c,d]	23.9 ± 9.3 (197)[c,d]	25.1 ± 11.7 (103)[c,d]
Birthweight ratio, mean ± SD[a] (n)	1.03 ± 0.16 (101)	1.02 ± 0.16 (101)	1.04 ± 0.16 (96)	0.98 ± 0.19 (195)[c]	0.99 ± 0.21 (187)	0.97 ± 0.18 (153)	0.97 ± 0.18 (244)[c]	0.97 ± 0.19 (191)[c]	0.94 ± 0.20 (100)[c]
Dexamethasone given on test day	0	4	9	1	2	2	0	0	0
Diamorphine given on test day	43	35	4	17	12	6	9	3	2
Aminophylline given on test day	31	27	9	50	27	4	11	7	1
Caffeine given on test day	23	43	33	82	106	35	42	20	2
Dopamine given on test day	14	9	1	0	0	1	0	0	0
Indomethacin given on test day	16	9	1	10	5	1	0	0	0
Mean, SD and n for continuous variables									
Enteral nutrition, kcal/kg·d[b] mean ± SD (n)	50 ± 39 (31)	82 ± 48 (57)	112 ± 38 (75)	80 ± 41 (142)[c]	115 ± 34 (150)[c]	124 ± 25 (125)	105 ± 28 (197)[c,d]	123 ± 27 (142)[c,d]	125 ± 27 (48)[c]
Total nutrition, kcal/kg·d mean ± SD (n)	83 ± 20 (99)	97 ± 24 (98)	115 ± 26 (92)	97 ± 21 (186)[c]	117 ± 31 (174)[c]	122 ± 23 (136)	109 ± 22 (214)[c,d]	122 ± 25 (153)[c]	122 ± 28 (53)

[a] These descriptors were recorded only as present or absent and are not time specific; all other data in the table. *i.e.* drugs, were recorded as in use or not on the test day of sampling.
[b] The totals of enteral intake and total nutrition do not add up as expected because of missing information in one or other of the data fields for a few infants.
[c] Significantly different from 23- to 27-wk gestation infants at $P < 0.02$.
[d] Significantly different from 28- to 30-wk gestation infants at $P < 0.03$.

TABLE 3. Organisms by site and grouped by day of onset and gestation

Site[a] and organism of infection	Onset of infection 3–8 d			Onset of infection 10–15 d			Onset of infection 24–28 d		
	23–27 wk	28–30 wk	31–34 wk	23–27 wk	28–30 wk	31–34 wk	23–27 wk	28–30 wk	31–34 wk
BLOOD									
Gram-positive organisms	**34**	**23**	**8**	**15**	**17**	**6**	**9**	**3**	
Staphylococcus coagulase-negative	32	23	7	14	16	6	8	3	
Staphylococcus aureus	1		1		1		1		
Enterococcus spp	1			1					
Gram-negative organisms	**2**	**1**		**1**	**2**		**1**	**1**	
E. coli	1							1	
Klebsiella		1			1				
Pseudomonas	1								
Acinobacter				1			1		
Serratia					1				
Fungi	**1**			**1**				**1**	
Candida albicans	1			1				1	
ENDOTRACHEAL TUBE SECRETIONS									
Gram-positive organisms	**11**	**3**	**2**	**6**	**1**				
Staphylococcus coagulase-negative	11	3	2	4					
Staphylococcus aureus				2	1				
Gram-negative organisms				**1**	**2**				
E. coli					1				
Klebsiella				1					
Enterobacter					1				
Fungi	**2**								
Candida albicans	2								
Other	**3**	**1**					**1**		
Mycoplasma hominis	1								
Ureaplasma urealyticum	2	1					1		
VASCULAR ACCESS CATHETER TIP									
Gram-positive organisms	**1**	**1**							
Staphylococcus coagulase-negative	1	1							
SURFACE[b]									
Gram-positive organisms		**2**							
Staphylococcus aureus		2							
Maximum n	101	198	252	101	190	197	97	155	103

[a] No urinary tract infections occurred within the days of onset used in this table.
[b] Including oropharyngeal and rectal swabs.

pmol/liter), and infection in blood or endotracheal tube (+293 pmol/liter) were associated (Table 5). By d 28, only gestation (−100 pmol/liter) remained associated with T_4S levels (Table 6).

Discussion

Two early studies of the effect of respiratory distress syndrome on serum thyroid hormone levels, which extended the study period beyond the first week of life, suggested a persistent effect (26, 28); additional reports have not confirmed these observations (22, 30), including our study where only marginal associations are present with T_4S and rT_3 levels. This lack of association is not surprising given the acute and time-limited nature of this syndrome to the early neonatal period and that more recently severity has been attenuated by the use of prenatal corticosteroids and postnatal surfactant therapies.

In our preterm infants with late-onset infections, there are associations with marked reductions in T_4, T_3, and TBG levels. The definition of late-onset blood infection in preterm infants remains ambiguous and without consensus (37–40). Our definition was based on the pragmatic clinical definition used by collaborators in this study. If we were to apply the most detailed and stringent definitions of late-onset blood infections to our data, our criteria of one positive blood culture and the patient treated with a course of antibiotics would fulfill the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network definition of possible infection (40). A definite infection requires two positive blood cultures drawn within 2 d of each other or one positive blood culture and elevated C-reactive protein within 2 d of blood culture. Data collection in our study anteceded publication of NICHD definitions; by comparison, our definition has led to dilution of the effect, and meeting the NICHD criteria for definite infection would have strengthened the negative associations with thyroid hormone levels.

The predominant organism associated with infection in our study was coagulase-negative staphylococcus, and this is consistent with previous reports of infection (37–40) in extreme preterm infants; its interpretation is notoriously difficult where sampling is more frequent and where there is a higher risk of contamination. The novelty of our approach was the consideration of up to three acquired infections of late onset. This necessitated a hierarchical approach when there was concurrent culture of the same organism at different sites. Bacteremia was considered clinically to be the most important, followed by the endotracheal tube secretions, vascular access catheter tips, and surface infections. The number of infants who had positive cultures from only

TABLE 4. Significant factors that influence levels of d-7 sera iodothyronines, TSH, and TBG

Variable	B	SE	Anti-log B (effect size)	Group geometric mean at 30 wk gestation	Change in predicted mean	*t* statistic	*P* value
T_4 (nmol/liter)							
Intercept	0.416	0.092	2.606	90.95 nmol/liter			
Gestation	0.051	0.003	1.125		102.28	17.367	<0.001
Infection in blood or endotracheal tube on d 3–8	−0.053	0.021	0.885		80.55	−2.579	0.010
Persistent ductus arteriosus	−0.073	0.021	0.845		76.88	−3.498	0.001
Necrotizing enterocolitis	−0.062	0.023	0.867		78.85	−2.695	0.007
Aminophylline d 7	0.049	0.018	1.119		101.81	2.664	0.008
FT_4 (pmol/liter)							
Intercept	0.440	0.075	2.754	24.99 pmol/liter			
Cranial ultrasound change	0.045	0.017	1.109		27.72	2.720	0.007
Gestation	0.031	0.002	1.074		26.84	12.527	<0.001
TSH (mU/liter)							
Intercept	0.681	0.085	4.797	3.52 mU/liter			
Caffeine d 7	−0.086	0.035	0.820		2.89	−2.455	0.014
Birthweight ratio	−0.231	0.086	0.587		2.07	−2.684	0.008
T_3 (nmol/liter)							
Intercept	−2.196	0.113	0.006	0.99 nmol/liter			
Infection in blood or endotracheal tube on d 3–8	−0.093	0.026	0.807		0.80	−3.665	<0.001
Aminophylline d 7	0.082	0.023	1.208		1.20	3.501	0.001
Total nutrition d 7	0.181	0.041	1.517		1.50	4.439	<0.001
Gestation	0.065	0.004	1.161		1.15	16.823	<0.001
rT_3 (nmol/liter)							
Intercept	−0.198	0.113	0.634	1.76 nmol/liter			
Caffeine d 7	−0.052	0.018	0.887		1.56	−2.904	0.004
Birthweight ratio	−0.118	0.045	0.762		1.34	−2.645	0.006
Gestation	0.017	0.003	1.040		1.83	5.154	<0.001
TBG (mg/liter)							
Intercept	0.670	0.060	4.677	20.6 mg/liter			
Gestation	0.022	0.002	1.052		21.67	11.053	<0.001
Infection in blood or endotracheal tube on d 3–8	−0.036	0.015	0.920		18.96	−2.357	0.019
T_4S (pmol/liter)							
Intercept	4.102	0.149	12647.4	1881.3 pmol/liter			
Infant gender	0.092	0.020	1.236		2325.2	4.569	<0.001
Oxygen dependence d 28	−0.064	0.031	0.863		1623.6	−2.086	0.038
Gestation	−0.032	0.005	0.929		1747.7	−6.809	<0.001
FiO_2 mean	0.002	0.001	1.005		1890.0	2.307	0.022

vascular access catheter tips, surface swabs, or urine and who were treated with antibiotics was few. This approach numerically weights the importance of bacteremia and conversely underrecognizes the contribution of similar organisms particularly in the endotracheal tube secretions. Despite this, we find strong and persistent associations between reduced levels of T_4 and T_3 on postnatal d 7 and 14 and coagulase-negative staphylococcal infection in endotracheal tube secretions. In extreme preterm infants, the local proinflammatory cytokine response to endotracheal colonization immediately after birth is highest in neonates colonized with a Gram-negative pathogen, but this response is also associated with infection with coagulase-negative staphylococci (41). The mortality associated with Gram-negative bacteria and fungal sepsis is very much higher (up to 4-fold) than that reported for coagulase-negative staphylococcus (38–40). We are unable to comment on the relationship between Gram-negative bacteria and fungal sepsis and iodothyronine levels because these infections were relatively uncommon. Because the proinflammatory cytokine response is relatively less in infants with coagulase-negative staphylococci, it is also highly probable that the thyroid hormone responses to sepsis with these organisms are also similarly attenuated.

Serum T_3 and FT_4 levels are reduced in adults with subarachnoid hemorrhage (42, 43). In very low birthweight infants, low serum T_4 levels during the first week of life are associated with intraventricular hemorrhage but not thereafter at 2–4 wk postnatal age (44, 45). In such low birthweight infants, low serum T_4 and TSH levels measured within 6 h after birth are associated with severe intraventricular hemorrhage and death (46). These studies emphasize the limited temporal effect of intraventricular hemorrhage on T_4 levels to the early postnatal period; this may be the reason for limited associations in our results.

In respiratory distress syndrome (47), sepsis (48), intracranial hemorrhage (49), and necrotizing enterocolitis (48), the effects on serum thyroid hormone levels are likely to be mediated in part through the acute inflammatory cytokine response (50). There is no direct evidence for this cytokine response in preterm infants with a persistent ductus arteriosus, but reduced plasma T_3 levels is a feature of cardiac failure in adults (51).

Aminophylline and caffeine are used as respiratory stimulants in preterm infants with recurrent apnea. Both anterior pituitary and thyroid cells have cAMP-dependent regulation of gene expression and are potential sites for theophylline (the active metabolite of aminophylline and caffeine), which acts as a phosphodiesterase inhibitor and so influences thyroid hormone metabolism. Elevation of pituitary intracellular cAMP levels increases the expression of the TSH α- and

TABLE 5. Significant factors that influence levels of d-14 sera iodothyronines, TSH, and TBG

Variable	B	SE	Anti-log B (effect size)	Group geometric mean at 30 wk gestation	Change in predicted mean	*t* statistic	*P* value
T_4 (nmol/liter)							
Intercept	1.107	0.117	12.794	95.46 nmol/liter			
Oxygen dependence d 28	−0.055	0.022	0.881		84.10	−2.515	0.012
Persistent ductus arteriosus	−0.113	0.023	0.771		73.59	−4.919	<0.001
Infection in blood or endotracheal tube d 10–15	−0.064	0.027	0.863		82.38	−2.381	0.018
Diamorphine d 14	−0.104	0.029	0.787		75.13	−3.554	<0.001
Dopamine d 14	−0.229	0.056	0.590		56.34	−4.090	<0.001
Gestation	0.029	0.004	1.069		102.05	7.825	<0.001
FT_4 (pmol/liter)							
Intercept	0.644	0.059	4.498	23.24 pmol/liter			
Dexamethasone d 14	−0.136	0.047	0.730		16.99	−2.916	0.004
Gestation	0.023	0.002	1.054		24.50	11.807	<0.001
TSH (mU/liter)							
Intercept	0.676	0.087	4.742	4.0 mU/liter			
Caffeine d 14	0.129	0.034	1.346		5.38	3.838	<0.001
Birthweight ratio	−0.268	0.087	0.540		2.16	−3.095	0.002
T_3 (nmol/liter)							
Intercept	−1.202	0.145	0.063	1.28 nmol/liter			
Oxygen dependence d 28	−0.074	0.026	0.843		1.08	−2.848	0.005
Cranial ultrasound change	−0.067	0.026	0.857		1.10	−2.599	0.010
Persistent ductus arteriosus	−0.092	0.028	0.809		1.04	−3.234	0.001
Infection in blood or endotracheal tube on d 10–15	−0.133	0.033	0.736		0.94	−4.058	<0.001
Dexamethasone d 14	−0.443	0.088	0.361		0.46	−5.021	<0.001
Dopamine d 14	−0.253	0.067	0.559		0.71	−3.772	<0.001
Diamorphine d 14	−0.076	0.037	0.840		1.07	−2.050	0.041
Gestation	0.044	0.005	1.107		1.42	9.462	<0.001
rT_3 (nmol/liter)							
Intercept	−0.369	0.085	0.428	1.28 nmol/liter			
Infection in blood on d 10–15	0.078	0.024	1.197		1.53	3.202	0.001
Infant gender	−0.032	0.013	0.929		1.19	−2.412	0.016
Indomethacin d 14	0.098	0.041	1.253		1.60	2.395	0.017
Gestation	0.012	0.003	1.028		1.32	4.687	<0.001
FiO_2 mean	0.002	0.001	1.005		1.29	3.611	<0.001
TBG (mg/liter)							
Intercept	0.984	0.068	9.638	20.95 mg/liter			
Diamorphine d 14	−0.044	0.021	0.904		18.93	−2.126	0.034
Dopamine d 14	−0.135	0.043	0.733		15.35	−3.132	0.002
Gestation	0.011	0.002	1.026		21.49	5.088	<0.001
T_4S (pmol/liter)							
Intercept	4.135	0.160	13645.83	853.3 pmol/liter			
Infection in blood or endotracheal tube on d 10–15	0.128	0.042	1.343		1145.8	3.071	0.002
Gestation	−0.046	0.005	0.900		767.6	−8.707	<0.001
FiO_2 mean	0.003	0.001	1.007		859.2	2.762	0.006

β-subunit genes (52). Many of the effects of TSH activation of the thyroid gland are mediated through stimulation of the adenyl cyclase cascade regulating the expression of many genes including TSH receptor and thyroglobulin (53).

In the majority of adults and children, the result of therapeutic doses of theophylline is to increase plasma T_4 levels with variable increases in rT_3 and T_3 (54). A single dose of iv aminophylline to adult asthmatics is followed by acute increases in TSH and T_4 (55), whereas effects are absent after chronic administration (>2 wk) to infants (56). The effect of caffeine on neonatal thyroid hormones is unknown. In our study, there is a dichotomy of effect of caffeine on TSH at d 7 and 14. Aminophylline is associated with increases of T_4 and T_3 levels on d 7, which may reflect recent administration.

High-dose glucocorticoids have multiple effects on the thyroid axis, including inhibition of TSH secretion (57), decreases in extrathyroidal conversions of T_4 to T_3 (58, 59), reductions in serum TBG levels (60), and an increase in renal clearance of iodine (61). Postnatal dexamethasone has been used variously in preterm infants to accelerate fetal lung maturity and for the prevention or therapy of chronic lung disease; follow-up studies on such infants have shown substantial adverse effects on neuromotor and cognitive function (*e.g.* Refs. 62 and 63). Dexamethasone use is confined to our extreme preterm infants who are not only the highest-risk group for transient hypothyroxinemia (15, 21, 22) but also for a less favorable neurodevelopmental outcome (*e.g.* 64). Maintaining serum FT_4 levels in extreme preterm infants may be a priority for sustaining postnatal brain development (65). In our infants, postnatal dexamethasone use is associated with a substantial reduction in serum FT_4 levels, and this may also contribute, in addition to a direct effect of dexamethasone (66), to the unfavorable neurodevelopmental outcome.

Dopamine infusions are administered to infants for inotropic support and for optimization of renal and splanchnic perfusion (67). In humans, dopamine has a physiological inhibitory role in the control of TSH release (68) and therapeutic infusions are associated with rapid reductions in serum TSH levels in adults as well as infants and children (69,

TABLE 6. Significant factors that influence levels of d-28 sera iodothyronines, TSH, and TBG

Variable	B	SE	Anti-log B (effect size)	Group geometric mean at 29 wk gestation	Change in predicted mean	*t* statistic	*P* value
T_4 (nmol/liter)							
Intercept	1.075	0.108	11.885	94.13 nmol/liter			
Diamorphine d 28	−0.289	0.051	0.514		48.39	−5.634	<0.001
Gestation	0.030	0.004	1.072		100.86	8.248	<0.001
FT_4 (pmol/liter)							
Intercept	0.855	0.071	7.161	20.58 pmol/liter			
Diamorphine d 28	−0.091	0.033	0.811		16.69	−2.754	0.006
Gestation	0.016	0.002	1.038		21.35	6.701	<0.001
TSH (mU/liter)							
Intercept	0.668	0.096	4.656	2.98 mU/liter			
Birthweight ratio	−0.234	0.096	0.584		1.74	−2.424	0.016
T_3 (nmol/liter)							
Intercept	−1.188	0.159	0.048	1.31 nmol/liter			
Diamorphine d 28	−0.575	0.071	0.423		0.35	−8.122	<0.001
Dopamine d 28	−0.440	0.172	0.286		0.48	−2.562	0.011
Gestation	0.040	0.006	1.099		1.44	7.124	<0.001
Total nutrition d 28	0.131	0.054	1.005		1.77	2.410	0.017
rT_3 (nmol/liter)							
Intercept	0.186	0.052	1.535	0.95 nmol/liter			
Necrotizing enterocolitis	0.080	0.029	1.202		1.14	2.813	0.005
Total nutrition d 28	−0.146	0.041	0.998		0.68	−3.537	<0.001
TBG (mg/liter)							
Intercept	1.212	0.034	16.293	21.46 mg/liter			
Diamorphine d 28	−0.092	0.033	0.809		17.36	−2.773	0.006
Birthweight ratio	0.130	0.034	1.349		28.95	3.846	<0.001
T_4S (pmol/liter)							
Intercept	4.891	0.183	77803.66	668.7 pmol/liter			
Gestation	−0.070	0.006	0.851		569.16	−11.282	<0.001

To convert T_3 and rT_3 to ng/dl, multiply by 65.1; T_4 to μg/dl, multiply by 0.0777; FT_4 to ng/dl, multiply by 0.0777; T_4S to ng/dl, multiply by 0.085.

70). In addition, dopamine may also have peripheral effects such as the inhibition of TSH-stimulated T_4 release from the thyroid (71) or alterations in hepatic T_4 to T_3 conversion (72). Prolonged use of dopamine even on low infusion rates may result in reduced T_4 and T_3 levels and in adults may induce or exacerbate the changes in serum thyroid hormones associated with nonthyroidal illness (73, 74). In very low birthweight infants (<32 wk gestation, <1500 g birthweight), dopamine is associated with reductions in serum TSH levels but also with a relatively greater decline in serum T_4 levels (75). In our study, there was no association of dopamine with serum TSH levels but instead with reduced T_3 and T_4 levels, a similar pattern to our infant groups previously described with the severest nonthyroidal illness (23). In our infants, dopamine is associated with a reduced serum TBG level; this is a novel finding, and this association has not been reported before. A previous analysis of this data set, using the BAPM score as a surrogate marker of illness severity (32), showed no differences in serum TBG levels between infant groups with variable illness severity (23). The reduction in TBG levels associated with dopamine use may also contribute to the decreased serum T_3 and T_4 levels.

Morphine suppresses TSH release (76, 77), but to our knowledge effects on other aspects of thyroid hormone metabolism have not been reported. The association of diamorphine use with marked reductions in serum levels of T_4, T_3, FT_4, and TBG is therefore surprising. It is possible that this is a spurious observation and diamorphine use is a surrogate for severity of illness, but this could also be said of the associations of dexamethasone or dopamine, where there is already substantive supportive experimental evidence for their direct effect on thyroid hormone metabolism.

Diamorphine is frequently prescribed in the early neonatal period, and the lack of association with d-7 T_4 levels was not immediately clear given the significant associations between its use and T_4 levels on postnatal d 14 and 28. However, we believe that the association at d 7 is obscured by the relative dominance of the illness prevalent at this time; this mechanism may explain the lack of expected temporal associations between drugs and specific iodothyronine levels or between illnesses and specific iodothyronine levels.

Transient hypothyroxinemia in preterm infants is associated with reductions in developmental quotients and an increased risk of cerebral palsy. The role of thyroid hormone status as a contributory factor to cognitive and motor disability remains unclear, and we are still left with the question of whether low serum T_4 levels, particularly those associated with severe illness in preterm infants, are causative *per se* of later neurodevelopmental deficits or simply an epiphenomenon of illness? This critical question remains unanswered for the present; because the causative factors for disability may be multiple and influence each other, it is possible that hypothyroxinemia and other pathophysiological changes of illness(es) are interactive in their contributions to cerebral damage. Our study establishes for the first time that there are more associations of particular illnesses (or drug uses) with low serum T_4 levels than had previously been considered in preterm infants. This etiological complexity of low serum T_4 levels highlights that consideration should be given to alternative strategies for correction of hypothyroxinemia

rather than sole reliance on the direct therapy of hormone replacement. A more oblique preventative approach may be necessary, for example through reduction in the incidence or severity of individual illness(es) that influence thyroid hormone levels in these infants; this has probably already occurred for respiratory distress syndrome.

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