

# Frequency of transient hypothyroxinaemia in low birthweight infants

## Potential pitfall for neonatal screening programmes

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**SUMMARY** Thyroid function was studied in 54 low birthweight infants during a 3-week period. Each infant was placed in one of three groups. Group 1 (n = 21), infants who were well and appropriately grown for gestational age; group 2 (n = 23), infants who were appropriately grown but who had hyaline membrane disease; group 3 (n = 10), infants who were small-for-gestational-age. In group 1, 5 (24%) infants had at least one serum thyroxine value  $<3.0 \mu\text{g}/100 \text{ ml}$  (39 nmol/l). There were 8 (35%) infants in group 2 who had similarly low serum thyroxine values, as did 5 (50%) of the 10 infants in group 3. Serum thyrotropin levels and serum binding of thyroid hormones, as measured by a T3-charcoal uptake test, were normal in all infants. In all instances but 2, serum thyroxine values were at least  $4.0 \mu\text{g}/100 \text{ ml}$  (51 nmol/l) by the end of the 3-week period. There is thus a high incidence of transient 'hypothyroxinaemia' in low birthweight infants, particularly if such infants have hyaline membrane disease or are small-for-gestational-age. These findings must be considered when interpreting results of screening programmes for congenital hypothyroidism and they lend further support to the use of a combination of serum thyroxine and thyrotropin determinations for optimum screening of such infants.

The high incidence of congenital hypothyroidism and the usefulness of serum thyroxine (T4) and thyrotropin (TSH) measurements in detecting the disorder has resulted in recommendations for neonatal screening programmes.<sup>1</sup> Gestational age<sup>2</sup> and birthweight<sup>3-4</sup> are known to affect values of hormones in cord blood. We have published results indicating that the postnatal changes in serum T4 and TSH concentrations in well, low birthweight infants are similar to those of term babies in the first 3 weeks of life, although mean T4 values are lower.<sup>5</sup> Findings are similar for infants who are small-for-gestational-age (SGA) and those with hyaline membrane disease.<sup>5-7</sup>

A review of our data showed a striking number of patients with serum T4 concentrations  $<3 \mu\text{g}/100 \text{ ml}$  (39 nmol/l). In all but 2 patients—who eventually proved to be normal—the hypothyroxinaemia was transient and not accompanied by raised serum TSH or abnormalities of serum thyroid hormone binding.

Since transient hypothyroxinaemia in the newborn infant has been reported,<sup>1 8-9</sup> we felt it was important to record its incidence in a population of low birthweight infants.

### Materials and methods

Fifty-four preterm infants had serum T4 and TSH measurements performed, when possible, on cord blood and blood collected by venepuncture at 24, 48, and 72 hours as well as at 1, 2, and 3 weeks of age. Informed consent was obtained from one or both parents.

Patients (Table 1) were assigned to group 1 (AGA, n = 21) if they were appropriately grown for gestational age and were well or had only mild illness. Group 2 (HMD, n = 23) comprised AGA infants with classical hyaline membrane disease,<sup>10</sup> and group 3 (SGA, n = 10) comprised infants who were SGA and who were well or had only mild illness.

Table 1 The three study groups, means  $\pm$  SD

Group	Gestational age (weeks)	Birthweight (g)
1 (AGA) n=21	32.6 $\pm$ 3.2	1692 $\pm$ 585
2 (HMD) n=23	32.7 $\pm$ 2.1	1850 $\pm$ 449
3 (SGA) n=10	32.8 $\pm$ 3.0	1260 $\pm$ 470

AGA = appropriately grown for gestational age; HMD = hyaline membrane disease; SGA = small-for-gestational age.

Measurements of serum T4 and TSH were made by radioimmunoassay as described previously.<sup>5 11-12</sup> All samples from an individual infant were analysed in the same assay run. Serum binding of thyroid hormones was measured indirectly by a modification of the T3-charcoal technique of Bermudez *et al.*<sup>5 13</sup>

The incidence of serum T4 results  $<3.0 \mu\text{g}/100 \text{ ml}$  was expressed as a percentage of the total number of samples collected. The value of  $3.0 \mu\text{g}/100 \text{ ml}$  was arbitrarily chosen as being very low for a neonatal screening result<sup>1 14</sup> and was 2.5 SDs below the mean reported by Cuestas<sup>15</sup> for healthy preterm infants in the first 3 months of life.

**Results**

Serum T4 results at each time period for the three groups are shown in Table 2; the ranges indicate the

wide variation in serum T4 concentrations in these infants. Table 3 shows the overall high incidence of serum T4 values  $<3.0 \mu\text{g}/100 \text{ ml}$  as a function of time, the peak incidence occurring between 3 days and 1 week. Of the total of 260 samples assayed, 25 (9.6%) had T4 values  $<3.0 \mu\text{g}/100 \text{ ml}$ . Of a total of 81 serum T4 measurements at 72 hours and 1 week (the age range generally recommended for screening), 17 (21%) were  $<3.0 \mu\text{g}/100 \text{ ml}$ . Five (24%) infants in group 1 had at least one serum T4 value  $<3.0 \mu\text{g}/100 \text{ ml}$ . There were 8 (35%) infants in group 2 who had similarly low values as did 5 (50%) of the 10 infants in group 3. The Figure shows the distribution of serum T4 and TSH results for the groups, expressed as a percentage of the total number of samples for all groups. With 2 exceptions (both infants with HMD who were subsequently normal), all patients had serum T4 concentrations of at least  $4.0 \mu\text{g}/100 \text{ ml}$  (51 nmol/l) by 3 weeks. Similarly, all infants had serum TSH concentrations  $<12 \mu\text{U}/\text{ml}$  at 3 weeks of age.

The T3-charcoal uptake value, an indirect measurement of serum T4-binding capacity (performed on all except 5 of the infants), was normal in all patients. These data exclude decreased serum thyroid hormone binding as the cause of the hypothyroxinaemia.

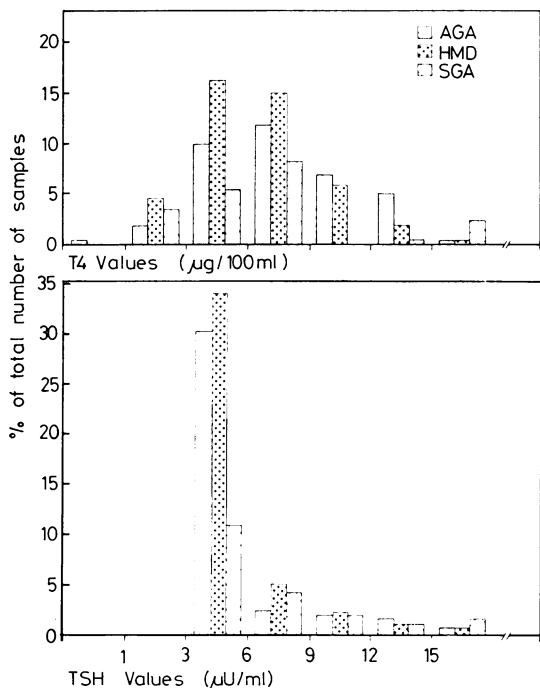
Table 2 Serum T4 values ( $\mu\text{g}/100 \text{ ml}$ ) at different ages in the 3 study groups

Group	Cord	Age					
		24 hours	48 hours	72 hours	1 week	2 weeks	3 weeks
1 (AGA)							
Mean	6.2	9.3	7.8	7.3	7.1	7.8	8.8
Range	(1.6-9.8)	(4.8-18.0)	(2.6-14.0)	(1.3-12.6)	(2.5-14.9)	(2.2-14.6)	(5.2-12.8)
	n=8	n=8	n=11	n=8	n=19	n=19	n=18
2 (HMD)							
Mean	8.9	5.4	5.7	5.8	5.9	6.9	8.0
Range	(4.5-16.0)	(2.0-9.5)	(2.4-9.0)	(2.5-10.0)	(1.6-14.0)	(1.7-14.3)	(2.6-14.4)
	n=7	n=15	n=18	n=15	n=22	n=21	n=20
3 (SGA)							
Mean	4.8	8.2	8.4	7.3	7.0	5.0	6.8
Range	(2.8-7.8)	(2.3-22.4)	(2.4-21.6)	(2.6-19.0)	(1.6-20.0)	(2.4-8.6)	(4.0-8.6)
	n=3	n=9	n=10	n=8	n=9	n=6	n=6

Conversion: traditional to SI units  $1 \mu\text{g}/100\text{ml} \approx 13 \text{ nmol}/\text{l}$ .

Table 3 Incidence of thyroxine values  $<3.0 \mu\text{g}/100 \text{ ml}$  at each time studied

	Age						
	Cord	24 hours	48 hours	72 hours	1 week	2 weeks	3 weeks
	(n=18)	(n=32)	(n=39)	(n=31)	(n=50)	(n=46)	(n=44)
Number (and %) with T4 $<3.0 \mu\text{g}/100 \text{ ml}$	2 (11)	1 (3)	2 (5)	5 (16)	9 (18)	5 (11)	1 (2)



AGA = appropriately grown for gestational age; HMD = hyaline membrane disease; SGA = small-for-gestational-age.

Figure Distribution of serum thyroxine and thyrotropin values in the study groups.

Conversion: traditional to SI units  $1 \mu\text{g}/100 \text{ ml} \approx 13 \text{ nmol/l}$ .

## Discussion

Our previous observations<sup>5</sup> that low serum T4 concentrations can occur transiently after birth in low birthweight infants have now been extended to show that a serum T4 concentration of  $<3.0 \mu\text{g}/100 \text{ ml}$  is a remarkably common occurrence. These low levels occurred at some point in the first 3 weeks of life in 24% of AGA babies, in 35% of babies with HMD, and in 50% of those who were SGA. The cases of transient hypothyroxinaemia reported earlier<sup>8-9</sup> differ from these because of increased serum TSH concentrations in the former group. Our findings of normal serum TSH levels with low serum T4 values are consistent with a hypothalamic-pituitary origin resulting from impaired thyrotropin-releasing hormone or TSH secretion. The results cannot be explained by abnormalities in serum thyroid hormone-binding proteins, since no abnormalities in T3-charcoal uptake were found. Whatever the explanation, our findings stress the difficulty in evaluating serum T4

measurements in low birthweight infants in the first 3 weeks of life, and show the importance of performing serum TSH determinations when low T4 values are found.<sup>1</sup> In every patient, the finding of a normal TSH ruled out primary hypothyroidism. The increase in serum T4 levels with age makes permanent TSH or thyrotropin-releasing hormone deficiency highly unlikely.

Despite the high incidence of low serum T4 measurements in this population of infants, prudence demands that serum T4 values  $<3$  or  $4 \mu\text{g}/100 \text{ ml}$  ( $39$ – $51 \text{ nmol/l}$ ) should be followed by repeat determinations of T4 and TSH until a decision for normality, or the institution of treatment can be made. Although with two exceptions the serum T4 levels in our patients returned to normal by 3 weeks of age, in some infants a longer period of follow-up may be necessary to ensure normality.<sup>9</sup> The particularly high frequency of very low serum T4 in infants with HMD and those who are SGA must be borne in mind when evaluating such patients.

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