Serum Thyroglobulin Levels in Preterm Infants with and without Respiratory Distress Syndrome.

II. A Longitudinal Study during the First 3 Weeks of Life

J. H. KOK, W. H. H. TEGELAERS, AND J. J. M. DE VIJLDER

Department of Neonatology and Department of Pediatrics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

ABSTRACT. Serum thyroglobulin (Tg) and thyroid-stimulating hormone (TSH) levels were measured in 182 preterm and term infants. Samples were taken from cord blood, and at 1, 3, 7, 14, and 21 days after birth. The infants were divided into groups according to their perinatal characteristics: infants who were appropriate for gestational age, infants who were small for gestational age, and preterm infants who developed respiratory distress syndrome. These groups were subdivided according to gestation age. Tg serum levels showed a significant increase in the 1st day in all groups, and decreased significantly after about 1 wk. The highest Tg levels were found in the 1st wk of life in respiratory distress syndrome infants, and in infants with the lowest gestation ages. TSH levels increased at day 1 but only in appropriate and small for gestational age infants of more than 30 wk of gestation. TSH levels at day 1 in the groups with gestation ages of less than 30 wk and in respiratory distress syndrome infants of more than 30 wk were low, reflecting a low TSH surge. We conclude that the neonatal increase of Tg is not merely caused by the TSH surge. We suggest that the Tg increase is due to an impaired degradation of Tg, and/or to hemoconcentration, which are more pronounced in respiratory distress syndrome infants compared with appropriate for gestational age infants. (*Pediatr Res* 20: 1001-1003, 1986)

Abbreviations

Tg, thyroglobulin
TSH, thyroid-stimulating hormone
AGA, preterm infants with a birth weight appropriate for gestational age
SGA, term and preterm infants with a birth weight small for gestational age
RDS, preterm infants who developed respiratory distress syndrome

The adaptation of pituitary-thyroid function in the first weeks of life has been described extensively with respect to iodothyronines and TSH in term and preterm neonates (1-3). On the other hand, little information on Tg levels in the early postnatal period is available. Pezzino *et al.* (4) demonstrated an increase

of serum Tg 6 h after birth in term neonates. They supposed that this reflects the endogenous TSH stimulation immediately after birth. Black *et al.* (5) measured a postnatal increase of Tg in healthy term infants; in ill term and in preterm infants they could not demonstrate such an increase.

This study was undertaken to investigate the changes of Tg serum levels in infants with and without RDS during the first 3 wk of life in relation to TSH serum levels in the observed period.

PATIENTS AND METHODS

Patients. Venous blood samples were collected from 182 infants, when possible, at birth (cord blood), and at 1, 3, 7, 14, and 21 days after birth. Tg and TSH serum concentrations of the samples were measured. In another paper (6) we demonstrated a dependence of Tg in cord serum on gestation age, birth weight, and RDS. Therefore these 182 infants were divided into groups according to their perinatal characteristics (AGA, SGA, and RDS, AGA infants who developed RDS). Each group was subdivided according to gestation age (I less than 30 wk; II 30-32 wk; III 33-36 wk; and IV more than 36 wk) (Table 1).

Definitions for gestation age and the RDS are given in our companion paper (6); the same exclusion criteria were used. In addition, infants who died during the observed period and infants who developed transient hypothyroidism after birth were excluded from this study. Infants with birth weights lower than the 10th percentile for their gestation age [according to Kloosterman's growth chart (7)] were considered SGA.

The study was approved by the Committee of Ethics of the Academic Hospital of the University of Amsterdam.

Methods. Tg and TSH levels were measured by radioimmunoassay methods (6). Due to the small volumes, Tg and TSH concentrations could not always be measured in all samples. In Figures 1 and 2 the number of samples in which determinations were performed is given for each sampling time.

All samples of one infant were assayed in the same run in order to avoid interassay variation.

Statistical analysis between groups of infants was performed with the use of Student's unpaired *t* test, or analysis of variance. Comparisons within the groups were made by paired *t* test; values were compared between cord and days 1, 3, and 21, and between days 1 and 3 in all groups. Because of skewness of the distribution of the data the Tg and TSH values were analyzed after logarithmic transformation.

RESULTS

Table 1 shows the relevant clinical data concerning the infants in the different subgroups. Mean gestation ages in the youngest

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Correspondence J. J. M. de Vijlder, Academic Medical Center, Department of Pediatrics, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands.
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Table 1. Clinical data of the investigated groups for longitudinal studies

	n	Birth wt		Gestational age		Sex
		Range	Mean $\pm$ SD	Range	Mean $\pm$ SD	Male/female
AGA I	15	890–1740	1275 $\pm$ 260	26–29	28.6 $\pm$ 0.8	7/8
AGA II	27	1160–2120	1605 $\pm$ 215	30–32	30.9 $\pm$ 0.8	18/9
AGA III	59	1570–3640	2250 $\pm$ 360	33–36	34.6 $\pm$ 1.1	32/27
SGA II	10	910–1285	1055 $\pm$ 135	30–32	31.7 $\pm$ 0.5	6/4
SGA III	21	890–2240	1560 $\pm$ 360	33–36	34.7 $\pm$ 1.3	16/5
SGA IV	19	1400–2350	1990 $\pm$ 280	37–41	37.7 $\pm$ 1.2	7/12
RDS I	18	810–1520	1190 $\pm$ 195	26–29	28.2 $\pm$ 0.9	9/9
RDS II	13	1190–1950	1570 $\pm$ 240	30–32	31.0 $\pm$ 0.9	8/5

Fig. 1. Geometric means and SEM of Tg concentrations during the first 3 wk of life in AGA infants, SGA infants, and in infants who developed RDS. Samples at day 0 are taken from cord blood. Significance values between subgroups with different gestational ages are indicated by an asterisk (* p < 0.05, ** p < 0.01). Number of samples at each sampling time is indicated. ●, I <30 wk; ○, II 30–32 wk; ■, III 33–36 wk; □, IV >36 wk of gestation.

Fig. 2. Geometric means and SEM of TSH concentrations during the first 3 wk of life in AGA infants, SGA infants, and in infants who developed RDS. Samples at day 0 are taken from cord blood. Significance values between subgroups with different gestational ages are indicated by an asterisk (* p < 0.05, ** p < 0.01). Number of samples at each sampling time is indicated. ●, I <30 wk; ○, II 30–32 wk; ■, III 33–36 wk; □, IV >36 wk of gestation.

groups (AGA I and RDS I) are comparable, as is the case for AGA III and SGA III. However, in infants of 30–32 wk mean gestational age in SGA infants (31.7 ± 0.5 wk) is significantly higher than that in AGA or RDS infants (30.9 ± 0.8 and 31.0 ± 0.9 wk, respectively) ($p < 0.05$). SGA I and RDS III groups were not composed because of too small a number of infants (two and four, respectively).

Tg. All groups show a characteristic pattern of Tg serum levels in the first 3 wk of life, as can be seen in Figure 1.

In all groups (except RDS II, because of short data in cord serum) a significant increase of Tg serum values is found 1 day after birth (AGA I, II, SGA II $p < 0.05$; AGA III, SGA III, RDS I $p < 0.01$; SGA IV $p < 0.001$). Although in group AGA II mean Tg in cord serum and day 1 serum are the same, there is a significant increase of Tg in 13 infants of whom paired data were available. RDS infants show the highest mean Tg values in the first 7 days. In AGA II and III Tg serum levels at day 21 are significantly lower than cord serum levels ($p < 0.001$ and < 0.01 , respectively). No differences between mean Tg levels on days 1 and 3 can be measured, except in SGA IV ($p < 0.05$).

Comparison of mean data between infants with the same perinatal characteristics but different gestation age shows that Tg values at day 1 are higher when gestation age is shorter (AGA I, II, III: $p < 0.05$, SGA II, III, IV: $p < 0.01$; analysis of variance; RDS I, II: NS, t test).

Differences between AGA, RDS, and SGA with comparable gestation ages are as follows. RDS I infants show higher Tg levels than AGA I during the period of observation. However, the difference is significant only on day 14 (t test, $p < 0.05$). In the groups between 30–32 wk, RDS II infants show significantly higher levels during the first 7 days (analysis of variance $p < 0.05$), while SGA II infants show the highest levels after this period ($p < 0.05$). SGA infants show the highest levels after 1 wk in the groups between 33–36 wk as well ($p < 0.05$).

TSH. The longitudinal pattern of TSH serum values in the investigated groups is shown in Figure 2. TSH levels of AGA I infants are significantly lower on day 1 than those of AGA II and III ($p < 0.05$). In SGA III and IV significantly higher TSH levels are found on day 1 compared with cord serum levels ($p < 0.01$ and < 0.05 , respectively). In the groups between 30–32 wk of gestation, RDS II infants show significantly lower TSH levels on day 1 than SGA II and AGA II infants (analysis of variance, $p < 0.01$). AGA I and RDS I infants show slightly but not significantly lower TSH levels on day 1 compared with cord serum. There are no significant differences in the course of TSH levels between AGA I and RDS I infants.

DISCUSSION

We found that Tg serum levels display a characteristic pattern in the first 3 wk of life in all groups. Between 1–3 days after birth maximal Tg values were found. The highest Tg levels were observed in RDS infants. These findings are in contrast to those of Black *et al.* (5), who did not find differences between cord levels of Tg and Tg levels in the first 2 wk of life in preterm infants. This is probably due to pooling of their data. De Nayer *et al.* (8) found high Tg cord serum concentrations and a decrease after the first weeks of life in preterm infants, in accordance with our data.

Pezzino *et al.* (4) suggested that the Tg increase after birth in term infants is caused by an endogenous TSH surge which can be demonstrated half an hour after birth (9). We did not measure the TSH surge, but others (10, 11) have shown a lower TSH surge in RDS infants than in healthy preterm infants of compa-

table gestation ages. Our finding that TSH concentrations on day 1 in RDS II infants are significantly lower than in AGA II or SGA II, probably reflects a low TSH surge in RDS infants. Because lower TSH levels were measured in both AGA I and RDS I infants on day 1, the TSH surge is probably low in the extreme premature infant as well. Therefore the TSH surge after birth cannot be the only factor responsible for the Tg increase after birth. This is particularly true in RDS infants, because these infants show the highest Tg values.

In addition to a given level of TSH stimulation, other factors leading to high Tg serum concentrations in preterm infants may include a higher permeability of the thyroid gland or a delayed degradation of Tg by an immature liver. A delayed degradation could be caused by a diminished binding of Tg, resulting from an altered structure of the receptor, or from an altered composition of the carbohydrate chains of Tg, as can also be found in thyroid cancer (12). Another factor may be the degree of hemoconcentration. Usually RDS infants show an increasing edema during the first days of life, with hypoalbuminemia (13) due to a higher capillary permeability. Since it is unlikely that Tg permeates the capillary wall (mol wt of Tg: 660,000) at the same rate as proteins of lower molecular weight, such as albumin, it is possible that the high Tg levels are due to hemoconcentration. However, in our study group mean hematocrit levels of RDS I and AGA I infants were not different during the 1st wk.

In conclusion, Tg levels in preterm infants show a significant increase between 1 and 3 days after birth. This increase is not entirely attributable to the TSH surge. In preterm infants with RDS significantly higher Tg serum concentrations are found than in preterm infants who do not develop the syndrome.

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