

High Incidence of Thyroid Dysfunction in Preterm Infants

To determine the validity of a repeat thyroid function test for preterm infants, and to investigate factors that influence thyroid function of preterm infants, thyroid functions of 105 infants born at <32 weeks' gestational age were evaluated. Initial serum free thyroxine (fT4) and thyrotropin (TSH) levels were measured during the first 10 days of life, and repeated tests were performed more than 2 weeks apart. We analyzed the effects of gestational age, systemic diseases, and nutrition on the development of thyroid dysfunction. Thirty-one infants (30%) had low fT4 levels (<0.7 ng/dL) in the absence of elevated TSH levels (<7 μ U/mL). Thirteen infants (12%) had hypothyroidism (fT4 <0.7 ng/dL, TSH \geq 10 μ U/mL) and mean age at diagnosis was 28 ± 17 days. Twelve infants had moderately elevated TSH (TSH 10-30 μ U/mL) with normal fT4 levels after 1 week of postnatal life. The history of undergone surgical procedure which needed iodine containing disinfectants was significantly frequent in the infant with hypothyroidism and transient TSH elevation. Repeated thyroid function tests are necessary for preterm infants, even though they initially show normal thyroid function, and are especially important for infants who have been exposed to excessive or insufficient levels of iodine.

Key Words : Preterm Infant; Thyroid hormones; Hypothyroidism

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INTRODUCTION

Postnatal thyroid function of preterm infants differs from that of term infants. Blunted postnatal thyrotropin (TSH) surges and low serum T4 levels are frequently observed in preterm neonates; this is generally referred to as hypothyroxinemia of prematurity (1). In contrast to typical congenital hypothyroidism, a normal TSH level upon initial screening followed by delayed TSH elevation is observed in some preterm infants (2).

The main factors that influence thyroid function in preterm infants are immaturity of the hypothalamic-pituitary-thyroid axis, immature thyroid hormone synthesis, immature thyroid hormone metabolism, and systemic diseases. Insufficient or excessive iodine intakes also influence preterm thyroid function (3).

Although the survival rate of very low birth weight infants has increased in recent years, guidelines for thyroid function monitoring have not been established for preterm infants. The aims of this study were to examine the characteristics of thyroid function of preterm infants, to determine the validity of a repeat thyroid function test for preterm infants, and to investigate factors that influence thyroid function of preterm infants.

MATERIALS AND METHODS

Patients and data

One hundred five preterm infants who were born at <32 weeks' estimated gestational age (GA) at the Seoul National University Children's Hospital and the Seoul National University Bundang Hospital between July 2004 and May 2006, and who underwent repeat thyroid function tests were included in the study. Infants with maternal thyroid diseases, multiple congenital anomalies, or who died within a month after birth were excluded from the study. The mean gestational age of these 105 infants was 28.4 ± 2.2 weeks, and mean birth weight was $1,112 \pm 320$ g.

We had routinely performed thyroid function test more than twice for preterm infants who were born at <32 weeks' GA. Initial serum levels of free thyroxine (fT4), triiodothyronine (T3), and thyrotropin (TSH) were measured within the first 10 days of life using radioimmunoassays and were repeated every 2 to 4 weeks after the first test.

Clinical data were retrospectively analyzed in terms of gestational age, birth weight, Apgar score at 5 min, the development of respiratory distress syndrome requiring surfactant supplementation, chronic lung disease (duration of oxygen requirement \geq 4 weeks), necrotizing enterocolitis (Bell stage

\geq II_A), intraventricular hemorrhage (grade \geq 3), and the history of surgical procedures. We obtained information on prenatal treatment with dexamethasone and the use of dopamine, dobutamine or morphine on the day on which the thyroid function test was performed. Nutritional status was estimated from the interval until tolerable feeding (\geq 100 mL/kg per day) was achieved. The study was approved by the institutional ethics committee of participating institution.

Definitions

Hypothyroxinemia of prematurity was defined as a free T₄ level $<$ 0.7 ng/dL and a TSH level $<$ 7 μ U/mL in the initial test. Hypothyroidism was defined as a free T₄ level $<$ 0.7 ng/dL in conjunction with a TSH level \geq 10 μ U/mL or as a TSH level \geq 30 μ U/mL in conjunction with any level of free T₄. Transient TSH elevation was defined as normal fT₄ levels with moderately elevated TSH levels (TSH 10–30 μ U/mL) after 1 weeks of postnatal life and TSH level was eventually normalized in the follow-up test without treatment. Preterm infants who did not have apparent thyroid dysfunction were included as controls.

Statistics

Data were expressed as means \pm standard deviations. Statistical analyses were performed using the t test or the Mann-Whitney U test. The Pearson chi-square test was used to compare categorical data. All calculations were performed using SPSS 12.0 (SPSS, Inc., Chicago, IL, U.S.A.), and a *P* value $<$ 0.05 was considered statistically significant.

RESULTS

Postnatal changes in thyroid function according to gestational age

Most infants born at $<$ 28 weeks' gestation had low free T₄ concentrations during the first week of postnatal life. Serum free T₄ levels gradually increased, and at 2 months of life,

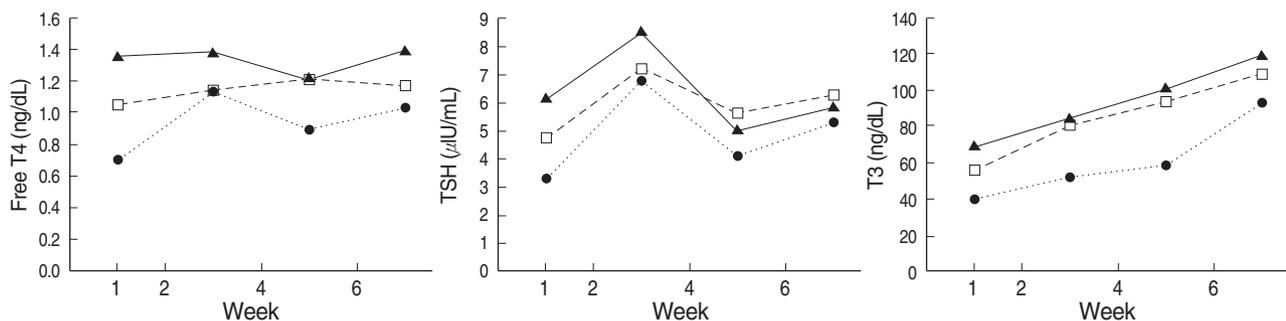


Fig. 1. Serum free T₄, TSH, T₃ concentration of 85 preterm infants during first 2 months after birth, grouped by gestational age. 20 infants who received L-thyroxine replacement were excluded. ●, $<$ 28 weeks (n=27); □, 28–30 weeks (n=32); ▲, 30–32 weeks (n=26).

reached levels equal to those of term infants. Infants of low gestational age had a tendency to show low TSH concentrations during the first week of postnatal life. TSH levels had a tendency to increase transiently between the second and fourth weeks of life in all groups. T₃ concentrations gradually increased during the first 2 months after birth in all infants (Fig. 1).

Thyroid function during the first 10 days of life

Hypothyroxinemia of prematurity was observed in 31 preterm infants (28%). Gestational age, birth weight, and Apgar score at 5 min were significantly lower in preterm infants with hypothyroxinemia than in the controls ($P<$ 0.01) (Table 1). Prenatal treatment with dexamethasone had no significant effect on the results of the initial thyroid function test. The incidence of respiratory distress syndrome and the incidence of bronchopulmonary dysplasia were significantly greater in preterm infants with hypothyroxinemia than in the controls ($P<$ 0.05; $P<$ 0.01).

Among 31 infants with hypothyroxinemia of prematurity, 7 infants received L-thyroxine supplementation; the remaining 24 infants did not receive L-thyroxine supplementation. Of 24 infants with hypothyroxinemia who did not receive L-thyroxine supplementation, three were diagnosed with overt hypothyroidism during follow-up; free T₄ levels of the remaining 21 infants normalized (\geq 0.7 ng/mL) during the first 3 weeks of postnatal life.

Hypothyroidism

Of 105 infants, 13 (12%) were diagnosed with hypothyroidism. Their mean age at diagnosis was 28 ± 17 days. Preterm infants with hypothyroidism had significantly lower gestational age and birth weights than the controls ($P<$ 0.05; $P<$ 0.01) (Table 1). Among these 13 infants, 8 infants who did not have overt hypothyroidism on the first thyroid function test were diagnosed as hypothyroidism on the repeated test. Especially infants of case 8 and 10 showed normal thyroid function on first test but turned out to have hypothyroidism on about 6 weeks of life (Table 2).

Table 1. Comparison between infants with hypothyroxinemia of prematurity, hypothyroidism, transient TSH elevation and control

	Hypothyroxinemia (n=24) [†]	Hypothyroidism (n=13)	Transient TSH elevation (n=12)	Control* (n=56)	P value
GA (week)	26.6±2.1	27.8±1.8	29.2±2.3	29.1±1.8	<0.01 [†] <0.05 [§]
BW (g)	900±261	967±236	1,158±386	1,225±292	<0.01 [†] <0.01 [§]
AS5	5.4±2.0	6.6±1.8	6.4±2.2	6.7±1.9	NS
Caesarean section	63%	85%	75%	79%	NS
Prenatal treatment with dexamethsone	75%	69%	75%	75%	NS
RDS	67%	62%	33%	40%	<0.05 [†]
BPD	83%	69%	42%	40%	<0.01 [†]
IVH, ≥Grade 3	13%	0%	1%	4%	NS
NEC	33%	15%	25%	9%	<0.05 [†] <0.05 [†]
Surgical procedure	21%	38%	17%	6%	<0.01 [§] <0.05 [‡]
Tolerable feeding (days)	35.3±21.3	36.3±33.2	27.0±24.3	17.6±13.4	<0.01 [†]

*Control: Preterm infants without hypothyroxinemia of prematurity, hypothyroidism and transient TSH elevation; [†]Among 31 infants who had hypothyroxinemia, 7 infants who were diagnosed as hypothyroidism or transient TSH elevation during follow-up were excluded; [‡]P value: Between infants with hypothyroxinemia and controls; [§]P value: Between infants with hypothyroidism and controls; [‡]P value: Between infants with transient TSH elevation and controls.

GA, gestational age; BW, birthweight; AS5, Apgar score at 5 min; RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NS, not significant.

Of 105 infants, 12 (11%) showed moderately elevated TSH levels (TSH 10-30 μ U/mL) with normal fT4 levels (>0.7 ng/dL) after 1 week of postnatal life and their clinical findings were not significantly different from controls. The history of undergone surgical procedure which needed iodine containing disinfectants was significantly frequent in the infant with hypothyroidism and transient TSH elevation ($P<0.01$; $P<0.05$) (Table 1).

In preterm infants with hypothyroidism, the interval until tolerable feeding was achieved tended to be prolonged, but the increase was not statistically significant (Table 1).

DISCUSSION

The incidence of thyroid dysfunction, especially hypothyroidism in preterm infants was high in this study. Thyroid hormone is associated with the neurodevelopment of preterm infants (4, 5). Despite many studies on thyroid function in preterm infants, its significance is still debated. Moreover, there has been much debate about the need for routine repeat thyroid function tests for preterm infants (6, 7) and thyroid hormone replacement in hypothyroxinemia of prematurity.

In term neonates, filter paper blood specimens are used to measure TSH levels and screen for congenital hypothyroidism during the first 2 to 5 days of postnatal life. However, the TSH surge and pituitary feedback for thyroid hormone are limited and TSH may not be increased even though serum thyroid hormone is low in preterm infants (8). In addition, very low birth weight infants usually have various systemic diseases and are given various drugs such as dopamine, dobutamine and morphine that affect the hypothalamic-pituitary-

Table 2. Clinical characteristics of 13 infants with overt hypothyroidism

No.	GA (week)	BW (g)	Age at diagnosis (days)	Initial		At diagnosis		Surgical procedure (Age at operation, days)	Tolerable feeding (days)
				free T4 (ng/dL)	TSH (μ U/mL)	free T4 (ng/dL)	TSH (μ U/mL)		
1	24 ⁺⁶	510	30	0.35	1.4	0.2	237	PDA ligation (10)	>100
2	25 ⁺³	680	45	0.6	2.4	<0.1	479	PDA ligation (24)	44
3*	25 ⁺⁵	710	64	0.26	9.4	0.5	41.7	Colostomy for NEC (17) EVD (31, 40, 54)	29
4	26 ⁺¹	970	7	0.59	13.5	-	-	-	26
5	27 ⁺¹	965	10	0.29	17.48	-	-	Colostomy for NEC (5) PDA ligation (14)	29
6	27 ⁺¹	870	20	0.64	4.3	0.8	58.5	-	18
7	28 ⁺³	1,140	21	0.91	30.5	0.54	111	-	12
8	28 ⁺⁴	1,320	42	2.1	6.5	0.31	67.5	-	9
9	29 ⁺¹	1,075	19	0.66	7	0.38	126.3	-	9
10	29 ⁺¹	1,100	45	1.29	2.3	0.61	26.8	-	15
11	29 ⁺¹	1,275	24	0.7	10.9	0.45	94.7	-	31
12	30 ⁺¹	870	28	1.42	20.1	0.42	95	PDA ligation (4)	16
13	30 ⁺¹	1,080	9	0.54	37.62	0.56	113.4	-	11

*Case 3: On 26 days of life, free T4 0.98 ng/dL, TSH 6.0 μ U/mL.

GA, gestational age; BW, birthweight; TSH, thyrotropin; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; EVD, external ventricular drain.

thyroidal axis. Thus, TSH levels are not representative of overall thyroid function in preterm infants.

In this study, eight preterm infants with hypothyroidism exhibited delayed TSH elevation and 2 of them showed normal thyroid function on the first test. The age at which hypothyroidism developed varied, and we could not anticipate which infants were at risk. Our findings justify repeated thyroid screening tests, including TSH and T₄ measurements, in preterm infants.

The incidence of persistent hypothyroidism among preterm infants does not differ from that among term newborns, but transient hypothyroidism is considerably more prevalent (1). Mandel *et al.* reported that the incidence of hypothyroidism in very low birth weight infants is 1:153 and that about half of these infants had atypical hypothyroidism (2). Larson *et al.* reported the incidence to be 1:250 (9). In studies conducted in Belgium, 5% to 18% of preterm infants had hypothyroidism, which was caused by an iodine deficiency (10, 11). The daily iodine requirement of preterm infants is more than twice that of term infants (12), and studies conducted in Europe demonstrated that most preterm infants have iodine deficiency (13-15).

In our study, the incidence of hypothyroidism was 12%, which was much higher than expected. Iodine intakes in Korea are thought to be sufficient because most Koreans eat various kind of seaweed, and the iodine content of human milk from lactating mothers is higher than that in other countries (12, 16). However, it takes about one month to achieve full enteral feeding in extreme preterm infants, before which most nutrition is supplied parenterally. According to Ibrahim *et al.*, most extremely preterm infants who receive parenteral nutrition have iodine deficiency (14). It is thought that preterm infants in Korea also have iodine deficiency, which might explain the high incidence of hypothyroidism in our patients.

In contrast, there is some evidence that the preterm neonate is more sensitive to the thyroid-suppressive effects of iodine exposure than the full-term neonate (17, 18). Escape from the Wolff-Chaikoff effect, that is the capacity of thyroid to reduce iodide trapping in response to excess iodine, does not appear until 36 to 40 weeks' gestation (19). The safe upper limit for daily iodine intake is lower for preterm infants than for term infants (20). Topical iodine can be absorbed through the skin. The skin of preterm infants is thin and may absorb iodine easily, and preterm infants have many chances that can be exposed to iodine-containing disinfectants. In addition, lactating women in Korea have seaweed soup containing abundant iodine traditionally and iodine concentration of breast milk of Korean women was reported very high (12). Although it is not clear whether such exposure to iodine can cause overt hypothyroidism in preterm infants, it may be one of the reasons for the high incidence of hypothyroidism.

Transient hypothyroxinemia is common in preterm infants and is more severe in infants born at a low gestational age.

Some studies suggest that low serum concentrations of thyroid hormone in the early period of life are associated with poor developmental outcomes (4, 5), although a definitive causal relationship between them is unclear. Thyroid hormone supplementation is frequently used for treatment of hypothyroxinemia, but there is no conclusive evidence that it is beneficial. Some authors have recommended that thyroid hormone supplementation should not be used for infants with low thyroid hormone levels unless they have elevated TSH levels (21, 22). However, in preterm infants born at <28 weeks' gestation, it usually takes more than one month for free T₄ levels to reach levels equal to those of term infants. It has been reported that thyroxine supplementation of infants born at <28 weeks' gestation results in a better neurodevelopmental outcome at 2, 5, and 10 yr of age (23-25). These findings suggest that thyroxine supplementation may be beneficial for preterm infants born at <28 weeks' gestation who have hypothyroxinemia.

In our study, free T₄ levels increased in most infants who had hypothyroxinemia and did not receive thyroxine supplementation during the first 3 weeks of postnatal life. This suggests that thyroxine supplementation should be considered if free T₄ levels are persistently low during the first 3 weeks after birth. Further studies are needed before clinical application of this finding.

It has been reported that low thyroid hormone levels are associated with the development of respiratory distress syndrome (26). In this study, respiratory distress syndrome was more frequent in preterm infants with hypothyroxinemia. However, gestational age was lower in preterm infants with hypothyroxinemia and specimens were obtained between 4 and 10 days of postnatal life. Thus, the low free T₄ and T₃ levels might have been caused by euthyroid sick syndromes or the low gestational age.

In conclusion, preterm infants born at <32 weeks' gestation have a high incidence of hypothyroidism. Repeated thyroid function tests are necessary for preterm infants, even though they may initially show normal thyroid function. The high incidence of hypothyroidism in preterm infants may be associated with excessive or insufficient iodine intake. Further studies are needed to elucidate the causal relationship between iodine balance and thyroid function in preterm infants.

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