Endocrinol. Japon. 1990, 37 (3), 369-379

Transient Hypothyroidism in Infants Born to Mothers with Chronic Thyroiditis- A Nationwide Study of Twenty-three Cases

NOBUO MATSUURA[1], JUNJI KONISHI[2] and the transient hypothyroidism study group in Japan

Member of the study group

NAOKO MOMOTANI, KAZUMI ARIKAWA, YACHIYO NOHARA, KENJI FUJIEDA, KANJI KASAGI, HIRONORI NAKAJIMA, HIROAKI INOMATA TORU MORI, TAKASHI ISHIHARA, SEIZO SUWA, KATSUHIKO TACHIBANA, MAKOTO SHIMIZU, HIROSHI IGARASHI, KAZURO KAISE, SHUICHI YAMAGUCHI, NAOYA KOODA, NORIHIDE OOYAMA, HIDEKI KURASHIGE, MICHINDO NINOMIYA, SEIGO HOSHI, YUTAKA YAMADA, NOBUYUKI TAKASU, TETSUO MORI, KAZUNORI MIKI, OSAMU NOSE, HIROKO KODAMA, ICHIRO OKABE, KAZUHIKO MASHIMO

Department of Pediatrics, Hokkaido University School of Medicine, Sapporo[1] and Department of Nuclear Medicine, Kyoto University School of Medicine, Kyoto[2] and a study group in Japan

Abstract

To define the difference in prognosis and the clinical features of transient neonatal hypothyroidism in infants born to mothers with chronic thyroiditis, we conducted a nationwide study of this condition. Sixteen mothers with chronic thyroiditis and twenty-three of their offspring with transient hypothyroidism were registered and reported in this paper. Five (group A) of twenty-two live infants showed physical, mental and/or psychomotor developmental delay (IQ below 80). No significant difference between TSH-binding inhibitor immunoglobulin (TBII) or thyroid-stimulation blocking antibody (TSBAb) activities in groups A and B (normal development) were noted. Moreover, there was no significant difference in thyroid function in the newborn period, ages at the start of thyroid medication or the dose and duration of treatment in the two groups. A striking difference observed between the two groups was the thyroid function of their mothers during pregnancy. In group A, four mothers were hypothyroid during pregnancy, and another mother discontinued thyroid medication in the last trimester and her baby was most delayed at the start of thyroid medication. On the other hand, the mothers of only two of seventeen live cases in group B had mild hypothyroidism during pregnancy. There were two sets of siblings whose mother received inadequate treatment during the first pregnancy and adequate treatment during the second pregnancy. The psychomotor, physical and mental developmental delay were observed in their first babies. These findings suggested that maternal thyroid function during pregnancy might be an important factor in the prognosis of infants born to mothers with chronic thyroiditis.

Table 1. Maternal thyroid function

Case No.			Thyroid function at diagnosis.					
Infant	Mother	Age (Years)	T_4 (ug/dl)	T_3 (ng/dl)	TSH (uU/ml)	^{123}I-uptake (% 24 hr)	TBII (%) (undiluted	TSBAb (%) serum)
1	M-1	28	3.3	66	104.8	1.2	83.3	91.7
2	M-2	25	1.0>	20	170.0	—	93.9	100.0
3	M-3	27	4.6	57	21.6	—	100.0	74.7
4	M-4	19	—	—	—	0.4	97.0	100.0
5	M-5	19	—	—	—	—	93.1	75.9
M±SD							93.5±5.6	88.5±11.2
6	M-6	30	0.1	*1 16.7	160.0	—	93.3	—
7	M-7	30	1.0	16	364.0	—	98.0	93.3
8	M-4	19	—	—	—	0.4	93.3	100.0
9	M-8	23	0.4	30	171.0	1.5	*4 —	—
10	〃	〃	〃	〃	〃	〃	—	—
11	M-9	24	2.3	30	146.0	—	96.0	100.0
12	〃	〃	〃	〃	〃	—	〃	〃
13	〃	〃	〃	〃	〃	—	〃	〃
14	〃	〃	〃	〃	〃	—	〃	〃
15	M-10	22	0.1	26	*2 14.2	0.4	90.0	100.0
16	M-11	26	1.3	50	480.0	*3 0	99.4	100.0
17	〃	〃	〃	〃	〃	〃	〃	〃
18	M-12	12	—	—	—	—	*5 84.8	—
19	M-13	17	—	—	—	2.0	77.2	—
20	M-14	24	1.4	25>	160<	—	*5 68.0	*6(+)
21	M-15	31	27.0	220	4.9	—	97.3	*6(+)
22	M-16	17	0.8	50	—	0.7	86.0	*6(+)
23	M-1	28	3.3	66	104.8	1.2	89.4	100.0
M±S.D.							92.0±6.4	98.9±7.5
P value							N.S	N.S.

*1 : Triosorb, *2 : 10 days after discontinuation ot medication, *3 : 99 mTc uptake,
*4 : Data for mother are not available, however, TBII was positive in fant in (Table ⇨

Transient neonatal hypothyroidism in infants born to mothers with chronic thyroiditis, first reported by Sutherland *et al.*, (1960), has been established as an important disease entity in the newborn period. Transplacental transfer of thyrosuppressive factors has been postulated as a cause of the disease (Goldsmith *et al.*, 1973). Recently TSH-receptor blocking antibody was defined as one such factor (Matsuura, *et al.*, 1980). Although similar cases have been reported (Iseki, *et al.*, 1983; Ninomiya,, *et al.*, 1983; Takasu, *et al.*, 1984; Karlsson, *et al.*, 1984; Ishikura, *et al.*,

Received November 24, 1989
Address reprint requests to Dr. NOBUO MATSUURA at the Department of Pediatrics, Hokkaido University School of Medicine, N-15, W-7, Kita-ku, Sapporo, Hokkaido, 060 Japan (011-716-1161 ext. 5954)

The study was supported in part by Grants-in-Aid for Scientific Research 58480248 and 62480223 from the Ministry of Education, Science and Culture, Japan.

at diagnosis and during pregnancy.

Thyroid medication and function during pregancy or shortly after delivered infant.

Drugs (ug or mg/day)	Dose	T_4 (ug/dl)	T_3 (ng/dl)	TSH (uU/ml)	Age at Pregnancy	Reference
None		3.3	66	104.8	28	Matsuura (1989)
〃		1.0>	20	170.0	25	
LT_4	40	0.9	10	55.9	27	
DT	120-30	5.3	135	45.0	21	Matsuura (1980)
—	? - 0	—	—	—	—	Yokota (1985)
		2.6±1.8	57.8±49.3	94.9±49.3		
DT	60	5.9	*1 19.0	—	37	
L-T_4	100	4.8	110	25.6	32	Inomata (1986)
DT	120	16.2	200	0.3>	33	Matsuura (1980)
L-T_4	100	*7—	—	—	25	
〃	〃	—	—	—	27	
L-T_4	150	Euthyroid			28	Iseki (1983)
〃	〃	〃			30	
〃	〃	〃			30	
〃	〃	〃			32	
L-T_4	200	9.1	142	0.5	29	Ninomiya (1983)
L-T_4	200	Euthyroid			28	Ishihara (1985)
〃	〃	〃			29	
L-T_4	150	*8 2.05	—	1.0	28	
DC	80	11.3	437	—	27	
L-T_4	150	16.9	159	13.2	27	Kanaya (1985)
MMI	5	9.7	120	4.4	30	Mashimo (1985)
L-T_4	150	10.2	120	3.8	25	Takasu (1984)
L-T_4	100	11.5	131	1.6	32	Matsuura (1989)
		10.6±3.8	177.4	6.2		
			±101.7	±8.3		
		P<0.001	P<0.05	P<0.05		

2), *5: Data for 50-fold dilution, *6: Refer to original paper, *7: Actual data were not available, *8: Free T4

1985; Yokota, *et al.*, 1985; Kanaya, *et al.*, 1985; Mashimo, *et al.*, 1985; Inomata, *et al.*, 1986) since then, the clinical features as well as the prognosis of each case varied a great deal. Although most infants recovered completely, some were physically, mentally or emotionally retarded in spite of intensive treatment during the newborn period (sutherland, *et al.*, 1960; Goldsmith, *et al.*, 1973). It is not clear whether the difference was due to the nature of TSH-receptor blocking antibodies in the mother or to the severity of thyroid suppression during the fetal and neonatal periods.

We conducted a nationwide study of this condition to find out which factors might influence the clinical course of affected infants. Results suggested that maternal hypothyroidism during pregnancy might be a cause of the delay in physical, mental and/or psychomotor development.

Materials and Methods

Sixteen mothers with chronic thyroiditis and twenty-three of their offspring with transient hypothyroidism were the subjects of this study. Questionaires were sent to the hospitals where transiently hypothyroid infants born to mothers with chronic thyroiditis were treated. Using a standardized form, the following data were collected; name, date of birth, gestational week, birth weight and length, thyroid function during the newborn period, treatment with thyroid drugs, physical, psychomotor and mental development of children, thyroid function of mothers during pregnancy, clinical course of mother's thyroiditis and analysis of TSH-receptor antibodies. TBII was assayed by means of a radioreceptor assay of TSH. TSBAb was assayed by measuring basal and TSH-induced cyclic AMP accumulation in the presence or the absence of test IgG with cultured thyroid adenoma cells or porcine thyroid cells as targets. Serum TSH, T_4 and T_3 were determined by radioimmunoassay with commercially available kits. The presence of antithyroid antibodies was determined by the hemagglutination technique with tanned sheep red cells, for both thyroglobulin (TGHA) and microsomal antibodies (MCHA), with commercially available kits (Fujirebio, Inc., Tokyo).

Physical development was evaluated by the standard deviation score of length obtained at the patient's last examination. Psychomotor development was estimated from the age of walking alone and mental development was evaluated by means of the development quotient (DQ) (Enjoji method) or intelligence quotient (IQ) (Tanaka-Binet). The subjects were divided into two groups, group A (cases 1 to 5) and group B (cases 6 to 23), according to the presence or absence of a delay in their mental development (IQ below 80).

Statistical analysis: Data were analysed for statistical significance by Student's *t*-test or X^2 test.

Results

A. Evaluation of mothers (Table 1)

1) Age at diagnosis of hypothyroidism

The average age at diagnosis of hypothyroidism with chronic thyroiditis was 23.4±5.4 (M±S.D.) (range 12–31) years, and none of the cases had developed hypothyroidism before in puberty.

2) Thyroid function at diagnosis

One of the sixteen cases showed mild hyperthyroidism at diagnosis and during pregnancy and was treated with 5 mg of methyl mercaptoimidazole. The mother developed hypothyroidism after delivery of her child (case 21). The remaining fifteen cases exhibited mild to severe hypothyroidism at diagnosis (Table 1). Three cases had a small goiter at diagnosis or during pregnancy, but there was no sign of goiter in the other cases.

3) Anti-thyroid antibodies

MCHA were detected in all cases and TGHA was positive in eight of the sixteen mothers (50%).

TBII was determined in fifteen cases and all patients possessed potent TBII activities. TSBAb was determined in twelve cases and all patients possessed potent TSBAb activities. TBII as well as TSBAb activities of group A and group B mothers were not significantly different (Table 1).

4) Number of offspring and transient hypothyroidism

Out of the total thirty-one children born to sixteen mothers, twenty-four offspring were born after the mother had developed hypothyroidism. Twenty-three out of twenty-four offspring were diagnosed as having transient hypothyroidism in the newborn period. The first child of mother, M–13, was transiently hypothyroid (case 19); while her second baby was normal. In contrast, another mother (M–1) gave birth to a child with only mild hypothyroidism (Case 1); however her second child showed severe hypothyroidism (Case 23). Four other mother (M–4, 8, 9, 11) gave birth to two to four siblings whose thyroid functions did not differ significantly from each other.

B. Evaluation of the children

1) Fetal growth

Cases 12 and 13, identical twins, were born at 31 weeks' gestation and one (case 13) died of respiratory distress syndrome and perforation of the stomach. Case 3 was a small-for-dates infant, and the remaining twenty cases were appropriate-for-dates infants (Table 2). Birth length and weight of infants in groups A and B were not significantly different (cases 12 and 13 were excluded because prematurity).

2) Epiphysis of the distal femur

Sixteen infants were evaluated for epiphysis of the distal femur, the size of which depends on the thyroid function in the newborn period. It was not visible in X-ray films of 3 among 4 in Group A or 6 among 13 infants in group B which was not significantly different (Table 1).

3) Thyroid function in the newborn period

Plasma levels of TSH were elevated in all cases, but serum T_4 and T_3 in four infants (Cases 1, 9, 10, and 15) were within the normal range and plasma TSH returned to normal without medication. Eighteen cases were treated with L-T_4 or desiccated thyroid for 5 to 117 months, after which the treatment was discontinued. Euthyroidism was confirmed without medication in all cases. TBII were determined in seventeen cases (at 0 to 52 days of age) and were strongly positive in all infants (Table 3). TSBAb activity was determined in four infants and was positive in all cases.

4) Physical development

The S.D. score of height was within-2 S.D. except in case 12 who was a premature baby and her psychomotor and mental development were within the normal range.

5) Psychomotor and mental development

Age of walking alone was delayed in Cases 2 to 5 and 22. DQ or IQ was low in Cases 1 to 5. DQ and IQ in Cases 6, 14, 16, 17, 18, 20 were not evaluated because they were too young to evaluate or it was reported to be within the normal range for their ages by the physician in charge judging from the age of walking alone or speech and psychomotor development.

6) Mother's thyroid function and outcome of their offspring

Seven mothers (M–1 to 7) were hypothyroid at the time of delivery or in the post partum period when first examined. The mothers of Cases 1 and 2 were not treated at all during the whole pregnancy period. The mothers of Cases 3 and 4 decided to reduce their doses of thyroid medication from one third to one fourth when they noticed their pregnancy out of fear of side effects in the fetus; therefore, they were in a hypothyroid state for the major part of the pregnancy. Thyroid medication was discontinued during the last trimester in case 5 and for a month before delivery in Case 6. Another mother (M–7) continued taking 100 μg of L–T_4 a day throughout the pregnancy, but the thyroid function at delivery was slightly low (Table 1). Psychomotor and/or mental development were delayed in Cases 1 to 5. Case 5 had sever hyperbililubinemia in infancy that needed exchange transfusion and was most delayed in the start of thyroid medication. These factors might also be responsible for mental retardation. Among seven sibling cases, in two of the sibling sets, that is Cases 1 and 23, and Cases 4 and 8, the mothers were once hypothyroid (Cases 1 and 4) and were euthyroid (Cases 23 and 8) during pregnancy. The IQ and DQ of Cases 8 and 23 were 103 and 106 respectively, and their height was −0.4 and ±0 S.D. at the age of 7 3/12 years and one year, respectively, and was within the normal range. On the other hand, the IQ of Cases 1 and 4 was 76 and 70, respectively, and their height was −1.8

Table 2. Clinical data for twenty-three infants with transient hypothyroidism

Case Infant	Number Mother	Sex	Gestational Age (wk)	Birth Weight (gm)	Birth Length (cm)	Epiphysis of dist. femur (mm)	Start of Therapy (day)	Max. $L-T_4$ Dose (ug/kg/day)	End of therapy (Month)
1	M-1	F	41	2970	48.0	8×6	None		
2	M-2	F	42	3046	48.5	0×0	24	8.9	10.5
3	M-3	F	41	2440	45.5	0×0	13	10.8	9.0
4	M-4	M	41	3083	49.0	0×0	14	6.1*	17.0
5	M-5	M	?	2880	N.D.	N.D.	45	3.1	117.0
(M±SD)				2884.8±232.5	47.8±1.4		24.4±12.9	7.2±2.9	
6	M-6	M	42	3400	48.5	0×0	16	6.7	14.0
7	M-7	M	42	3750	50.0	4×5	43	10.0	5.0
8	M-4	M	39	2600	45.0	0×0	4	5.0*	12.0
9	M-8	M	40	3240	52.5	6.5×5.0	None		
10	M-8	M	40	3050	53.5	3×5	2	5.0	10.0
11	M-9	F	40	3370	50.0	(+)	31	5.0	35.0
12	M-9	F	31	953	N.D.	0×0	12	10.0	22.2
13	M-9	F	31	1426	N.D.	0×0	None		
14	M-9	M	39	3130	47.0	N.D.	15	11.0	6.0
15	M-10	F	40	3030	49.2	3×5	None		
16	M-11	F	41	3420	49.7	N.D.	37	8.5	7.0
17	M-11	M	39	2820	47.0	N.D.	3	10.0	5.0
18	M-12	M	41	2786	50.0	N.D.	3	6.6	7.0
19	M-13	M	41	3150	49.0	0×0	26	8.6	13.0
20	M-14	F	39	2960	N.D.	0×0	4	11.4	10.0
21	M-15	F	41	3575	N.D.	(+)	37	7.3	11.0
22	M-16	F	41	3720	57.0	N.D.	6		18.0
23	M-1	M	41	2860	48.3	2×2	13	10.0	8.0
(M±S.D.)				3178.8±329.1	49.8±2.9		16.8±13.8	8.2±2.1	
P value				N.S.	N.S.		N.S.	N.S.	

* Desiccated thyroid (mg/kg/day) (Calculated as 1 mg DC=1 ug T_4) N.D: Not determined $L-T_4$: L-thyroxine

Table 3. Clinical data for twenty-three infants with transient hypothyroidism

Case No.	Thyroid function at diagnosis							Age of walking alone (months)	IQ or DQ (age when studied) (years)	Physical development Height (age examined)		
	Age (days)	T_4 (ug/dl)	T_3 (ng/dl)	TSH (uU/ml)	MCHA	TGHA	TBII (%)			(years)	(cm)	(S.D.)
1	5	17.2	30	28.4	1600	100>	41.2	12	76 (5)	4 5/12	96.2	−1.8
2	19	1.8	60	380.5	1600	100	78.5	20<	75 (2)	11/12	70.2	−1.6
3	11	0.1	10	122.8	25600	100>	98.5	21	54 (4 2/12)	4 2/12	95.5	−1.0
4	3	0.4	27	150.0	6400	1600	N.D.	18	70 (9)	9 4/12	121.5	−1.7
5	45	1.0	N.D.	50.0	N.D.	N.D.	N.D.	24<	60 (2)	12	134.5	−1.9
M±S.D.												−1.6±0.3
6	15	4.8	99	624.0	6400	100>	93.3	14	N.D.	1 1/12	73.4	−0.5
7	42	3.9	159	370	100>	100>	87.0	12	105 (1)	1	75.8	+0.2
8	0	2.0	N.D.	320	25600	6400	71.6	12	103 (7)	7 3/12	119.1	−0.4
9	26	11.0	217	93.1	400	100>	N.D.	11	122 (3)	3	88.9	−1.5
10	21	6.5	118	405	400	100>	75.3	10	111 (6/12)	1 6/12	79.0	−0.6
11	30	1.0	50	320	6400	100>	N.D.	12	106 (3)	6	110.0	−1.2
12	6	1.0	25	320	1600	100>	96.0	19	104 (4)	2 11/12	80.6	−2.8
13	6	3.1	25	320	1600	100>	96.0	Died at the age of 4 days.				
14	0	0.58*	40	550	100	100>	94.9	17	N.D.	2 1/12	83.0	−1.2
15	31	7.4	210	81.9	10^4	100>	100.0	12	104 (1)	1	74.3	+0
16	3	3.8	52	214	100>	100>	81.5	14	N.D.	N.D.		
17	4	3.0	60	190	N.D.	N.D.	92.5	Stood at 9 months		N.D.		
18	3	0.24*	N.D.	400	N.D.	N.D.	98.9	**—	—	N.D.		
19	26	2.0	92	867	6400	100	N.D.	13	92 (2 7/12)	4	96.8	−1.1
20	4	2.2	25	961	320	100>	65.0	14	107 (2)	2	79.8	−1.3
21	0	3.6	20	487	800	100>	N.D.	11	N.D.	10/12	74.6	+0.6
22	6	4.0	80	90	6400	100	62.0	18	86 (5 6/12)	5 3/12	118.0	+2.7
23	13	0.9	47	1768	3200	100>	86.1	12	106 (6/12)	1	73.8	−0.5
M±S.D.												−0.4±1.1
Normal range		6–13	95–210	5>	100>	100>	15>					
P value												P<0.01

*: free T^4 **: too young to evaluate N. D.: Not determined

and −1.7 S.D. at the age of 5 6/12 and 9 4/12 years, respectively, and was delayed.

Discussion

Transient neonatal hypothyroidism in infants born to mothers with chronic thyroiditis, especially those with atrophic autoimmune thyroiditis, was confirmed as an important disease entity in the newborn period. It was first reported by Sutherland *et al.*, (1960), and was recognized in cases in this paper. There have been at least three other cases reported in the literature. (Connors and Styne, 1986; Fort, *et al.*, 1988; Cho, *et al.*, 1988)

The presence of TSH receptor blocking antibodies, which were detected by radioreceptor assay of TSH (TBII) and TSBAb assay have been considered pathogenetic in this condition. These activities were confirmed in the serum of fifteen mothers and their 17 newborn infants. Clinical features, such as the severity of hypothyroidism were not correlated with TBII nor with TSBAb activities of undiluted sera. However, it has recently been confirmed that the titers of mother's serum determined by diluting the serum with normal pool serum to obtain 50% inhibition of labelled TSH binding to its receptor or 50% inhibition of TSH-induced cAMP accumulation is correlated with the severity of neonatal hypothyroidism and the size of the epiphysis of the distal femur of the offspring (Matsuura, *et al.*, 1989; Tamaki, *et al.*, 1989). The mechanisms of thyroid suppression were suggested to be trapping, as well as organification defects, in the newborn period, which was confirmed in *in vivo* as well as in *in vitro* studies (Matsuura, *et al.*, 1980; Takasu, *et al.*, 1984 a, b).

As to the prognosis for the infants, physical, psychomotor and/or mental development differed significantly among reported cases. The siblings reported by Sutherland, *et al.*, (1960) and Goldsmith, *et al.* (1973) were physically, mentally and emotionally retarded in spite of intensive treatment given immediately after birth. The present study revealed delayed psychomotor and/or mental development in five of the twenty-two live infants studied. These figures are much larger than those found in cases of congenital hypothyroidism, as reported in Japan (Nakajima, *et al.*, 1985) as well as in other countries (Glorieux, *et al.*, 1985; New England Congenital hypothyroidism Collaborative. 1985; Ilick, *et al.*, 1988; Komianov, *et al.*, 1988). The mechanisms of the delay in psychomotor and/or mental development delay are not clear; but at least four mechanisms might be speculated. First, the delayed development might depend on the severity of thyroid suppression during the fetal period as well as the degree of hypothyroidism during the newborn period. The second consideration is the period of hypothyroidism and the age at the start of treatment. The nature of the TSH-receptor blocking antibodies, and finally, the degree of maternal hypothyroidism during pregnancy might also be important factors. The mean serum T_4 level of Cases 2 to 5 at diagnosis was 1.8, 0.1, 0.4, 1.0 ug/dl, respectively, the mean of which was lower than that of the cases in group B ($p<0.05$) (Table 3). However, Case 1 showed only mildly increased TSH at diagnosis, and the level returned to normal without medication. The age at the start of medication was comparable in groups A and B. TBII as well as TSBAb activities of mothers in groups A and B were not significantly different (Table 1). Birth weight and birth length were also not significantly different in the groups (Table 2).

Since the titers of TSH-receptor blocking activities well correlated with serum T_4 levels and the size of the epiphysis of the distal femur (Matsuura, *et al.*, 1989), it was speculated that they were not markedly

different in the mothers of the two groups.

On the other hand, the thyroid function status of mothers in groups A and B was quite different. Four mothers in group A were hypothyroid during throughout pregnancy and another mother was hypothyroid during the last trimester. On the other hand, the mothers of only two of seventeen live infants in group B had mild hypothyroidism during pregnancy. The siblings of Sutherland's cases were mentally and emotionally retarded in spite of intensive treatment, including exchange transfusion immediately after birth (Sutherland, *et al.*, 1960; Goldsmith, *et al.*, 1973). The mother of these siblings had also been treated inadequately and was severely hypothyroid during the whole pregnancy period.

Reports of the high incidence of mental retardation occurring in children whose mothers suffered from severe endemic goiter during pregnancy are available (Pharoach, *et al.*, 1980). But investigations relating psychomotor and mental development in children to maternal hypothyroidism are not well documented. Man *et al.*, (1976) made an extensive study of the relationship between the thyroid function of pregnant women and the outcome of their progeny, and found that the progeny of hypothyroid women showed lower psychomotor and neurological scores.

It is well known that the placenta is essentially impermeable to the natural iodothyronines, T_3, T_4 and rT_3 as well as TSH (Fisher and Klein, 1981). On the other hand, many animal experiments proved that the direct transfer of T_4 from the maternal system to the fetus does take place in early pregnancy (Devaskan, *et al.*, 1986); Morreale de Escobar, *et al.*, 1985; 1987). Judging from the above evidence, maternal T_4 might play a vital role in early fetal neurologenesis before the onset of fetal thyroid function (Ekins, 1984; Morreale de Escobar, *et al.*, 1987). Transfer of T_4 from the mother to the fetus near term was also confirmed in rats (Morreale de Escobar, *et al.*, 1988) as well as in humans (Vulsma, *et at.*, 1989) and might play an important role in the development of brain function when the fetal thyroid function is impaired. The mothers in groups A were not treated at all in cases 1 and 2, had their dose of thyroid medication reduced from the early phase of pregnancy in cases 3 and 4, and discontinued medication in the last trimester as well as being most delayed in the start of medication in case 5. These might be the causes of the mental retardation in the cases in group A. Although the transport of T_4 from mother to fetus in man is not clear, the evidence presented in this report suggests that the role of thyroid function in early embryogenesis be given serious reconsideration.

We wish to thank Prof. S. Matsumoto for his valuable comments.

References

Cho, Y., Y. K. Shong, H. K. Lee, C. S. Koh, H. K. Min and M. Lee (1988). Transient neonatal hypothyroidism due to transplacental transfer of maternal immunoglobulins that inhibit TSH-induced cAMP increase and cell growth. *Endocrinol. Japan.* **35**, 819–826.

Connors, M. H. and D. M. Styne (1986). Transient neonatal "Athyreosis" resulting from thyrotropin-binding inhibitory immunoglobulins. *Pediatrics* **78**, 287–290.

Devaskar, U. P., S. U. Devaskar, H. F. Sadiq and V. Chechani (1986). Ontogeny of plasma-free thyroxine and triiothyronine concentrations during the perinatal period and maternofetal transfer of thyroid hormone in the rabbit. *Dev. Pharmacol. Ther.* **9**, 115–123.

Ekins, R. (1984). Roles of serum thyroxine-binding proteins and maternal thyroid hormones in fetal development. *Lancet* **I**, 1129–1132.

Fisher, D. A. and A. H. Klein (1981). Thyroid development and disorders of thyroid function in the newborn. *N. Engl. J. Med.*

304, 702–712.

Fort, P., F. Lifshitz, M. Pugliese and I. Klein (1988). Neonatal thyroid disease: Differential expression in three successive offspring. *J. Clin. Endocrinol. Metab.* **66**, 644–647.

Glorieux, J., J. H. Dussalt, J. Morissette, J. Letarte and H. Guyda (1985). Follow-up at ages 5 and 7 years on mental development in children with hypothyroidism detected by Quebec screening progman. *J. Pediatr.* **107**, 913–915.

Goldsmith, R. E., A. J. McAdams, P. R. Larsen, M. MacKenzie and E. V. Hess (1973). Familial autoimmune thyroiditis: Maternal-fetal relation and the role of generalized autoimmunity. *J. Clin. Endocrinol. Metab.* **37**, 265–275.

Ilicki, A. and A. Larsson (1988). Psychomotor development of children with congenital hypothyroidism diagnosed by neonatal screening. *Acta Pediatr. Scand.* **77**, 142–147.

Inomata, H., N. Sasaki, K. Tamaru, H. Ushiku, H. Niimi and H. Nakajima (1986). Relationship between potency of blocking type thyrotropin-binding inhibitor immunoglobulin in three women with primary myxedema and thyroid function of their neonates. *Endocrinol. Japon* **33**, 353–359.

Iseki, M., M. Shimizu, T. Oikawa, H. Hojo, K. Arikawa, Y. Ichikawa, N. Momotani and K. Ito (1983). Sequential serum measurements of thyrotropin binding inhibitor immunoglobulin G in transient familial neonatal hypothyroidism. *J. Clin. Endocrinol. Metab.* **57**, 384–387.

Ishihara, T., N. Waseda, K. Ikekubo, K. Kuroda, T. Akamizu and T. Mori (1985). A predicted case with neonatal transient hypothyroidism due to blocking type thyrotropin binding inhibitor immunoglobulins (TBII). *Endocrinol. Japon* **32**, 189–194.

Kanaya, S., T. Harada, I. Maki, S. Kimura, K. Shimizu, Y. Seino, O. Nose, H. Yabuuchi, H. Tamaki, N. Amino, K. Miyai, M. Mori and O. Tanizawa (1985). A predicted case of transient hypothyroidism due to TSH-receptor blocking antibody (TBII). *J. Jap. Pediatr. Soci.* **89**, 1291–1296. (in Japanese)

Karlsson, F. A., P. A. Dahlberg and M. Ritzen (1984). Thyroid blocking antibodies in thyroiditis. *Acta Med. Scand.* **215**, 461–466.

Komianou, F., G. Makaronis, J. Lambadaridis, E. Sarafidou, F. Vrachini, C. Mengreli and S. Pantelakis (1988). Psychomotor development in congenital hypothyroidism. The Greek screening programme. *Europ. J. Pediatr.* **147**, 275–278.

Man, F. B. and B. A. Serunian (1976). Thyroid function in human pregnancy. IX Development or retardation of 7-year-old progeny of hypothyroxinemic women. *Am. J. Obstet. Gynecol.* **125**, 949–957.

Mashimo, K., T. Shimizu, K. Tajima, T. Harada, M. Sato, M. Nakamu and S. Tarui (1985). Cases of mother and her infant with hypothyroidism due to TBII. *Horumon to Rinsho.* **35** (supp), 133–136. (in Japanese)

Matsuura, N., Y. Yamada, Y. Nohara, J. Konishi, K. Kasagi, K. Endo, K. Kojima and K. Wataya (1980). Familial neonatal transient hypothyroidism due to maternal TSH-binding inhibitor immunoglobulins. *N. Engl. J. Med.* **303**, 738–741.

Matsuura, N., J. Konishi, S. Harada, K. Yuri, S. Fujieda, K. Kasagi, J. Iida, S. Fujimoto, M. Fukushi and N. Takasugi (1989). The prediction of thyroid function in infants born to mothers with chronic thyroiditis. *Endocrinol. Japan.* **36**, 865–871.

Morreale de Escobar, G., R. Pastor, M. J. Obregon and F. Escobar del Ray (1985). Effects of maternal hypothyroidism on the weight and thyroid hormone concentration of rat embryonic tissues before and after onset of fetal thyroid function. *Endocrinology* **117**, 1890–1900.

Morreale de Escobar, G., M. J. Obregon and F. Escobar del Rey (1987). Fetal and Maternal thyroid hormones. *Hormone. Res.* **26**, 12–27.

Morreale de Escobar, G., M. J. Obregon, C. Ruiz de Ona and F. Escobar del Rey (1988). Transfer of thyroxine from the mother to the rat fetus near term; Effects on brain 3, 5, 3'-triiodothyronine deficiency. *Endocrinology* **122**, 1521–1531.

Nakajima, H. and M. Irie (1985). Treatment and follow-up study children with congenital hypothyroidism detected by neonatal screening in Japan. *Igakuno Ayumi* **115**, 965–968 (In Japanese).

New England Congenital Hypothyroidism Collaborative. (1985) Neonatal hypothyroidism screening: status of patients at 6 years of age. *J. Pediatr.* **107**, 915–919.

Ninomiya, M., K. Goji, T. Takahashi, Y. Mo-

rishita, S. Kodama, Y. Iida, K. Kasagi and J. Konishi (1983). Transient hypothyroid in infants due to TSH-binding inhibitor immunoglobulin (TBII). *J. Jap. Pediat. Soci.*, **87**, 939–944. (in Japanese)

Pharoach, P. O. D., I. H. Buttfield and B. S. Hetzel (1980). Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. *Lancet* **I**, 308–310.

Sutherland, J. M., V. M. Esselborn, R. L. Burket, T. B. Skillman and J. T. Benson (1960). Familial nongoitrous cretinism apparently due to maternal antithyroid antibody. Report of a family. *N. Engl. J. Med.* **263**, 336–341.

Takasu, N., T. Mori, Y. Koizumi, S. Takeuchi and T. Yamada (1984a). Transient neonatal hypothyroidism due to maternal immunoglobulins that inhibit thyrotropin-binding and post-receptor processes. *J. Clin. Endocrinol. Metab.* **59**, 142–146.

Takasu, N., M. Naka, T. Mori and T. Yamada (1984b). Two types of thyroid function-blocking antibodies in autoimmune atrophic thyroiditis and transient neonatal hypothyroiditis due to maternal IgG. *Clin. Endocrinol.* **21**, 345–355.

Tamaki, H., N. Amino, M. Aozasa, M. Mori, Y. Iwatani, J. Tachi, O. Nose, O. Tanizawa and K. Miyai (1989). Effective method for prediction of transient hypothyroidism in neonates born to mothers with chronic thyroiditis. *Am. J. Perinatol.* **6**, 296–303.

Vulsma, T., M. H. Gons and J. J. M. de Vijlder (1989). Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. *N. Engl. J. Med.* **321**, 13–16.

Yokota, Y., N. Ooyama, K. Ootsuka and T. Koshimizu (1985). A case of cretinism due to maternal TSH binding inhibitor immunoglobulins. *Horumon to Rinsho* **33**, 601–605. (in Japanese)