0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(8):2984–2991

doi: 10.1210/jc.2006-2042

Loss of Integrity of Thyroid Morphology and Function in Children Born to Mothers with Inadequately Treated Graves' Disease

Marlies J. E. Kempers, A. S. Paul van Trotsenburg, Rick R. van Rijn, Anne M. J. B. Smets, Bert J. Smit, Jan J. M. de Vijlder, and Thomas Vulsma

Emma Children's Hospital, Academic Medical Center, University of Amsterdam, Departments of Pediatric Endocrinology (M.J.E.K., A.S.P.v.T., J.J.M.d.V., T.V.) and Radiology (R.R.v.R., A.M.J.B.S.), 1100-DE Amsterdam, The Netherlands; and Erasmus Medical Center, Sophia Children's Hospital, Department of Neonatology (B.J.S.), 3000 CB Rotterdam, The Netherlands

Context: Central congenital hypothyroidism (CH-C) in neonates born to mothers with inadequately treated Graves' disease usually needs T_4 supplementation. The thyroid and its regulatory system have not yet been extensively studied after T_4 withdrawal, until we observed disintegrated thyroid glands in some patients.

Objective: The aim was to study the occurrence and pathogenesis of disintegrated thyroid glands in CH-C patients.

Design, Setting, Patients, Participants: Thyroid function was measured and thyroid ultrasound imaging was performed in 13 children with CH-C due to inadequately treated maternal Graves' disease after T_4-supplementation withdrawal (group Aa). In addition, thyroid ultrasound imaging was performed in six children with CH-C born to inadequately treated mothers with Graves' disease, in whom T_4 supplementation was not withdrawn yet (group Ab) or never initiated (group Ac), in six euthyroid children born to adequately treated mothers with Graves' disease (group B), and in 10 T_4-supplemented children with CH-C as part of multiple pituitary hormone deficiency (group C).

Main Outcome Measures: Thyroid function and aspect (volume, echogenicity, echotexture) were measured.

Results: In group A, five children had developed thyroidal hypothyroidism characterized by persistently elevated TSH concentrations and exaggerated TSH responses after TRH stimulation. In the majority of patients in groups A and C, thyroid echogenicity and volume were decreased, and echotexture was inhomogeneous. Thyroid ultrasound imaging was normal in group B children.

Conclusions: Inadequately treated maternal Graves' disease not only may lead to CH-C but also carries an, until now, unrecognized risk of thyroid disintegration in the offspring as well. We speculate that insufficient TSH secretion due to excessive maternal-fetal thyroid hormone transfer inhibits physiological growth and development of the child's thyroid. **(*J Clin Endocrinol Metab* 92: 2984–2991, 2007)**

CENTRAL HYPOTHYROIDISM IS a condition characterized by impaired secretion of thyroid hormone due to a defect in the thyroid's regulatory system. In The Netherlands, neonates with central congenital hypothyroidism (CH-C) are detected by a T_4-based neonatal screening program (1, 2). Usually, permanent CH-C is part of multiple pituitary hormone deficiencies (2). Recently, we have reported on the occurrence of isolated CH-C in neonates born to mothers with Graves' disease, presumably with a transient course. Although maternal characteristics were heterogeneous with respect to timing of diagnosis, thyroid antibody concentrations, and treatment, one consistent feature in all mothers was inadequate treatment during pregnancy, resulting in hyperthyroidism (3). Although this type of CH-C has been reported frequently (4–13), the course of thyroid function after withdrawal of T_4 supplementation has been studied less extensively. It has been reported that plasma concentrations of free T_4 (FT_4) and TSH remain within their reference ranges when T_4 supplementation was withdrawn after a few months (5, 6, 8, 10, 11) and that the TSH response after TRH administration recovers (5, 11, 13), suggesting a transient condition.

When evaluating the thyroid function after withdrawal of T_4 supplementation in our patients with CH-C due to inadequately treated maternal Graves' disease, we disclosed a persistent thyroid dysfunction in some of them, as a novel outcome. To gain more insight into the occurrence and pathogenesis of this finding, we analyzed thyroid function and performed thyroid ultrasound imaging in these patients in the phase without T_4 treatment. In addition, we performed thyroid ultrasound imaging in children with CH-C as part of multiple pituitary hormone deficiencies and in children born to mothers with adequately treated Graves' disease during pregnancy.

First Published Online May 15, 2007

Abbreviations: CH-C, Central congenital hypothyroidism; FT_4, free T_4.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

Patients and Methods

Children with CH-C due to inadequately treated maternal Graves' disease (group A, n = 19)

In the Academic Medical Center (AMC), records are kept of patients whose blood and/or urine samples were sent for confirmation of di-

agnosis of congenital hypothyroidism, or whose pediatrician consulted our pediatric endocrinology team. When this report was prepared, 28 children with CH-C due to inadequately treated maternal Graves' disease were known in the pediatric endocrinology department of the Emma Children's Hospital AMC.

Inadequate treatment was concluded when Graves' disease was either not treated at all during pregnancy (obviously in those diagnosed after pregnancy and also those who stopped medication themselves) or insufficiently treated, resulting in persistently high-plasma FT_4 concentrations during pregnancy. The children were followed in the AMC or a local Dutch hospital. All but one started T_4 supplementation after diagnosis of CH-C. Timing of diagnosis of maternal Graves' disease, maternal thyroid function determinants measured during pregnancy or after delivery, and neonatal thyroid function determinants before the start of T_4 supplementation were known.

In 13 children, T_4 supplementation was stopped (group Aa). Their thyroid function determinants after withdrawal were monitored. In six of them, TSH response after TRH administration was measured. In 11 children, thyroid ultrasound imaging was performed (two children were not able to visit the AMC). In three of five children with persistently elevated TSH concentrations, a thyroid $^{123}I^-$-uptake study was performed.

In the five children whose T_4 supplementation could not be withdrawn yet because of young age (group Ab), exclusively thyroid ultrasound imaging was performed. Also in the child in whom T_4 supplementation was never initiated (group Ac), thyroid ultrasound imaging was performed.

Of nine children with the same type of CH-C, follow-up data were not (yet) available because they had moved abroad, were lost to follow-up, or were considered too young to withdraw T_4 supplementation and thyroid ultrasound imaging. The characteristics of these nine patients, in terms of maternal characteristics or neonatal thyroid function determinants, were not different from the 19 presented.

Children born to mothers with adequately controlled Graves' disease (group B, n = 6)

Adequate treatment was concluded when Graves' disease was diagnosed before or in the first trimester of pregnancy, for which patients received adequate treatment resulting in normal plasma FT_4 concentrations throughout pregnancy or, when diagnosis was made in the first trimester, within a few weeks after initiation of antithyroid drugs.

To evaluate thyroid function and structure in children born to mothers with adequately controlled Graves' disease, group B was formed. Three children already participated in an earlier study on psychomotor outcome (14). Another three children were recruited among the younger sibs from group A children. Neonatal thyroid function determinants were recorded, thyroid ultrasound imaging was performed, and thyroid function was measured again.

Children with CH-C as part of multiple pituitary hormone deficiencies (group C, n = 10)

To evaluate thyroid function and morphology in children with permanent CH-C as part of multiple pituitary hormone deficiencies, group C was formed. There were 10 patients detected by the neonatal screening program and treated since then in the AMC who were willing to participate. During one of their routine visits for treatment control, thyroid ultrasound imaging was performed.

Methods

The study protocol was approved by the institutional review board of the AMC. All parents, and patients older than 12 yr, gave their written informed consent.

Thyroid ultrasound imaging was performed in the pediatric radiology department in the AMC. Thyroid volume (if the age of the child allowed accurate measurement), echogenicity, and echotexture were recorded by one of the pediatric radiologists (R.R.v.R. or A.M.J.B.S.), and blindly reexamined by the other (A.M.J.B.S. or R.R.v.R.), as well as a pediatric endocrinologist (T.V.). All observers had to have made the same interpretation about the ultrasound to score it as being abnormal. The volume (in ml) of each thyroid lobe was estimated as follows: transversal × sagittal × longitudinal maximum diameters × 0.479 (15), and was compared with age-matched reference values (16–18). Echogenicity was scored as "decreased," "normal," or "increased." Echotexture was scored as "normal," "inhomogeneous," or "abnormal" (when substantial irregularities were visible, *e.g.* nodules or cysts).

In the TRH test, plasma TSH was measured 15, 30, 45, 60, 120, and 180 min after iv administration of TRH (10 μg/kg). An adequate response was defined as a maximum TSH concentration between 15 and 35 mIU/liter after 20–40 min (2, 19).

Thyroid $^{123}I^-$-imaging was performed by administering 2-MBq $Na^{123}I^-$ iv; an uptake of 10–15% after 2 h was considered normal [extrapolated from the reported uptake after 24 h (20)].

The plasma FT_4 and TSH reference ranges, measured by time-resolved fluoroimmunoassays (Delfia Free T_4 and Delfia hTSH Ultra; Wallac Oy, Turku, Finland), as established in our laboratory, are 0.78–1.79 ng/dl (10.0–23.0 pmol/liter) and 0.4–4.0 mIU/liter, respectively; for neonates, the lower limit of the FT_4 reference range is 0.93 ng/dl (12.0 pmol/liter). When "FT_4" and "TSH" are mentioned in the text, their plasma concentrations are meant, unless otherwise mentioned. TSH receptor antibodies were measured using the TRAK assay (Brahms, Berlin, Germany), either with radioactive label or by luminescence.

Results

Group Aa

The mothers were diagnosed with Graves' disease before (n = 2, one twin pregnancy), during (n = 4), or after pregnancy (n = 6). As presented in Table 1, maternal FT_4 measured during or shortly after pregnancy was markedly elevated and accompanied by suppressed TSH (data not shown). In the neonatal period, all children had FT_4 less than 0.93 ng/dl (<12.0 pmol/liter), while TSH never exceeded 8.0 mIU/liter (Table 1). TSH-receptor antibodies were measurable in variable concentrations in both mothers and children (Table 2).

Patients with persistently elevated TSH after T_4 withdrawal (Table 3)

In patient Aa:4, T_4 withdrawal appeared successful at the age of 0.5 yr when both FT_4 and TSH remained within their reference ranges and maximum TSH response in the TRH test was normal (21.7 mIU/liter after 30 min). However, after 8 months TSH increased more than 4.0 mIU/liter, and T_4 supplementation was restarted. After another withdrawal at the age of 4.9 yr, TSH remained elevated up to 9 months (11.3 mIU/liter), and T_4 supplementation was restarted again. Also in patient Aa:5, whose TSH was within the reference range 5 months after T_4 withdrawal, TSH increased more than 4.0 mIU/liter after 1 yr. In patients Aa:8 and Aa:9, TSH increased immediately after T_4 withdrawal and remained elevated until supplementation was restarted a few months later. The maximum TSH response in the TRH test, performed during the T_4 withdrawal period, in patients Aa:4, Aa:5, Aa:8, and Aa:9 was exaggerated (47.9, 37.2, 53.0, and 127.0 mIU/liter, respectively; Fig. 1). In none of the patients were thyroid antibodies (TSH receptor antibodies > 1.5 IU/liter, thyroid peroxidase antibodies > 60 kIU/liter, or antithyroglobulin) detectable at ages 5.0, 2.3, 3.8, and 3.7 yr, respectively. The $^{123}I^-$-uptake, performed in patients Aa:4, Aa:8, and Aa:9, was low (4.4%, 5.2%, and 3.4%, respectively, after 120 min). In addition, in patient Aa:13, TSH increased immediately after withdrawal of T_4 and remained elevated up till 6 months after withdrawal. Because T_4 supplementation was restarted, no stimulation test could be performed yet.

Thyroid ultrasound imaging showed decreased echoge-

TABLE 1. Characteristics of thyroid function of children and their mothers in group A

Patient no.	Timing of diagnosis	Mother FT_4 ng/dl (pmol/liter)	Timing	GA (wk)	BW (g)	Child FT_4 ng/dl (pmol/liter)[a]	TSH (mIU/liter)[a]	Days postpartum
Aa:1	Before pregnancy	2.5 (32.2)	33.4 wk GA	34.6	1970	0.9 (11.5)	1.1	61
Aa:2	Before pregnancy	2.5 (32.2)	33.4 wk GA	34.6	1840	0.8 (10.8)	1.1	71
Aa:3	Before pregnancy	1.8–4.0 (23.2–51.5)	During pregnancy	37.0	2580	0.6 (7.9)	0.7	50
Aa:4	During pregnancy	>5.4 (>70.0)	31.1 wk GA	38.3	1940	0.6 (7.5)	4.1	2
Aa:5	During pregnancy	4.7 (60.0)	30.0 wk GA	38.0	4445	0.8 (10.8)	7.5	6
Aa:6	During pregnancy	>5.4 (>70.0)	30.7 wk GA	36.9	2480	0.6 (7.6)	0.7	96
Aa:7	During pregnancy	3.5 (45.0)	30.0 wk GA	36.9	2150	0.5 (6.4)	0.9	40
Aa:8	After pregnancy	2.7 (34.7)	First wk pp[b]	38.0	3100	0.4 (5.0)	1.2	12
Aa:9	After pregnancy	>5.4 (>70.0)	Seventh wk pp[b]	39.9	3660	0.6 (8.0)	3.3	24
Aa:10	After pregnancy	3.5 (45.0)	Third wk pp[b]	38.0	2825	0.9 (11.3)	2.4	16
Aa:11	After pregnancy	4.6 (59.0)	Second wk pp[b]	38.3	3470	0.5 (6.5)	5.9	11
Aa:12	After pregnancy	5.0 (64.0)	Third wk pp[b]	36.7	3330	0.5 (6.2)	1.8	11
Aa:13	After pregnancy	4.4 (56.0)	Third wk pp[b]	38.9	2900	0.8 (10.9)	2.1	17
Ab:1	Before pregnancy	>5.4 (>70.0)	First wk pp[b]	28.0	1200	0.7 (8.7)	0.1	15
Ab:2	During pregnancy	>5.4 (>70.0)	14.3 wk GA	35.4	2250	0.8 (10.0)	0.1	9
Ab:3	After pregnancy	3.1 (40.0)	Third wk pp[b]	40.0	3385	0.8 (10.1)	3.0	18
Ab:4	After pregnancy	4.8 (61.8)	Second wk pp[b]	38.0	2750	0.3 (4.0)	2.8	7
Ab:5	After pregnancy	>5.4 (>70.0)	Third wk pp[b]	38.0	3260	0.4 (5.1)	3.4	18
Ac:1	After pregnancy	3.5 (45.0)	Third wk pp[b]	40.9	3530	0.6 (8.2)	1.2	10

BW, Birth weight; GA, gestational age.

[a] Measurement before initiation of T_4 supplementation.

[b] If no FT_4 concentration during pregnancy was determined (because of undiagnosed or uncontrolled Graves' disease), the first measurement after pregnancy is presented.

nicity in all five patients, with a cyst and a nodule in patient Aa:4, inhomogeneous echotexture in patients Aa:5, Aa:9 (Fig. 2), and Aa:13, and decreased volume in patients Aa:8 and Aa:9 (Table 4).

Patients with transiently elevated TSH after T_4 withdrawal (Table 3)

In four patients (Aa:1, Aa:2, Aa:11, and Aa:12), TSH spontaneously returned into the reference range, after a transient elevation (>4.0 mIU/liter) after withdrawal of T_4 supplementation. Thyroid echogenicity was decreased in patients Aa:11 and Aa:1, in combination with an inhomogeneous echotexture. Thyroid volume was decreased in patients Aa:1 and Aa:2 (Table 4).

Patients with normal TSH after T_4 withdrawal (Table 3)

In four patients (Aa:3, Aa:6, Aa:7, and Aa:10), TSH remained within the reference range after T_4 withdrawal. In patient Aa:7, T_4 was withdrawn for the first time at the age of 3.2 yr but was immediately restarted when FT_4 decreased to 0.5 ng/dl (5.9 pmol/liter) after 1 month. After a second attempt (age 3.5 yr) to withdraw T_4 supplementation, FT_4 decreased again and remained low up to 4 months (0.6 ng/dl, 8.1 pmol/liter). Also, in patient Aa:10, FT_4 was borderline (0.8 ng/dl, 10.3 pmol/liter) 6 months after withdrawal. In patients Aa:7 and Aa:10, the maximum TSH response in the TRH test was within the normal range (17.0 and 15.1 mIU/liter, respectively; Fig. 1) and substantially higher than in the neonatal period (2.3 and 8.5 mIU/liter, respectively). In patient Aa:10, thyroid echogenicity was decreased with inhomogeneous texture (Table 4).

Group Ab

Mothers of group Ab children were diagnosed with Graves' disease before (n = 1), during (n = 1), or after pregnancy (n = 3). FT_4 during or after pregnancy was markedly increased (Table 1), and TSH was suppressed.

In the neonatal period, all children had FT_4 less than 0.93 ng/dl (<12.0 pmol/liter) and TSH less than 4.0 mIU/liter (Table 1). Thyroid echogenicity was decreased in two patients, echotexture inhomogeneous in one, and thyroid volume decreased in one patient (Table 4).

Group Ac

In patient Ac:1, who was never treated with T_4, FT_4 increased from 0.6–1.0 ng/dl (8.2–12.8 pmol/liter) within 4 wk after birth. TSH remained within the reference range, except at the age of 1 yr, when once 4.2 mIU/liter was measured. Maximum TSH response in the TRH test was insufficient at the age of 1 month (4.4 mIU/liter after 30 min) but normal at the age of 1.1 yr (26.4 mIU/liter after 40 min). He was released from out-clinic controls at the age of 1.5 yr [FT_4 1.1 ng/dl (14.2 pmol/liter), TSH 4.0 mIU/liter]. At the age of 9.5 yr, both FT_4 (1.1 ng/dl, 13.7 pmol/liter) and TSH (2.6 mIU/liter) were within their reference ranges. His thyroid gland had a normal volume with inhomogeneous echotexture (Table 4).

Group B

The four mothers of the six group B children were known to have Graves' disease before pregnancy (five pregnancies), or diagnosed already in the sixth week of pregnancy (one pregnancy). During pregnancy, mothers were treated with antithyroid drugs throughout pregnancy (three pregnancies), with T_4 after $^{131}I^-$-treatment before pregnancy (two pregnancies), or without any medication (one pregnancy). One of the mothers, diagnosed before pregnancy, was hyperthyroid until antithyroid drug treatment became intensified, resulting in FT_4 less than 1.94 ng/dl (<25.0 pmol/liter) from the 18th week of pregnancy onwards. In the mother with hyperthyroidism diagnosed in early pregnancy, FT_4

TABLE 2. TSH-receptor antibody concentrations in groups A and B

Case no.	Mother		Child	
	Concentrations (IU/liter)[a]	Time of sampling	Concentrations (IU/liter)[a]	Time of sampling
Aa:1	41	33.4 wk GA	nd	
Aa:2	41	33.4 wk GA	nd	
Aa:3	18.4[b]	18 wk GA	91	Cord blood
Aa:4	26	31.1 wk GA	8	Cord blood
Aa:5	59	34 wk GA	20	Cord blood
Aa:6	247	34.9 wk GA	1.3[b]	114 d pp
Aa:7	nd		<5	40 d pp
Aa:8	19	4 d pp	nd	
Aa:9	43	43 d pp	<5	85 d pp
Aa:10	1.2[b]	21 d pp	nd	
Aa:11	<9	14 d pp	nd	
Aa:12	12	22 d pp	9	22 d pp
Aa:13	2.4[b]	28 d pp	nd	
Ab:1	nd		1.4[b]	38 d pp
Ab:2	37.6[b]	22.3 wk GA	21.9[b]	1 d pp
Ab:3	<1.0[b]	23 d pp	21.0[b]	21 d pp
Ab:4	nd		1.8[b]	8 d pp
Ab:5	4.8[b]	18 d pp	3.7[b]	18 d pp
Ac:1	24	17 d pp	11	24 d pp
B:1	62	15.1 wk GA	10	Cord blood
B:2	8	30.1 wk GA	nd	
B:3	7	24.4 wk GA	<5	Cord blood
B:4	22	14.1 wk GA	7	4 d pp
B:5	14	13.7 wk GA	5	11 d pp
B:6	nd		nd	

BW, Birth weight; GA, gestational age; nd, not determined; pp, postpartum.
[a] <6 IU/liter negative, 6–10 IU/liter dubious, and >10 IU/liter positive.
[b] TSH-receptor antibodies measured by luminescence; < 1.0 IU/liter negative, 1.0–1.5 IU/liter dubious, and > 1.5 IU/liter positive.

was less than 1.94 ng/dl (<25.0 pmol/liter) from the 16th week of pregnancy onwards, after antithyroid drug treatment became effective. In the other four pregnancies, FT_4 was less than 1.94 ng/dl (<25 pmol/liter) throughout pregnancy. TSH-receptor antibodies were measurable in variable concentrations in both mothers and children (Table 2).

Neonatal thyroid function was normal in all six children. At recall (median age 8.8 yr, range 1.3–11.4), all children were considered healthy. FT_4 was within the reference range in all six children, while TSH was in five (Table 5). Of note, child B:2 had been very nervous for the blood sampling and was extremely stressed during the venepuncture. His TSH was slightly elevated (4.8 mIU/liter), which we ascribed to his nervousness. To support this, two more stress-responsive determinants [prolactin (51 ng/ml) and cortisol (20.1 μg/dl, 555 nmol/liter)] were analyzed retrospectively and were indeed found to be elevated. Thyroid echogenicity, texture, and volume were normal in all children (Table 5 and Fig. 3).

Group C

Nine CH-C patients had multiple pituitary hormone deficiencies and were treated with T_4 (n = 9), growth hormone (n = 8), hydrocortisone (n = 7), and testosterone (n = 2); 1 patient had isolated CH-C and was treated with T_4. In all patients FT_4 was within the reference range, and TSH suppressed (Table 5).

Thyroid ultrasound imaging showed decreased echogenicity in two patients, increased echogenicity in three, nodules in one, inhomogeneous echotexture in five, and decreased thyroid volume in six patients (Table 5).

Discussion

Disturbance of the fetal and neonatal thyroid hormone state, as one of the adverse effects of maternal Graves' disease during gestation, is an important issue because it constitutes the risk of damage to the developing brain. The occurrence, type, and severity of thyroid dysfunction in the offspring are dependent on the presence of maternal thyroid antibodies and the use of antithyroid drugs (6, 21). Recently, we reported on children with CH-C born to mothers with gestational hyperthyroidism due to inadequately treated Graves' disease. This entity illustrates that disturbances in the maternal thyroid hormone state during gestation may influence pre- and postnatal thyroid function in the offspring too (3). We followed these children extensively, especially after withdrawal of T_4 supplementation, to establish whether the condition would be transient or permanent. In all patients the pituitary dysfunction, as observed in the neonatal period, improved later on. However, until now, in five children, the apparently transient CH-C appeared to be succeeded by persistent thyroidal hypothyroidism. This novel finding constitutes another, unexpected adverse effect of maternal Graves' disease.

The thyroid condition in these five patients was characterized by persistent hyperthyrotropinemia, an exaggerated TSH response in the TRH test, and thyroid glands with small volume and inhomogeneous echotexture. The onset of this thyroid condition is uncertain because thyroid ultrasound imaging was not performed systematically after birth. Besides, the initially coexistent TSH deficiency as well as subsequent (adequate) T_4 supplementation will have masked

TABLE 3. Characteristics of thyroid function just preceding withdrawal and after withdrawal of T_4 supplementation in group Aa

Patient no.	Preceding withdrawal of T_4 supplementation			Age at withdrawal (yr)	After withdrawal of T_4 supplementation		
	Age (yr)	FT_4 ng/dl (pmol/liter)	TSH mIU/liter		Age after withdrawal (yr)	FT_4 ng/dl (pmol/liter)	TSH mIU/liter
Persistent TSH elevation after withdrawal							
Aa:4	4.9	1.2 (14.9)	3.3	0.5/3.2/4.9	5.4	0.9 (11.3)	14.3
					5.7	0.8 (9.7)	11.3
Aa:5	1.0	1.2 (15.1)	1.7	1.1	1.2	1.0 (12.8)	4.5
					1.5	1.0 (13.0)	2.1
					2.1	1.2 (15.3)	6.0
					2.2	1.0 (13.4)	4.9
					2.3	1.0 (13.4)	5.2
Aa:8	2.0	1.2 (15.0)	2.0	2.3	2.5	0.7 (9.0)	6.0
					2.6	0.7 (9.0)	7.8
Aa:9	3.0	1.1 (14.4)	0.2	3.0	3.1	0.4 (5.0)	36.1
					3.2	0.6 (7.1)	22.1
					3.3	0.8 (10.7)	13.0
					3.7	0.6 (7.4)	18.8
Aa:13	1.5	1.3 (16.2)	2.2	2.0	2.1	0.9 (11.0)	8.7
					2.2	1.0 (12.7)	8.3
					2.5	0.9 (11.7)	6.3
Transient TSH elevation after withdrawal							
Aa:1	4.0	2.0 (25.3)		4.0	4.1	0.9 (11.6)	7.2
					4.3	0.9 (11.9)	2.7
Aa:2	4.0	2.0 (25.4)		4.0	4.1	0.8 (9.8)	8.3
					4.2	0.8 (10.9)	5.8
					4.3	0.9 (12.2)	3.5
Aa:11	0.3	1.2 (15.3)	3.1	0.3	0.4	1.2 (15.1)	5.9
					0.5	1.1 (14.2)	2.2
					1.6	1.2 (15.9)	2.2
Aa:12	1.8	1.0 (13.0)	2.7	1.8	2.2	1.2 (15.0)	4.8
					2.6	1.2 (15.0)	2.3
					3.1	1.2 (15.0)	4.3
					3.6	1.2 (16.0)	2.8
Normal TSH after withdrawal							
Aa:3	3.0	1.5 (18.8)	0.9	3.0	3.3	1.2 (15.3)	1.4
					3.6	1.1 (14.8)	0.9
Aa:6	1.1	1.3 (17.3)	1.4	1.3	1.4	1.0 (12.8)	1.7
					1.8	1.1 (14.0)	1.4
					2.4	1.0 (13.4)	1.6
Aa:7	3.5	1.0 (13.0)	0.3	3.2/3.5	3.6	0.6 (7.6)	3.2
					3.7	0.8 (10.4)	2.3
					3.8	0.6 (8.1)	1.4
Aa:10	2.0	0.8 (10.7)	1.2	2.2	2.3	0.9 (12.0)	2.4
					2.7	0.8 (10.3)	1.9

and prevented the biochemical expression of the thyroid dysfunction (3).

The other eight patients with CH-C due to gestational hyperthyroidism ended up (after withdrawal) with plasma TSH concentrations within the reference range, sometimes after a transient elevation. In six of them, concomitantly measured FT_4 concentrations were within the reference range; the two with low and low-normal FT_4 concentrations, respectively, had normal TSH responses in the TRH test, so hypothyroidism could not be established in either of them. On the other hand, the inhomogeneous echotexture and/or decreased thyroid echogenicity or volume, in the majority of patients with CH-C due to gestational hyperthyroidism, suggests that thyroid tissue is affected. The fact that TSH was not (persistently) increased in some patients in whom T_4 was withdrawn might be explained by ongoing pituitary-hypothalamic insufficiency (CH-C). In addition, the fetal hyperthyroidism to which our patients had been exposed might have shifted the pituitary's set point for TSH secretion [in analogy to the shift in the opposite direction as observed in children exposed to fetal or perinatal hypothyroidism (22)], explaining the tendency to lower FT_4 in the subgroup of patients with persistently normal TSH. Although none of the patients had clinical problems after withdrawal, T_4 supplementation was restarted when either FT_4 or TSH continued to be outside the reference range.

Permanent and transient congenital hypothyroidism of thyroidal origin, occasionally described in children born to mothers with autoimmune hypothyroidism, has been attributed to cytotoxic effects of maternal antibodies (23–25). Although thyroid antibodies were not demonstrated in any of our patients with persistent thyroid dysfunction at the time T_4 supplementation was withdrawn, they had been detected (in variable concentrations) in the neonatal period (Table 2), as reported previously (3). To gain more insight into the possible role of antibodies in the thyroid problem in our group A patients, we also investigated thyroid function and structure in a group of children born to mothers with Graves'

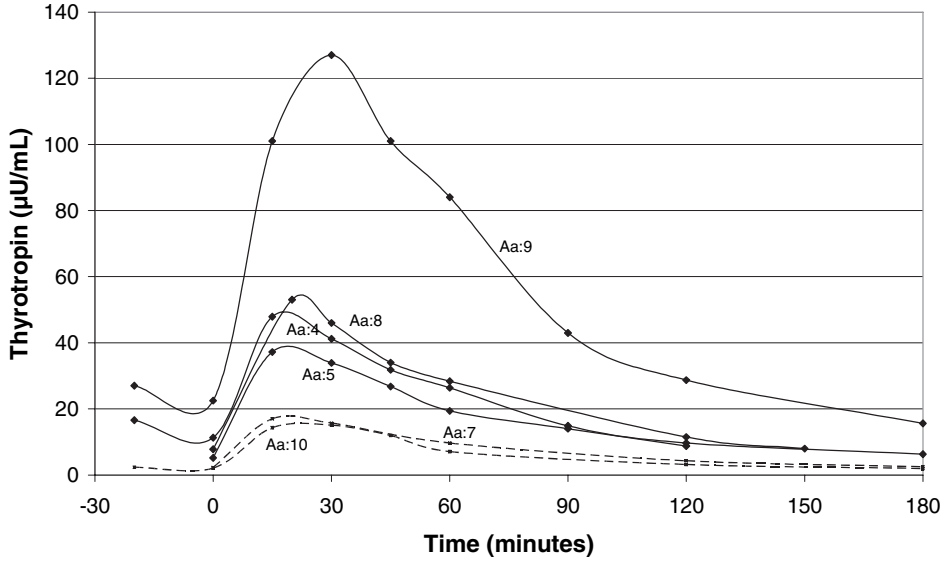

FIG. 1. TRH test with normal and exaggerated TSH response. *Dashed lines* indicate normal TSH response, *continuous lines* exaggerated TSH response.

disease adequately treated during pregnancy, in other words, in whom autoimmunity was not associated with hyperthyroidism. In their children, obviously without CH-C, we did not observe biochemical or ultrasound signs of a thyroid problem. So, this novel disease entity appeared to be restricted to children in whom CH-C preceded, rather than to be associated with thyroid antibodies of maternal origin, although our data do not allow exclusion of antibodies as an additional causal factor. A suitable (additional) control group (gestational hyperthyroxinemia without autoimmunity) would have been "not affected" children born to mothers with thyroid hormone resistance, but such cases never came to our attention. Indeed, the report of Anselmo *et al.* (26) dealing with this subject has shown that maternal thyroid hormone resistance can lead to pituitary dysfunction in the child, in line with our observations, but these authors did not (yet) report on the long-term consequences for thyroid morphology and function in the offspring.

In the control group of CH-C patients with multiple pituitary hormone deficiencies, in whom adequate T_4 supplementation invariably caused longstanding extremely low TSH concentrations (22), we observed extremely decreased thyroid volumes. Likewise, in patients with inactivating mutations in the TSH receptor gene, thyroid hypoplasia is a common feature (27). These observations led us to the hypothesis that early and longstanding insufficient TSH action hampers normal thyroid growth and development. A unique feature of the group of patients with CH-C born to mothers with gestational hyperthyroidism is that after a period of insufficient TSH action, the pituitary still started functioning several months after birth. Subsequently, persistent TSH elevation enables the disclosure of irreversible thyroid dysfunction, and demonstrates that the ultrasound features represent severely affected thyroid tissue. The loss of integrity of both thyroid morphology and function, after a phase in which the development and function of the thyroid's regulatory system was hampered, suggests a developmental defect at the follicular level. We believe that the term "thyroid disintegration" best describes this phenomenon, which somehow combines thyroid dysgenesis and thyroid destruction.

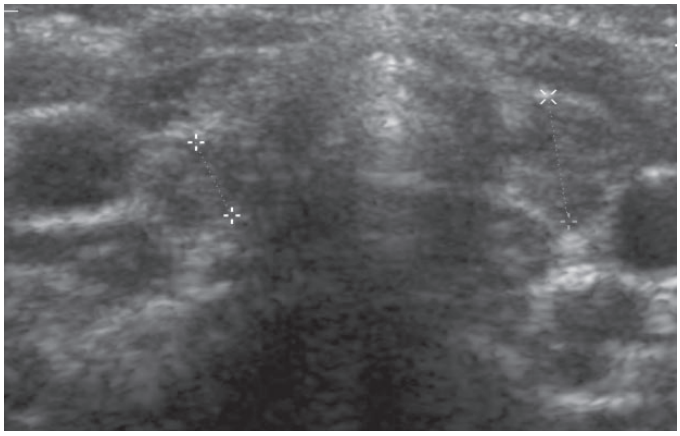

FIG. 2. Thyroid ultrasound image of child Aa:9 with thyroid disintegration, showing decreased echogenicity and inhomogeneous echotexture.

Thyroid hormone plays an essential role in brain development during pre- and early postnatal life. Therefore, T_4 supplementation was initiated in our patients with CH-C as soon as the diagnosis was established. Although it might be that the institution of T_4 supplementation (further) impaired thyroid growth and integrity, we consider well-established preservation of brain development by instituting adequate T_4 supplementation a higher priority than the eventual preservation of thyroid tissue.

Because of its retrospective character, our study had some limitations, *e.g.* variation in the age of the children at the time of investigation. Whenever possible, a prospective design is more suitable to provide complete and structured information, but for obvious ethical reasons, the present issue cannot be studied in a prospective design. Monitoring maternal thyroid function will lead to immediate correction of any tendency to hypothyroidism or hyperthyroidism, aiming to prevent disturbance of the thyroid hormone state in both mother and child. Based on our previous (3) and present observations, we suppose that once maternal hyperthyroidism is prevented, the occurrence of the described type of central and thyroidal hypothyroidism in the offspring will

TABLE 4. Thyroid ultrasound characteristics in group A

Patient no.	Age (yr)	Echogenicity	Echotexture	Estimated volume (ml)			Reference[a]
				Left lobe	Right lobe	Total	
Aa:1	4.1	Decreased	Inhomog	0.8	0.7	1.5	1.8–4.6[b]
Aa:2	4.1	Normal	Normal	0.3	0.4	0.7	1.8–4.6[b]
Aa:3	3.3	Normal	Normal				1.8–4.6[b]
Aa:4	5.1	Decreased	Cyst and nodule	0.6	0.7	1.3	0.9–3.7[c]
Aa:5	2.1	Decreased	Inhomog				
Aa:7	3.8	Normal	Normal	0.8	1.0	1.8	1.8–4.6[b]
Aa:8	3.3	Decreased	Normal	0.2	0.3	0.5	1.8–4.6[b]
Aa:9	3.7	Decreased	Inhomog	0.2	0.1	0.3	1.8–4.6[b]
Aa:10	2.3	Decreased	Inhomog	0.5	0.8	1.3	0.3–4.0[d]
Aa:11	1.6	Decreased	Normal				
Aa:13	1.2	Decreased	Inhomog				
Ab:1	1.2	Decreased	Normal				
Ab:2	2.3	Normal	Normal	0.3	0.4	0.7	0.5–2.9[e]
Ab:3	1.1	Normal	Normal				
Ab:4	2.0	Decreased	Inhomog	0.1	0.2	0.3	0.5–2.9[e]
Ab:5	1.1	Normal	Normal				
Ac:1	8.5	Normal	Inhomog	2.6	2.5	5.1	3.6 ± 1.3[f]

Inhomog, Inhomogeneous.
[a] Reference values are obtained from patients with sufficient iodine supply.
[b] Range is presented [3–5 yr (females) (16)].
[c] Range is presented [3–5 yr (males) (16)].
[d] Range is presented [0–2 yr (females) (16)].
[e] Range is presented [0–2 yr (males) (16)].
[f] Mean ± SD is presented [9 yr (17)].

also be prevented. So, we got a rather unique opportunity to learn about the pediatric consequences of inadequately treated maternal Graves' disease.

In summary, inadequately treated maternal Graves' disease resulting in gestational hyperthyroidism might not only lead to (transient) hyperthyroidism in the fetus and (presumably transient) CH-C in the newborn infant but also carries the until now unrecognized risk of thyroid tissue

TABLE 5. Thyroid function and ultrasound characteristics in groups B and C

Patient no.	Age (yr)	FT_4 ng/dl (pmol/liter)	TSH (mIU/liter)	Echogenicity	Echotexture	Estimated volume (ml)			Reference[a]
						Left lobe	Right lobe	Total	
B:1	10.3	1.0 (12.4)	2.5	Normal	Normal	2.3	3.9	6.2	4.0 ± 1.5[b]
B:2	11.4	1.4 (17.6)	4.8	Normal	Normal	1.8	2.2	4.0	4.9 ± 1.5[c]
B:3	8.8	1.2 (15.0)	3.2	Normal	Normal	1.4	2.5	3.9	3.6 ± 1.3[d]
B:4	2.5	0.9 (11.5)	2.0	Normal	Normal	0.7	0.7	1.4	0.5–2.9[e]
B:5	1.3	0.9 (11.8)	0.8	Normal	Normal	0.6	0.6	1.2	0.5–2.9[e]
B:6	4.0	1.2 (14.9)	0.9	Normal	Normal	0.7	0.8	1.5	0.9–3.7[f]
C:1	10.8	1.3 (16.1)	0.01	Normal	Inhomog	0.6	0.9	1.5	4.9 ± 1.5[c]
C:2	5.8	1.2 (15.9)	0.01	Normal	Inhomog	0.2	0.3	0.5	2.7 ± 1.2[g]
C:3	6.2	1.7 (22.2)	0.01	Normal	Inhomog	0.5	0.6	1.1	2.7 ± 1.2[g]
C:4	8.0	1.4 (18.1)	0.01	Decreased	Normal	0.4	0.6	1.0	3.3 ± 1.2[h]
C:5	8.8	1.2 (15.6)	0.01	Increased	Normal	0.6	0.2	0.8	3.6 ± 1.3[d]
C:6	4.5	1.4 (17.8)	0.11	Normal	Normal	0.2	0.3	0.5	1.8–4.6[i]
C:7	5.0	1.3 (16.4)	0.01	Decreased	Normal	0.5	0.6	1.1	0.9–3.7[f]
C:8	13.1	1.4 (17.8)	0.01	Increased	Inhomog	0.5	0.5	1.0	6.1 ± 1.6[j]
C:9	17.5	0.9 (11.0)	0.02	Increased	Nodule	0.6	0.7	1.3	9.9[k]
C:10	13.5	1.5 (18.9)	0.01	Normal	Inhomog	0.1	0.2	0.3	6.3 ± 1.5[l]

Inhomog, Inhomogeneous.
[a] Reference values are obtained from patients with sufficient iodine supply.
[b] Mean ± SD is presented [10 yr (17)].
[c] Mean ± SD is presented [11 yr (17)].
[d] Mean ± SD is presented [9 yr (17)].
[e] Range is presented [0–2 yr (males) (16)].
[f] Range is presented [3–5 yr (males) (16)].
[g] Mean ± SD is presented [6 yr (17)].
[h] Mean ± SD is presented [8 yr (17)].
[i] Range is presented [3–5 yr (females) (16)].
[j] Mean ± SD is presented [13 yr (17)].
[k] Mean is presented for adult males (18).
[l] Mean ± SD is presented [14 yr (17)].

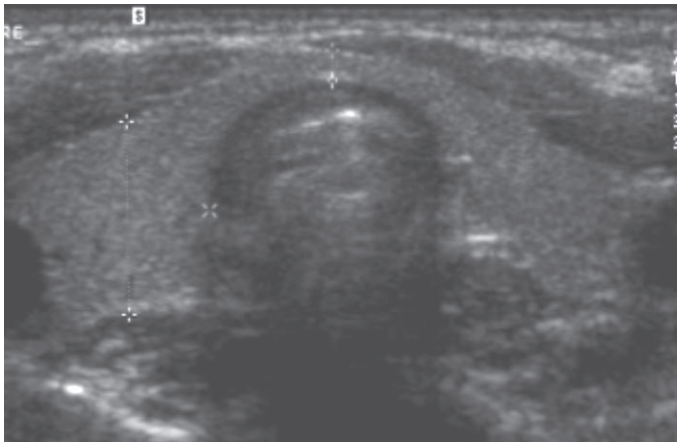

FIG. 3. Thyroid ultrasound image of child B:4 with a normal thyroid, showing normal echogenicity and normal echotexture.

disintegration, resulting in (presumably permanent) loss of the patient's capacity to maintain euthyroidism. We speculate that the long-term lack of TSH action due to the hyperthyroid fetal environment, possibly prolonged by the postnatal T_4 supplementation, interferes with thyroid development and results in loss of integrity in terms of thyroid morphology and function.

Long term follow-up is needed to evaluate the incidence and further consequences of this novel pathological entity, and to reveal the most appropriate diagnostic and treatment approach. In the meantime, careful monitoring of thyroid function determinants and thyroid imaging should be part of the diagnostic workup in children born to mothers with Graves' disease.

Acknowledgments

We thank all patients and their parents for their participation. We also thank the pediatricians, internists, and gynecologists for providing clinical data of their patients. Special thanks go to Brenda Wiedijk (Pediatric Endocrinology Department of the Emma Children's Hospital Academic Medical Center) for her assistance in collecting all clinical data.

Received September 20, 2006. Accepted May 8, 2007.

Address all correspondence and requests for reprints to: Marlies J. E. Kempers, M.D., Ph.D., Academic Medical Center, University of Amsterdam, G8-205, Emma Children's Hospital Academic Medical Center, Department of Pediatric Endocrinology, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands. E-mail: m.j.kempers@amc.uva.nl.

Disclosure Statement: The authors have nothing to declare.

References

1. **Lanting CI, van Tijn DA, Loeber JG, Vulsma T, de Vijlder JJ, Verkerk PH** 2005 Clinical effectiveness and cost-effectiveness of the use of the thyroxine/thyroxine-binding globulin ratio to detect congenital hypothyroidism of thyroidal and central origin in a neonatal screening program. Pediatrics 116:168–173
2. **van Tijn DA, de Vijlder J, Verbeeten Jr B, Verkerk PH, Vulsma T** 2005 Neonatal detection of congenital hypothyroidism of central origin. J Clin Endocrinol Metab 90:3350–3359
3. **Kempers MJ, van Tijn DA, van Trotsenburg AS, de Vijlder JJ, Wiedijk BM, Vulsma T** 2003 Central congenital hypothyroidism due to gestational hyperthyroidism: detection where prevention failed. J Clin Endocrinol Metab 88:5851–5857
4. **Matsuura N, Konishi J, Fujieda K, Kasagi K, Iida Y, Hagisawa M, Fujimoto S, Fukushi M, Takasugi N** 1988 TSH-receptor antibodies in mothers with Graves-disease and outcome in their offspring. Lancet 1:14–17
5. **Matsuura N, Harada S, Ohyama Y, Shibayama K, Fukushi M, Ishikawa N, Yuri K, Nakanishi M, Yokota Y, Kazahari K, Oguchi H** 1997 The mechanisms of transient hypothyroxinemia in infants born to mothers with Graves' disease. Pediatr Res 42:214–218
6. **Tamaki H, Amino N, Takeoka K, Iwatani Y, Tachi J, Kimura M, Mitsuda N, Miki K, Nose O, Tanizawa O, Miyai K** 1989 Prediction of later development of thyrotoxicosis or central hypothyroidism from the cord serum thyroid-stimulating hormone level in neonates born to mothers with Graves-disease. J Pediatr 115:318–321
7. **Mitsuda N, Tamaki H, Amino N, Hosono T, Miyai K, Tanizawa O** 1992 Risk-factors for developmental disorders in infants born to women with Graves disease. Obstet Gynecol 80:359–364
8. **Mandel SH, Hanna CE, LaFranchi SH** 1989 Neonatal hypopituitary hypothyroidism associated with maternal thyrotoxicosis. J Pediatr Endocrinol 3:189–192
9. **Mandel S, Hanna C, Lafranchi S** 1990 Thyroid-function of infants born to mothers with Graves disease. J Pediatr 117:169–170
10. **Slyper AH, Shaker JL** 1993 Neonatal hypothyroxinemia with normal thyrotropin. Clue to maternal Graves' disease. Clin Pediatr (Phila) 32:121–123
11. **Hashimoto H, Maruyama H, Koshida R, Okuda N, Sato T** 1995 Central hypothyroidism resulting from pituitary suppression and peripheral thyrotoxicosis in a premature infant born to a mother with Graves disease. J Pediatr 127:809–811
12. **Lee YS, Loke KY, Ng SCY, Joseph R** 2002 Maternal thyrotoxicosis causing central hypothyroidism in infants. J Paediatr Child Health 38:206–208
13. **Higuchi R, Miyawaki M, Kumagai T, Okutani T, Shima Y, Yoshiyama M, Ban H, Yoshikawa N** 2005 Central hypothyroidism in infants who were born to mothers with thyrotoxicosis before 32 weeks' gestation: 3 cases. Pediatrics 115:e623–e625
14. **Smit BJ, Kok JH, Vulsma T, Briet JM, Boer K, Wiersinga WM** 2000 Neurologic development of the newborn and young child in relation to maternal thyroid function. Acta Paediatr 89:291–295
15. **Brunn J, Block U, Ruf G, Bos I, Kunze WP, Scriba PC** 1981 [Volumetric analysis of thyroid lobes by real-time ultrasound (author's transl)]. Dtsch Med Wochenschr 106:1338–1340 (German)
16. **Tas F, Bulut S, Egilmez H, Oztoprak I, Ergur AT, Candan F** 2002 Normal thyroid volume by ultrasonography in healthy children. Ann Trop Paediatr 22:375–379
17. **Vitti P, Martino E, Aghini-Lombardi F, Rago T, Antonangeli L, Maccherini D, Nanni P, Loviselli A, Balestrieri A, Araneo G** 1994 Thyroid volume measurement by ultrasound in children as a tool for the assessment of mild iodine deficiency. J Clin Endocrinol Metab 79:600–603
18. **Maravall FJ, Gomez-Arnaiz N, Guma A, Abos R, Soler J, Gomez JM** 2004 Reference values of thyroid volume in a healthy, non-iodine-deficient Spanish population. Horm Metab Res 36:645–649
19. **Rapaport R, Sills I, Patel U, Oppenheimer E, Skuza K, Horlick M, Goldstein S, Dimartino J, Saenger P** 1993 Thyrotropin-releasing hormone stimulation tests in infants. J Clin Endocrinol Metab 77:889–894
20. **Vulsma T, de Vijlder JJM** 2005 Genetic defects causing hypothyroidism. In: Werner SC, Ingbar SH, Braverman LE, Utiger RD, eds. Werner & Ingbar's the thyroid: a fundamental and clinical text. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 714–730
21. **Mortimer RH, Tyack SA, Galligan JP, Perrykeene DA, Tan YM** 1990 Graves' disease in pregnancy: TSH receptor binding inhibiting immunoglobulins and maternal and neonatal thyroid function. Clin Endocrinol (Oxf) 32:141–152
22. **Kempers MJ, van Trotsenburg AS, van Tijn DA, Bakker E, Wiedijk BM, Endert E, de Vijlder JJ, Vulsma T** 2005 Disturbance of the fetal thyroid hormone state has long-term consequences for treatment of thyroidal and central congenital hypothyroidism. J Clin Endocrinol Metab 90:4094–4100
23. **Blizzard RM, Chandler RW, Landing BH, Pettit MD, West CD** 1960 Maternal autoimmunization to thyroid as a probable cause of athyrotic cretinism. N Engl J Med 263:327–336
24. **Ritzen EM, Mahler H, Alveryd A** 1981 Transitory congenital hypothyroidism and maternal thyroiditis. Acta Paediatr Scand 70:765–766
25. **Goldsmith RE, McAdams AJ, Larsen PR, MacKenzie M, Hess EV** 1973 Familial autoimmune thyroiditis: maternal-fetal relationship and the role of autoimmunity. J Clin Endocrinol Metab 37:265–275
26. **Anselmo J, Cao DC, Karrison T, Weiss RE, Refetoff S** 2004 Fetal loss associated with excess thyroid hormone exposure. JAMA 292:691–695
27. **Biebermann H, Schoneberg T, Krude H, Schultz G, Gudermann T, Gruters A** 1997 Mutations of the human thyrotropin receptor gene causing thyroid hypoplasia and persistent congenital hypothyroidism. J Clin Endocrinol Metab 82:3471–3480

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.