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Central Congenital Hypothyroidism due to Gestational Hyperthyroidism: Detection Where Prevention Failed

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Much worldwide attention is given to the adverse effects of maternal Graves' disease on the fetal and neonatal thyroid and its function. However, reports concerning the adverse effects of maternal Graves' disease on the pituitary function, illustrated by the development of central congenital hypothyroidism (CCH) in the offspring of these mothers, are scarce. We studied thyroid hormone determinants of 18 children with CCH born to mothers with Graves' disease. Nine mothers were diagnosed after pregnancy, the majority after their children were detected with CCH by neonatal screening. Four mothers were diagnosed during pregnancy and treated with antithyroid drugs since diagnosis. Another four mothers were diagnosed before pregnancy, but they used antithyroid drugs irregularly; free T_4 concentrations less than 1.7 ng/dl (<22 pmol/liter) were not encountered during pregnancy. All neonates had decreased plasma free T_4 concentrations (range 0.3–0.9 ng/dl, 3.9–11.5 pmol/liter); plasma TSH ranged between 0.1 and 6.6 mU/liter. TRH tests showed pituitary dysfunction. Seventeen children needed T_4 supplementation. Because all mothers were insufficiently treated during pregnancy, it is hypothesized that a hyperthyroid fetal environment impaired maturation of the fetal hypothalamic-pituitary-thyroid system. The frequent occurrence of this type of CCH (estimated incidence 1:35,000) warrants early detection and treatment to minimize the risk of cerebral damage. A T_4-based screening program appears useful in detecting this type of CCH. However, the preferential and presumably best strategy to prevent CCH caused by maternal Graves' disease is preserving euthyroidism throughout pregnancy. (*J Clin Endocrinol Metab* 88: 5851–5857, 2003)

THE INFLUENCE OF the maternal thyroid hormone state on the development of the fetal thyroid and its regulatory system is an important issue, particularly because lack of thyroid hormone in fetus and infant constitutes a major risk for damage to the developing brain. This is dramatically demonstrated by conditions in which both fetus and mother are unable to produce adequate amounts of thyroid hormone, as in severe iodine deficiency or in fetomaternal POU1F1 (*i.e.* PIT1) deficiency (1, 2). In contrast, when the condition is confined to fetal thyroid dysfunction as in classical forms of congenital hypothyroidism (CH), brain damage can largely be prevented by early postnatal T_4 supplementation, presumably because transfer of T_4 from mother to fetus compensates, at least in part, for impaired fetal thyroid hormone production (3, 4). Along with these observations, even subtle changes in the maternal thyroid hormone state have been a subject of major interest in recent years (5, 6).

In case of maternal gestational autoimmune Graves' disease, the preservation of a normal fetal thyroid hormone state to ensure normal brain development is a complex issue. Dependent on the presence of antithyroid antibodies, the use of antithyroid drugs, and the maternal thyroid hormone state, the fetal and neonatal thyroid function can be disturbed with high variability in type of effects as well as in severity (7–11). Remarkably, only a minority of newborns from mothers with gestational autoimmune thyroid disease demonstrates a disturbed thyroid hormone state (8, 12–14). A probably undervalued risk is the occurrence of central CH, in infants of mothers with Graves' disease, first described in 1988 by Matsuura *et al.* (7). The published reports on this condition suggest a rare occurrence (7, 8, 12, 15–21), but because of its clinical course, we speculate that it often remains unrecognized unless it is given specific attention.

Because the Dutch T_4-based neonatal CH screening also detects congenital hypothyroidism of central origin, we explored this issue. The case histories of 18 infants with central CH, born to 17 mothers with untreated or inadequately treated Graves' disease are presented.

Materials and Methods

Data collection

The Department of Pediatric Endocrinology in the Emma Children's Hospital Amsterdam Medical Center functions as a national center for consultation on diagnostics and treatment of children with thyroid diseases. Since the start of the Dutch CH screening, the department has been involved in at least half of all cases of CH. In 1994 the first patient with central CH born to a mother with Graves' disease was recognized and since 1999, 19 more children were diagnosed. Detailed information could be retrieved from 18 patients.

Neonatal screening

The Dutch screening, performed 4 to 7 d after birth, is based on measurement of T_4 in filter paper blood spots. T_4 concentrations are compared with the day mean and expressed as SD scores. If heel puncture blood spot concentration of T_4 is -0.8 SD or less, TSH is additionally measured in the blood spot. If T_4 is -1.6 SD or less, TSH and T_4-binding globulin concentration are additionally measured in the blood spot. Depending on T_4, and if measured TSH and T_4-binding globulin concentrations, the test is interpreted as abnormal, borderline, or normal. Children with borderline tests undergo a second screening. Children with one abnormal test ($T_4 \leq -3.0$ SD and/or TSH $\geq$50 mU/liter) or two consecutive borderline tests (T_4 moderately decreased, not caused by

Abbreviation: CH, Congenital hypothyroidism.

T_4-binding globulin deficiency and/or TSH moderately increased) are referred to a pediatrician. This method enables detection of CH of thyroidal origin (decreased T_4, elevated TSH concentration) and central origin (decreased T_4, not caused by T_4-binding globulin deficiency with normal TSH concentration).

Diagnosis of CH of central origin

The criteria for diagnosis of central CH are a free T_4 concentration of less than 0.9 ng/dl (<12 pmol/liter) in combination with a TSH concentration of less than 20 mU/liter and at least one other entity that suggests disintegrity of the thyroid's regulatory system (*e.g.* abnormal response to TRH administration, multiple pituitary hormone deficiencies, anatomical abnormalities on brain magnetic resonance imaging, mutations in genes involved in embryogenesis, or function of hypothalamus or pituitary).

Diagnosis of maternal thyroid disease

Based on the moment the diagnosis of maternal Graves' disease is made, three groups were composed: group A, after delivery, group B, during pregnancy, and group C, before pregnancy. Because all mothers were supposedly hyperthyroid during (part of) pregnancy, the maternal condition was defined as gestational hyperthyroidism; the fetal condition was defined as hyperthyroid fetal environment.

Laboratory measurements

The plasma free T_4 and plasma TSH concentration were measured by time-resolved fluoroimmunoassays (Delfia Free T4 and Delfia hTSH Ultra, Wallac Oy, Turku, Finland). The free T_4 normal range at the age of 2–3 wk is 0.9–2.3 ng/dl (12–29 pmol/liter) (22, 23). The TSH normal range at the age of 0–3 months is 1–10 mU/liter (22, 23), thereafter 0.4–4.0 mU/liter. TSH receptor antibodies were measured using the TRAK assay (Brahms, Berlin, Germany) either with radioactive label or by luminescence.

Results

Diagnostics in mothers

Group A. Mothers A1–9 were diagnosed with hyperthyroidism because of Graves' disease during the first weeks after delivery (Table 1), seven of them after their children were diagnosed with central CH. Mother A4 was diagnosed a few days after delivery because she experienced tachycardia; simultaneously her daughter was referred to the pediatrician because of an abnormal CH-screening result. Mother A9 was diagnosed 2 wk after delivery, after she encountered problems with breast-feeding. No information was available on maternal thyroid function during pregnancy, except that mother A1 had noticed a neck swelling from the third month of pregnancy.

Group B. Mothers B1–4 were diagnosed with hyperthyroidism because of Graves' disease during the second (B4) or third (B1–3) trimester of pregnancy (Table 1) and were treated since then with antithyroid drugs and propranolol. At the time of delivery, plasma free T_4 concentrations had normalized, except for those of mother B4.

Group C. Mothers C1–5 were diagnosed with Graves' disease before pregnancy, but none of them was treated adequately. The mothers of children C1and C2 (twin pregnancy) and C3 stopped using antithyroid drugs in the first trimester. Mother C4 stopped using antithyroid drugs a few months before pregnancy. Only mother C5 was treated with antithyroid drugs throughout pregnancy. Plasma free T_4 concentrations measured throughout pregnancy were all above 1.7 ng/dl (22 pmol/liter).

Table 1 shows that in the three groups together 44% of the parents (50% of the mothers) were not native Dutch, whereas in group A even 89% of the mothers were not native Dutch.

Table 2 shows that in the majority of the mothers TSH-receptor antibodies were present. In two subjects in whom TSH-receptor antibody measurements in the mothers were lacking, they were detectable in the children.

TABLE 1. Patient characteristics

Case no.	Sex	Native Dutch mother/father	GA (wk)	BW (g)	Heel puncture			Maternal thyroid function	
					T_4 (μg/dl)	TSH (mU/liter)	Day	Free T_4 (ng/dl)	Day
A1	M	No/No	40.9	3530	4.4	3	7	3.5	17 d pp
A2	F	No/No	39.9	3660	5.4	<2	14	>5.4	43 d pp
A3	F	No/No	36.7	3330	4.4	3	4	5.0	18 d pp
A4	F	No/Yes	38.0	3100	1.9	5	10	2.7	4 d pp
A5	F	No/Yes	38.3	3470	3.2	n.d.	4	4.6	14 d pp
A6	M	No/No	37.0	2500	4.7	3	9	4.2	36 d pp
A7	F	No/Yes	38.0	2825	8.4	3	12	3.5	21 d pp
A8	M	No/No	38.0	2750	3.1	3	5	4.8	8 d pp
A9	F	Yes/Yes	37.4	3125	8.9	2	[a]	>5.4	17 d pp
B1	M	No/No	38.3	1940	T	T	T	>5.4	31.1 wk GA
B2	F	Yes/No	36.9	2150	6.8	3	8	3.5	30.0 wk GA
B3	M	Yes/Yes	36.9	2480	16.9	n.d.	4	>5.4	30.7 wk GA
B4	M	Yes/Yes	35.4	2256	7.1	2	4	>5.4	14.3 wk GA
C1[b]	F	Yes/Yes	34.6	1970	16.6	n.d.	4	2.5	33.4 wk GA
C2[b]	F	Yes/Yes	34.6	1840	11.8	3	4	2.5	33.4 wk GA
C3	F	Yes/Yes	37.0	3090	5.1	3	5	1.9–>5.4	Range during pregnancy
C4	F	Yes/Yes	36.0	2400	7.5	3	4	2.5–4.0	
C5	F	Yes/Yes	37.0	2580	12.8	3	8	1.8–4.0	

T_4 and TSH concentrations of the children represent the heel puncture blood spot concentrations expressed in μg/dl and mU/liter, respectively. T, Child was already treated at the time of heel puncture blood spot sampling; n.d., not determined; GA, gestational age; BW, birth weight; pp, postpartum. To convert T_4 to Systeme Internationale (SI) Units, multiply by 12.87. To convert free T_4 to Systeme Internationale (SI) Units, multiply by 12.87.

[a] Day of sampling not exactly known.

[b] Twin pregnancy.

TABLE 2. TSH-receptor antibody concentrations

Case no.	Mother		Child	
	Concentration (IU/liter)[a]	Time of sampling	Concentration (IU/liter)[a]	Time of sampling
A1	24	17 d pp	11	24 d pp
A2	43	43 d pp	<5	85 d pp
A3	12	22 d pp	9	22 d pp
A4	19	14 d pp	n.d.	
A5	<9	14 d pp	n.d.	
A6	10.3[b]	36 d pp	n.d.	
A7	1.2[b]	21 d pp	n.d.	
A8	n.d.		1.8[b]	8 d pp
A9	4.9[b]	17 d pp	n.d.	
B1	26	31.1 wk GA	8	Cord blood[c]
B2	n.d.		<5	40 d pp
B3	247	34.9 wk GA	1.3[b]	114 d pp
B4	37.6[b]	22.3 wk GA	21.9[b]	1 d pp
C1	41	33.4 wk GA	n.d.	
C2	41	33.4 wk GA	n.d.	
C3	26	9.7 wk GA	11	5 d pp
C4	n.d.		12	8 d pp
C5	18.4[b]	18 wk GA	91	Cord blood[c]

pp, Postpartum; n.d., not determined; GA, gestational age.

[a] <6 IU/liter = negative, 6–10 IU/liter = dubious, >10 IU/liter = positive.

[b] TSH receptor antibodies measured by luminescence; <1.0 IU/liter = negative, 1.0–1.5 IU/liter = dubious, >1.5 IU/liter = positive.

[c] Cord blood determination at delivery.

Diagnostics in children

Group A. Children A1–8 were referred to the pediatrician because of abnormal CH-screening results (Table 1); child A9 was referred at the age of 4 wk after disclosure of maternal hyperthyroidism 2 wk earlier. All children had, when measured in venous blood samples, abnormally low plasma free T_4 concentrations and plasma TSH concentrations within the age-specific normal range, except for child A6 whose TSH was initially suppressed (Fig. 1). The children A1 and A3–7 underwent a TRH test, demonstrating a blunted TSH response (Fig. 2). CRH tests, performed in three children, revealed normal ACTH and cortisol responses (data not shown). Because maternal hyperthyroidism was diagnosed before the diagnostic work-up was completed, investigation of the other hormonal systems were not performed. Magnetic resonance imaging of the hypothalamic-pituitary region performed in children A4and A6 showed no abnormalities.

Group B. Children B1 and B2 had decreased plasma free T_4 concentrations with normal and initially suppressed plasma TSH concentration respectively (Fig. 1). In child B3 plasma free T_4 was initially normal but increased to above the normal range after a few days. Without intervention plasma free T_4 decreased to below the normal range within a few weeks although with suppressed TSH. In child B4 plasma free T_4 was initially normal, which gradually decreased to below the normal range; plasma TSH was suppressed. TRH tests, performed in the children B2–4, showed blunted TSH responses.

Group C. Cord blood examination in the children C1–3 and C5 showed normal plasma free T_4 concentrations and low TSH concentrations (Fig. 1). Child C4 had low-normal plasma free T_4 1 d after birth [1.0 ng/dl (13 pmol/liter)]; TSH was not measured. In the children C3 and C4 plasma free T_4 decreased in the first week after birth; in the other children, free T4 increased initially but decreased after a few weeks below the normal range. Children C1–2 and C4–5 underwent a TRH test that showed a blunted TSH response (Fig. 2).

Treatment in children

Child A1 was not treated because his plasma free T_4 concentration spontaneously normalized, already during the phase of diagnostic work-up. Although the TSH response after TRH administration was blunted in the neonatal period, the response had become normal when retested at the age of 1 yr (Fig. 2). In all other children, T_4 supplementation was initiated. In child A5 T_4 supplementation was interrupted at the age of 4 months; she remained euthyroid afterward. In child B1 T_4 supplementation was interrupted at the age of 6 months. At the age of 1 yr, his TRH test showed a normal TSH response (Fig. 2). However, because at that time plasma free T_4 concentration was below the normal range [0.8 ng/dl (10.7 pmol/liter)] with slightly increased TSH (7.1 mU/liter), T_4 supplementation was restarted and has continued to date. In the other patients, the effect of interruption of T_4 supplementation was not sorted out because of the potential risk of cerebral damage under the age of 3 yr.

Discussion

Eighteen infants with central CH were born to mothers with Graves' disease. The endocrine characteristics of the mothers varied considerably with respect to time of diagnosis, antibody concentrations, and treatment, but the common denominator was the lack of adequate treatment during pregnancy leading to elevated maternal plasma free T_4 concentrations when measured after or during pregnancy.

All children developed moderately to extremely decreased neonatal free T_4 concentrations in combination with normal or suppressed TSH concentrations. Most children were already hypothyroid at the first thyroid function measurements within a few days after birth, although one child became hypothyroid after a short hyperthyroid phase and six children after an initial euthyroxinemic phase. The blunted TSH response on TRH administration confirmed the disturbance of the child's thyroid regulatory system. As shown in Fig. 1, the initiation of T_4 treatment was incidentally delayed for several weeks, presumably as a consequence of the unfamiliarity with this specific thyroid entity in children of mothers with Graves' disease.

The reported incidence of permanent central CH detected by neonatal screening in The Netherlands is around 1 in 20,000 children, *i.e.* about 10 patients every year (24, 25), of whom the great majority has permanent deficiency of multiple pituitary hormones. Although the Dutch T_4-based screening was introduced in 1981, the first patient with central CH because of maternal gestational hyperthyroidism was detected as late as 1994. The other 17 children presented here were born over a 3-yr period since 1999; they represent an incidence of central CH because of maternal gestational hyperthyroidism of 1:35,000. However, the total number of children with central CH because of maternal gestational hyperthyroidism is probably even higher because not all patients might have come to our attention. Therefore, the

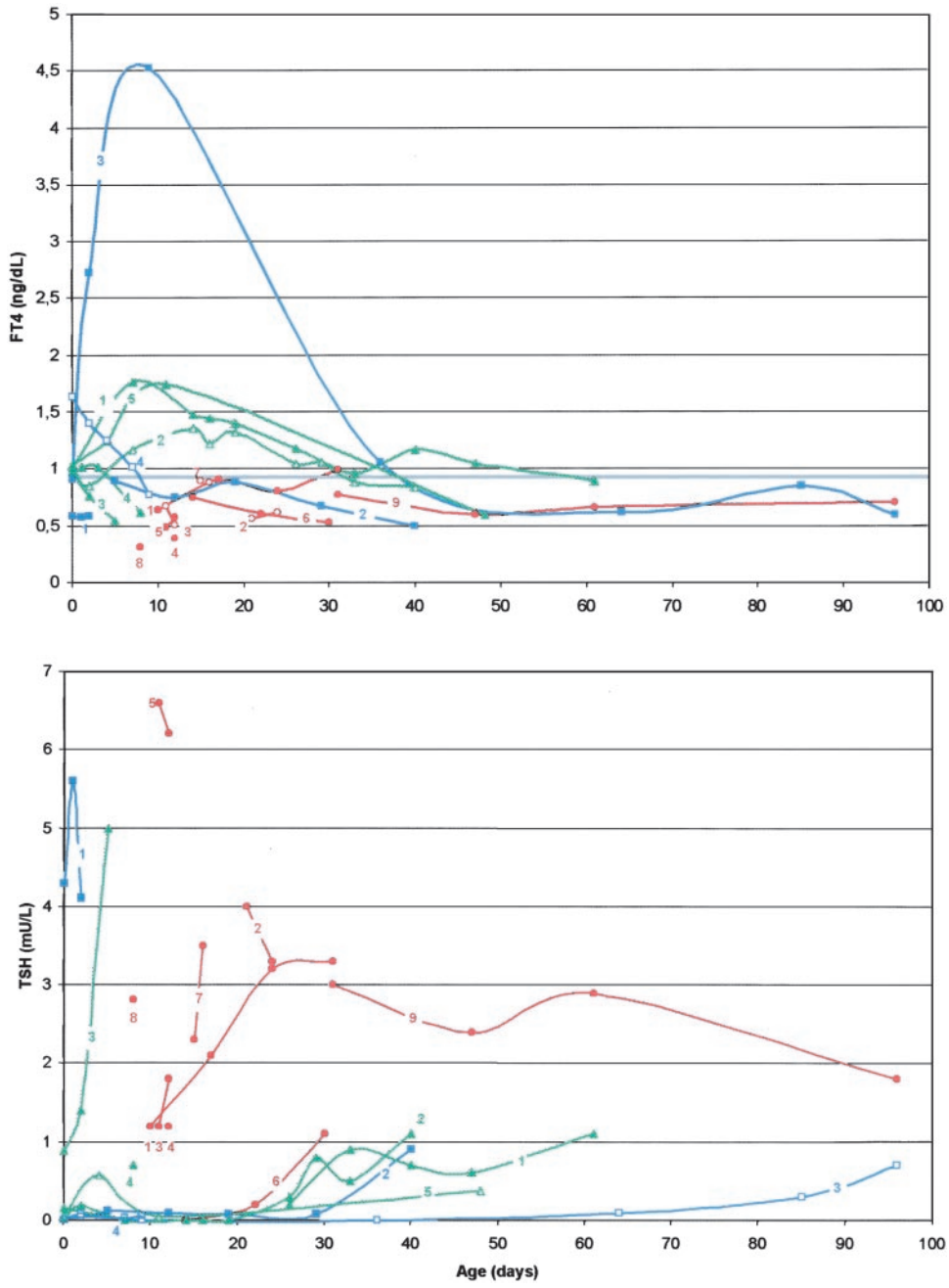

FIG. 1. Plasma free T_4 and TSH concentrations in the children. Plasma free T_4 (*upper panel*) and TSH concentrations (*lower panel*) are shown for group A (*red*), group B (*blue*), and group C (*green*). The results represent measurements before T_4 supplementation was started. *Open* and *closed symbols* are used to discriminate between different lines. The *gray line* in the upper panel represents the lower limit of the plasma free T_4 normal range [*i.e.* 0.9 ng/dl (12 pmol/liter)]. To convert free T_4 to Systeme Internationale (SI) units, multiply by 12.87.

total incidence of central CH in The Netherlands is at least 1 in 15,000 newborns.

For the Dutch population, accurate incidence figures of Graves' disease during pregnancy are not available. International estimations of the incidence of Graves' disease during gestation of about 1 in 500 (26–29) indicate that about 1 in 70 women (1.5%) with Graves' disease gives birth to a child with central CH. However, because all presented children were born to inadequately treated mothers, the risk seems to be restricted to these mothers. This implies that, within the spectrum of neonatal thyroid dysfunction related to maternal Graves' disease, the occurrence of central CH seems of the same magnitude as that of congenital hyperthyroidism, estimated as 1–5% (26, 27, 30). Neonatal screening appeared to be indispensable in the diagnosis of at least seven mother-child pairs (*i.e.* 40%). However, also in the Dutch T_4-based neonatal screening program, several cases might remain undetected because they became hypothyroid after an initial euthyroid or hyperthyroid phase (40% of the present cohort).

Intriguingly, an impressive percentage (44%) of the parents originated from outside The Netherlands, mostly underdeveloped countries. Especially in group A, 70% of parents (and even 90% of mothers) were not native Dutch; language problems together with the unfamiliarity with the Dutch health care system might have led to insufficient medical care.

The finding that all women with Graves' disease who gave birth to children with central CH were inadequately treated

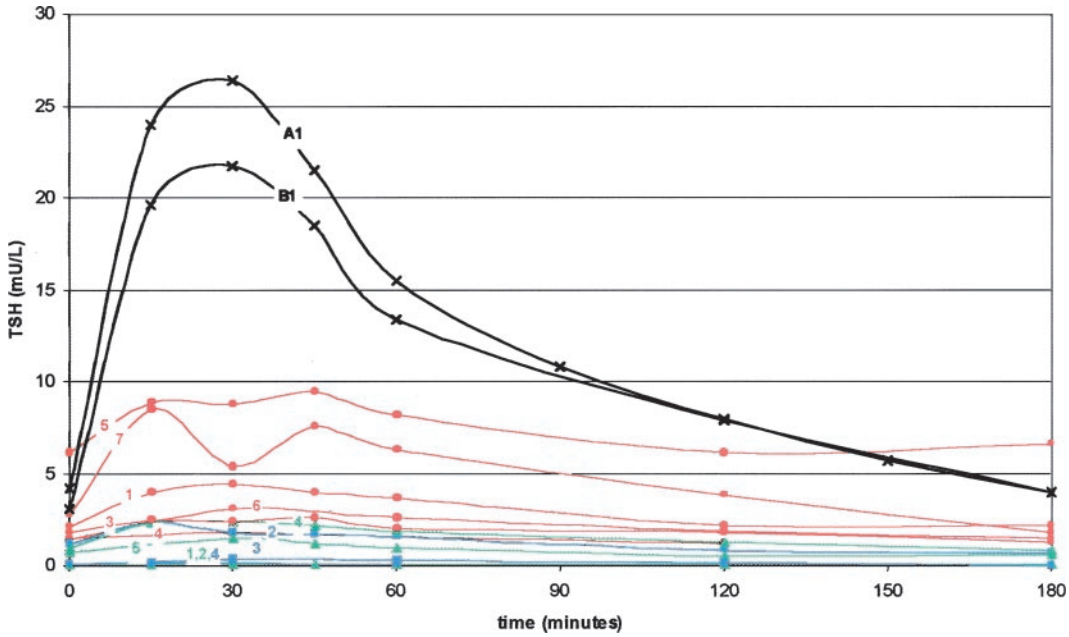

FIG. 2. TSH response after administration of TRH. TRH test results at neonatal age are shown for group A (*red*), group B (*blue*), and group C (*green*). In child A1 (who also underwent a TRH test in the neonatal period) and child B1 (after T_4 supplementation was interrupted for a few months) a TRH test was performed at the age of 1 yr (*black*).

suggests a causal relationship. We hypothesize that the maternal gestational hyperthyroidism causes a hyperthyroid fetal environment. Because substantial maternal-fetal transfer of T_4 occurs in euthyroid mothers pregnant with children with thyroidal CH (3), maternal hyperthyroidism may result in increased T_4 transfer. The exposure of the fetal hypothalamic-pituitary-thyroid system to higher-than-normal thyroid hormone concentrations might have impaired its physiologic maturation during intrauterine life. The system was not triggered to produce its own thyroid hormone through TSH and TRH secretion and not prepared to become self-supporting. After birth pituitary TSH secretion in response to dropping plasma (free) T_4 concentrations as well as to TRH administration is inadequate; likewise, hypothalamic TRH secretion might be inadequate as well.

Hyporesponsiveness of the pituitary is also observed in adult patients with hyperthyroidism; after initiation of treatment (antithyroid drugs or ^{131}I) and normalization of thyroid hormone concentrations, the reinstitution of adequate TSH secretion, either basal or after TRH administration, takes weeks to months (31, 32).

Other factors (putatively) involved in pituitary hyporesponsiveness during Graves' disease are *e.g.* TSH-receptor antibodies occupying the pituitary TSH receptor (33) or pituitary autoantibodies associated with lymphocytic hypophysitis (34), which is especially seen in women during or shortly after pregnancy, sometimes associated with autoimmune thyroid disease. However, these factors fail to explain why central CH is strictly confined to inadequately treated maternal gestational hyperthyroidism. For the fetal thyroid system, the only relevant feature, distinguishing pregnant mothers with overt hyperthyroidism from those mothers with adequately treated Graves' disease, is the presence of a hyperthyroid fetal environment. Therefore, it is very likely that instituting adequate maternal treatment might have prevented the central CH in the children we studied.

According to reports in literature (8, 15, 17–20) discussing the course of central congenital hypothyroidism related to maternal Graves' disease, this type of central CH has a transient expression; thyroid hormone concentrations remain within the normal range after withdrawal of T_4 treatment or the TSH response in response to TRH administration normalizes. In one of our patients who demonstrated a spontaneous normalization of free T_4 concentration, the TSH response to TRH administration became normal within a year. In two other patients, interruption of T_4 supplementation was evaluated: One remained euthyroid and the other became hypothyroid within a few months, despite a normal TRH test result. At the moment we cannot exclude that subtle changes in the thyroid regulatory system may persist. The hypothesized overexposure of the fetal hypothalamic-pituitary-thyroid system to thyroid hormone might have permanently altered the tuning of the pituitary set point of TSH secretion. Consequently, plasma free T_4 and TSH concentrations, albeit in the normal range after interruption of T_4 supplementation, might differ from those of children prenatally exposed to a euthyroid environment. Animal studies suggest that short-term overexposure of neonatal rats to T_4 results in permanent alterations of the hypothalamic-pituitary regulatory system (35–37). Besides, patients with CH of thyroidal origin, prenatally underexposed to thyroid hormone, need plasma free T_4 concentrations in the high normal range to normalize TSH secretion during postnatal thyroxine treatment (38). This suggests that their regulation in the negative feedback system differs from children without CH.

Maternal Graves' disease during pregnancy carries the risk of a variety of adverse effects for the offspring with a wide spectrum of abnormalities in the thyroid function. All patients presented here experienced a phase of central hypothyroidism, starting before or just after birth, which we explained by postulating a prenatal phase of hyperthyroidism that affected the thyroid's regulatory system. Especially because both conditions are known to impair brain development (39, 40), preventive action or timely correction is important.

Certainly, the most effective management would be the preservation of euthyroidism in all pregnant women. This, however, would imply routine screening on thyroid function during gestation because at least some of the women with Graves' disease appear to escape from recognition of this diagnosis. As long as such a preventive maternal screening method is not available, the neonatal CH screening, on the condition that it is T_4 based, seems helpful to detect central congenital hypothyroidism. In the diagnostic work-up of patients with central CH, evaluation of maternal thyroid function should be incorporated.

The thyroid function of the offspring of mothers with Graves' disease, especially those with inadequate treatment throughout pregnancy, should be controlled carefully, at least up to a few weeks after birth. If there is any doubt about the integrity of the child's thyroid regulatory system [free $T_4 < 0.9$ ng/dl (<12 pmol/liter) and TSH < 20 mU/liter], a TRH test should be performed. In case of a (partly) suppressed TSH response after administration of TRH, the presence of central CH is proven and T_4 supplementation should be given for at least several months.

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References

1. **De Zegher F, Pernasetti F, Vanhole C, Devlieger H, van den Berghe G, Martial JA** 1995 The prenatal role of thyroid hormone evidenced by fetomaternal Pit-1 deficiency. J Clin Endocrinol Metab 80:3127–3130
2. **Dunn JT, Delange F** 2001 Damaged reproduction: the most important consequence of iodine deficiency. J Clin Endocrinol Metab 86:2360–2363
3. **Vulsma T, Gons MH, de Vijlder JJM** 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
4. **Calvo RM, Jauniaux E, Gulbis B, Asuncion M, Gervy C, Contempre B, Morreale de Escobar G** 2002 Fetal tissues are exposed to biologically relevant free thyroxine concentrations during early phases of development. J Clin Endocrinol Metab 87:1768–1777
5. **Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga W, Drexhage HA, Vader HL** 1999 Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol 50:149–155
6. **Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waibren SE, Faix JD, Klein RZ** 1999 Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 341:549–555
7. **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
8. **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
9. **Mortimer RH, Tyack SA, Galligan JP, Perry-Keene DA, Tan YM** 1990 Graves' disease in pregnancy: TSH receptor binding inhibiting immunoglobulins and maternal and neonatal thyroid function. Clin Endocrinol 32:141–152
10. **Momotani N, Noh JY, Ishikawa N, Ito K** 1997 Effects of propylthiouracil and methimazole on fetal thyroid status in mothers with Graves' hyperthyroidism. J Clin Endocrinol Metab 82:3633–3636
11. **Gallagher MP, Schachner HC, Levine LS, Fisher DA, Berdon WE, Oberfield SE** 2001 Neonatal thyroid enlargement associated with propylthiouracil therapy of Graves' disease during pregnancy: a problem revisited. J Pediatr 139: 896–900
12. **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
13. **Mestman JH** 1999 Diagnosis and management of maternal and fetal thyroid disorders. Curr Opin Obstet Gynecol 11:167–175
14. **Laurberg P, Nygaard B, Glinoer D, Grussendorf M, Orgiazzi J** 1998 Guidelines for TSH-receptor antibody measurements in pregnancy: results of an evidence-based symposium organized by the European Thyroid Association. Eur J Endocrinol 139:584–586
15. **Mandel SH, Hanna CE, LaFranchi SH** 1989 Neonatal hypopituitary hypothyroidism associated with maternal thyrotoxicosis. J Pediatr Endocrinol 3:189–192
16. **Mandel S, Hanna C, LaFranchi S** 1990 Thyroid function of infants born to mothers with Graves disease. J Pediatr 117:169–170
17. **Slyper AH, Shaker JL** 1993 Neonatal hypothyroxinemia with normal TSH. Clue to maternal Graves' disease. Clin Pediatr 32:121–123
18. **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
19. **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
20. **Higuchi R, Kumagai T, Kobayashi M, Minami T, Koyama H, Ishii Y** 2001 Short-term hyperthyroidism followed by transient pituitary hypothyroidism in a very low birth weight infant born to a mother with uncontrolled Graves' disease. Pediatrics 107:E57
21. **Lee YS, Loke KY, Ng SCY, Joseph R** 2002 Maternal thyrotoxicosis causing central hypothyroidism in infants. J Paediatr Child Health 38:206–208
22. **Fisher DA** 1991 Management of congenital hypothyroidism. J Clin Endocrinol Metab 72:523–529
23. **Nelson JC, Clark SJ, Borut DL, Tomei RT, Carlton EI** 1993 Age related changes in serum free thyroxine during childhood and adolescence. J Pediatr 123:899–905
24. **Vulsma T** 1991 Etiology and pathogenesis of congenital hypothyroidism. Evaluation and examination of patients detected by neonatal screening in The Netherlands, Thesis, University of Amsterdam
25. **Lanting CI, van Tijn DA, Loeber JG, Vulsma T, de Vijlder JJM, Verkerk PH** 2002 Screening for CH in the Netherlands: use of thyroxine/TBG ratio. Proc 5th Meeting of the International Society for Neonatal Screening, Genova, Italy, June 2002, p 93 (Abstract P24)
26. **Burrow GN** 1985 The management of thyrotoxicosis in pregnancy. N Engl J Med 313:562–565
27. **Polak M** 1998 Hyperthyroidism in early infancy: pathogenesis, clinical features and diagnosis with a focus on neonatal hyperthyroidism. Thyroid 8:1171–1177
28. **Lazarus JH** 2002 Epidemiology and prevention of thyroid disease in pregnancy. Thyroid 12:861–865
29. **Anonymous** 2002 Thyroid disease in pregnancy. Obstet Gynecol 37:387–396
30. **Weetman AP** 2000 Graves' disease. N Engl J Med 343:1236–1248
31. **Fischer HRA, Hackeng WHL, Schopman W, Silberbusch J** 1982 Analysis of factors in hyperthyroidism, which determine the duration of suppressive treatment before recovery of thyroid stimulating hormone secretion. Clin Endocrinol 16:575–585
32. **Uy HL, Reasner CA, Samuels MH** 1995 Pattern of recovery of the hypothalamic-pituitary-thyroid axis following radioactive iodine therapy in patients with Graves' disease. Am J Med 99:173–179
33. **Brokken LJS, Scheenhart JWC, Wiersinga WM, Prummel MF** 2001 Suppres-

sion of serum TSH by Graves' Ig: evidence for a functional pituitary TSH receptor. J Clin Endocrinol Metab 86:4814–4817

34. **O'Dwyer DT, Smith AI, Matthew ML, Andronicos NM, Ranson M, Robinson PJ, Crock PA** 2002 Identification of the 49-kDa autoantigen associated with lymphocytic hypophysitis as α-enolase. J Clin Endocrinol Metab 87:752–757
35. **Azizi F, Vagenakis AG, Bollinger J, Reichlin S, Braverman LE, Ingbar SH** 1974 Persistent abnormalities in pituitary function following neonatal thyrotoxicosis in the rat. Endocrinology 94:1681–1688
36. **Bakke JL, Lawrence NL, Bennett J, Robinson S** 1975 The late effects of neonatal hyperthyroidism upon the feedback regulation of TSH secretion in rats. Endocrinology 97:659–664
37. **Dussault JH, Coulombe P, Walker P** 1982 Effects of neonatal hyperthyroidism on the development of the hypothalamic-pituitary-thyroid axis in the rat. Endocrinology 110:1037–1042
38. **Bakker B, Kempers MJ, De Vijlder JJM, van Tijn DA, Wiedijk BM, van Bruggen M, Vulsma T** 2002 Dynamics of the plasma concentrations of TSH, FT4 and T3 following thyroxine supplementation in congenital hypothyroidism. Clin Endocrinol (Oxf)57:529–537
39. **Daneman D, Howard NJ** 1980 Neonatal thyrotoxicosis: intellectual impairment and craniosynostosis in later years. J Pediatr 97:257–259
40. **Van Vliet G** 1999 Neonatal hypothyroidism: treatment and outcome. Thyroid 9:79–84