

# Short-Term Hyperthyroidism Followed by Transient Pituitary Hypothyroidism in a Very Low Birth Weight Infant Born to a Mother With Uncontrolled Graves' Disease

Ryuzo Higuchi, MD; Takeshi Kumagai, MD; Masakazu Kobayashi, MD; Takaomi Minami, MD; Hirofumi Koyama, MD; and Yuki Ishii, MD

**ABSTRACT.** Transient hypothyroxinemia in infants born to mothers with poorly controlled Graves' disease was first reported in 1988. We report that short-term hyperthyroidism followed by hypothyroidism with low basal thyroid-stimulating hormone (TSH) levels developed in a very low birth weight infant born at 27 weeks of gestation to a noncompliant mother with thyrotoxicosis attributable to Graves' disease. We performed serial thyrotropin-releasing hormone (TRH) tests in this infant and demonstrated that TSH unresponsiveness to TRH disappeared at 6.5 months of age.

The maternal thyroid function was free triiodothyronine (FT<sub>3</sub>), 21.1 pg/mL; free thyroxine (FT<sub>4</sub>), 8.1 ng/dL; TSH, <0.03 μU/mL; thyroid-stimulating hormone receptor antibody, 52% (normal: <15%); thyroid-stimulating antibody, 294% (normal: <180%); and thyroid-stimulation blocking antibody, 9% (normal: <25%) on the day of delivery. A nonstress test revealed fetal tachycardia >200 beats per minute, and a male infant weighing 1152 g was born by emergency cesarean section. Thyroid-stimulating hormone receptor antibody was 16% and thyroid-stimulating antibody was 370% in the cord blood. We administered 10 mg/kg per day of oral propylthiouracil from day 1. Tachycardia along with elevated FT<sub>4</sub> and FT<sub>3</sub> levels in the infant decreased from 200/minute to 170/minute, 4.7 ng/dL to 2.9 ng/dL, 7.0 pg/mL to 4.8 pg/mL, respectively, in the first 33 hours. At 5 days, FT<sub>4</sub> and FT<sub>3</sub> were 1.1 ng/dL and 2.9 pg/mL, respectively, and we stopped propylthiouracil administration. Although FT<sub>4</sub> decreased to 0.4 ng/dL, TSH was quite low and did not respond to intravenous TRH by 14 days of age. We began daily levothyroxine 5-μg/kg supplementation. The responsiveness of TSH to TRH did not become significant until 4 months old and normalized at 6.5 months old. At this time, levothyroxine was stopped.

We conclude that placental transfer of thyroid hormones may cause hyperthyroidism in the fetal and early neonatal periods and lead to transient pituitary hypothyroidism in an infant born to a mother with uncontrolled Graves' disease. *Pediatrics* 2001;107(4). URL: <http://www.pediatrics.org/cgi/content/full/107/4/e57>; *pituitary hypothyroidism, Graves' disease, thyroxine, triiodothyronine, placental transfer*.

**ABBREVIATIONS.** FT<sub>3</sub>, free triiodothyronine; FT<sub>4</sub>, free thyroxine; TSH, thyroid-stimulating hormone; TRAb, thyroid-stimulating hormone receptor antibody; TSAb, thyroid-stimulating antibody; TRH, thyrotropin-releasing hormone; T<sub>4</sub>, thyroxine; T<sub>3</sub>, triiodothyronine.

## CASE REPORT

A male infant was born at 27 weeks 2 days of gestational age to a 27-year-old G2P0 mother who was diagnosed at age 13 years with thyrotoxicosis attributable to Graves' disease. She was noncompliant with medication and had an elective abortion at age 26 years because of thyrotoxicosis. Premature rupture of the membranes occurred at 27 weeks 2 days of the second gestation and a nonstress test revealed fetal tachycardia >200 beats per minute. The mother was transferred to our hospital because of threatened premature labor and abruptio placenta. Her thyroid function was free triiodothyronine (FT<sub>3</sub>), 21.1 pg/mL; free thyroxine (FT<sub>4</sub>), 8.1 ng/dL; thyroid-stimulating hormone (TSH), <0.03 μU/mL; thyroid-stimulating hormone receptor antibody (TRAb), 52% (normal: <15%); thyroid-stimulating antibody (TSAb), 294% (normal: <180%); and thyroid-stimulation blocking antibody, 9% (normal: <25%). On the day of her admission, a male infant was born by emergency cesarean section. He had a 1-minute Apgar score of 8 and weighed 1152 g. Cord blood revealed TRAb was 16% and TSAb was 370%. On the day of birth, the infant required tracheal intubation for respiratory distress. He had tachycardia at 200 beats per minute but did not show goiter or exophthalmos. Radiographs did not reveal any ossification centers in the distal femurs. His thyroid function was FT<sub>4</sub>, 4.7 ng/dL; FT<sub>3</sub>, 7.0 pg/mL; and TSH, 0.12 μU/mL at 1 hour of life. We diagnosed thyrotoxicosis according to the reference FT<sub>4</sub> level (0.5–3.3 ng/dL) for 25 to 30 weeks of gestation<sup>1</sup> and tachycardia and administered 10 mg/kg per day of oral propylthiouracil from day 1.

Thirty-four hours after birth, the heart rate was 170 beats per minute and thyroid function decreased to normal levels: FT<sub>4</sub>, 2.9 ng/dL and FT<sub>3</sub>, 4.8 pg/mL. At 5 days of life, FT<sub>4</sub> and FT<sub>3</sub> were 1.1 ng/dL and 2.9 pg/mL, respectively, and we stopped propylthiouracil administration. Determined by the log linear regression method of the 3 points in the first 5 days, serum elimination half-life of FT<sub>4</sub> and FT<sub>3</sub> measured 50.3 hours and 84.9 hours, respectively. By day 14, FT<sub>4</sub> was 0.4 ng/dL and basal TSH 0.03 μU/mL (normal: 0.5–29 μU/mL) indicating hypothyroidism.<sup>1</sup> A thyrotropin-releasing hormone (TRH) test (10 μg/kg) showed no TSH response after 30 minutes (0.04 μU/mL). We diagnosed pituitary hypothyroidism and started administering 5 μg/kg per day of oral levothyroxine. In 14 days, FT<sub>4</sub> concentration became euthyroid (Fig 1). However, basal TSH remained extremely low and a TRH test did not show TSH response by 2 months old (postmenstrual age: 37 weeks). TSH was 0.17 μU/mL before testing and 0.54 μU/mL at 30 minutes after the TRH test. At 4 months old, for the first time, TSH increased significantly from 1.68 μU/mL before testing to 6.02 μU/mL at 30 minutes after testing. TSH was 4.05 μU/mL and increased to 18.05 μU/mL at 30 minutes after a TRH test at 6.5 months old. We stopped levothyroxine therapy and thyroid function was normal 2 weeks after its discontinuation.

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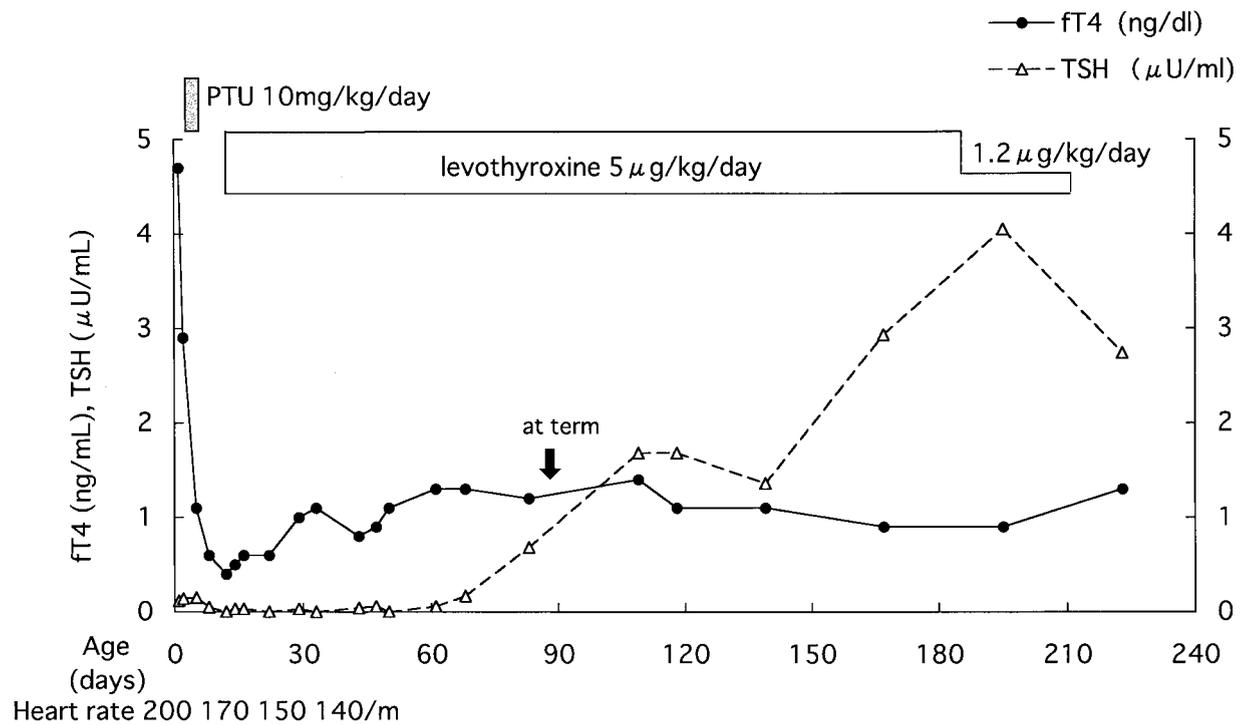


Fig 1. Clinical course of the patient. High FT<sub>4</sub> levels declined in the first 2 days of life and low FT<sub>4</sub> levels normalized after levothyroxine administration. Basal TSH levels remained quite low in the first 2 months of life and then gradually increased.

## DISCUSSION

Transient hypothyroxinemia in infants born to mothers with poorly controlled Graves' disease was first reported in 1988.<sup>2</sup> Hashimoto et al<sup>3</sup> speculated that this type of hypothyroidism may become overt when pituitary thyrotropin secretion is suppressed during fetal thyrotoxicosis, and TSAb activity is relatively weak compared with TRAb activity after birth. Matsuura et al<sup>4</sup> showed that the blood thyroxine (T<sub>4</sub>) levels at birth were higher than those infants 5 days old with transient hypothyroxinemia born after 34 weeks of gestation. They suggested that the fetal T<sub>4</sub> level might have been elevated because of the transfer of maternal T<sub>4</sub> to the fetus during the last trimester when the maternal thyroid function was elevated. TRAb was much lower in the cord blood than in the maternal blood probably because placental transfer of immunoglobulin G is limited in the second trimester. TSAb was slightly higher in the cord blood than in the maternal blood, and both were increased above the reference range. TRAb does not necessarily correlate to TSAb because TRAb consists of diverse, polyclonal antibodies. Slightly increased TSAb and the difference in responsiveness to the TSAb between the maternal and fetal thyroids may cause increased cord blood FT<sub>3</sub>. This case and the one of Hashimoto et al<sup>3</sup> indicate that the fetal thyrotoxicosis during the second trimester may be the mechanism that causes the transient hypothyroidism in a term infant.

The mother had thyrotoxicosis and her thyroid function was higher than this very low birth weight infant. Tachycardia and elevated thyroid function subsided within 2 days after birth in this infant. T<sub>4</sub>

transferred passively from the noncompliant mother with thyrotoxicosis is thought to cause hyperthyroidism in fetal and early neonatal life and lead to the development of pituitary hypothyroidism. FT<sub>4</sub> and FT<sub>3</sub> decreased so soon after birth that hyperthyroidism may have been missed. The elimination half-life of T<sub>4</sub> and triiodothyronine (T<sub>3</sub>) in acute thyroxine ingestion is 2.8 days and 6 days, respectively.<sup>5</sup> Because the half-life of FT<sub>3</sub> in this infant is shorter than that of T<sub>3</sub>, FT<sub>3</sub> could be transferred across the placenta when the maternal level is high, although T<sub>3</sub> is considered unable to cross the placenta. Dussault et al<sup>6</sup> reported that the administration of T<sub>3</sub> to pregnant participants caused a rise in both maternal and newborn T<sub>3</sub>.

The duration of passive hyperthyroidism during fetal life that leads to pituitary hypothyroidism is unknown. TRH tests in this infant demonstrated pituitary unresponsiveness and recovery from the suppression after 6.5 months, which supports the theories of Hashimoto et al<sup>3</sup> and Matsuura et al.<sup>4</sup> An increase in responsiveness to the TRH test coincided with an increase in basal TSH levels and confirmed the appropriate duration for levothyroxine supplementation. It remains a concern in neonatal screening for congenital hypothyroidism by TSH determination that this type of hypothyroidism may be overlooked.

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