

## PRENATAL TREATMENT OF THYROTOXICOSIS TO PREVENT INTRAUTERINE GROWTH RETARDATION

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A woman with hypothyroidism and Graves ophthalmopathy was treated with propylthiouracil during her second pregnancy. This was employed because her first pregnancy resulted in an infant with severe intrauterine growth retardation and neonatal thyrotoxicosis. The antithyroid drug used during the second pregnancy crossed the placenta and treated the infant in utero. The infant was delivered by elective cesarean section at 36 weeks and was a live-born male with appropriate height and weight without evidence of thyrotoxicosis. The therapeutic benefit of propylthiouracil during this second pregnancy seems likely, based on the development of neonatal thyrotoxicosis after 4 days of life and on the presence of high thyroid-stimulating immunoglobulin levels in the mother and the infant. (*Obstet Gynecol* 60:122, 1982)

Graves disease in pregnancy is uncommon, occurring in 0.02 to 3.7% of all pregnancies.<sup>1</sup> Neonatal Graves disease is even more uncommon, occurring in only 1 in 70 births to thyrotoxic mothers.<sup>2</sup> Occasionally, a thyrotoxic mother will give birth to an infant somewhat small for gestational age. Thyrotoxicosis has been reported as a cause of intrauterine growth retardation.<sup>3,4</sup> Recent studies in patients with Graves disease have demonstrated the presence of thyroid-stimulating immunoglobulins, 7S IgG antibodies, which have the ability to attach to thyroid-stimulating hormone recep-

tor sites on the thyroid and to stimulate the gland to produce thyroxine (T<sub>4</sub>) and triiodothyronine (T<sub>3</sub>).<sup>5</sup> These immunoglobulins may also cross the placenta and in rare circumstances (less than 1%) cause thyrotoxicosis.

One of the first immunoglobulins described was termed LATS (long-acting thyroid stimulator), a nonthyrotropin substance in the plasma of thyrotoxic individuals that could stimulate mouse thyroid membranes.<sup>6</sup> It was subsequently found that more sensitive but technically more difficult assays using human thyroid cell membranes could be employed.<sup>7</sup>

Graves ophthalmopathy may be present in a hyperthyroid individual (most common instance), or in a euthyroid or hypothyroid person.<sup>8</sup> The case report presented describes a woman with hypothyroidism and Graves ophthalmopathy who delivered an infant with intrauterine growth retardation and neonatal thyrotoxicosis in her first pregnancy. The procedures and rationale used to manage this patient during her second pregnancy, which led to the delivery of an infant of appropriate size for gestational age, are described.

### Case Report

The patient is a 34-year-old woman with a past medical history of hypothyroidism probably due to Hashimoto disease. This diagnosis was based on the bosselated texture of an enlarged thyroid gland along with significantly elevated antimicrosomal and antithyroglobulin antibodies, elevated thyroid-stimulating hormone levels, and Graves ophthalmopathy. The patient's first pregnancy culminated in a cesarean section at 33 weeks' gestation by dates because of fetal distress, amnionitis, and prolonged spontaneous premature rupture of membranes. An ultrasound scan taken 4 days before delivery showed a fetal biparietal diameter compatible with 29 weeks' gestation. A decision had been made to manage the patient conservatively in an effort to achieve fetal growth compatible with viability. A female infant weighing 1446 g with a developmental age of 33 weeks died at 30 hours of life of group  $\beta$  Streptococcus septicemia. Autopsy revealed hyperplasia of the thyroid follicles, intrauterine growth retardation, and meconium aspiration pneumonia. At 4 hours of life T<sub>4</sub> was elevated at 24.5  $\mu$ g/dl (normal cord serum, 10.9  $\mu$ g/dl  $\pm$  1.6) and the T<sub>3</sub> by radioimmunoassay was 230 ng/dl (normal, 48 ng/dl  $\pm$  1.6).

When the patient became pregnant for the second time,

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there was clinical concern for the possible development of intrauterine growth retardation or premature synostosis in the second infant. Although the mother's serum was LATS negative, it was reasoned that she had circulating thyroid-stimulating immunoglobulins capable of crossing the placenta and causing neonatal thyrotoxicosis. Unfortunately, the results of the thyroid-stimulating immunoglobulin assay were not available at the time a clinical decision regarding treatment had to be made. A high thyroid-stimulating immunoglobulin titer was thought likely. On this basis, the patient was treated with 150 mg/day propylthiouracil in addition to the 100 µg L-T<sub>3</sub> that she was taking. This strictly arbitrary dosage was based on the average dose used in the authors' experience with hyperthyroid individuals. A smaller dosage of propylthiouracil might have been equally effective. Because propylthiouracil readily crossed the placenta, it was reasoned that the drug might actually treat and limit the complications of intrauterine thyrotoxicosis.

At 36 weeks' gestation amniocentesis revealed a lecithin: sphingomyelin (L:S) ratio greater than 2:1. An elective repeat cesarean section was performed, delivering a live-born male with an Apgar score of 8 and 8 at 1 and 5 minutes, respectively; weight, 2530 g; head circumference, 33.5 cm; and total length, 45 cm. There was no evidence of a thyroid goiter. The infant was not given propylthiouracil following delivery.

At 4 days of life the infant developed tachycardia and a goiter was noted. Two days later, increasing tachycardia, irritability, and elevated T<sub>4</sub> and T<sub>3</sub> as ascertained by radioimmunoassay (Table 1) prompted treatment with methimazole and Lugol iodine solution. A response was noted in 3 days, with a decrease in heart rate, T<sub>4</sub> levels, and in the size of the goiter. Therapy with Lugol iodine solution was discontinued at that time. The methimazole dosage was reduced to maintenance levels 11 days after initiation of treatment. The infant was discharged home and was euthyroid on a maintenance dose of 0.6 mg methimazole twice a day.

Thyroid-stimulating immunoglobulin sera from the first pregnancy were frozen and assayed after the second delivery (Table 2). They demonstrated extremely high levels in the first infant. The maternal levels of thyroid-stimulating immunoglobulins during the second pregnancy, as well as cord blood and neonatal serum levels for the second infant, were significantly elevated.

**Table 1.** Serum Thyroid Hormone Levels in the Second Infant

Infant age	T <sub>4</sub> * (µg/dl)	T <sub>3</sub> † (ng/dl)
At birth (cord)	24.3	151
At birth (infant)	24.2	167
Day 6	>32	630
Day 8	21.8	350
Day 9	13.8	243
Day 12	8.3	
Day 16	10.3	

T<sub>4</sub> = thyroxine; T<sub>3</sub> = triiodothyronine.

\* Normal = 6.2 to 19 µg/dl.

† Normal = 99 to 195 ng/dl.

**Table 2.** Thyroid-Stimulating Antibody in Both Infants and Mother<sup>12</sup>

Patient	Percent increase/mg IgG*
First infant	725/5.5
Mother (second pregnancy)	2429/15
Mother (post partum)	2011/15
Second infant (cord)	561/15
Second infant (at 1 mo)	171/15

\* Percent increase in adenosine 3'5'-cyclic phosphate (cyclic AMP) generated from human thyroid slices as compared with controls. Levels greater than 500% considered as a high titer.

## Discussion

Serup<sup>9</sup> reported a previous case in which the mother was treated with antithyroid drugs to manage fetal hyperthyroidism. In that case, the mother was euthyroid but had a positive LATS titer. The fetal thyrotoxicosis was not documented by laboratory studies, and the diagnosis was based on the presence of intrauterine tachycardia. Weighing against this clinical diagnosis was the fact that neonatal thyrotoxicosis did not develop. Furthermore, it is not clear that the treatment given in Serup's case had any effect on neonatal outcome. In the 2 present cases, neonatal thyrotoxicosis was documented by T<sub>4</sub> and T<sub>3</sub> uptake measurements and there is a strong suggestion that untreated intrauterine thyrotoxicosis resulted in significant intrauterine growth retardation in the first infant. In contrast, maternal antithyroid medication may have prevented this complication from occurring in the second infant. Although thyrotoxicosis did occur several days after birth in the second infant, it was easily treated without adverse sequelae.

The usual clinical circumstances under which neonatal thyrotoxicosis is found include a pregnancy in which the mother has classic Graves hyperthyroidism with or without ophthalmopathy. Unless there is existing thyroid disease, a thyroid-stimulating immunoglobulin level capable of causing neonatal thyrotoxicosis should also cause hyperthyroidism in the mother. In the present case, the mother had high thyroid-stimulating immunoglobulin levels that caused neonatal thyrotoxicosis in her 2 infants. However, she did not develop thyrotoxicosis herself because her thyroid was previously affected by Hashimoto disease.

The physician often is faced with deciding the appropriate management of Graves disease in a woman contemplating pregnancy. Some physicians are concerned about using antithyroid drugs in pregnancy for fear of fetal goiter, rare teratogenic effects, or potential but not proved deleterious effects on fetal neurologic development by fetal hypothyroidism.<sup>10,11</sup> A decision may be made for a thyroid ablative procedure,

eg, radioactive I<sup>131</sup> treatment or subtotal thyroidectomy, even though medical therapy may have been the physician's and patient's first choice if pregnancy was not contemplated. This case suggests a possible harmful effect on intrauterine fetal growth and thyroid function by not using antithyroid drugs during pregnancy. These drugs may serve to limit fetal growth retardation, premature synostosis, and severe neonatal thyrotoxicosis in mothers with high thyroid-stimulating immunoglobulin titers because the antithyroid drugs suppress the development of intrauterine thyrotoxicosis.

Thus it seems reasonable to measure LATS in any individual with Graves disease who is euthyroid or hypothyroid and would thus not normally be treated with antithyroid drugs. If the LATS titer is positive, consideration of treatment with an antithyroid drug should be given. Until the more difficult thyroid-stimulating immunoglobulin titers (which have fewer false-negative results than LATS assays) become commercially available, it may be reasonable to monitor the fetal heart rate if LATS titers are negative in an individual with euthyroid or hypothyroid Graves ophthalmopathy. If the fetal heart rate increases, consideration for treatment with antithyroid drugs should be given.

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