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Fetal Goitrous Hyperthyroidism in a Pregnant Woman with Triiodothyronine-Predominant Graves' Disease

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Triiodothyronine (T3)-predominant Graves' disease is characterized by increased serum free T3 (FT3) levels after free thyroxine (FT4) levels become normal or even low during antithyroid drug treatment. We encountered a 34-year-old pregnant woman, gravida 5 para 4, who was complicated by T3-predominant Graves' disease. She was diagnosed with Graves' disease at 20 years old, and had received methimazole. Methimazole was changed to potassium iodide to reduce the risk of congenital anomalies during the first trimester. The dose of antithyroid drugs was adjusted based on maternal FT4 levels, so that maternal Graves' disease deteriorated and fetal goitrous hyperthyroidism appeared during the second trimester. Since the fetus presented goiter and tachycardia at 27-28 gestational weeks, doses of methimazole and potassium iodide were increased. A male newborn weighing 2604 g was delivered by a cesarean section at 35 gestational weeks. The newborn was diagnosed with neonatal hyperthyroidism, and received methimazole for six months. He developed normally with normal thyroid function at 1 year old. In pregnancies complicated by T3-predominant Graves' disease, the kinds and doses of antithyroid drugs have to be carefully selected to maintain maternal levels of FT4 as well as FT3 within the normal range, considering trimesters of pregnancy, teratogenicity of medication, and maternal levels of thyroid-stimulating hormone receptor antibody.

INTRODUCTION

The prevalence of hyperthyroidism in pregnancy ranges from 0.1% to 0.4%, with Graves' disease accounting for 85% of these cases [6]. Pregnant women with Graves' disease have a high risk of pregnancy loss, preterm birth, fetal growth restriction, hypertensive disorders of pregnancy, and maternal heart failure [3, 10, 12]. As uncontrolled thyrotoxicosis during pregnancy significantly increases the risk of neonatal thyroid dysfunction [14], the disease activity has to be controlled prior to and throughout pregnancy.

In Graves' disease, high levels of serum free thyroxine (FT4) and free triiodothyronine (FT3) usually fall to their respective normal ranges with antithyroid therapy. However, it has been noted that in ~12% of patients with Graves' disease, serum levels of FT3 remain raised while FT4 levels become normal or even low during therapy. This condition has been named triiodothyronine (T3)-predominant Graves' disease [13]. The monodeiodination of FT4 to FT3 activates the major secretory product of the iodine-sufficient human thyroid gland, and type 1 (D1) and type 2 iodothyronine deiodinase (D2) catalyze this reaction. In T3-predominant Graves' disease, D1 and especially D2 activities in the thyroid tissues increases, and the FT4 to FT3 conversion catalyzed by these deiodinases is responsible for the higher serum FT3-to-FT4 ratio [9]. The clinical features of T3-predominant Graves' disease are as follows: being young, having a large goiter, a high serum level of FT3 compared with FT4, a high level of thyroid-stimulating hormone receptor antibody (TRAb), and refractory to antithyroid drug treatment [9].

The main antithyroid drugs used in pregnancy are methimazole (MMI) and propylthiouracil (PTU). Since there have been reports of severe PTU-related liver failure, MMI is the first-line drug in non-pregnancy due to its higher adherence rates and lesser toxicity [4]. However, exposure to MMI during the first trimester of pregnancy increases the risk of congenital anomalies, including aplasia cutis congenita, omphalocele and symptomatic omphalomesenteric duct anomaly [15]. Recently, there have been reports that exposure to PTU in early pregnancy is also associated with an increased prevalence of congenital anomalies, including anomalies of the face, neck, and urinary tract [1, 2]. However, these defects tended to be less severe than with MMI. Therefore, PTU is recommended as the first-line drug for the treatment of hyperthyroidism during the first trimester.

Switching from MMI to potassium iodide (KI) in order to control hyperthyroidism in women with Grave's disease during the first trimester may reduce the risk of congenital anomalies, at least in iodine-sufficient regions

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such as Japan [16]. Japan Thyroid Association recommends that MMI should be avoided during the first trimester, especially during 5-9 GW, and MMI is the first-line drug after the first trimester. Graves' disease during pregnancy should be treated with the lowest dose of antithyroid drugs to keep the maternal serum FT4 levels at or slightly above the upper limit of the reference range for non-pregnant women.

Here, we report a case of fetal goitrous hyperthyroidism in pregnancy complicated by T3-predominant Graves' disease.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

CLINICAL CASE

Patient: A 34-year-old woman

Family history: None

Medical history: She was diagnosed with myasthenia gravis at 32 years old, but she was in remission and had received no treatment during pregnancy.

Obstetric history: Gravida 5 para 4. She delivered the first baby vaginally at 40 gestational weeks (GW) at 25 years old. She delivered her second baby vaginally at 39 GW at 27 years old. She delivered her third baby vaginally at 40 GW at 29 years old. The baby developed neonatal hyperthyroidism. She delivered her fourth baby by a cesarean section indicated to premature rupture of the membranes at 25 GW at 30 years old.

History of present illness: She was diagnosed with Graves' disease when she was 20 years old and started to take MMI. She had neither received radioiodine therapy nor underwent thyroidectomy. Her thyroid function (thyroid-stimulating hormone [TSH] 0.003 μIU/ml, FT4 1.34 ng/dl) was controlled using MMI (25 mg/day) and levothyroxine sodium hydrate (LT4, 50μg/day) before conception. After she became pregnant, a physician changed her prescription from MMI and LT4 to KI (100 mg/day) at 4 GW. She was referred to our department in the Kobe University Hospital at 5 GW.

Physical examinations and laboratory findings at 5 GW: A BMI of 19.1 kg/m^2, a heart rate of 105 beats per minute (bpm), and a blood pressure of 121/71 mmHg. She had tachycardia and goiter, but not thymoma. The estimated volume of thyroid grand was 132g (normal: 15-20g). Complete blood counts, coagulation/fibrinolytic system, and serum chemistry were normal. Blood tests showed the following: TSH 0.003 μIU/ml (normal: 0.30-5.00), FT3 4.40 pg/ml (normal: 1.70-3.70), FT4 0.82 ng/dl (normal: 0.70-1.60), anti-thyroglobulin antibody (aTg) 473 IU/ml (normal: <28), anti-thyroid peroxidase antibody (aTPO) 375.10 IU/ml (normal: <16), TSH receptor antibody (TRAb) ≥400 IU/L (normal: <2.0), and anti-acetylcholine receptor antibody (AChR) 1.9 nmol/l (normal: 0-0.2).

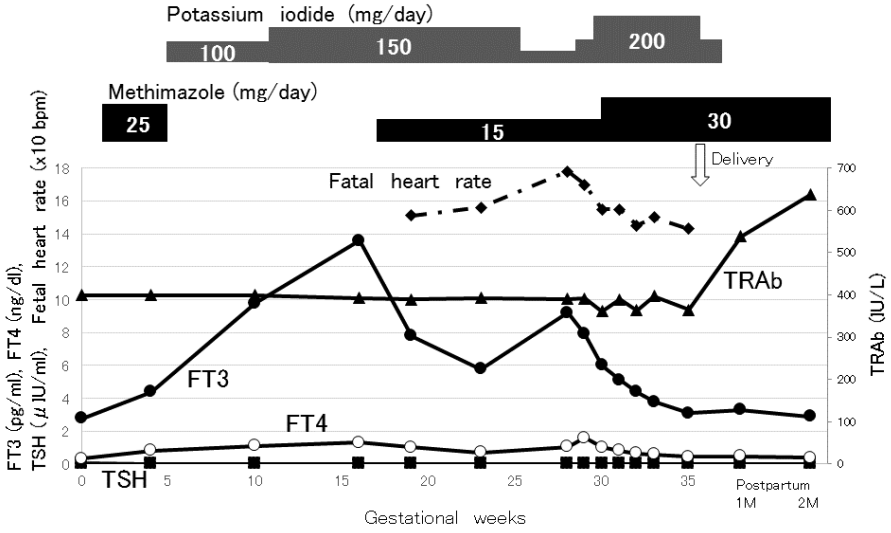

Figure 1. The course of the pregnancy. After switching from methimazole to potassium iodide at 4 gestational weeks (GW), maternal Graves' disease got worse. MMI was added at 16 GW. We controlled the doses of maternal medications based on fetal heart rate and maternal FT3 serum levels. The woman underwent a repeated cesarean section at 35 GW.

The course of the pregnancy: MMI (25 mg/day) was changed to KI (100 mg/day) at 4 GW, because MMI may cause a series of malformations when it is used during the first trimester of pregnancy. After that, serum FT3 level increased to 13.58 pg/ml at 16 GW (Figure 1). It was difficult to control her Graves' disease activity using KI (150 mg/day), so that MMI (15 mg/day) was added at 16 GW. These treatments decreased serum levels of FT3 and

FT4. At 22 GW, TSH was 0.003μIU/ml, FT3 5.78 pg/ml, and FT4 0.77 ng/dl. The dose of KI was reduced from 150 mg/day to 50 mg/day because serum levels of FT4 were low (0.70 ng/dl) at 24 GW, but this caused a paradoxical increase in FT3 levels (9.2 pg/ml) at 28 GW. Throughout her pregnancy, levels of FT4 were almost within the normal range, although TSH was low and FT3 was high (Figure 1). The FT3/FT4 ratio was >5.5 and TRAb was extremely high (400 IU/L). She was diagnosed with T3-predominant Graves' disease. At 27 GW, the fetus developed tachycardia and cardiomegaly. Additionally, ultrasound examinations revealed an enlarged thyroid gland of the fetus at 28 GW. A fetal pericardial effusion was observed temporarily, and the fetal ejection fraction was maintained around 70%. The fetal development was appropriate for gestational age, and the amniotic fluid volume was within the normal range. The fetus was strongly suspected to have hyperthyroidism based on tachycardia, goiter, and high maternal levels of TRAb. Cordocentesis was not performed. The doses of oral maternal MMI and KI were increased to 30mg/day and 200mg/day respectively, as intrauterine therapies for fetal hyperthyroidism at 29 GW and were maintained according to fetal heart rate and maternal FT3 levels. Thereafter, the fetal heart rate was normalized and cardiomegaly was improved (Figure 2). The ultrasound examination found a homogeneous, symmetrical, hyperechogenic, and hyper-vascular mass in the anterior region of the fetal neck (Figure 3). Fetal magnetic resonance imaging (MRI) revealed a hyperintensity neck mass on the T1-weighted image at 30 GW (Figure 4). Since airway obstruction was not detected by ultrasonography and MRI, ex utero intrapartum treatment was not considered. The patient was hospitalized for the onset of labor at 35 GW and delivered a male newborn weighing 2604 g (+0.3 SD) by cesarean section, with Apgar scores of 9 (1') and 10 (5'). She was discharged on postoperative day 6 without complications. Eight months later, she underwent total thyroidectomy and parathyroid transplantation.

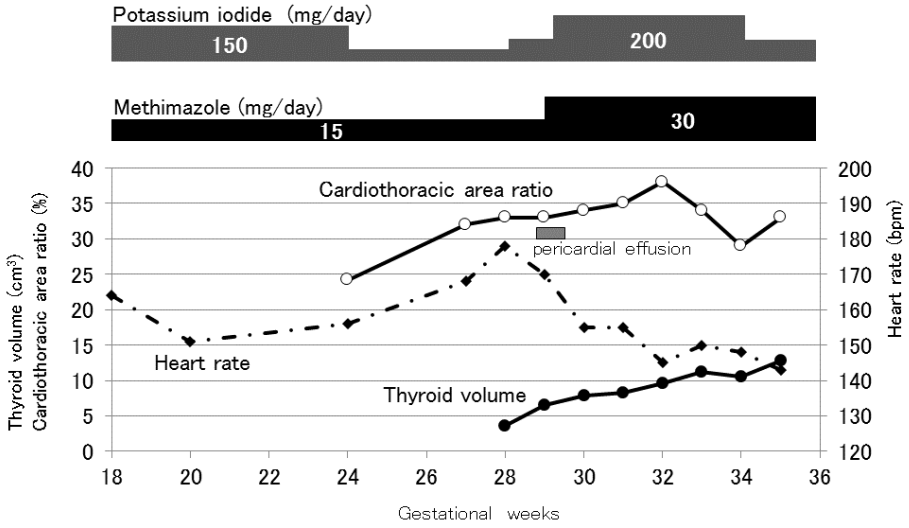

Figure 2. Changes in fetal sonographic measurements. The fetus developed tachycardia and cardiomegaly at 27 GW. Fetal goiter had been noted since 28 GW. The fetal pericardial effusion was observed temporarily. The transplacental treatment improved fetal tachycardia.

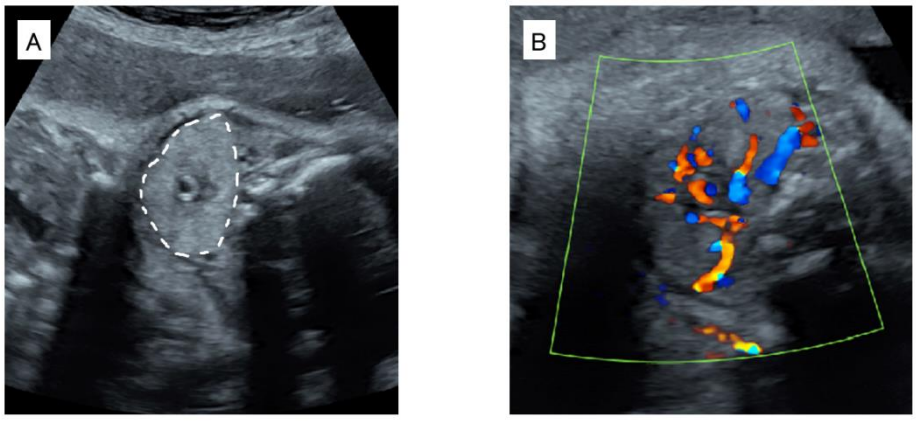

Figure 3. Sonographic features of the fetal goiter

(A) Transverse view of the fetal neck at 30 gestational weeks showing the enlarged thyroid gland. The estimated volume of the mass was 7.8cm^3. The trachea is shown in the middle of the mass.

(B) Color-flow Doppler imaging demonstrating the mass surrounded by abundant blood flow.

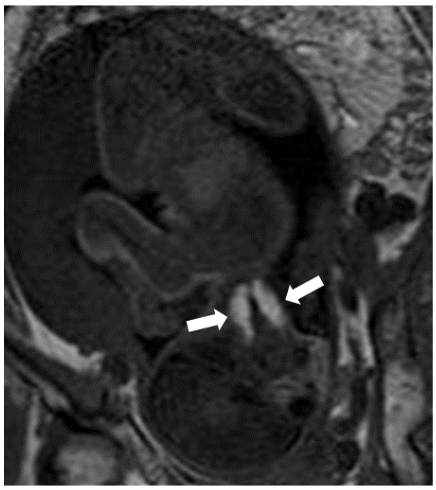

Figure 4. Fetal magnetic resonance imaging at 30 gestational weeks showing a hyperintensity neck mass on the T1-weighted image (arrow).

The clinical course of the newborn: At birth, he had an enlarged thyroid gland without any malformations or symptoms of hyperthyroidism. Blood levels of thyroid function on day 1 of life were as follows: TSH 0.011 μIU/ml, FT3 3.90 pg/ml, FT4 0.50 ng/dl, and TRAb 399.2 IU/L. Serum FT3 and FT4 levels increased to ≥30 pg/ml and 2.4 ng/dl respectively while the heart rate increased to 200 bpm on day 3. The newborn was diagnosed with neonatal hyperthyroidism, then MMI and propranolol were commenced (Figure 5). Serum FT3 and FT4 levels were 7.2 pg/ml and 0.22 ng/dl respectively on day 44. He was discharged with therapies of MMI (2 mg/day) on day 50. LT4 (20 μg/day) was used because serum FT4 level decreased to 0.60 ng/dl on day 100. MMI and LT4 therapies were stopped when TRAb became negative at 6 months old. He had normal thyroid function and psychomotor development at 1 year old.

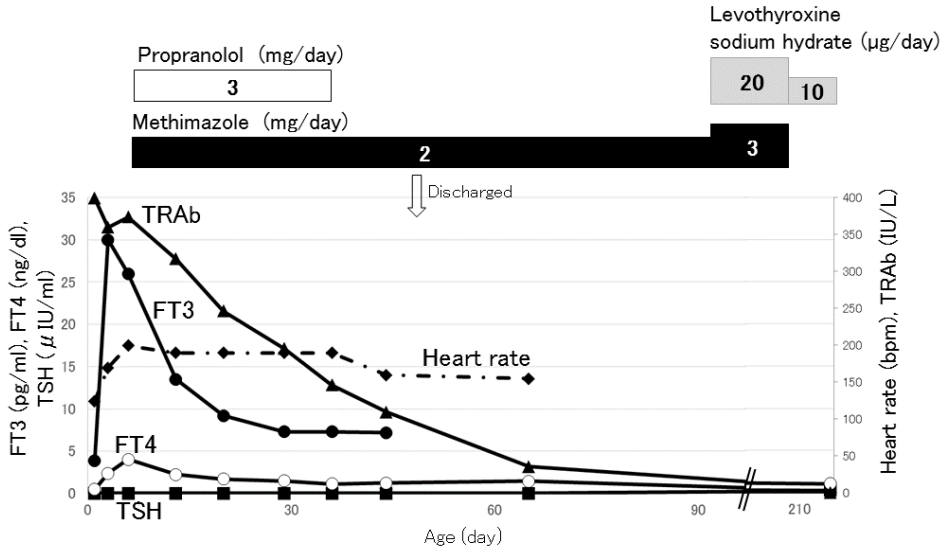

Figure 5. The clinical course of the newborn. Since the newborn developed hyperthyroidism, MMI and propranolol were initiated on day 3. He was discharged on day 50. LT4 replacement was initiated on day 100. We discontinued MMI and LT4 after we confirmed that TRAb was negative at 6 months old.

DISCUSSION

T3-predominant Graves' disease is characterized by high serum FT3 levels, even after FT4 becomes normal, or even low during antithyroid drug treatment. The condition is defined by a high FT3-to-FT4 ratio, high level of TRAb, large goiter, and refractory to antithyroid drug therapy.

In this report, both a mother and her newborn developed Graves' disease characterized by persistently high levels of serum T3 and normal or even lower levels of T4 during antithyroid drug therapy. MMI (25 mg/day) was changed to KI (100 mg/day) at 4 GW to reduce the risk of congenital anomalies that could be caused by the use of

MMI during the first trimester. The doses of MMI (0-15 mg/day) and KI (100-150 mg/day) were determined according to serum levels of FT4 during the first and second trimesters. It is likely that this inappropriate medication caused a deterioration of maternal T3-predominant Graves' disease and fetal goitrous hyperthyroidism with tachycardia. Since the doses of MMI and KI during the third trimester were increased to 30 mg/day and 200 mg/day respectively, fetal heart rate and maternal FT3 levels were successfully decreased to normal levels. Cordocentesis was not performed, since it is an invasive procedure that is risky for a fetus, and because fetal hyperthyroidism was diagnosed undoubtedly due to fetal tachycardia and high levels of maternal TRAb.

Maternal TRAb crosses the placenta, and can overstimulate the fetal thyroid gland causing hyperthyroidism [11]. Antithyroid drugs also can cross the placenta, and high doses of them can expose the fetus to hypothyroidism. Fetal goiter, an extremely rare complication of pregnancy, indicates fetal thyroid dysfunction. The incidence of goitrous hypothyroidism is approximately one per 40,000 live births [5], while the incidence of goitrous hyperthyroidism is still unknown. Fetal goiter causes perinatal and postnatal complications attributable either to the physical effects of the goiter itself or to the attendant thyroid dysfunction, which can be life-threatening.

Recently, two cases of fetal goiter in pregnancy complicated by T3-predominant Graves' disease have been reported [7, 8]. One fetus developed goitrous hypothyroidism after the dose of antithyroid drugs was increased to reduce maternal serum FT3 levels to fall within the normal range, but maternal levels of TRAb were not so high. It is likely that high doses of antithyroid drugs caused fetal goitrous hypothyroidism. Another fetus developed goitrous hyperthyroidism after the dose of antithyroid drugs was decreased to adjust the maternal levels of FT4 within the normal range, while the maternal levels of TRAb were extremely high. In Graves' disease, high levels of serum FT4 and FT3 usually fall to their respective normal ranges with antithyroid therapy. However, in T3-predominant Graves' disease, serum levels of FT3 remain raised while FT4 levels become normal or even low during therapy. There is a discrepancy between serum FT4 levels and FT3 levels in T3-predominant Graves' disease, and it makes perinatal management more difficult. In order to avoid causing fetal thyroid dysfunction in pregnancy complicated by T3-predominant Graves' disease, the kinds and doses of antithyroid drugs have to be carefully selected to bring the maternal levels of FT4 as well as FT3 to lie within the normal ranges, considering the trimesters of pregnancy, teratogenicity of medication, and maternal TRAb levels.

Moreover, patients with T3-predominant Graves' disease have larger thyroid glands and their sizes tend to increase rapidly, it is likely related to stimulation by higher TRAb, resulting in resistance to antithyroid drug treatment. Surgery should be considered to achieve remission prior to conception for patients with T3-predominant Graves' disease, especially with large goiters, high titers of serum TRAb levels, and resistance to antithyroid drug treatment.

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