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**Case Report**

# Maternal Graves Disease Postthyroidectomy With Fetal Thyrotoxicosis and Goiter

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## Abstract

Fetal thyrotoxicosis is a rare condition with high morbidity and mortality. It may complicate pregnancies in women with a history of Graves disease (GD) when transplacental passage of maternal TSH receptor antibodies stimulate the fetal thyroid gland and cause hyperthyroidism. We report the case of a 34-year-old woman with a history of GD and prior thyroidectomy, where fetal thyrotoxicosis at 21 weeks of gestation was suspected due to prenatal ultrasound findings of cardiac failure and fetal goiter. She was treated with high-dose carbimazole and followed closely by a multidisciplinary team. Her baby was delivered in good condition at 34 weeks' gestation and developed hyperthyroidism in the days after birth, which was successfully treated medically. This case highlights the importance of awareness of the condition among women with a history of GD, as well as the necessity for prompt diagnosis and treatment of this complex disease.

**Key Words:** Graves, hyperthyroidism, thyrotoxicosis, pregnancy, fetal

## Introduction

Autoimmune hyperthyroidism, or Graves disease (GD), is an uncommon condition that affects approximately .2% of pregnancies. It is caused by TSH receptor antibodies (TRAb), which stimulate the thyroid gland, and is characterized by high-circulating T4 and/or T3 levels with suppression of TSH [1, 2]. It is distinct from gestational transient thyrotoxicosis, which typically affects patients with hyperemesis gravidarum and high-circulating human chorionic gonadotropin levels and occurs in 1% to 5% of pregnancies. Though gestational transient thyrotoxicosis causes a similar pattern of thyroid function test abnormalities, they quickly normalize without treatment [2].

Fetal and neonatal thyrotoxicosis occurs in between 1% and 5% of patients with a history of active or prior GD. Transplacental passage of maternal TRAb stimulates the fetal thyroid to cause hyperthyroidism, typically in those with TRAb levels greater than 5 IU/L, or 3 times the upper limit of normal. The likelihood increases with higher concentrations of TRAb. It can cause serious morbidity and mortality in the fetus and/or neonate, and prompt identification and treatment of the condition is imperative [3, 4].

The fetal thyroid is sensitive to the effects of TRAb from approximately 20 weeks' gestation, though neonatal thyrotoxicosis has been identified as early as 18 weeks [3]. Clinical signs identifiable on ultrasound include fetal tachycardia, goiter, intrauterine growth restriction, accelerated bone maturation, and oligo/polyhydramnios, as well as cardiac failure, fetal hydrops, and fetal demise. While direct measurement of fetal thyroid hormone levels is possible with cordocentesis, it is not usually required to make the diagnosis and is generally avoided due to risks associated with the procedure—pregnancy loss in particular [2, 3].

Clinical guidelines recommend checking maternal TRAb in the first trimester and repeating at 18 to 22 weeks' gestation if elevated. Ultrasound surveillance is recommended in the second half of pregnancy to monitor for signs of fetal thyrotoxicosis in those with elevated TRAb levels [3].

Treatment of the condition involves administration of antithyroid drugs to the mother. Transplacental passage of the medication decreases fetal thyroid hormone levels. Clinical response to treatment is monitored by measuring fetal heart rate (HR) and goiter size, with targets aimed at normalising fetal HR (110-160bpm). The lowest effective dose of medication to normalize fetal HR is used [1].

In patients treated for GD with total thyroidectomy, it is expected that serum TRAb levels will fall over time [5]. Clinical guidelines suggest surgery has potential as a more favorable definitive treatment in those with high levels of TRAb and seeking future pregnancy, due to the persistence of higher antibody titres in those who receive radioactive iodine therapy [3]. However, antibody titres may remain detectable at high levels for several years after thyroidectomy [5], and this warrants consideration. Preconceptual counseling is important for all women with a history of GD, including those with previous

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thyroidectomy, as while they may be considered to have received definitive treatment for their hyperthyroidism, the fetus may still be at risk of morbidity due to the presence of TRAb. Our case highlights the significant morbidity the disease can cause in a patient whose GD was previously treated surgically.

## Case Presentation

A 34-year-old female was referred from a regional hospital at $21^{+2}$ weeks' gestation due to findings of a fetal tachycardia (180-190bpm) and enlarged right-sided heart noted on routine prenatal ultrasound. The patient had TRAb-positive GD diagnosed 2 years previously, with moderate thyroid ophthalmopathy. Total thyroidectomy was performed 10 months prior to presentation to our center, due to uncontrolled thyrotoxicosis and the patient's wish for pregnancy. She subsequently had hypothyroidism for which she was on thyroid hormone replacement of L-thyroxine 100 micrograms daily. Laboratory studies revealed inadequate thyroid hormone replacement in early pregnancy with a TSH of 13.2 μIU/mL (.27-4.2) and free T4 13.4 pmol/L (1.04 ng/dL) (reference range 11-21.0 pmol/L, .85-1.63 ng/dL) and her L-thyroxine dose was increased to 150 micrograms daily. In her obstetric history, she had an emergency cesarean delivery due to placental abruption at 31 weeks' gestation 5 years previously and a midtrimester fetal loss at 17 weeks' gestation 1 year prior in the setting of uncontrolled thyrotoxicosis, with placental histology showing chronic inflammation. TRAb was measured at 12.3 IU/L (.0-.9) in this pregnancy.

## Diagnostic Assessment

Upon presentation to our center, a fetal tachycardia of 170-180 bpm was observed (Fig. 1). An ultrasound (US) scan showed fetal right ventricular hypertrophy and a small pericardial effusion (Fig. 2), as well a neck mass measuring $1.9 \times 2.7 \times 2.8$ cm, strongly suspicious for fetal goiter (Fig. 3). Fetal magnetic resonance imaging confirmed a $2.9 \times 1.7 \times 2.7$ cm neck mass with homogenous signal, compatible with fetal goiter. Maternal laboratory studies showed a TSH of 2.38 mIU/L (.27-4.2), free T4 16.0 pmol/L (1.24 ng/dL) (reference range 12-22 pmol/L, .93-1.71 ng/dL), thyroid peroxidase antibody negative <3.0 IU/mL and TRAb markedly elevated >30 IU/L (0-1.8). Following multidisciplinary discussion, a diagnosis of fetal thyrotoxicosis secondary to placental passage of stimulating maternal TRAb was made, with resultant fetal goiter and cardiac dysfunction.

## Treatment

The patient was commenced on high-dose carbimazole (20 mg twice daily) at $21^{+6}$ weeks of gestation as treatment for fetal thyrotoxicosis. Maternal thyroid function tests were closely monitored, and she remained euthyroid on L-thyroxine 200 micrograms daily. She received weekly follow-up, and US scanning showed interval improvement, with resolution of the pericardial effusion and fetal HR normalization.

Concern was expressed regarding the size of the fetal goiter and the risk for airway obstruction at delivery. Fetal echocardiogram at $31^{+1}$ weeks noted "septal bounce," a paradoxical motion of the interventricular septum during early diastole associated with pulmonary hypertension, and concerns for potential pulmonary hypertension after delivery were raised as a result. Following a multidisciplinary discussion to plan optimal timing for delivery, a healthy boy weighing 2.73 kg was delivered by planned cesarean section at 34 weeks' gestation. Despite his goiter (Fig. 4), he breathed spontaneously without difficulty and had normal HR at delivery, with Apgar scores of 9 and 9 at 1 and 5 minutes. His umbilical cord blood thyroid function test showed free T4 13.1 pmol/L (1.02 ng/dL) (reference range 11-32 pmol/L, .85-2.49 ng/dL), free T3 5.9 pmol/L (3.84 pg/mL) (reference range 2.6-4.9 pmol/L, 1.69-3.19 pg/mL), and TSH .03 mIU/L (5-40). Maternal carbimazole was

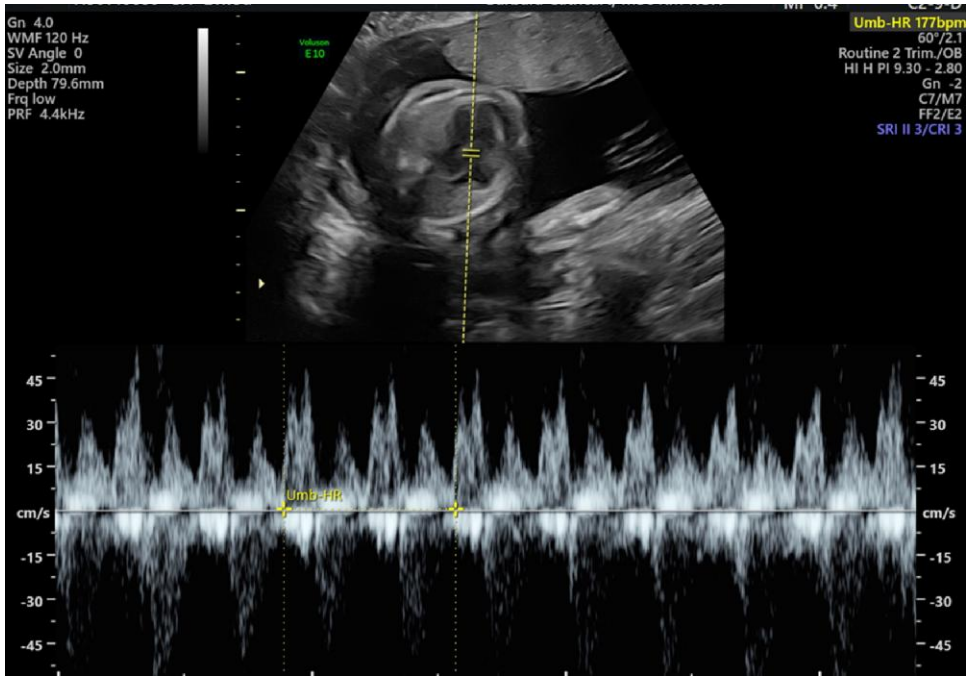


**Figure 1.** Doppler study showing fetal tachycardia 177 bpm.

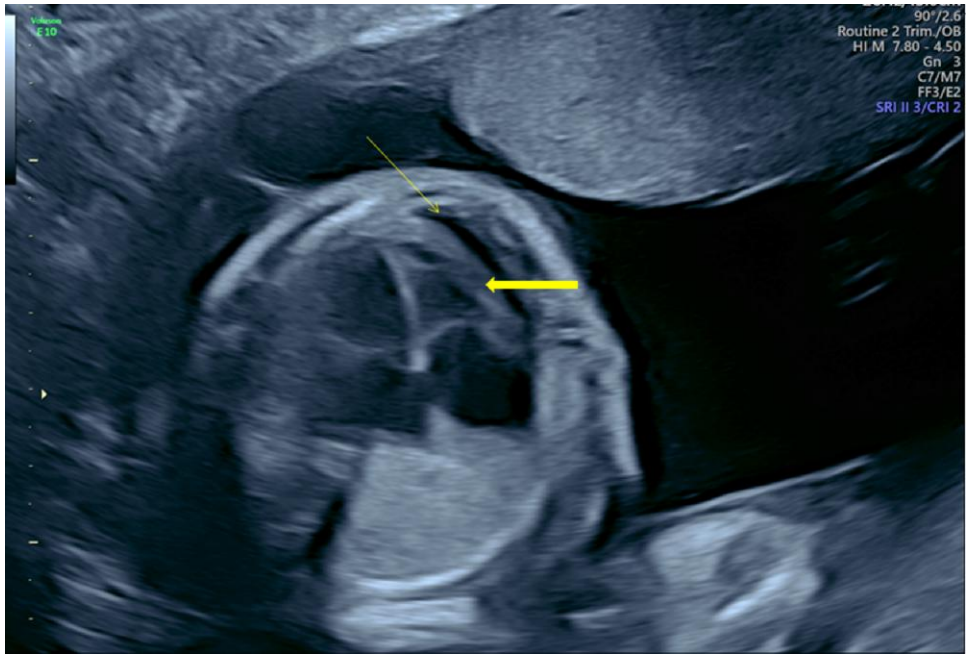


**Figure 2.** Fetal cardiac ultrasound showing pericardial effusion (thin arrow) and thickened right ventricular wall (thick arrow).

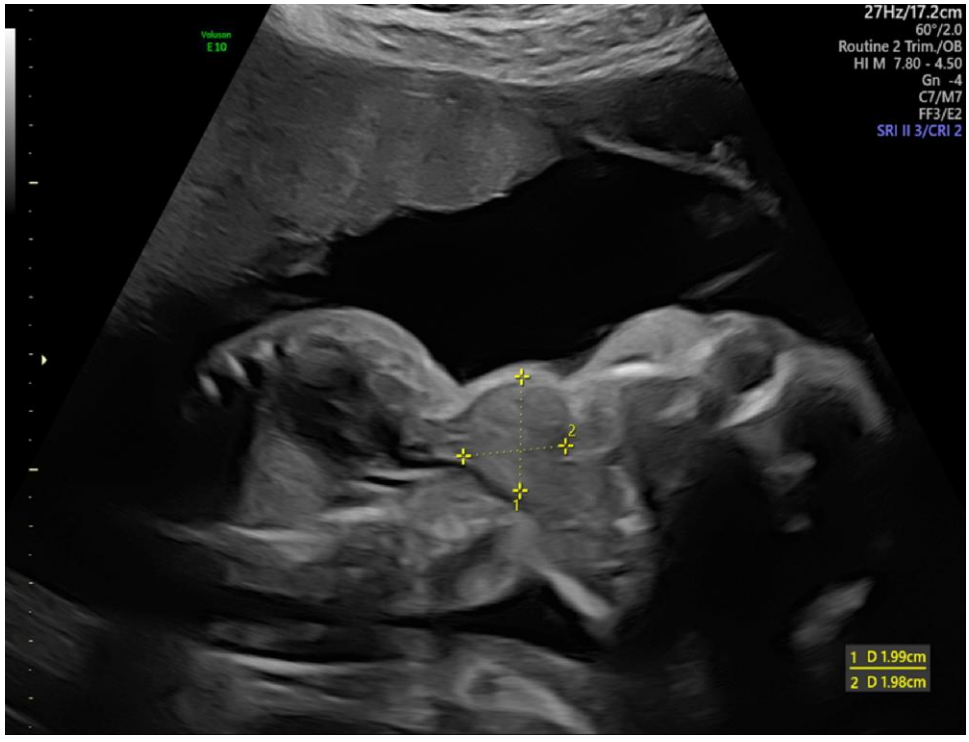


**Figure 3.** Ultrasound showing fetal neck mass with size indicated by yellow markings.

immediately discontinued postdelivery and the L-thyroxine dose reduced to 150 micrograms daily.

## Outcome and Follow-up

The mother had an uncomplicated course post cesarean section. The infant was closely monitored in the neonatal intensive care unit. On day 4 of life, he had desaturations and developed a supraventricular tachycardia. Thyrotoxicosis was confirmed on laboratory studies [free T4 > 100 pmol/L (>7.77 ng/dL)]. TRAb later returned at >100 IU/L. Initial treatment consisted of carbimazole .5 mg/kg/day in 2 divided doses, propranolol 2 mg/kg/day in 2 divided doses, and Lugol's iodine 1 drop (.05 mL) 3 times daily. Lugol's iodine was continued for 4 days. His thyroid hormone levels normalized within days. He had gradual clinical improvement and was discharged home well at 4 weeks of age on propranolol .3 mg/kg 4 times daily and carbimazole .5 mg twice daily.

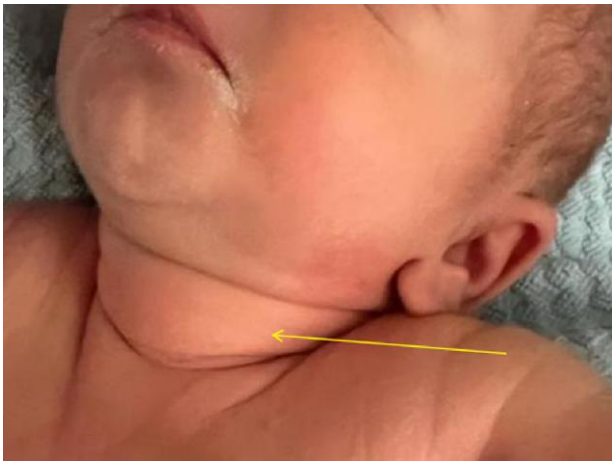

**Figure 4.** Image of neonatal goitre (arrow), taken postdelivery.

With close pediatric outpatient follow-up, all medications were weaned and stopped over 4 months.

## Discussion

The alarming US findings of tachycardia, pericardial effusion, and right ventricular hypertrophy suggested that this fetus was at risk of significant morbidity at the time of presentation. Without prompt recognition and treatment of the disease, the outcome may have been more unfavorable. Fetal thyrotoxicosis is extremely rare, and clear evidence-based guidelines for treatment of the condition are lacking. Previously, mortality rates for neonatal thyrotoxicosis were reported at 12% to 20% [6]. It is difficult to accurately estimate mortality for fetal thyrotoxicosis, though multiple publications report intrauterine fetal demise and neonatal death as a result of the condition [7, 8]. One case mentions a female who had 3 intrauterine deaths in the third trimester, with autopsy findings showing features of fetal thyrotoxicosis. The same patient received treatment with carbimazole in the fourth and fifth pregnancies, which both resulted in live births, though the fourth pregnancy resulted in a neonatal death and the fifth child survived [8]. In surviving cases, significant neonatal morbidity is often described, with cardiac failure and pulmonary hypertension common, which improved with treatment [9, 10].

The optimal timing for delivery of these cases is unclear. Fetal HR is used as a surrogate marker for fetal thyroid status, in place of direct laboratory sampling of fetal thyroid hormone with cordocentesis, which confers a nontrivial associated risk of fetal loss. However, this may not be an accurate reflection, as in 1 particular case, which proceeded with normal fetal HR throughout and reducing doses of methimazole, until a sudden onset of fetal arrhythmia occurred at 36 weeks' gestation, resulting in an emergency cesarean delivery of a profoundly acidotic infant with pronounced biochemical thyrotoxicosis [10]. Fetal complications are common during the late stages of pregnancy, and elective preterm cesarean section could be considered.

While guidelines suggest consideration of surgery as treatment for GD in those who are seeking future pregnancy, due to its associated reduction in TRAb, it is important to remember that the risk of fetal thyrotoxicosis is not eliminated in these patients. This case highlights the importance of preconceptual counseling and early TRAb measurement for patients with a history of GD and previous thyroidectomy or radioactive iodine treatment, in addition to those who are on antithyroid treatment. Those with TRAb levels >5 IU/L, or greater than 3 times the upper limit of normal, are at risk and should be monitored closely. Careful history-taking is important; not all those who are on thyroid hormone replacement may volunteer a history of GD. The risk of developing the condition is small, but it can have devastating consequences, so an awareness of this disease among specialists is important.

The management of this condition is challenging, complex, and often uncertain. What is clear, however, is that multidisciplinary collaboration including fetal medicine, endocrinology, neonatology, radiology, and cardiology specialists, alongside meticulous and regular clinical follow-up, are necessary for favorable outcomes.

## Learning Points

- Fetal thyrotoxicosis is an uncommon condition, though it is an important diagnosis to consider in patients with a personal history of thyrotoxicosis who present with fetal tachycardia and/or cardiac complications in utero.
- Preconceptual counseling is important for all prospective mothers with a history of hyperthyroidism.
- While thyroidectomy can be employed as definitive management for GD, this case reminds us that circulating TRAb levels may remain high for prolonged periods postoperatively, and this can have important and serious complications when patients are planning pregnancy.
- The management of this condition is complex and requires specialist input across multiple disciplines including fetal medicine, endocrinology, neonatology, radiology, and cardiology.

## Contributors

All authors made individual contributions to authorship. D.F. was involved in the clinical diagnosis and management of the patient and prepared the primary draft manuscript. J.W. was involved in the diagnosis and management of the patient and manuscript review. B.C. was involved in the clinical care and in preparation of images for submission. C.O.D. was involved in the clinical care and manuscript review. M.H. was involved in the diagnosis and management of the patient and is the senior supervising author of the manuscript.

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## Disclosures

None declared.

## Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

## Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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