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CASE REPORT

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Prenatal management of fetal goiter alternating between hypothyroidism and hyperthyroidism in a mother with Graves' disease

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Abstract

We present a rare documented case with consecutive hypo- and hyperthyroidism during fetal life. First, hypothyroidism was due to transplacental passage of antithyroid drugs. After the mother's thyroidectomy, fetal hyperthyroidism was due to transplacental passage of persistent anti-thyrotropin receptor antibodies. Fetal goiter disappeared after adjusting maternal treatment.

KEYWORDS

endocrinology and metabolic disorders, fetal goiter, maternal Grave's disease, obstetrics and gynecology, prenatal management

1 | INTRODUCTION

Graves' disease is the most common cause of hyperthyroidism[1] and occurs in 0.1%-0.4% of the pregnancies.[2] When it remains untreated, it can lead to materno-fetal complications such as preeclampsia, preterm birth, placental abruption, miscarriage, and intrauterine fetal death due to cardiac failure.[3] It is also the most common cause of fetal goiter. Because of risks of fetal hyperthyroidism due to transplacental passage of antithyrotropin receptor antibodies (TRAb) and fetal hypothyroidism due to transplacental passage of antithyroid drugs (ATD), patients with Graves' disease should be carefully monitored during pregnancy. We report here a case of management of a fetal goiter in which the mother had Graves' disease. We documented a switch between fetal hypothyroidism and hyperthyroidism necessitating appropriate therapy.

2 | CASE PRESENTATION

The patient was a 37 years old Asian woman, fifth gravida, with only past history of Graves' disease. Since the diagnosis after her third delivery, she underwent three recurrences. Because dysthyroidism was difficult to balance, a total thyroidectomy was scheduled but had to be delayed because of a new pregnancy.

Since the beginning of the pregnancy, the disease was imbalanced with very high level of stimulating TRAbs

(700 UI/L, NR: <1.6 UI/L), high level of f-T4 (26 pmol/L, NR: 10.0-22.5 pmol/L), and f-T3 (27.6 pmol/L, NR: 3.1-6.5 pmol/L) which necessitated the increase of propylthiouracil from 200 mg per to 300 mg a day since 16 weeks. The first-trimester ultrasound showed no abnormalities, but a fetal goiter appeared at 18 weeks: Fetal thyroid was > 99 percentile with hyperextension of the neck. According to European Thyroid Association Guidelines,[4] the treatment was replaced by carbimazol 40 mg and soon after 60 mg a day. At 22 weeks and 2 days, ultrasound showed the persistence of fetal goiter with peripheral hypervascularization (shown in Figure 1A). A cordocentesis was performed at 22 weeks and 5 days diagnosing moderate fetal hypothyroidism with free thyroxin dosage (f-T4) at 6.1 pmol/L (NR: 9.7-16.4 pmol/L) and a TSH dosage of 0.15 mU/L (NR: 4-13 mU/L). At that point lowering of carbimazol was considered but the mother clinical (bilateral exophthalmos, tachycardia and large vascular goiter) and biological state was so difficult to control that a total thyroidectomy was performed at 23 weeks and 3 days. The patient was then supplemented by levothyroxin 150 µg a day permitting the normalization of maternal thyroid function. Maternal TRAbs' levels decreased to 153 UI/l. The monitoring of the fetal thyroid gland did not show a frank regression of its size. The following ultrasound showed the persistence of fetal goiter and fetal hyperthyroidism symptoms: tachycardia, central hypervascularization (shown in Figure 1B) of the thyroid, and accelerated skeletal maturation. As the carbimazol had been withdrawn since the mother's thyroidectomy, fetal hyperthyroidism was the obvious diagnosis; after multidisciplinary discussion, we preferred to establish the diagnosis by a fetal blood sample which confirmed, at 29 weeks and 3 days, hyperthyroidism with f-T4 at 54.9 pmol/L (NR: 9.7-16.4 pmol/L) and TSH < 0.01 mU/L (NR: 4-13 mU/L), of note fetal TRAbs' assays was at 34 UI/L. Levothyroxin was decreased at 100 µg a day and carbimazole was reintroduced with a daily dosage of 60 mg, gradually decreased to 20 mg. Fetal thyroid diameter progressively decreased until 32 weeks and 3 days when ultrasound examinations showed a normal thyroid size and normal heart beat until the end of pregnancy. It is interesting to note that fetal heart rate was normal on all ultrasound examination. Figure 2 shows evolution of fetal thyroid diameter and circumference and evolution of maternal dosage medication.

Delivery was induced because of fetal heart rate abnormalities at 37 weeks of gestation and 4 days. The patient gave birth to a girl, weighing 2830 g, measuring 48 cm, arterial pH was 7.34, and Apgar score was 10/10. Thyroid hormones of the newborn showed hypothyroxinemia (TSH was 2.64 mI/L, NR: 0.3-7 mu/L, f-T4 was 8.0 pmol/L, NR: 14-35 pmol/L, and f-T3 was 1.4, NR: 3.1-6.5 pmol/L) at birth but she quickly developed hyperthyroidism at 6 days of life (TSH was 0.11 mI/L, NR: 0.3-7 mu/L, f-T4 was 44.2 pmol/L, NR: 14-35 pmol/L, and f-T3 was 13.6, NR: 3.1-6.5 pmol/L). At that point, TRAbs were positive at 14.7 UI/L (NR < 1.6 U/L). A treatment was introduced at 8 days of life. It was stopped at 9 weeks of life, and the last control we know at 11 weeks of life showed normal thyroid function and normal clinical evolution.

3 | DISCUSSION

Fetal goiter is a rare condition that results of either fetal hypothyroidism or hyperthyroidism. It can cause several complications[5] and has several etiologies: congenital dyshormonogenesis, deficiency or excess of iodine or transplacental passage of maternal TRAb or ATD.[6] Maternal Graves' disease accounts for more than 60% of fetal goiter.[7] The goiter itself can be responsible of tracheal and esophageal compression that leads to polyhydramnios, anasarca and, at the very last, cardiac insufficiency. In the most extreme cases, polyhydramnios leads to preterm birth and fetal cervical hyperextension causes dystocic labor and neonatal asphyxia. Fetal hyperthyroidism causes accelerated bone maturation, intrauterine growth restriction, cardiac insufficiency (leading to intrauterine fetal death), and craniostenosis. On the other hand, fetal hypothyroidism is often less severe and leads to delay of both bone maturation and potentially different degree of psychomotor development depending on maternal thyroidal status.[8]

Graves' disease is an autoimmune condition in which TRAb cross the placenta and bind to hormonal fetal receptors. A correlation between high level of TRAb and development of fetal hyperthyroidism symptoms has previously been demonstrated.[9] This is all the more likely in our case since TRAb were showed to be stimulating one (>1000%).

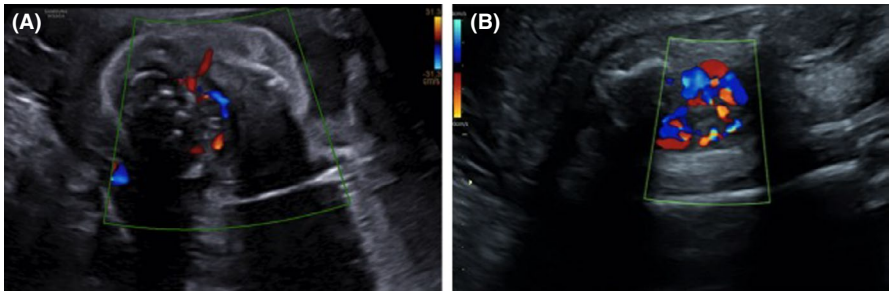

FIGURE 1 A, Thyroid peripheral hypervascularization in an axial ultrasound section at 22 weeks B, Thyroid central hypervascularization in an axial ultrasound section at 28 weeks and 6 days

Treatment is based on ATD (imidazole or thiouracil).[10] The strategy consisting in "combined" or "block-replace" treatment is not recommended during pregnancy because the proportion of thyroxine crossing the placenta is lower than the ATDs' leading therefore to a fetal hypothyroidism. Surgery is reserved for allergy to ATD or poor control of maternal hyperthyroidism. Thus, the balance between the risk of fetal hypothyroidism due to ATD placental passage and hyperthyroidism due to TRAb placental passage can be difficult to manage in Graves' disease.

The presence of fetal goiter on ultrasound requires a precise diagnosis before introduction of any treatment. Indeed, it can be associated with hypothyroidism, hyperthyroidism, or more rarely euthyroid state.[11] Experienced physician can assume fetal thyroid hormone status by describing the appearance of fetal goiter (thyroid diameter and circumference, vascularization) and bone maturation at ultrasound examination. However, direct measure of fetal cordonal blood sample remains the gold standard diagnostic method in difficult cases, as recommended by the American Thyroid Association.[5,12] In our case, the first diagnosis of the fetal goiter was hypothyroidism due to relatively high dose of ATD in the mother; this was necessary due to maternal clinical and hormonal status. However, low dosage of TSH at that point was surprising. We

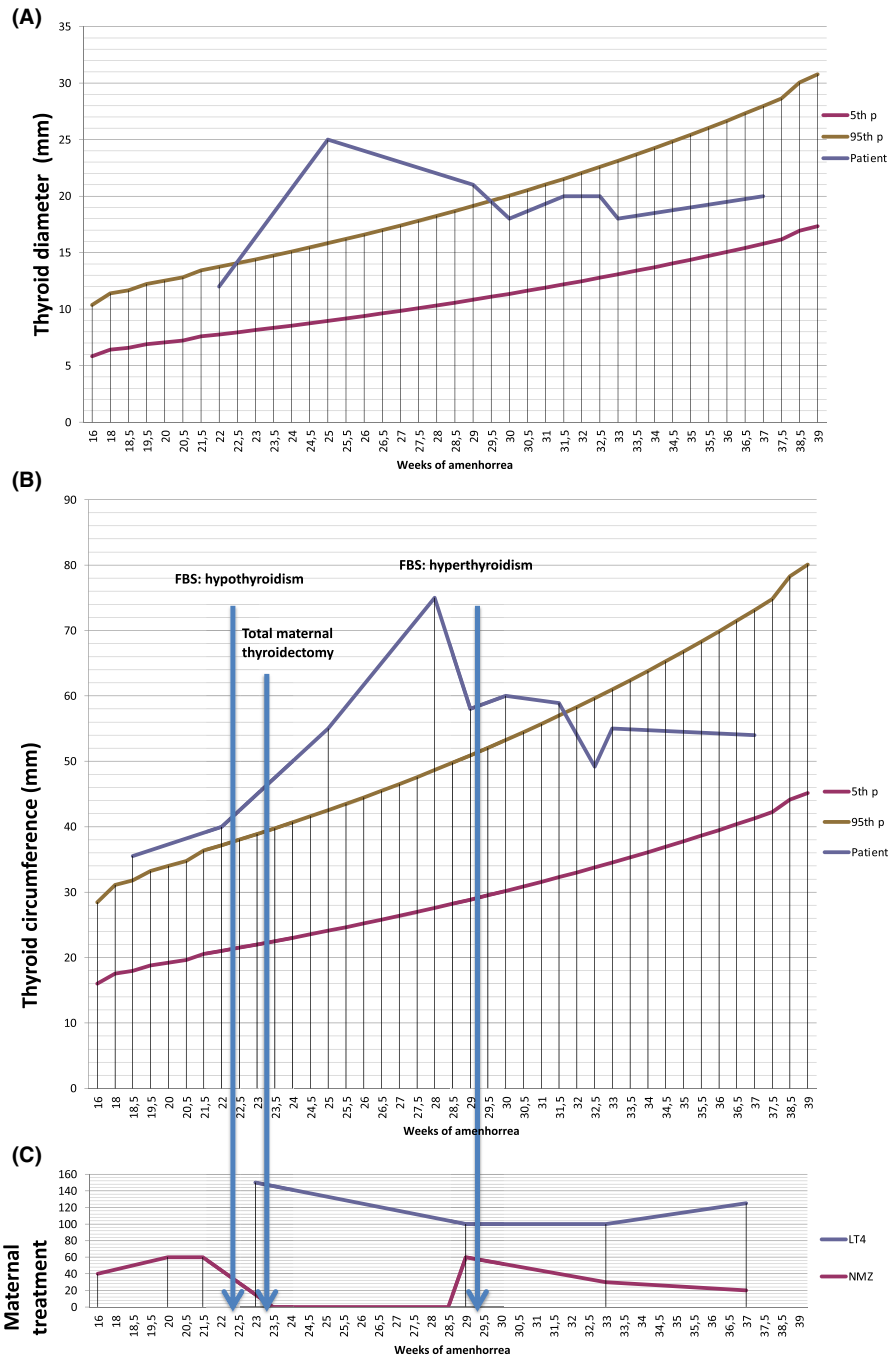

FIGURE 2 A, Evolution of fetal thyroid diameter. B, Evolution of fetal thyroid circumference. C, Medication dosage of carbimazol (NMZ) and levothyroxine (L-T4). FBS, fetal blood sample

supposed it was due to balancing between TRAb and ATD, resulting in changeover between fetal hypo and hyperthyroidism. Once the mother's disease was "cured" by thyroidectomy, a second problem arised in the fetus due to the only persistence of a significant TRAb level not counterbalanced by ATD; this led the fetus to switch from an hypo- to an hyperthyroid state. Challenge of our fetal medicine approach consisted in identifying this switch and choosing the good option, that is, reintroducing carbimazol with fine monitoring of the fetal thyroid gland. Previous study showed that one-third of thyroidectomized patients have residual TRAb levels,[2] even though other series suggested that the activity of these antibodies is lower due to loss antigen stimulation.[13,14] Nevertheless, our patient kept significant levels of TRAb. This case is emblematic of fetal medicine challenge dealing with a fetus that experienced consecutive hypo- and hyperthyroidism with appropriate medical intervention.

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Published with written consent of the patient.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

HD-M: wrote the original draft preparation; DL, HB, JY, M-VS: wrote, reviewed, and edited; DL: involved in supervision.

All authors have read and agreed to the published version of the manuscript.

ETHICAL APPROVAL

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

DATA AVAILABILITY STATEMENT

Anonymized data will be shared on request from any qualified investigator.

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