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Fetal hyperthyroidism associated with maternal thyroid autoantibodies: A case report

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ABSTRACT

A 33-year-old Caucasian woman was referred at 24 + 3 weeks of gestation due to fetal tachycardia and hydrops. She had an uncomplicated pregnancy 16 years previously and was on levothyroxine after total thyroidectomy for Graves' disease 6 years previously, when she developed moderate exophthalmos. Laboratory evaluation revealed appropriate thyroid function for this time of gestation: thyroid stimulating hormone (TSH) 1.7 μU/ml (1–3), fT4 18.53 pmol/l (12−22), with positive antibodies: anti-TPO 157 U/ml (<35), TSH receptor antibodies (TRAb) 171.95 U/l (<1.75). The diagnosis was fetal hyperthyroidism due to transplacental passage of stimulating maternal TRAb. Methimazole and digoxin were initiated. The patient remained euthyroid, with fT4 levels in the upper normal range. The fetus showed intrauterine growth retardation, oligohydramnios, aggravating hydrops, goiter with increased central vascularization and improved heart rate without signs of cardiac failure. At 30 + 3 weeks a hydropic hyperthyroid male newborn (birthweight 1560 g) was delivered by cesarean section and admitted to the neonatal intensive care unit. Cord serum showed neonatal hyperthyroidism. Methimazole and propranolol were administered to the newborn. On the 5th postnatal day the infant died because of severe infection inducing respiratory dysfunction, hemodynamic deterioration and cardiac asystole. Graves' disease occurs in about 0.2% of pregnancies. Hyperthyroidism occurs in 1–5% of neonates born to mothers with Graves' disease and the risk correlates with the maternal TRAb titer. Early diagnosis and treatment are crucial not only in pregnant women with active disease, but also in mothers with a history of Graves' disease, even after definitive treatment such as thyroidectomy or ablative therapy.

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1. Introduction

Maternal hyperthyroidism occurs in about 0.2% of pregnancies and in most cases the cause is Graves' disease. Graves' disease is an autoimmune disorder due to stimulation of TSH receptor antibodies (TRAb). Fetal hyperthyroidism occurs in 1–5% of pregnant mothers with Graves' disease, when maternal TRAb cross the placenta and stimulate the thyroid gland, leading to excessive thyroid hormone secretion. The risk correlates with the TRAb titer [1,2]. We describe a case of fetal hyperthyroidism in a pregnant woman who had previously had a thyroidectomy for her Graves' disease.

2. Case presentation

A 33-year-old Caucasian woman was referred at 24 + 3 weeks of gestation due to fetal tachycardia and hydrops. She had an uncomplicated pregnancy 16 years previously and was on levothyroxine after total thyroidectomy for Graves' disease 6 years previously, when she had developed moderate exophthalmos. Her medical history was otherwise uneventful.

On admission, a fetal ultrasound revealed fetal supraventricular tachycardia (SVT) (200 b.p.m), no structural heart abnormalities, facial skin edema (Fig. 1), mild pleural, pericardial and ascetic effusions (Fig. 2) and oligohydramnios. Laboratory evaluation revealed appropriate thyroid function for this time of gestation: TSH 1.7 μU/ml (normal range 1–3), free T4 18.53 pmol/l (12–22). However, tests were positive for auto-antibodies: anti-TPO 157 U/ml (<35), TSH receptor antibodies (TRAb) 171.95 U/l (<1.75).

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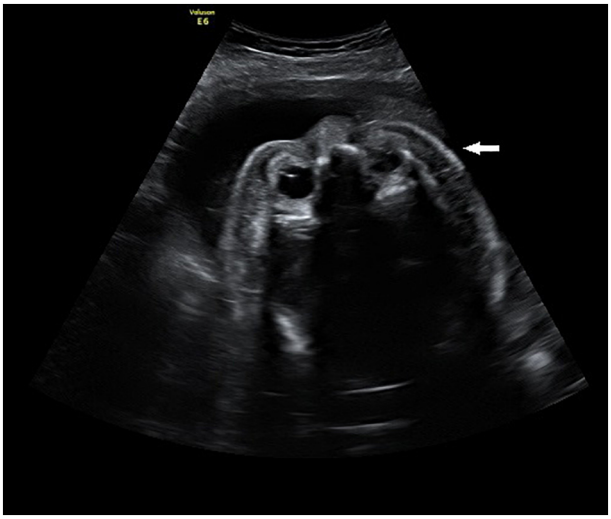

Fig. 1. Facial skin edema of the fetus. Arrow indicates fluid under the fetal skin.

The diagnosis was fetal hyperthyroidism due to transplacental passage of stimulating maternal TRAb. Methimazole (20 mg/day) and digoxin (0.25 mg × 2/day) were initiated. Fetal blood sampling (FBS) performed at 26 + 4 weeks (seven days after methimazole initiation) showed a normal level FT4 16.09 pmol/l (normal mean ± SD 16.5 ± 5.3), a mildly suppressed TSH level 0.594 μU/ml (6.8 ± 2.93) and a high TRAb level 121.9 U/l (<1.75) [3]. Based on these findings, methimazole was reduced to avoid iatrogenic fetal hypothyroidism and propranolol (20 mg twice daily) was added.

The mother remained euthyroid, with fT4 levels in the upper normal range. A fetal ultrasound scan at 29 weeks) showed intrauterine growth retardation, oligohydramnios, aggravating hydrops, goiter with increased central vascularization of the thyroid gland (Fig. 3) and improved heart rate (148 bpm with episodes of SVT), without signs of cardiac failure [4]. A second FBS, at 29 + 1 weeks, that is, after 27 days of treatment, showed frank hyperthyroidism with high fT4 35.13 pmol/l (normal mean ± SD 18.6 ± 5.5) and suppressed TSH 0.009 μU/ml (7.0 ± 3.73) [3]. Methimazole was increased to 25 mg/day. However, hydrops persisted, with excessive pleural and ascetic effusions, while maternal transaminase levels increased. At 30 + 3 weeks a hydropic hyperthyroid male newborn (birthweight 1560 g) was delivered by cesarean section and admitted to the neonatal intensive care unit. Cord serum showed - neonatal hyperthyroidism [fT4: 35.07 pmol/l (normal range 10.68–39.77), TSH: 0.007 μU/ml (0.8–5), TRAb: 98.5 U/l (<1.75)]. Methimazole and propranolol were administered to the newborn. On the 5th postnatal day the newborn died because of severe infection inducing respiratory dysfunction, hemodynamic deterioration and cardiac asystole.

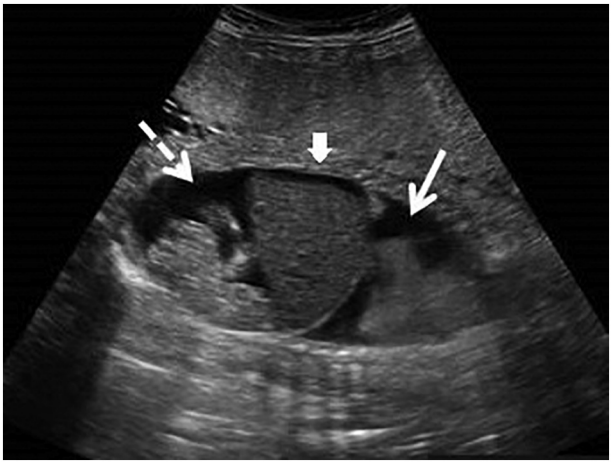

Fig. 2. Fetal ascites (dashed arrow) and pleural effusion (longer solid arrow). Short arrow indicates fetal liver.

3. Discussion

Fetal hyperthyroidism occurs when maternal TRAb cross the placenta. These antibodies stimulate the adenylate cyclase in fetal thyrocytes and lead to hyperthyroidism. It develops when fetal TSH receptors physiologically respond to these antibodies, mostly during the second half of gestation and particularly in women with high TRAb levels [1,5]. This case highlights that this clinical condition can present not only in pregnant women with active Graves' disease, but also in mothers previously treated, in whom circulating TRAb persist.

According to current guidelines, TRAb measurements should be performed at the start of pregnancy in all women with Graves' disease or a history of the condition, both in euthyroid ones and in those on long-term levothyroxine treatment after radio-iodine treatment or thyroidectomy [6]. TRAb determinations should be also performed at 20–24 weeks of gestation. If TRAb levels exceed two to three times the upper limit of the normal range, close monitoring is essential. Repeated ultrasound examination of the fetal thyroid gland is also important and should be performed by highly experienced ultrasound operators [1,4,6].

Treatment with anti-thyroid drugs (ATD) such as methimazole or carbimazole, which are able to cross the placenta, should aim to keep both maternal and fetal thyroid function at a normal level. If there is any indication of fetal hypothyroidism, the dose should be reduced [1]. A combination of fetal (heart rate, thyroid Doppler signal, bone maturation) as well as maternal criteria (TRAb titer, ATD dose) should be considered by a multidisciplinary team, including endocrinologists, obstetricians and pediatricians, to achieve a balance between fetal hypothyroidism and hyperthyroidism [1,3,4,6].

The offspring of mothers with negative TRAb test results during the second half of pregnancy and negative cord blood test results can be discharged with no further follow-up. However, hyperthyroidism may develop in neonates in the first days or weeks after delivery and is strongly associated with maternal TRAb levels at the end of pregnancy. Where TRAb are detected, thyroid function tests on cord blood should be repeated every two days, even if TSH levels are normal or high due to ATD treatment [3,6]. Neonatal hyperthyroidism is generally transient, but it is associated with a high risk of short-term and long-term mortality and of morbidity. Therefore ATD should be given to the infant shortly after birth where there is any suspicion of hyperthyroidism [1].

In conclusion, early diagnosis and treatment of fetal hyperthyroidism are crucial not only in pregnant women with active disease but also in mothers with a history of Graves' disease even after definitive treatment such as thyroidectomy or ablative therapy. Diagnosis and treatment need to be undertaken by a multidisciplinary team that includes endocrinologists, obstetricians and pediatricians.

Contributors

Paraskevi Kazakou wrote the article.
Christina Kanaka-Gantenbein revised the article.
Stavroula A. Paschou wrote the article.
Eleni Anastasiou revised the article.
All authors approved the final content of article.
All authors took care of the patients (mother or neonate).

Conflict of interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

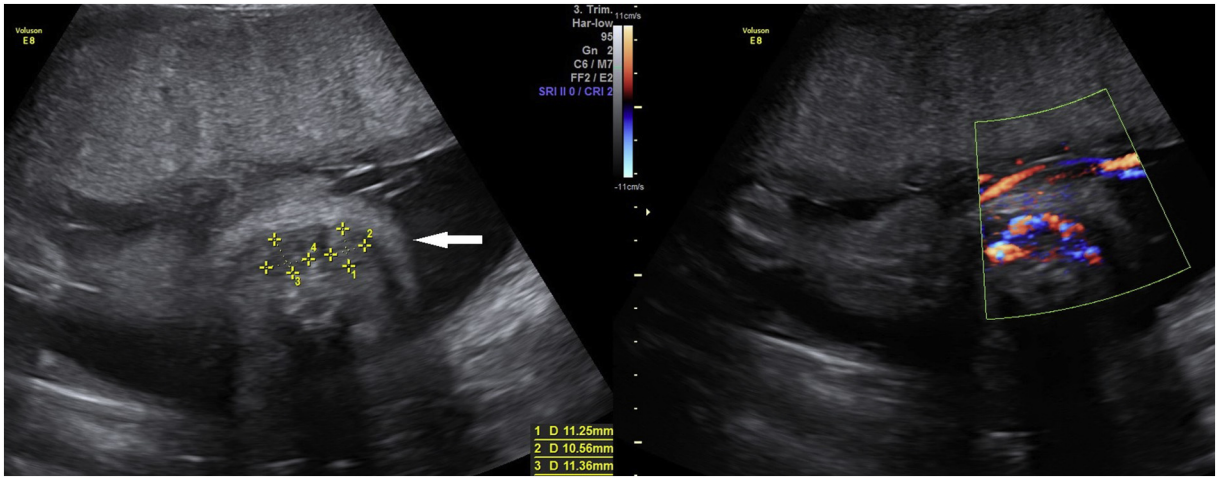

Fig. 3. Enlargement of the fetal thyroid gland (solid arrow) with increased central vascularization on the color Doppler.

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Patient consent

Obtained.

Provenance and peer review

This case report was peer reviewed.

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