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Fetal Thyrotoxicosis due to Maternal TSH Receptor Stimulating Antibodies Causes Infant Central Hypothyroidism

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Established Facts

- Women with a current diagnosis or past history of Graves' disease are at risk of developing fetal thyrotoxicosis during pregnancy because of placental passage of TSH receptor antibodies.
- The chance of reaching remission of TSH-receptor autoimmunity may be lower after I^{131} therapy than after medical or surgical therapy.
- Fetal thyrotoxicosis induced by high *maternal* thyroid hormone concentrations may result in (central) hypothyroidism.

Novel Insights

- Fetal thyrotoxicosis due to high *fetal* thyroid hormone concentrations stimulated by high maternal TSH receptor antibodies levels might also result in (central) hypothyroidism, requiring long-term evaluation of the hypothalamus-pituitary-thyroid axis in these children.

Keywords
Fetal thyrotoxicosis · Graves' disease · Maternal TSH receptor antibodies · Infant central hypothyroidism

Abstract
Introduction: Women with a current diagnosis or past history of Graves' disease (GD) are at risk of developing fetal thyrotoxicosis (FT) during pregnancy when they are inadequately

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treated, or because of placental passage of TSH receptor antibodies (TRAb). It is known that FT induced by high *maternal* thyroid hormone concentrations may result in infant (central) hypothyroidism. ***Case Presentation:*** In a euthyroid woman with a history of GD treated with radioactive iodide (I^{131}), persistently high levels of maternal TRAb resulted in recurrent FT during two separate pregnancies, followed by neonatal hyperthyroidism and infant central hypothyroidism. ***Discussion:*** This case demonstrates the novel insight that FT due to high *fetal* thyroid hormone concentrations stimulated by high maternal TRAb levels might also result in (central) hypothyroidism, requiring long-term evaluation of the hypothalamus-pituitary-thyroid axis in these children.

Introduction

Women with a current diagnosis or past history of Graves' disease (GD) are at risk for fetal thyrotoxicosis (FT) during pregnancy when they are inadequately treated, or because of placental passage of TSH receptor antibodies (TRAb) [1]. It is known that FT induced by high *maternal* thyroid hormone concentrations may result in infant (central) hypothyroidism [2, 3].

In this case report, we present a euthyroid woman with a history of GD treated with radioactive iodide (I^{131}). Remarkably, persistently high levels of TRAb resulted in recurrent FT in two separate pregnancies, followed by neonatal hyperthyroidism and infant central hypothyroidism, indicating that FT due to maternal TRAb stimulated high *fetal* thyroid hormone concentrations might also result in (central) hypothyroidism.

Case Report

A 31-year-old woman was diagnosed with GD (TSH <0.01 mIU/L, reference interval [RI] 0.5–4.0; FT4 26.7 pmol/L, RI 11–19.5; TRAb titer 8.5 IU/L, RI <1.8, Kryptor assay, Thermo Fisher, Hennigsdorf, Germany) in a general hospital in 2016. After treatment with I^{131}, she developed iatrogenic hypothyroidism for which levothyroxine (LT4) replacement therapy was started. Since then, she was euthyroid. In 2019, she became pregnant. LT4 dose was increased by 25% to 125 μg levothyroxine once daily, with biochemical euthyroidism throughout pregnancy. During the first trimester, there was no hyperemesis. At 15 weeks pregnancy, TRAb were measured for the first time and were found to be 39.6 IU/L (RI <1.8). Fetal heart rate (FHR) was 150 beats per minute (bpm) (RI for gestational age 120–160). The 20-week anomaly scan was unremarkable. At 24 weeks pregnancy, TRAb was 34.1 IU/L, TSH 0.5 mIU/L, and FT4 18 pmol; FHR was normal. At 27 weeks pregnancy, FHR had increased to 170 bpm; fetal ultrasound showed normal fetal movements with no signs of structural cardiac dysfunction, but a fetal goiter was seen with a circumference of 4.7 cm (>p90; 10th–90th percentile 3.0–4.6 cm [4]; shown in Fig. 1). FT was suspected and the woman was referred to the outpatient clinic of the Department of Endocrinology of the University Medical Center Groningen, The Netherlands. Methimazole 5 mg once daily was started. Within 1 week, FHR normalized (shown in Fig. 2) and ranged between 132 and 150 bpm throughout pregnancy. Follow-up ultrasound showed a slight decrease of the fetal goiter to values around p90 for gestational age (5.2 cm at 31 weeks, 5.3 cm at 33 weeks). Fetal growth was stable along the 60–70th percentile. Maternal thyroid function remained stable (TSH ranging from 0.23 to 0.60 mIU/L). The TRAb level in the third trimester was 27.9 IU/L.

After an uncomplicated, spontaneous vaginal delivery at 38 weeks and 3 days of pregnancy a girl was born with a birth weight of 2,910 g (p10-p50). Based on cord blood laboratory testing, neonatal hyperthyroidism was diagnosed (TSH <0.005 mIU/L, RI 0.7–15.2; FT4 30.9 pmol/L, RI 12–32; TRAb 31.8 IU/L, RI <1.8). According to good clinical practice at that time at the University Medical Center Groningen, methimazole treatment was started, combined with LT4 2 weeks later (i.e., block-replace regimen). At 8 days of age, TRAb levels had decreased to 15.9 IU/L and normalized to 0.48 IU/L at 10 weeks, i.e., maternal TRAb had disappeared from the child's circulation. Methimazole and LT4 were stopped at 11 weeks. Three days after stopping LT4, the girl's FT4 was low (FT4 8.4 pmol/L, RI 12–28.3) in combination with a low TSH (TSH 0.21 mIU/L, RI 0.7–8). Because of suspected central hypothyroidism, LT4 was restarted. At the age of 2.5 years another attempt to stop LT4 was made resulting in a FT4 of 11.1 pmol/L (RI 12.3–22.8) and a TSH of 2.68 mIU/L (RI 0 0.70–5.97) which was considered to indicate persistent central hypothyroidism. LT4 was then reinitiated.

The mother stopped methimazole treatment directly after the birth of her daughter and LT4 was continued in the prepregnancy dose, after which she remained clinically and biochemically euthyroid. One month later, her TRAb level, however, had increased to 33.8 IU/L. Ten months after giving birth, the woman reported being pregnant again. TRAb in the first trimester was 45.5 IU/L. At 25 weeks pregnancy, again FT was diagnosed based on FHR of 160–170 bpm and a goiter on ultrasound (circumference p90 for gestational age). The mother was started on methimazole 5 mg once daily again, after which FHR normalized (shown in Fig. 2), and the fetal thyroid remained just below p90. After 37 weeks pregnancy, a girl was born with a birth weight of 3,100 g after an uncomplicated spontaneous vaginal delivery. Like the first girl, this baby girl had neonatal hyperthyroidism. Subsequently, she developed a biochemical profile of low-normal thyroid function tests (Table 1); in light of the disease course of the eldest daughter, there were concerns that central hypothyroidism was evolving. It was decided to initiate treatment directly in order not to compromise her developing brain. Because of her young age, an attempt to stop LT4 has not been made so far. At the moment, she is stable on LT4 supplementation with check-ups every 3 months.

Discussion

FT is an infrequent condition which develops in 1–5% of pregnancies in women with past or current (treated) GD [1]. Recurrent FT is very rare [5–7].

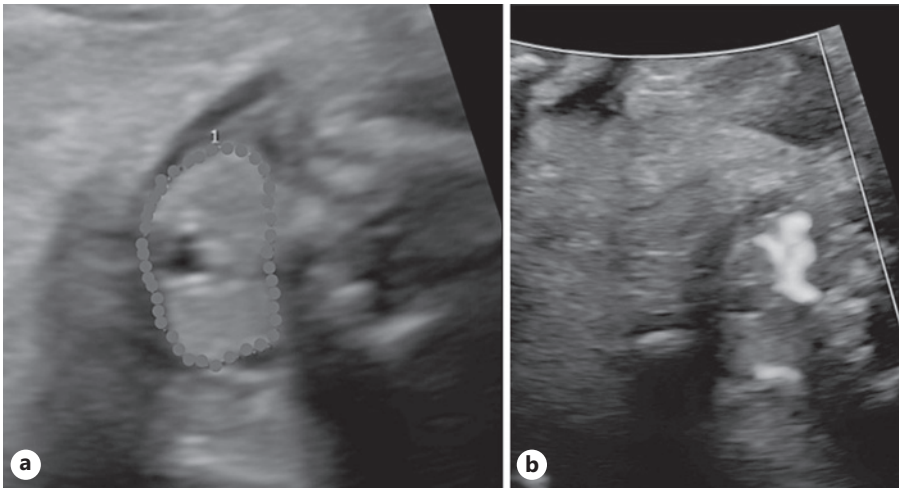

Fig. 1. Ultrasound of the thyroid gland of the fetus at 28 weeks, showing: (**a**) transverse view. The thyroid gland is within the ellipse. The carotid arteries are visible lateral to the thyroid gland. **b** Thyroid hypervascularization.

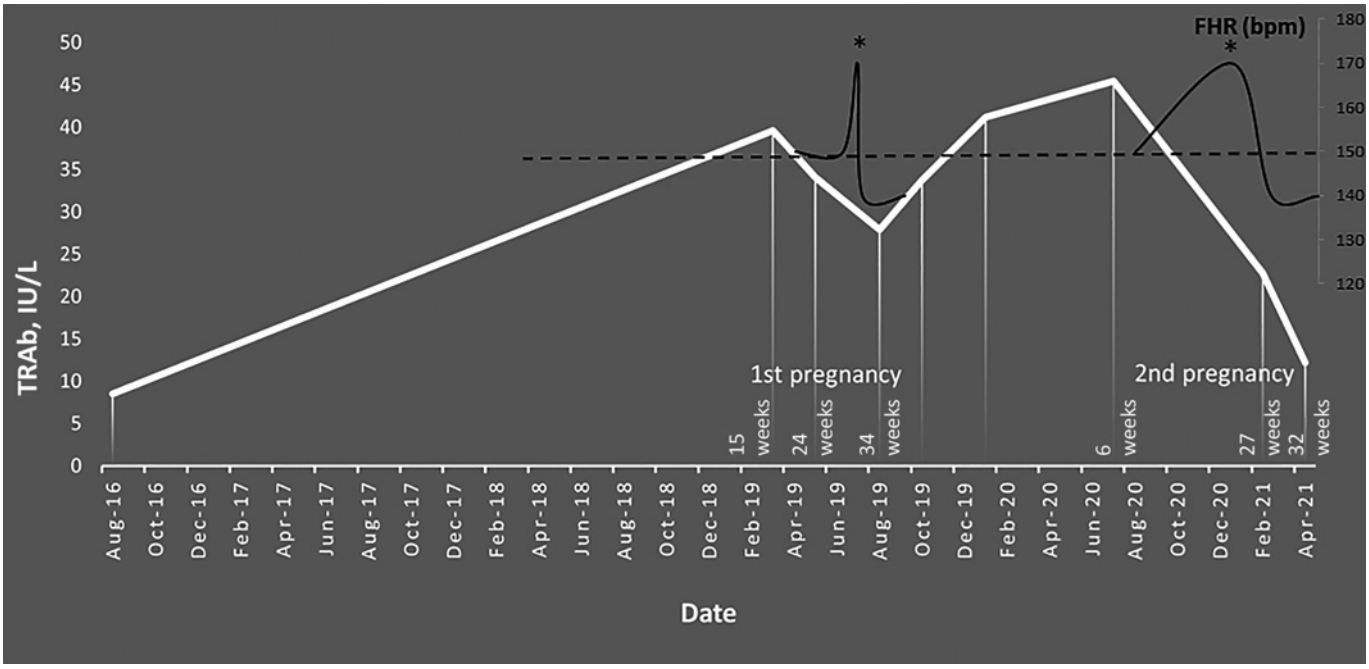

Fig. 2. Maternal TSH receptor antibodies (TRAb) and fetal heart rate (FHR) throughout both pregnancies. bpm, beats per minute. * indicates start methimazole.

FT is associated with fetal morbidity and a reported intrauterine fetal death rate of up to 20% of cases [1].

Three case reports in literature describe recurrent FT in two separate pregnancies (Table 1). Two women had a history of GD treated with subtotal thyroidectomy, of which one had subsequent I^{131} therapy, and one woman had been diagnosed with Hashimoto thyroiditis. All had very high maternal TRAb concentrations during pregnancy. Three of these six pregnancies resulted in stillbirth.

Our patient had been treated with I^{131} therapy as first-line therapy because of a pregnancy wish. To avoid fetal thyroid dysfunction and to abolish any unnecessary radiation dose to the fetus, it is usually recommended that women do not conceive within 6 months after I^{131} therapy (and only after a stable euthyroid state is reached) [8]. After I^{131} therapy for GD, however, there can be a transient increase in TRAb levels, lasting months up to 5 years [9]. Therefore, the chance of entering remission of TSH-receptor autoimmunity is considerably

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Table 1. Characteristics of reported cases of recurrent fetal thyrotoxicosis

	Maternal medical history	Pregnancy	Moment of FT diagnosis						FT treatment	Outcome
			gestation	presenting finding	other fetal findings	maternal TRAb	maternal biochemical thyroidal state	cordocentesis results		
Present case	I^{131} for GD 6 years before 1st pregnancy – on LT4 supplementation since	1st	27 weeks	Fetal tachycardia	Goiter	34.1 IU/L (RI <1.8)	TSH 0.09 mIU/L (RI during pregnancy 1.0–2.0), FT4 18 pmol/L (RI 11–19.5)	n.p.	Methimazole 5 mg daily	Live birth at 38 weeks. FT: TSH <0.005 mIU/L (RI 0.7–15.2 mU/L), FT4 30.9 pmol/L (RI 12–32 pmol/L), and TRAb 31.8 IU/L (RI <1.8 IU/L) (blood drawn from umbilical cord), followed by central hypothyroidism at 12 weeks of age TSH 0.21 mIU/L (RI 0.7–8) FT4 8.4 pmol/L (RI 12–28.3)
		2nd	25 weeks	Fetal tachycardia	Goiter	45.5 IU/L (RI <1.8)	TSH 0.76 mIU/L (RI during pregnancy 1.0–2.0), FT4 18.1 pmol/L (RI 11–19.5)	n.p.	Methimazole 5 mg daily	Live birth at 37 weeks. FT: TSH 0.029 mIU/L (RI 0.7–15.2 mU/L), FT4 20 pmol/L (RI 12–32 pmol/L), and TRAb 8.77 IU/L (RI <1.8 IU/L) (blood drawn from umbilical cord), followed by central hypothyroidism at 12 weeks of age TSH 2.37 mIU/L (RI 0.7–8) FT4 12.5 pmol/L (RI 12–28.3)
Matsumoto et al. [5]	Subtotal thyroidectomy and I^{131} for GD – on LT4 supplementation since, time between treatment and 1st pregnancy not mentioned	1st	23 weeks	Fetal tachycardia	Goiter, fetal growth restriction	381 IU/L (RI <2.0)	TSH 0.09 µU/mL (RI 0.2–3.0) FT4 1.7 ng/dL (RI 0.7–1.8) FT3 2.7 pg/mL (RI 2.0–4.5)	n.p.	Potassium iodide 50 mg and propylthiouracil 150 mg (increasing to 300 mg) daily	Live birth at 36 weeks. FT, followed by central hypothyroidism at 6 weeks of age TSH <0.01 µU/mL (RI 0.5–6.5) FT4 0.8 ng/dL (RI 0.9–2.2) FT3 3.8 pg/mL (RI 2.4–5.6) At 2 years of age, normalization of thyroidal state but failure to thrive (length and weight <5th percentile)
		2nd	21 weeks	Fetal tachycardia	Goiter, pericardial effusion, cardiomegaly, cardiac failure	223 IU/L (ref. <2.0)	TSH 0.10 µU/mL (RI 0.2–3.0) FT4 1.8 ng/dL (RI 0.7–1.8) FT3 3.6 pg/mL (RI 2.0–4.5)	n.p.	Potassium iodide 50 mg (increasing to 100 mg) and propylthiouracil 300 mg daily	Live birth at 35 weeks. Neonatal subclinical hyperthyroidism. Growth and gross motor development delayed
Rodó et al. [6]	Hashimoto thyroiditis 2 years before 1st pregnancy – on LT4 supplementation since	1st	27 weeks	Fetal tachycardia	Pericardial effusion, hydrothorax, cardiac insufficiency, suspected fetal anemia	n.p.	Euthyroid on LT4 suppletion	n.p.	Not started	Stillbirth at 27 weeks 2 days
		2nd	27 weeks	Fetal tachycardia	Bilateral ventriculomegaly, cardiomegaly, tricuspid	422.4 IU/L (RI <1.8) Anti	Hypothyroid 1st trimester,	TSH <0.008 mIU/L (RI 0.64–6.27)	Not started	Stillbirth at 27 weeks 2 days

Table 1 (continued)

	Maternal medical history	Pregnancy	Moment of FT diagnosis						FT treatment	Outcome
			gestation	presenting finding	other fetal findings	maternal TRAb	maternal biochemical thyroidal state	cordocentesis results		
Ting et al. [7]	Subtotal thyroidectomy for GD 6 years before 1st pregnancy – on LT4 supplementation since	1st	21 weeks	Fetal tachycardia	insufficiency, goiter, hepatomegaly, bilateral hydrothorax, bilateral hydrocele, enlarged hydropic placenta	TPO >6500 IU/mL (RI <60)	euthyroid after increasing LT4 dosage	FT4 4.03 ng/dL (RI 0.8–1.876) FT3 9.92 pg/mL (RI 2.3–4.2) TRAb n.p.		
		2nd	26 weeks	Fetal tachycardia	Cardiomegaly, goiter	n.p.	Not mentioned	n.p.	Not started	Stillbirth at 21 weeks 2 days
			26 weeks	Fetal tachycardia	Cardiomegaly, hepatosplenomegaly, placentomegaly	85.9% (ref. <15)	TSH <0.03 µlU/mL (RI 0.4–4.5) FT4 1.84 ng/dL (RI 0.6–1.83) T3 184 ng/dL (RI 62–168)	TSH <0.03 µlU/mL (RI 0.4–4.5) T4 18 µg/dL (RI 5.0–12.4) T3 65.3 ng/dL (RI 62–168) TRAb 77.6% (RI <15)	Propranolol 40 mg and methimazole 15 mg daily in divided doses	Live birth at 35 weeks, infant TRAb 41.2% 4 weeks and 1.4% 12 weeks after birth, biochemical thyroidal state or treatment not mentioned

FT, fetal thyrotoxicosis; TRAb, TSH receptor antibodies; I^{131}, radioactive iodide; GD, Graves' disease; RI, reference interval; LT4, levothyroxine; n.p., not performed.

lower after I^{131} therapy than after medical or surgical therapy [9, 10]. The American Thyroid Association (ATA) guidelines therefore argue in favor of surgical therapy to achieve a stable euthyroid state on thyroid hormone substitution therapy in women with high TRAb levels and a pregnancy wish [11], although evidence is still lacking.

Measurement of maternal TRAb could identify fetuses at risk for FT. TRAb are immunoglobulin G class antibodies, which can cross the placenta from around mid-gestation. TRAb can be stimulating, or block binding of TSH to its receptor, and can therefore result in fetal hyper- or hypothyroidism, even when the mother is euthyroid. This usually occurs after week 20 of pregnancy [12]. Therefore, the ATA guidelines recommend to measure the maternal TRAb concentration in the first trimester of pregnancy of women with (a history of) GD to assess the risk of developing FT [8], and repeat them at 18–22 and 30–34 weeks when elevated three times or more above the reference range or >5 IU/L. During pregnancy autoimmunity usually decreases, resulting in a gradual fall of TRAb concentrations during the second and third trimesters [13]; therefore, a normal TRAb concentration in the first trimester does not require follow-up measurements.

Findings of FT include (fetal) growth restriction, tachycardia, and cardiac decompensation [14]. In addition to clinical parameters, fetal ultrasound can be a useful tool to determine the effects of FT (fetal goiter with a Doppler signal throughout the gland and/or accelerated bone maturation) [15].

FT can be treated via the mother since antithyroid drugs (ATDs) cross the placenta. Although both PTU and methimazole treatment in the first trimester can cause birth defects (2–3% and 2–4%, respectively), PTU is preferred because its teratogenic effects tend to be less severe [6, 16]. In the second and third trimesters, methimazole is preferred over PTU because of PTU-associated risk of hepatotoxicity in the mother [8]. Since FT due to elevated maternal TRAb levels does not occur before 20 weeks pregnancy, methimazole is the drug of choice in such cases. Our patient had iatrogenic hypothyroidism after I^{131} therapy for GD so her FT4 levels depended solely on exogenous LT4 administration and were not influenced by methimazole use. Serial umbilical cord blood samples to measure fetal FT4 were deemed too invasive, and therefore FHR was used as the primary clinical parameter for the fetal thyroidal state and titration of methimazole. Because ATDs are more potent in the fetus than in the

mother, it is recommended to dose as low as possible to avoid inducing fetal hypothyroidism [17, 18]. We started with methimazole 5 mg daily, after which FHR normalized. Because of the persistently high levels of maternal TRAb titers, methimazole was continued until delivery. However, blood drawn from the umbilical cord directly postpartum showed biochemical thyrotoxicosis in both neonates. Although we believe that serial ultrasound should be central in the management of FT, in our case the normalization of FHR did not appear to be a fully accurate reflection of the fetal thyroid state.

After delivery, there is a direct drop of maternal regulatory T cells which can result in rebound postpartum thyroid autoimmunity and therefore worsening or re-exacerbation of GD in the mother [19]; illustrated in our case showing the rise in TRAb after first pregnancy (see Fig. 2). In the infant, transient (neonatal) hyperthyroidism may develop because of the presence of TRAb obtained from the mother, with a half-life of about 2 weeks [1]. Hyperthyroidism may be masked during the first 48–72 h after birth due to the lasting effects of ATDs from the mother's circulation [20]. Signs of neonatal hyperthyroidism may include tachycardia, tachypnea, hypertension, and heart failure [2]. When present, the recommended treatment consists of methimazole 0.5–1 mg/day [8]. If severe, propranolol 2 mg/kg/day should be added.

In our case, the laboratory data of both infants obtained after cessation of methimazole and LT4 therapy were interpreted as suggestive for central hypothyroidism. It is thought that high *maternal* thyroid hormone concentrations due to inadequately treated GD during pregnancy negatively influence development of the fetal hypothalamus-pituitary-thyroid axis [2, 3]; the findings in our case, and that of Matsumoto et al. (Table 1), indicate that high *fetal* thyroid hormone concentrations stimulated by high levels of maternal TRAb may have the same effect. Notably, while a situation of delayed recovery of an intact hypothalamic-pituitary-thyroid axis after medical treatment of hyperthyroidism may take weeks to months in adults [21, 22], it can be followed by central or even primary hypothyroidism in infants as a result of impaired physiologic maturation of the hypothalamic-pituitary-thyroid axis due to intrauterine exposure to high thyroid hormone concentrations [23]. This may become manifest up until 1 year after withdrawal of LT4 therapy [3]. Because of the deleterious effects of neonatal hypothyroidism on growth and neurodevelopment, treatment must be started immediately [24].

Although pituitary function in children with central hypothyroidism due to exposure to high *maternal* thyroid hormone concentrations in utero tends to improve over time, thyroidal function may remain compromised resulting in persistent primary hypothyroidism [3]. Less is known about the possible recovery of pituitary and thyroidal function in children with central hypothyroidism due to exposure to high *fetal* thyroid hormone concentrations in utero. In one of the two children with FT described by Matsumoto et al. (Table 1), subsequent central hypothyroidism recovered after 2 years [5]. Both daughters in our case report still require LT4 replacement therapy, respectively, 2.5, and 1 year after birth, so it is not yet known whether hypothyroidism will be transient or permanent. Long-term follow-up and re-evaluation of these children is warranted; to assess if hypothyroidism is transient or permanent it is advised to re-evaluate the hypothalamus-pituitary-thyroid axis after the age of 2–3 years, 4 weeks after phasing out or stopping LT4 levothyroxine; in children with a goiter and requiring a low LT4 dose (<3 μg/kg) this may be done safely already after 6 months of age [24]. In conclusion, this case demonstrates the novel insight that besides FT due to high *maternal* thyroid hormone concentrations, FT due to high *fetal* thyroid hormone concentrations stimulated by high maternal TRAb levels might also result in (central) hypothyroidism, requiring long-term evaluation of the hypothalamus-pituitary-thyroid axis in these children.

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Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent for publication of her clinical details and clinical images was obtained from the patient.

Conflict of Interest Statement

We declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author Contributions

L.T.H. conceived this case report and wrote the paper. J.R.P. provided ultrasound images and critically reviewed, commented on, and revised the paper. M.E.A.S.-R., A.S.P.T., T.P.L., and R.P.F.D. critically reviewed, commented on, and revised the paper.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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