

# Treatment of Resistance to Thyroid Hormone in Pregnancy: How to Address the Challenge

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**R**esistance to thyroid hormone (RTH) is a syndrome characterized by reduced target organ responsiveness to thyroid hormones. In a majority of cases, RTH is caused by mutations in the thyroid hormone receptor beta gene (TR $\beta$ ; OMIM 190160). The disorder is characterized by high serum concentrations of free thyroxine (FT4) and usually free triiodothyronine (FT3), and is accompanied by normal or slightly elevated serum thyroid-stimulating hormone (TSH) concentrations [1]. Most patients with RTH are clinically asymptomatic, but some show signs of elevated thyroid hormone (TH) levels, such as goiter and tachycardia. Some patients may exhibit hypothyroid symptoms, such as poor growth and slow weight gain, or have a mixture of hypo- and hyperthyroidism features. Additional symptoms include attention deficit, hyperactivity, and learning disabilities. Typically, anti-thyroid treatment is unnecessary; however, treatment for RTH in patients during pregnancy remains challenging and is based on fetal genotype [1].

We present the case of a young woman who was diagnosed with RTH in childhood and followed in our clinic. Genetic testing of amniotic fluid performed while she was pregnant demonstrated that her fetus did not carry the maternal mutant gene.

Clinical data has shown that fetal exposure to high maternal TH levels during pregnancy may cause fetal thyrotoxicosis, low birth weight, and fetal loss. It may also cause transient hypothyroidism in neonates due to overtreatment with anti-thyroid drugs and fetal TSH suppression during pregnancy. Thus, it is important to determine the fetal genotype and to treat a pregnant woman who has an RTH mutation if she is carrying an unaffected fetus. In the same way, prenatal fetal genotyping will reveal fetuses affected with the mutation. In such circumstances, if the fetus is resistant to TH, no treatment is recommended.

## PATIENT DESCRIPTION

The probanda was a 28 year old female who was initially seen in the endocrinology clinic for goiter, tachycardia, and poor weight gain when she was 8 years old. At the first visit, her weight was 20 kg (10th percentile) and her height was at the 25th percentile. She was a student in first grade with fair performance at school. Her physical examination was insignificant except for congenital nystagmus and bilateral sensorineural hearing loss. Mild learning disabilities were reported as well. A product of a consanguineous marriage of first-degree cousins, she was born at term after an uneventful pregnancy. Her family was of Jewish Caucasian descent that had immigrated to Israel from Dagestan in 1995. Her two brothers were healthy. The family history was otherwise unremarkable.

The patient had a diffusely enlarged thyroid gland, no tremor, and no exophthalmos. Her thyroid function tests on the first visit were: FT4 4.85 ng/dl (normal range 0.6–1.8), FT3 343 ng/dl (normal range

80–180), and TSH 0.78 mU/l (normal range, 0.2–3.8). A radioactive iodine uptake test with I131 revealed a high uptake (42% and 84% at 2 and 24 hours, respectively). Graves' disease was suspected, and she was treated with propylthiouracil. Despite the treatment, FT4 and FT3 levels remained high and TSH levels increased. Thyroid stimulating immunoglobulin was normal and thyroperoxidase and thyroglobulin antibodies were negative. A computed tomography (CT) scan of the pituitary did not reveal any abnormalities. A thyrotropin releasing hormone (TRH) stimulation test was performed under propylthiouracil treatment and revealed an exaggerated TSH elevation: 36  $\mu$ IU/ml at 10 minutes to 156.8  $\mu$ IU/ml after 30 minutes. Based on the patient's clinical picture, her thyroid test results, and the normal pituitary imaging on the CT, a diagnosis of RTH was suspected.

Sequencing analysis of four exons (7–10) of the TR $\beta$  gene identified a heterozygous mutation, 10 c.1357C>A; p.P453T, in exon 10. There was no evidence for this mutation in nine other family members. The patient continued to be monitored in our endocrinology clinic without treatment.

At the age of 27 the patient married and successfully conceived. She underwent genetic counseling to estimate the recurrence risk of RTH syndrome and to clarify the genetic status of her fetus. Sequencing analysis of the TR $\beta$  gene was performed by Illumina NeXTSeq 500 technology (Illumina Inc., San Diego, CA, USA) and revealed two changes in a heterozygote state: the already known c.1357C>A; p.P453T in exon 10 as well as a variant, c.735C>T; p.F245F, in exon 7, which was also found in her mother. Fetal genotyping was obtained by amniocentesis performed at week 16 of

the pregnancy. The patient began propylthiouracil treatment while waiting for the results from the amniocentesis. The patient's thyroid function tests during the pregnancy and data on propylthiouracil treatment are shown in Table 1.

The fetus was found to be unaffected. Fetal development and well-being was assessed by prenatal ultrasound performed at weeks 15, 23, 30, and 37. Cardiotocography for fetal heart rate assessment, performed at weeks 32 and 37, revealed normal heart rate with moderate variability. Fetal thyroid ultrasound was performed at week 34 and revealed a normal thyroid size according to the pregnancy age.

A healthy male infant was born at term. His birth weight was 2930 g. Physical examination revealed a normal size anterior fontanelle, a symmetric head, normal skin color, and normal heart examination. Cord blood TSH concentration was 4.65 IU/ml (normal for reference range). The neonate did well without jaundice and was discharged on postpartum day 3.

### COMMENT

RTH is a rare disorder characterized by reduced end-organ responsiveness to TSH. The prevalence of the condition is 1:40,000 live births and is equal in both genders [1]. The inheritance is autosomal dominant. Autosomal recessive transmission has been found in approximately 10% of families; 15% of subjects with RTH have no detectable mutation in the TR $\beta$  gene [2]. Different mutations in the TR $\beta$  gene have varying effects on the receptor function

according to their ligand binding capacity, but the clinical severity of the syndrome is not necessarily correlated with the degree of functional impairment of the receptors. Moreover, significant differences in clinical symptoms are observed in patients harboring the same mutation [2].

A characteristic feature of the syndrome is the preservation of the TSH response to TRH despite elevated TH levels. In this respect, it is notable that our patient underwent a TRH test twice. The first test was under propylthiouracil treatment and the results showed an exaggerated response of TSH, whereas the second time was without propylthiouracil treatment and the results showed a very flat TSH slope with maximum TSH 6 mIU/L after 15 minutes. In healthy euthyroid subjects, the minimum peak TSH following a TRH test is 5 mIU/L, whereas the maximum peak ranges between 17.2 and 19.5 mIU/L.

We speculate that the results of the TRH test in our patient were probably related to a recent propylthiouracil treatment that she had received, which caused some degree of hypothyroidism.

Due to a lack of prospective studies on pregnant subjects with RTH, there are no definite recommendations for the management of pregnancy in women with this condition. It is also unlikely that such studies would be performed because this condition is very uncommon and is often not diagnosed before pregnancy, as the patients are usually clinically euthyroid with normal TSH levels. There are sparse published data on the course and outcome of pregnancy in women with RTH and even fewer reports

on interventions during gestation [1]. The appropriate management of pregnant women with RTH is ideally based on the prenatal identification of the fetal genotype and on maternal thyroid function tests.

Several situations may be encountered in pregnant women with RTH. In a first scenario, both the mother and the fetus harbor the same mutation. In this case, the fetus is resistant to TH and tolerates the high maternal TH levels. No treatment is recommended during pregnancy.

In a second scenario, a normal mother is carrying an affected fetus. Surprisingly, in this situation no increased rates of miscarriage or birth complications have been observed. Such neonates, born to normal mothers and affected fathers, do not show symptoms of TH deprivation or elevations of TSH.

In a third scenario, the RTH mother has undergone previous ablative therapy (radioiodine, surgery) or is affected by Hashimoto's thyroiditis. In this situation, the outcomes (birth weight, TSH at birth) are normal, whether the fetus harbors the mutation or not. In this case, it is suggested to maintain FT4 levels within a maximum of 20% above the upper limit of normal (ULN) [3].

A fourth scenario is illustrated by the case we report here. In this situation, a normal fetus is carried by a woman with RTH. Consequently, the fetus is exposed to incongruent high maternal TH levels, while the mother remains clinically euthyroid.

A study of a large Azorean family harboring the R243Q TR $\beta$  gene mutation found that affected pregnant women carrying unaffected fetuses had a threefold to fourfold higher miscarriage rate [1]. In addition, the unaffected infants born to RTH mothers had significantly lower birth weight compared to infants with RTH. Their postnatal TSH level was suppressed in all cases. This situation indicates that the normal fetuses were exposed to high maternal TH levels, inappropriate to their genotype, and developed fetal hyperthyroidism. Moreover, in a recent study, intrauterine exposure to high TH levels was shown to cause persistent

**Table 1.** Thyroid function tests and treatment during pregnancy

Date	Weeks of pregnancy	TSH (IU/ml)	FT4 (pmol/L)	FT3 (pmol/L)	PTU treatment
20/10/2014	0	0.58	43.3	–	None
26/02/2015	13	0.03	54	19	None
25/03/2015	17	0.2	29.9	–	150 mg
21/04/2015	20	0.17	36.2	9.2	450 mg
20/05/2015	25	0.26	31.5	8.8	450 mg
25/06/2015	30	0.7	28.9	9.1	450 mg
23/07/2015	34	1.01	32	–	450 mg
16/08/2015	37	1.36	28.5	7.8	450 mg

FT3 = free triiodothyronine, FT4 = free thyroxine, PTU = propylthiouracil, TSH = thyroid stimulating hormone

pituitary resistance to TH in adult life in normal adults born to mothers with RTH [4]. According to the standard clinical practice, as reported by Weiss and colleagues [1], prenatal identification of the fetal genotype by amniocentesis and judicious treatment of RTH mothers carrying unaffected fetuses to reduce TH levels should be used to maintain FT4 levels under 20% above the ULN. This treatment can prevent the predictable low birth weight and TSH neonatal suppression. Moreover, prenatal determination of the fetal genotype can prevent unnecessary treatment of RTH mothers carrying fetuses harboring the mutation [1]. However, it should be noted that in women with RTH, miscarriages occur early in the first trimester of pregnancy, prior amniocentesis. There is also a small risk of miscarriage associated with amniocentesis (about 1%) that should be considered.

In our patient, we opted for a cautious approach and began propylthiouracil treatment at a low daily dose (150 mg) before we knew the fetal genotype. The standard

practice is to maintain FT4 levels below 20% of the ULN in women with RTH who are carrying wild type fetuses. In this respect, it is important to consider the reliability of thyroid function tests in pregnancy (i.e., to use gestational age-specific reference ranges) and to remember that in women with RTH the evolution of thyroid function tests in pregnancy is poorly known. In a recent retrospective study of 18 pregnancies in 13 women with RTH, Pappa and colleagues [5] emphasized the role of prenatal diagnosis in pregnant women with RTH. They suggested that it may be safe to delay prenatal diagnosis until FT4 levels exceed 150% of the ULN for gestational age. Their suggestion was based on the uneventful outcomes of six pregnancies in which the FT4 values of the mothers were close to 50% above the ULN [5].

**CONCLUSIONS**

Pregnancy in women with RTH should be planned, if possible, and closely followed. Given the rarity of this condition, we think it would be helpful for the medical commu-

nity to share information about pregnancies and outcomes in these patients.

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**Capsule**

**Stressed out by influenza virus**

Viral infection leads to cellular stress, which can act to the host's advantage to curb infection; however, the virus can also subvert stress responses for its own gain. **Zhao** et al. found that influenza A virus (IAV) infection led to global deregulation of transcription. After IAV infection, RNA polymerase II runs through the transcription termination site of almost all active genes. This process down-regulates gene expression by affecting the splicing of some transcripts and delaying

the next rounds of transcription initiation. The viral protein NS1 is responsible for this effect and can be modulated by SUMOylation. Although whether this stress response tilts in favor of host survival or facilitates viral replication is unknown, it might help explain the differences in pathogenicity seen in different IAV strains with divergent NS1.

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**Capsule**

**Impaired constriction in Duchenne muscular dystrophy**

Duchenne muscular dystrophy (DMD) is a hereditary disease caused by mutations in the gene that encodes the protein dystrophin. Dystrophin is also expressed in vascular smooth muscle cells (SMCs). A lack of dystrophin during disease causes damage to both skeletal and cardiac muscle. **Pritchard** and co-authors used superresolution microscopy to show that clusters of ryanodine receptors, which release Ca<sup>2+</sup> from the sarcoplasmic reticulum, are larger in SMCs from a mouse

model of DMD than in controls. These clusters colocalize with Ca<sup>2+</sup>-activated K<sup>+</sup> (BK) channels on the channel membrane. The resulting higher activity of the BK channels causes impaired vasoconstriction in the cerebral microvessels of mutant mice. This effect might contribute to DMD-associated cognitive impairment.

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