

## Development of Postpartum Graves' Hyperthyroidism in a Woman with Hashimoto's Hypothyroidism

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Received: February 9, 2011

Accepted: February 30, 2011

**Abstract.** Transformation of Hashimoto's hypothyroidism to Graves' hyperthyroidism is extremely rare, but does occur. The course and severity of autoimmune thyroid diseases are altered during pregnancy and the postpartum period. We report the clinical course, laboratory findings, and treatment of a female patient with Hashimoto hypothyroidism. She had a past medical history of Hashimoto hypothyroidism and had been on LT<sub>4</sub> replacement therapy for two years. Six-months postpartum, however, she developed Graves' hyperthyroidism. LT<sub>4</sub> was discontinued, and the patient was started on methimazole, 30 mg daily. Methimazole was discontinued one month later due to severe side effects, and 131 radioiodine therapy was applied. We suggest that patients with preexisting Hashimoto's hypothyroidism are not immune to developing Graves' disease. When such patients have unexpected symptoms and changes in thyroid function tests, especially during pregnancy or in the postpartum state, this unlikely diagnosis should be entertained and treated accordingly.

**Keywords** Autoimmune thyroid disease • Graves' disease • Hashimoto's • Hyperthyroidism • Hypothyroidism • LT<sub>4</sub> • Methimazole

### Introduction

Hashimoto thyroiditis and Graves' disease are the most two common autoimmune thyroid diseases. They are generally thought to be discrete entities. The autoantibodies thyroid peroxidase (TPO) and thyroglobulin (Tg) are the classic markers of Hashimoto's thyroiditis, a condition in which thyroid lymphocytic infiltration and thyrocyte damage may progress to hypothyroidism.

Graves' disease is caused by autoantibodies that induce thyrotoxicosis by mimicking the action of TSH and activating the TSH receptor. Reports showed that antibodies that either stimulate or block TSH receptors in Graves' disease patients were present in concentrations similar to those in Hashimoto thyroiditis.<sup>[1]</sup> Studies also show a link between Graves' disease and Hashimoto thyroiditis.<sup>[2]</sup>

The course and severity of autoimmune thyroid diseases are altered during pregnancy and the postpartum period. The thyroidal response to a fluctuating immune status, combined with changes in thyroid economy during pregnancy, may result in a need to adjust the treatment regimen for thyroid disease during pregnancy. These and other not yet completely

elucidated factors lead to partial tolerance and a dominant T-helper subset 2 (Th2) immune profile, which explains the positive influence of pregnancy on the clinical course of many (albeit not all) autoimmune diseases and, characteristically, the generalized improvement of thyroid autoimmune diseases during pregnancy.

Patients with Hashimoto's hypothyroidism who are on thyroid hormone replacements are frequently observed to have an increased requirement for levothyroxine early in pregnancy. This, however, is not true of all patients.<sup>[3,4]</sup>

Graves' disease usually improves during pregnancy but flares up after delivery. Due to the profound autoimmune modifications that occur post-delivery, it is understandable that the postpartum period has been associated with a greater frequency of onset, recurrence, or exacerbation of thyrotoxicosis from Graves' disease and postpartum thyroiditis.<sup>[5]</sup> Spontaneous conversion from hypothyroidism to hyperthyroidism, although not common, has been reported before.<sup>[6-10]</sup> Development of Graves' disease in the first trimester of pregnancy and later stages of pregnancy has also been reported.<sup>[8,10,11]</sup>

Spontaneous transformation from Hashimoto

hypothyroidism to postpartum Graves' hyperthyroidism, however, has not previously been reported. We report a patient with a 2-year history of Hashimoto hypothyroidism and replacement therapy who developed Graves' hyperthyroidism 6-months postpartum.

### Case Presentation

A 34-year-old female presented to the emergency department with complaints of palpitations and dizziness that was worsening. Three months previously, she had undergone a work up for fatigue following a miscarriage in June 2005. At that time, her TSH was < 0.1 mIU/L, her free T<sub>4</sub> was within range at 1.0 ng/dL, and her 123 Iodine uptake and scan showed a 6-hour RAI uptake of 9.7% and 24-hour RAI uptake of 13% with patchy and heterogeneous activities. The patient was sent to an endocrinologist for evaluation.

After five months of observation, when her TSH rose to 32 mIU/L and her free T<sub>4</sub> dropped to 0.8 ng/dL, the patient was diagnosed with Hashimoto's thyroiditis.

Anti-TPO antibodies at that time were positive at 67.7 IU/mL. Two months after initiation of treatment with LT<sub>4</sub>, 100 µg daily, her TSH dropped to 0.032

mIU/L and her free T<sub>4</sub> elevated to 2.13 ng/dL. Her LT<sub>4</sub> dose was subsequently decreased to 50 µg daily. Two months later, the patient became euthyroid and remained stable until becoming pregnant in August 2006.

During her first trimester, her TSH rose to 98 mIU/L and her LT<sub>4</sub> was increased back to 100 µg daily. However, her thyroid function tests again normalized, and she remained euthyroid through her third trimester. She had an uncomplicated delivery. Postpartum, she remained on 100 µg of LT<sub>4</sub> until she presented to her endocrinologist on September 2007 with symptoms of thyrotoxicosis.

At this time, her TSH was undetectable and her free T<sub>4</sub> was markedly elevated at 10.44 ng/dL. A 123 iodine uptake and scan revealed a homogenous 4-hour uptake of 66% and a 24-hour uptake of 73%. LT<sub>4</sub> was discontinued, and the patient was started on methimazole, 30 mg daily.

The patient's thyrotoxic symptoms persisted four weeks after she initiated methimazole, and she developed skin rashes, nausea, dizziness, and had episodes of syncope. Because of this, she sought treatment at our emergency department.

Upon admission, her TSH was undetectable, her

**Table 1.** Time course of TFTs, 123 Iodine uptake, thyroid antibodies and treatments.

Date	TSH	Free T <sub>4</sub>	24 hour RAI Uptake	TPO	TSI	LT <sub>4</sub> Dose
6/05	< 0.01	1.0	13%			None
10/05	31.19	0.8		67.7	Start	Start 100 µg
12/05	0.032	2.13				100 µg
2/06	0.009	1.79				100 µg
4/06	0.86	1.24				50 µg
7/06	0.71	1.31				50 µg
8/06 (1st trimester)	98.070	0.97				50 µg
9/07 (6 months post partum)	0.049	10.44	73%			100 µg, off T <sub>4</sub> and start Tapazole
10/07	< 0.01	2.02				Off Tapazole
11/07	< 0.01	1.03			357%	131RAI therapy
2/7/08	15.38	0.94				50 µg
4/7/08	0.288	1.23				88 µg
7/14/08	0.228	1.33				88 µg

**Reference ranges:** 123Iodine uptake, 24 hour 15-35%; TPO Ab, < 30 IU/mL; TSI, 0-129%; TSH, 0.35-5.50 mIU/mL; FreeT<sub>4</sub>, 0.61-1.76 ng/dL.

free T<sub>4</sub> was 2.02 ng/dL, and her thyroid stimulating immunoglobulin (TSI) level was elevated at 357%. Methimazole was discontinued due to her skin rashes and because she had transaminase elevations greater than two times the upper limit of normal. She was hydrated with intravenous fluid and administered propranolol and prednisone while waiting for 131 RAI therapy.

Seven days after discontinuing methimazole, the patient received 10 mCi of <sup>131</sup>I during her admission for definitive treatment. One month later at outpatient follow-up, the patient was found to be clinically euthyroid with a reference range free T<sub>4</sub>. Three months later, however, the patient complained of fatigue, dry skin, and was found to be clinically hypothyroid. Her TSH was high at 15.38 mIU/L, and her free T<sub>4</sub> was low in its reference range at 0.94 ng/dL. Treatment with LT<sub>4</sub> was then reinitiated (Table 1).

## Discussion

Hyperthyroidism is known to occur early in the course of Hashimoto's thyroiditis and is commonly termed "Hashitoxicosis."<sup>[12]</sup> At this time, the inflamed thyroid gland leaks preformed hormone. In patients who have already entered the hypothyroid phase of Hashimoto's thyroiditis, the injured thyroid gland has lost its synthetic ability and the patient needs life long replacement therapy. Affected patients are not expected to subsequently develop hyperthyroidism.

In the case we report here, however, the clinical course and treatment are unique. The patient was initially noted to have subclinical hyperthyroidism with low <sup>123</sup>I uptake in June 2005, which indicated Hashitoxicosis. Four months later, she developed hypothyroidism and had elevated TPO antibodies. She began T<sub>4</sub> replacement therapy. This, of course, was the typical course for a patient with Hashimoto hypothyroidism.

During the first trimester of her pregnancy, her LT<sub>4</sub> replacement dose had to be increased. This indicated that she had reduced thyroid reserve because Hashimoto's thyroiditis had injured or destroyed her thyroid gland.

Six months postpartum, she developed typical signs and symptoms of hyperthyroidism. She was found to have a high <sup>123</sup>I uptake, high TSI titer, low TSH, and a high free T<sub>4</sub>. These findings confirmed the diagnosis of Graves' hyperthyroidism.

The patient was treated with methimazole. However, she developed skin rashes and liver toxicity one month later. Because of this, Methimazole was discontinued and propranolol was used to control her hyperthyroidism while waiting for 131RAI thera-

py.<sup>[13,14]</sup>

Spontaneous conversion from hypothyroidism to hyperthyroidism, as in the patient we describe here, is not common, although it has been reported before.<sup>[6-11]</sup> Some of the described changes in clinical course that researchers have reported were associated with pregnancy or previous treatment with antithyroid medications; others occurred spontaneously. Nearly all of the patients in these cases expressed more than one type of thyroid auto-antibody concomitantly or over time. These observations are in accordance with a series of studies from the 1990's. These studies established that the same patient may express one or more different TSH receptor antibodies in addition to anti-TPO or anti-thyroglobulin antibodies.<sup>[15-17]</sup>

Factors influencing the relative concentrations of each antibody and how the different antibodies interact with one another are likely responsible for the prevailing clinical manifestations. Spontaneous transformation from Hashimoto hypothyroidism to Graves' hyperthyroidism postpartum, however, has never been reported before. The etiology of Graves' disease in a postpartum-patient already on replacement for Hashimoto's hypothyroidism remains to be elucidated at the present time.

Our patient had both positive TSI and positive TPO antibodies at two different points in her clinical course. She had Hashimoto hypothyroidism and had already been on replacement for two years. She also had a sufficiently reduced thyroid reserve to require an increase in LT<sub>4</sub> replacement during her first trimester of pregnancy. There should not have been enough thyroid hormone in reserve in her thyroid gland to respond to the stimulating antibodies postpartum.

Literature review revealed several case reports describing patients who transitioned from one form of autoimmune thyroid disease to another.<sup>[15-17]</sup> It appears that the course and severity of autoimmune thyroid disease are altered during or in the postpartum period. The pregnant woman's immune state may have changed from predominant anti-TPO antibody or thyroid-binding inhibiting immunoglobulin (TBII) to TSI.<sup>[16-18]</sup> Serum levels of TBII and TSI have been shown to consistently decrease or disappear during pregnancy and increase after delivery.<sup>[15-18]</sup> Progesterone (P) and estrogen (E) exert these immuno-modulating effects. Whereas progesterone decreases reactivity of both the humoral and cellular arms of the immune system, estrogen exerts opposite effects. Because pregnancy is characterized by an overall increase in the P:E ratio, the reactivity of both arms of the immune system is inhibited.<sup>[9]</sup> Thyroid

autoantibodies and antibodies directed against other tissues are partially suppressed during pregnancy and are exacerbated after delivery. The precise mechanism of these immune effects remains obscure. Presumably, the rapid reduction in immune suppressor function of the P:E ratio following delivery leads to the reestablishment and exacerbation of these conditions.<sup>[20-22]</sup>

The postpartum rebound of thyroid autoimmune diseases is a striking example of this phenomenon.<sup>[22]</sup> We suggest that our patient had thyroid hormone in reserve in her thyroid gland for two reasons: her anti-TPO antibody level was low and did not completely destroy her thyroid gland, and her relatively low LT<sub>4</sub> dosage before pregnancy allowed thyroid hormone production to proceed. During her pregnancy and postpartum period, her autoimmune status changed predominant to TSI (359%). The antibodies may have stimulated her remaining thyroid gland to produce enough thyroid hormone to produce Graves' hyperthyroidism six months postpartum.

## Conclusion

We report a case of Graves' hyperthyroidism that developed in a woman with Hashimoto's hypothyroidism six month postpartum. Transformation of Hashimoto's hypothyroidism to Graves' hyperthyroidism is extremely rare. However, patients with Hashimoto's hypothyroidism are not immune to the development of Graves' disease. When such patients have unexpected symptoms and changes in thyroid function tests that characterize hyperthyroidism, especially during pregnancy or the postpartum state, this unlikely diagnosis should be entertained and treated accordingly.

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