

Recurrent Hyperthyroidism Following Postpartum Thyroiditis in a Woman with Hashimoto's Thyroiditis

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Postpartum thyroid dysfunction occurs in 5-10% of women within one year after delivery. Women with hypothyroidism antedating pregnancy are at high risk for postpartum thyroiditis and should be closely monitored during the first year post-partum. Here, we report a case of recurrent hyperthyroidism between two episodes of postpartum thyroiditis in a woman diagnosed with subclinical hypothyroidism prior to pregnancy. It is of particular interest that spontaneously remitting hyperthyroidism as a sequela of postpartum thyroiditis can occur.

Key Words: Hyperthyroidism, Postpartum, Thyroiditis, Hypothyroidism

Introduction

Postpartum thyroid dysfunction occurs in 5-10% of women within one year after delivery.¹⁾ A strong correlation exists between the presence of thyroid peroxidase (TPO) antibodies and postpartum thyroid autoimmune dysfunction. Such thyroid dysfunction can manifest in various forms (hyperthyroid or hypothyroid, transient or persistent), each of which necessitates different treatment. The development of postpartum thyroiditis (PPT) in patients with a history of Graves' disease (GD) appears to be common during the postpartum period;^{2,3)} however, the development of GD in patients with a history of PPT and no prior history of GD appears to be far less common.⁴⁻⁸⁾ Here, we report a case of recurrent hyperthyroidism associated with GD between two episodes of PPT in a woman diagnosed with subclinical hypothyroidism prior to pregnancy.

Case Report

A 29-year-old female visited our clinic with slow enlargement of the anterior neck. There was no history of pregnancy or abortion, and she had no family history of thyroid disorders. Upon her initial evaluation at our clinic, her weight, height and body mass index were 154 cm, 45 kg and 19 kg/m², respectively. On physical examination, palpation of the neck revealed a mild goiter without tenderness. Blood pressure was 110/70 mmHg and heart rate was 78 beats per minute and regular. Thyroid panel showed elevated thyroid stimulating hormone (TSH) (17.4 μ IU/mL, normal range, 0.34 to 3.5) and free T4 at the lower limit of normal (0.81 ng/dL, normal range, 0.8 to 2.2). A repeat TSH test confirmed an elevated level, although the free T4 was normal. Ultrasonography demonstrated a diffusely enlarged thyroid gland with diffuse heterogeneous parenchyma, showing an antero-po-

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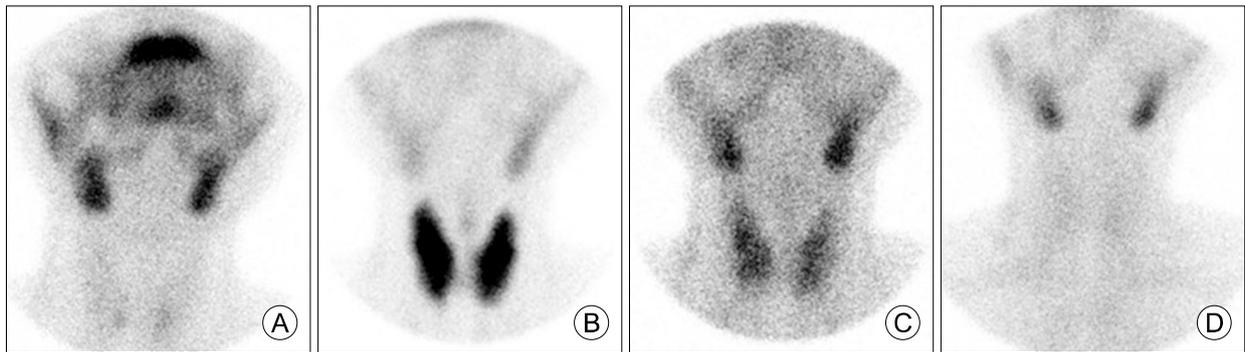


Fig. 1. Anterior view images of a Tc-99m pertechnetate scan in thyrotoxic phase. (A) Postpartum thyroiditis, (B) The first episode of hyperthyroidism, (C) The second episode of hyperthyroidism, (D) A relapse of postpartum thyroiditis. The normal range of thyroid trapping index in our laboratory is 2.5–6.0. In this case, they were 1.2 (A), 11.3 (B), 3.4 (C), and 1.1 (D).

sterior diameter of 21 mm for the right lobe and 15.8 mm for the left lobe, without any mass or nodule. Further testing for thyroid antibodies revealed the presence of TPO antibody (73.85 U/mL, >0.3 U/mL positive). The patient was treated with levothyroxine 50 μ g/day for goiter shrinkage and elevated TSH (above 10 μ IU/mL) in the context of future pregnancy.

Seven months after her first visit to our clinic, the patient became pregnant. She remained in a euthyroid state with no changes in levothyroxine dosing during pregnancy. At six weeks postpartum, follow-up thyroid function tests showed a mild thyrotoxic state (TSH 0.09 μ IU/mL, normal range 0.3 to 4; free T4 1.29 ng/dL, normal range 0.8 to 2.2) without symptoms of thyrotoxicosis. Over-replacement of thyroxine was considered, and levothyroxine was discontinued.

A thyroid panel obtained three months postpartum and after cessation of levothyroxine demonstrated low TSH (0.1 μ IU/mL), high free T4 (5.05 ng/dL), and elevated TPO antibody (55.87 IU/mL, >0.3 U/mL positive) with an absence of TSH receptor antibody (TRAb) (thyrotropin binding inhibitory immunoglobulin [TBII] 9.07%, >15% positive). The patient also experienced palpitations and tremor. There were no reported weight changes, eye changes, neck pain, or prior viral syndromes. Complete blood count, comprehensive metabolic panel, erythrocyte sedimentation rate, and C-reactive protein were within normal range. The patient had not been breastfeeding due to her illness and thus demonstrated a low milk volume. Technetium-99m pertechnetate (^{99m}Tc) scintigraphic

thyroid imaging noted decreased thyroid uptake (Fig. 1A).

Two months after her thyrotoxic episode, the patient reverted back to a hypothyroid state (elevated TSH of 107.46 μ IU/mL and low free T4 of 0.09 ng/dL). Her diagnosis was confirmed as PPT. She restarted levothyroxine 100 μ g/day due to elevated TSH with hypothyroid symptoms, including edema, fatigue, and sluggishness. Later, levothyroxine was reduced to the pre-pregnancy dose (50 μ g/day).

At 11 months postpartum (eight months after the diagnosis of PPT), the patient visited our clinic complaining of 3 kg weight loss with anxiety and hand tremors. Thyroid panel revealed suppressed TSH (0.06 μ IU/mL) and elevated free T4 (2.68 ng/dL). Levothyroxine was stopped entirely to avoid exacerbation of her thyrotoxicosis, and she was closely observed for the subsequent four weeks. The patient still remained clinically and biochemically hyperthyroid with a repeat TSH of 0.04 μ IU/mL and free T4 of 3.89 ng/dL (Table 1). The thyroid scan was reevaluated to distinguish between the occurrence of GD and a repeat episode of painless thyroiditis. Scintigraphic thyroid imaging showed increased homogeneous tracer uptake with an enlarged thyroid gland (Fig. 1B), and sonography demonstrated increased Doppler flow. These results suggested endogenous hyperthyroidism, although repeat TBII was negative (14%, >15% positive). On examination, the patient had a mild goiter and no optical symptoms. In light of her history of transient thyrotoxicosis, her uncertain diagnosis, and the

Table 1. Temporal profile of thyroid function tests and levothyroxine treatment for a patient with recurrent hyperthyroidism following postpartum thyroiditis

Dates and events	Free T4, ng/dL (normal range)	TSH, μIU/mL (normal range)	TPO–Ab, U/mL (normal range)	TBII (%) (normal range)	L–T ₄ treatment	Diagnosis
Early February 2007	0.81 (0.8–2.2)	17.4 (0.34–3.5)	73.85 (0–0.3)	N/A	0 → 50 μg/d	Subclinical hypothyroidism (Hashimoto’s thyroiditis)
Early May 2008	Delivery of the first child					
Late June 2008 (6 weeks from first delivery)	1.29	0.09	N/A	N/A	50 μg/d → 0	Thyrotoxic state
Late August 2008 (3 months from first delivery)	5.05	0.1	55.87	9.07 (0–15)	0	Postpartum thyroiditis
Early November 2008	0.09	107.46 (0.3–4)	N/A	N/A	0 → 100 μg/d	Hypothyroid state
Late December 2008	2.14	1.3	N/A	N/A	100 → 50 μg/d	Euthyroid state
Mid–April 2009	2.68	0.06	N/A	N/A	50 μg/d → 0	Thyrotoxic state
Mid–May 2009 (12 months from first delivery)	3.89	0.04	N/A	14 (0–15)	0	The first episode of hyperthyroidism
Late June 2009	2.91	0.13	N/A	N/A	0	Hyperthyroid state
Late September 2009	0.87	0.82	N/A	N/A	0	Euthyroid state
Early June 2010 (25 months from first delivery)	3.66	0.13	52.8 (0–0.3)	18.56 (0–15)	0	The second episode of hyperthyroidism
Early August 2010	2.19	0.3	N/A	13.08 (0–15)	0	Euthyroid state
Mid–January 2013	Delivery of the second child					
Mid–April 2013 (3 months from second delivery)	5.65 (0.77–1.94)	0.07	969.9 (0–60)	12.33 (0–15)	0	A relapse of postpartum thyroiditis
Late June 2013	0.64	36.6	N/A	N/A	0 → 50 μg/d	Hypothyroid state
Early August 2013	1.19	0.53	N/A	N/A	50 μg/d	Euthyroid state
Early August 2014	1.52	0.45	N/A	N/A	50 μg/d	Euthyroid state

L–T₄: levothyroxine, N/A: not applicable

tolerable symptoms, we chose to observe without treatment. She chose to take intermittent propranolol to control her palpitations and tremors. Serial thyroid function tests showed gradual recovery of thyroid function over five months. She had experienced transient hyperthyroidism (Table 1) (Fig. 2).

The second episode of hyperthyroidism occurred 12 months after the first episode. She presented with palpitations and fatigue without neck tenderness, which was unrelated to pregnancy. Thyroid panel (low TSH of 0.13 μIU/mL and an elevated free T4 of 3.66 ng/dL), scintigraphic thyroid scan images with normal radiotracer accumulation in spite of low TSH level (Fig.

1C) and positive TBII level (18.56%, >15% positive) were consistent with GD. Thyroid sonographic images showed a mild increase in blood flow through the parenchyma. In this episode of hyperthyroidism, she once again chose to take intermittent propranolol to control her palpitations. Two months later, her TBII titer became negative without administration of antithyroid drugs, indicating a euthyroid state (Table 1) (Fig. 2). During the following two years, the patient remained clinically and biochemically euthyroid despite a lack of thyroid medication and experiencing a second pregnancy.

The recurrent episode of thyrotoxicosis happened

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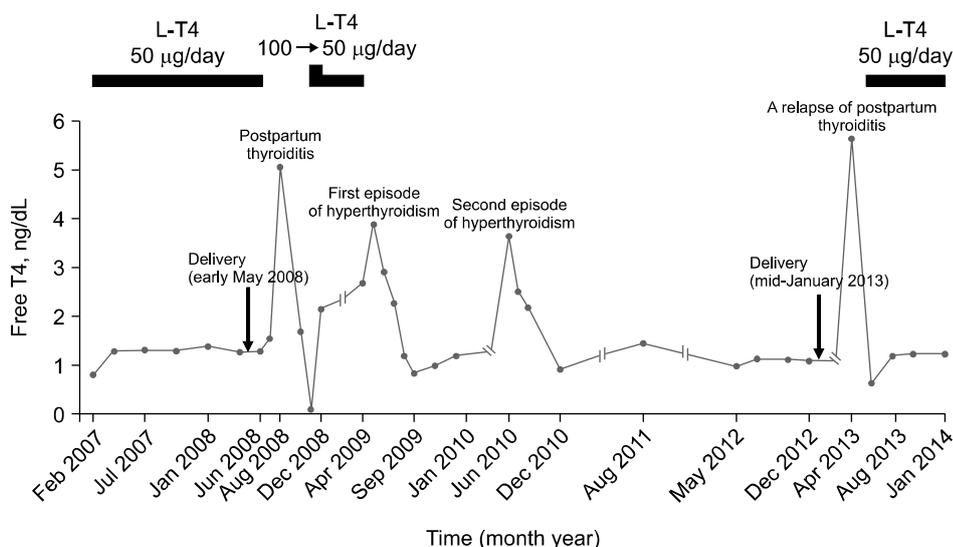


Fig. 2. Serum free T4 change during pregnancy and after delivery in our patient with Hashimoto's thyroiditis. The dosages of L-T4 (levothyroxine) are shown at the top.

Table 2. Summary of literature describing cases of Graves' disease following postpartum thyroiditis

Case number (reference)	Age	Family history of thyroid disease	Personal history of pre-pregnancy	PPT (months after delivery)	GD (months after delivery)	Anti-thyroid treatment	Final thyroid outcome
1 (4)	23	No	No	3	9	PTU → Methimazole	Hypothyroidism due to Hashimoto's thyroiditis
2 (5)	36	No	PPT (at age 30)	4	48 [†]	Methimazole	N/A
3 (5)	17	Yes*	Latent lupus	1	5	No	N/A
4 (6)	47	No	No	4	25	PTU & ¹³¹ I	Post- ¹³¹ I hypothyroidism
5 (7)	30	No	No	5	28	Methimazole	N/A
6 (8)	31	Yes [†]	PPT (3 years ago)	2.5	10.5	PTU	Euthyroid state
7 (our case)	29	No	Hashimoto's thyroiditis	3	12 (first) 25 (second)	No	L-T4 treatment

GD: Graves' disease, N/A: not-applicable, PPT: postpartum thyroiditis, *mother: permanent hypothyroidism after postpartum thyroiditis, maternal grandmother: Hashimoto's thyroiditis, [†]older sister: Graves' disease, [‡]: in 24 months after recurrent painless thyroiditis

three months after her second delivery. Thyroid panel (TSH 0.07 μ IU/mL, normal range 0.3 to 4; high free T4 5.65 ng/dL, normal range 0.77 to 1.94), thyroid antibody tests (TPO-Ab, 969 U/mL, >60 positive and TBII, 12.33%, >15% positive) and reduced uptake in a scintigraphic thyroid scan (Fig. 1D) were all consistent with the thyrotoxic phase of PPT. The patient reverted back to a hypothyroid state (elevated TSH of 36.6 μ IU/mL and low free T4 of 0.64 ng/dL) after two months. She resumed levothyroxine 50 μ g/day (1 μ g/kg/day) after complaining of anterior neck swelling associated with a goiter and lack of energy. She re-

mained euthyroid and ultrasonography revealed the thyroid gland to be normal in size of thyroid gland 14 months after her second episode of postpartum thyroiditis without changes in levothyroxine dose or a recurrence of thyrotoxicosis (Table 1) (Fig. 2). We are continuing to monitor the progression of her autoimmune thyroid disease.

Discussion

The course and severity of autoimmune thyroid disease can vary during pregnancy and in the post-

partum period. Women with TPO antibodies in early pregnancy have a 30 to 50% chance of developing PPT. Recently, one retrospective cohort study demonstrated that the incidence rate of PPT in women with hypothyroidism treated before pregnancy is nearly 10 times higher than that observed in the general population (5–9%).⁹⁾ Predictably, our patient at high risk for PPT experienced two episodes of PPT after childbirth.

PPT and GD are two clinical entities belonging to a wide spectrum of autoimmune thyroid diseases. In contrast to the high incidence of PPT or recurrence of GD in the postpartum period in women with a history of GD,^{2,10)} the development of endogenous hyperthyroidism in patients with a history of PPT, as in our case, is infrequent; however, it has been reported previously in the literature.^{4–8)} These patients were first diagnosed with PPT within six months after delivery, and subsequently developed GD after PPT (Table 2). One patient had a relapsed episode of painless thyroiditis 24 months before occurrence of GD.⁵⁾ The time period between PPT and GD varied from 4 months to 44 months in previous reports. The transition from hypothyroidism to hyperthyroidism suggests that the autoimmune tissue damage that initially occurred caused the hypothyroidism and was followed by sufficient recovery to allow for stimulation by TRAb. The pathogenesis of the association between the two entities is not clear; however, these cases might be associated with an etiological role of thyroid antigen release during the destructive process and genetic susceptibility to the development of GD.⁶⁾ Therefore, it is important that patients with PPT should be followed long after their recovery from the acute episode.

In contrast to all of the above reported cases,^{4–8)} our patient experienced two consecutive episodes of hyperthyroidism following PPT. Her first episode occurred 12 months after her first delivery and the recurrent hyperthyroidism occurred 8 months after recovery. Five of the previously reported cases were treated with antithyroid medications, while one was not because the patient remained asymptomatic (Table 2).⁵⁾ However, our patient's recovery from two episodes of hyperthyroidism was most likely spontaneous and part of the natural course of the disease because symp-

tom-controlling β -adrenergic antagonists are devoid of antithyroid and immunosuppressive actions. In several reports, the treatment of patients with GD with only β -adrenergic antagonist drugs was followed by remission of hyperthyroidism in 16–30% of patients,¹¹⁾ but there are very few reports of spontaneous remission of GD following painless thyroiditis (including PPT).^{12,13)}

In the present case, although TBII was not detected at the time of the hyperthyroid state, the first episode of hyperthyroidism was likely due to GD. Initially, a discrepancy between TBII negativity and thyroid scan images led to confusion regarding diagnosis. However, her history of persistent hyperthyroidism (>1 months), increased radioisotope uptake, and augmented Doppler flow on ultrasound were compatible with a diagnosis of GD.^{1,14)} Several studies have shown that a minority of individuals with GD remain TRAb-negative even when modern TBII assays are used.¹⁵⁾ Tamaki et al.¹⁶⁾ showed that postpartum initiation of hyperthyroidism in GD is not always associated with an increase in circulating TRAbs. In their small study, TBII was not undetectable in 8 of 10 patients with GD at the time of postpartum onset or relapse. There are possible explanations for the dissociation between thyroid function and TRAb titer as in our case. First, the assays for TRAb might not have been sensitive enough to detect antibody at the time of hyperthyroidism initiation. Unfortunately, the newer and more sensitive third-generation TBII assays were not available in our case. Second, our patient might have had intrathyroidal TRAb production that did not spill over to the circulation. If so, circulating antibodies may become detectable only after saturation of thyroid TSH receptors.¹⁷⁾ Third, a rise in TRAb after hyperthyroidism has developed may stem from the effect of hyperthyroidism itself on the immune system, which would act to exaggerate the production of TRAbs. However, in our case, TBII was only measured at the time of diagnosis, without follow-up measurements despite of the possibility of a delayed increase of TBII. In spite of these limitations, we suggest that this patient had a less severe clinical course and spontaneously improved without intervention because her thyrotoxicosis represented TBII-

negative GD.¹⁵⁾

During the second occurrence of hyperthyroidism, the patient's thyroid function panel, increased TBII activity in the hyperthyroid phase, and increased thyroid blood flow on the Doppler ultrasonography prompted a diagnosis of GD.^{1,14)} She experienced a reduction in TBII titer level and a gradual decrease in thyroid hormones without the administration of antithyroidal drugs. This patient had normal, rather than lower, scintigraphic thyroid uptake and also showed diffuse and discrete trappings in the enlarged glands. One study showed that Graves' patients with normal thyroidal ^{99m}Tc uptake had significantly smaller goiters, a lower serum thyroid hormone level, and lower TBII, when compared with other high ^{99m}Tc uptake groups with GD, and their condition could be easily controlled with small dosages of antithyroid drugs.¹⁸⁾ In addition, we could not exclude the simultaneous occurrence of painless thyroiditis and active GD, which is revealed by normal radioisotope uptake, masking GD (2). Therefore, further studies are required to understand the mechanisms of spontaneous remission following her second episode of hyperthyroidism.

In summary, this case illustrates the need for continued follow-up of patients with autoimmune thyroid disease and supports a very wide spectrum of clinical and biochemical measurements in the postpartum period. Furthermore, physicians should consider causes other than over-replacement of thyroid hormone when contemplating conversion from hypothyroidism to hyperthyroidism. It is of particular interest that recurrent transient hyperthyroidism can occur as a sequela of PPT. In addition, since we believe that some patients may spontaneously remit, as in our case, caution should be exercised in treating hyperthyroidism following PPT.

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