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ORIGINAL ARTICLE

A Preventive Trial of Short-Term Immunosuppressive Therapy in Postpartum Thyroid Dysfunction

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Autoimmune diseases, once developed, are often hard to control and thus prevention of disease development is obviously of great importance. Postpartum onset of autoimmune diseases, especially autoimmune thyroid disease, is frequently observed and postpartum hypothyroidism is a good candidate for investigation of prediction and a trial of prevention of disease development.

Materials and Methods: In order to clarify the method of prediction of postpartum onset of hypothyroidism, 9 patients who had had previous episodes of postpartum hypothyroidism and high titers (more than 5×10^3) of anti-thyroid microsomal antibodies were examined during the postpartum period of their current pregnancies. Thyroid function, size of goiter and titer of anti-microsomal antibodies were observed every month for 12 months after delivery. The other two patients, who were expected to develop postpartum hypothyroidism after present parturition and had high anti-thyroid microsomal antibody titers of more than 5×10^3, were treated with short-term glucocorticoid therapy.

Results: All 9 patients, who had previous postpartum transient hypothyroidism and had had high anti-thyroid microsomal antibodies, developed recurrence of postpartum hypothyroidism at almost the same postpartum time. A short-term glucocorticoid therapy was tried for two other cases who were expected to have recurrence of postpartum hypothyroidism. In the first case, occurrence of postpartum hypothyroidism was delayed by 2 months and peak value of TSH was lower than that of the previous episode. In the second case, duration and dose of predonisolone was doubled and development of postpartum hypothyroidism was successfully prevented.

Conclusion: Postpartum recurrence of hypothyroidism was predicted in patients who had previous episodes of postpartum transient hypothyroidism and higher titers of anti-thyroid microsomal antibodies. The short-term predonisolone therapy successfully prevented postpartum development of hypothyroidism in one case.

Key Words: Postpartum thyroiditis, Prevention, Glucocorticoid therapy, Postpartum hypothyroidism

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Introduction

Autoimmune diseases, once developed, are often hard to control and the treatment takes a long time. Therapy in the early phase of the disease or ideally before the onset of disease is obviously a desirable approach, but generally it may not be possible because the diagnosis depends mostly on clinical signs and there are no reliable predictive clinical tests. However, in autoimmune thyroid disease, as an exception, thyroid autoantibodies are found in the sera of the patients before clinical onset of the disease, and play an espe-

cially important role in the prediction of the onset of postpartum thyroid dysfunction.[1] Here, we tried to prevent the development of postpartum thyroid dysfunction by a short-term immunosuppressive therapy.

Postpartum thyroid dysfunction is known to occur during an exacerbation of autoimmune thyroid disease after delivery, and has been observed in 1.1 – 16.7 percent of postpartum women in the general population.[1-4] It often occurs repeatedly after subsequent deliveries in the same woman[1,5] and in particular, it almost always occurs for mothers who previously suffered severe destructive thyrotoxicosis followed by hypothyroidism.[1] Development of postpartum thyroid dysfunction is highly probable for patients who had previous episodes of postpartum thyroid dysfunction, and who have high titers($>5\sim10\times10^3$) of anti-thyroid microsomal antibodies.[6,7] According to the "immune rebound hypothesis" postpartum exacerbation occurs due to enhanced rebound of immune activity from the immune-suppressed state during pregnancy.[8] Actually, the counts and activity of lymphocytes,[9] the amount of immunoglobulins,[10] and the titers of anti-thyroid autoantibodies[11] decrease during pregnancy and then increase after delivery. A recent study on cytokine production in peripheral lymphocytes also revealed similar serial changes.[12]

As for the recurrence of postpartum thyroid dysfunction, there are few reports[13–16] but the number of cases in each report has been too small to clarify the predictive factors. Only one report by Lazarus et al,[5] says recurrence rate is no more than 70% (9/13 cases), but the rate may depend on "the basal severity" of autoimmunity and on how closely the patients were observed after parturition. Therefore, we tried to confirm the recurrent development of postpartum thyroid dysfunction, especially postpartum hypothyroidism, in patients with high microsomal antibodies titers of more than 5×10^3. Reported here are two case trials conducted to prevent recurrent development of postpartum thyroid dysfunction by a short-term immunosuppressive therapy.

Materials and Methods

In order to clarify the recurrence of postpartum thyroid dysfunction, we examined 9 patients (cases 1 ~ 9) who had had postpartum transient hypothyroidism after their previous deliveries and now had anti-thyroid microsomal antibody titers of over 5×10^3 in early pregnancy. This cut-off value for antibodies was supported by the fact that almost all patients with Hashimoto's thyroiditis whose anti-microsomal antibody titers were over 5,000 developed postpartum hypothyroidism.[6] These 9 patients repeatedly visited our thyroid clinic for their following pregnancy and were observed monthly for a year after their deliveries. The times of the hypothyroid phase were compared, because the thyrotoxic phase is often short and sometimes difficult to specify precisely without an error.

A short-term glucocorticoid therapy was then tried for two other cases (cases 10 and 11) who had experienced postpartum hypothyroidism after their previous parturition and had high titers of anti-thyroid microsomal antibodies. In these 2 patients (cases 10 and 11), the development of postpartum thyroid dysfunction was expected. They were treated with predonisolone orally immediately after delivery, and their thyroid function, size of goiter and titers of anti-microsomal antibodies were observed for a year. Breast-feeding was suspended during therapy. The patients were well informed about the therapy and gave consent to the study.

Serum free T_4 and TSH were measured with commercially available kits, Eiken FT_4 kits (Eiken Immunochemical Laboratory, Tokyo, Japan) and Daiichi TSH kits (Daiichi Radioisotope Laboratories, Tokyo, Japan), respectively. The intra- and inter-assay variations of FT4 assay were 4.6 – 8.6 % and 6.3 – 11.6 %, respectively and the intra- and inter-assay variations of TSH assay were 0.9 – 4.1 % and 1.5 – 14.0 %, respectively.[17] Anti-thyroid microsomal antibodies (MCHA) were measured with commercially available particle agglutination kits (Fuji Rebio, Tokyo, Japan).

Results

Recurrence of postpartum hypothyroidism was examined in 9 patients (cases 1 ~ 9) with anti-thyroid microsomal antibodies in titers of more than 5×10^3 in early pregnancy (Table 1). Two patients (case 8 and 9) had spontaneous abortions before the first pregnancy. As described in Table 1 they had had two or three previous pregnancies. All patients developed similar postpartum hypothyroidism after the next delivery. The time of the nadir of hypothyroidism (lowest FT_4 and highest TSH) was compared to that in their previous episode (Table 1). Of these nine cases, in case 1, the postpartum time of second episode was delayed 1.1 months compared to the first episode and, in case 8, the second episode developed one month earlier than the previous episode. In the other patients, the time of nadir of hypothyroidism was the same between the first and second episode. None of patients showed a difference of two months or more between each episode.

The two other cases (cases 10 and 11), who were strongly suspected for recurrence of postpartum development of hypothyroidism, were enrolled for preventive trial using short-term glucocorticoid therapy.

Case 10 was a 33-year-old female who had been diagnosed with transient hypothyroidism at 3 months after her first delivery when she was 27 years old (Fig. 1). She had hypothyroid symptoms but was followed without being given any medication. She had a small goiter with 4.3 cm of transverse width, and had remained euthyroid until the present episode. The anti-thyroid microsomal particle agglutination test was highly positive with a titer of 8×10^4 but the anti-thyroglobulin antibody test was negative in early pregnancy. In the 38th week of the current (second) pregnancy, serum free thyroxine was 1.4 ng/dl (normal range: 0.8-1.4), triiodothyronine; 169 ng/dl (150-250), and

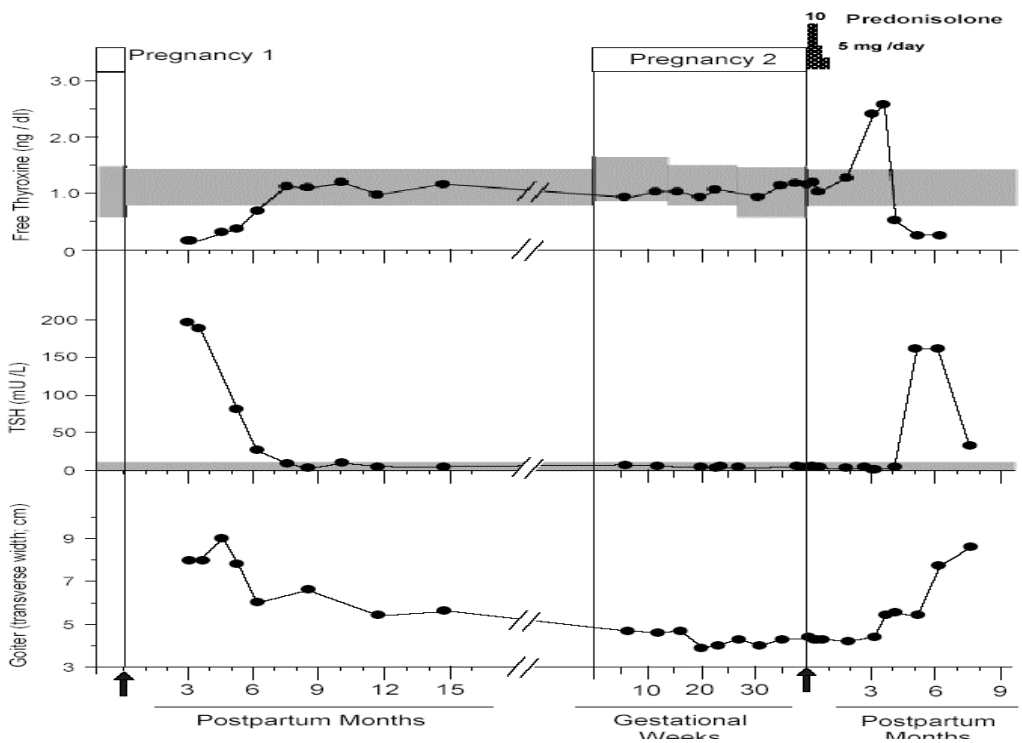

Fig 1: Serial changes in serum free thyroxine, serum thyrotropin (TSH), and goiter size in the first case during the pregnant and postpartum periods. The meshed area denotes the normal reference range.

TSH; 3.6 mU/l (0.3-4.5). She delivered a baby (2810g; female) in the 39th week of pregnancy. We started 10mg per day of predonisolone on the next day, decreased it to 5 mg per day at 10 days postpartum, further decreasing it to 5 mg every other day at 17 days postpartum, and discontinued it at one month postpartum. However, she developed destructive thyrotoxicosis at 3 months postpartum followed by transient hypothyroidism at 5 months postpartum. Occurrence of postpartum hypothyroidism was delayed by 2 months as compared to that in the first episode. The peak value of serum TSH during the current episode was lower than that of the first episode.

Case 11 was a 30-year-old female who was found to have transient hypothyroidism, 3 months after her first delivery, when she was 25 years old (Fig. 2). She suffered a relapse of destructive thyrotoxicosis followed by transient hypothyroidism after her second delivery (at the age of 27). She also had obvious hypothyroid symptoms both in her first and second episodes of postpartum hypothyroidism but agreed to spontaneous recovery and did not receive any medication. The anti-thyroid microsomal particle agglutination test was positive at the titer of 3×10^5 and anti-thyroglobulin antibody was negative in the first trimester of her current (3rd) pregnancy. She had a small goiter with 4.4 cm of transverse width, and remained euthyroid except for postpartum periods. In 39th week of the pregnancy, serum free thyroxine was 1.9 ng/dl, triiodothyronine; 221 ng/dl, and TSH; 2.2 μU/ml. She delivered a baby (3610g; male) in the 40th week of pregnancy. We started 20mg per day of predonisolone the next day, decreased it to 10 mg per day at 18 days postpartum, further decreasing it to 5 mg per day at 30 days postpartum, and discontinued it at two months postpartum.

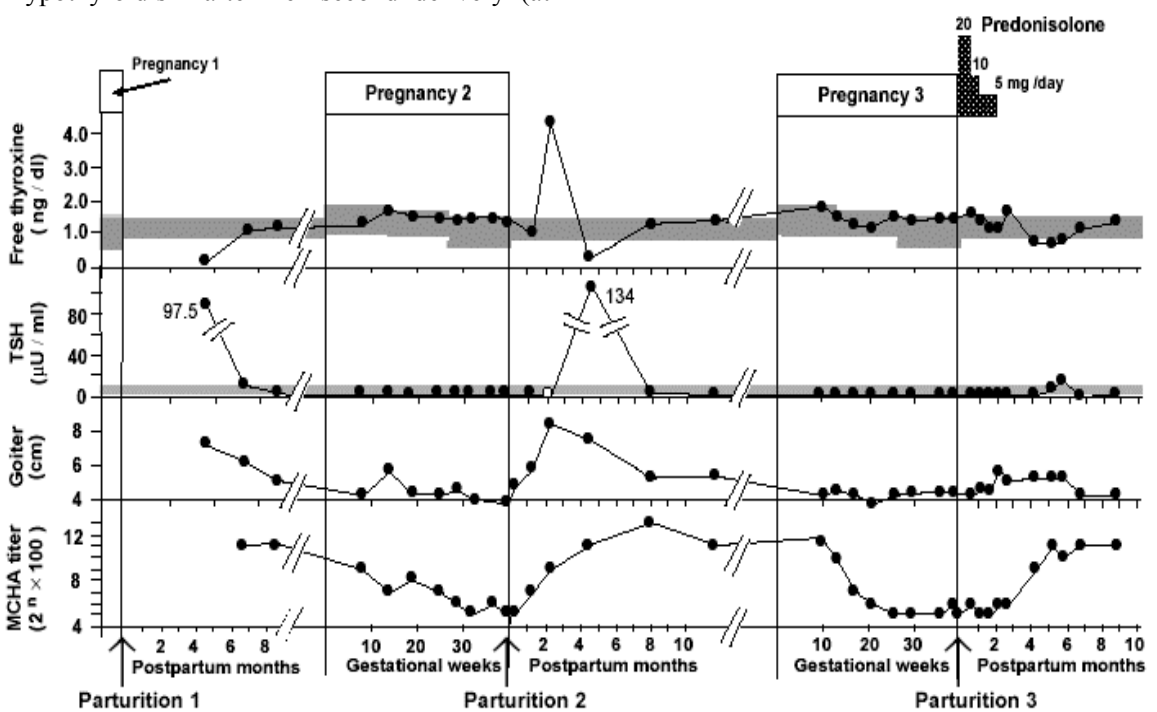

Fig 2: Serial changes in serum free thyroxine, serum thyrotropin (TSH), goiter size, and the titers of anti-microsomal antibody (MCHA) in the second case during the pregnant and postpartum periods. Open circle indicates undetectable TSH value. The meshed area denotes the normal reference range.

Postpartum thyroid dysfunction was successfully prevented and the patient was very pleased, since she had no symptoms related to thyroid dysfunction and found it easy to take care of her baby. She remained euthyroid thereafter. Postpartum enlargement of goiter size ceased, although elevation in the titer of anti-thyroid microsomal antibodies was not totally suppressed by glucocorticosteroid therapy.

Discussion

It is important to predict postpartum onset of thyroid dysfunction. Lazarus et al,[5] reported that among the 13 patients who developed postpartum thyroiditis after their first pregnancy, nine (69.2%) had a recurrence of thyroid dysfunction after their following pregnancies. In their study, patients with anti-thyroid peroxidase antibody titers above the 2SD or 3SD of upper normal limit were enrolled. Patients with low titer of antibodies do not always have recurrent episodes of postpartum thyroid dysfunction. When subjects were selected, the more severe cases, as judged by the appearance of hypothyroidism, all patients seemed to have recurrence of postpartum hypothyroidism.[5] In this study, we observed the postpartum hypothyroid patients with microsomal antibody titers more than 5×10^3. All the patients had relapses of postpartum hypothyroidism at almost the same time. These data clarified that recurrence of postpartum "hypothyroidism" could be predicted in patients who had had previous episode(s) of postpartum hypothyroidism and had high titers of anti-thyroid microsomal antibodies of more than 5×10^3 in early pregnancy.

We therefore selected two other patients (cases 10 and 11) in this study, who had transient postpartum hypothyroidism and high titers of microsomal antibodies. In case 10, although we were unsuccessful in preventing the development of postpartum thyroid dysfunction with glucocorticosteroid therapy, the onset of transient hypothyroidism was however delayed for two months as compared to that in her first episode and peak value of TSH was lower than that of the first episode. As summarized in Table 1, none of the nine patients showed two months difference of postpartum time between the occurrences of each episode. Thus, results in case 10 strongly suggest that the therapy was partially effective. Based on these findings, we increased the dose and duration of glucocorticoid therapy for case 11, and successfully prevented the development of postpartum thyroid dysfunction. Although postpartum increase in titers of anti-thyroid mi-

Table 1. Recurrence of postpartum hypothyroidism in patients with microsomal antibodies in titers more than 5×10^3. Comparison of the time of nadir of hypothyroidism

Case No.	Age at first pregnancy	The time of the nadir of hypothyroidism (months postpartum)		
		1st episode	*2nd episode*	*3rd episode*
1	28	*4.4*	*5.5*	*5.5*
2	26	*4*	*4*	*None**
3	30	*3*	*3*	*None**
4	25	*5*	*5*	*None**
5	30	*4*	*4*	*None**
6	26	*4*	*4*	*None**
7	21	*4*	*4*	*None**
8	27	*4*	*3*	*None**
9	30	*6*	*6*	*None**

* The third episode could not be examined because the patient had only two pregnancies

crosomal antibodies was not completely suppressed, relief obtained by the patient, from the symptoms of postpartum thyroid dysfunction dramatically improved her quality of life.

Our trial is too limited to discuss the effectiveness and the optimal protocol of short-term immunosuppressive therapy, and a systematic prospective study is necessary. However, the results obtained seem to be encouraging for the preventive therapy of autoimmune disease, because it is expected that autoimmune diseases may be tractable with currently available therapy before or in the ultra-early stage of their onset, although stages of the fully activated disease are hard to control. The problem is how to predict disease occurrence. This may also be applicable in the prevention of postpartum Graves' disease, the onset of which, according to one study is predictable.[18] The prevention of postpartum onset is of clinical importance for Graves' thyrotoxicosis, because 40% of female Graves' patients at childbearing age contract their disease during the postpartum period.[19] Prevention of the subgroups of patients with postpartum Graves' disease could reduce the total prevalence of patient populations with the disease. Furthermore, the same strategy could be used in the prevention of postpartum onset of other autoimmune diseases,[1] if their onset could be reliably predicted.

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