

Immunological Study on Autoimmune Postpartum Thyroiditis

Hyeon Man Kim,¹ Kap Bum Huh,¹ Hyun Chul Lee,¹
Sung Kil Lim,¹ Kil Park,² Jung Koo Youn,³ and Sang Yong Lee¹

Autoimmune postpartum thyroiditis (PPT) has been thought of as one of the organ-specific autoimmune diseases. The present study was designed to investigate whether the immunological changes during the postpartum period might induce this disease, by comparing the circulating lymphocyte subsets and antibody-dependent cell-mediated cytotoxicity (ADCC) between normal postpartum women and PPT patients. The results were as follows: 1) No significant differences in the circulating total T lymphocyte population, or suppressor T lymphocyte subsets, or in Th/Ts ratio were found among 25 PPT patients, 11 normal postpartum women and 11 normal non-pregnant women. 2) In PPT patients, helper T lymphocyte subsets were fewer in proportion than those of normal postpartum or non-pregnant women. However, B lymphocyte population ($19.7 \pm 7.8\%$) and ADCC activity ($.41 \pm .13$) in PPT patients were comparable to those in normal postpartum women ($18.3 \pm 4.8\%$, $.42 \pm .11$), although they were significantly greater than those in normal non-pregnant women ($13.3 \pm 5.9\%$, $.29 \pm .07$).

In conclusion, the enhancement of immune activities observed in PPT patients was comparable to that in normal postpartum women, suggesting that some other causative or triggering factors might be responsible for the occurrence of this disease.

Key Words: Autoimmune postpartum thyroiditis, lymphocyte subsets, postpartum women

Autoimmune postpartum thyroiditis (PPT) shares clinical features with Hashimoto's disease, with its characteristic occurrence following delivery or abortion and complete recovery within 10 months postpartum (Amino *et al.* 1976; Huh *et al.* 1980). As mentioned by Jansson *et al.* (1985), the reversibility and the organ-specificity of PPT apparently provide a unique human model for *in situ* studies on target organ destruction and functional impairment by autoimmune mechanisms. However, the study they conducted was one in which they compared PPT patients with healthy, non-pregnant and non-postpartum women.

There have been extensive studies done on immune activities during pregnancy (Damer *et al.* 1977).

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Department of Internal Medicine¹, Department of Surgery² and Department of Microbiology³, Yonsei University College of Medicine, Seoul, Korea.

Address reprint requests to Dr. K. B. Huh, Department of Internal Medicine, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul, Korea.

However, there are few reports on immune activities during the postpartum period, although it has been suggested that they are transiently enhanced (Jansson *et al.* 1984b). Considering the various immunological changes during pregnancy and the postpartum period, one could easily see why it was necessary to the investigation of organ-specific autoimmune disease, to compare PPT patients with healthy postpartum women.

The present study was designed to investigate whether the immune state during the postpartum period could be a primary factor in initiating PPT, by comparing the circulating lymphocyte subsets and antibody-dependent cell-mediated cytotoxicity (ADCC) between healthy postpartum women and PPT patients.

SUBJECTS AND METHODS

Subject and diagnosis

Twenty-five patients with PPT (group I) were studied. Their ages ranged between 23 and 33 (mean age: 28). Age-matched controls, 11 healthy postpartum women (group II) and 11 healthy non-pregnant

and non-postpartum women (group III) were used to establish normal values.

Based on classical clinical and biological criteria (Huh *et al.* 1980), the patients were diagnosed as having PPT. In each case, there was no previous history of thyroid disease except PPT, and there was diffuse goiter without fever or cervical tenderness within 10 months following delivery or abortion, lower serum thyroid hormone level combined with a higher thyroid-stimulating hormone (TSH) level and above normal radioactive iodine uptake (RAIU) value. Serum thyroid hormones and TSH were measured by radioimmunoassay (RIA); triiodothyronine (T_3) (normal range: 80-220ng/dl) and thyroxine (T_4) (normal range: 5-13 μ g/dl) by the solid phase RIA (Abbott Lab., U.S.A.), free T_4 (FT_4) (normal range: 0.6-1.6ng/ml) by the RIA using magnetic separation (Serono, Italy), and TSH (normal range: less than 8 μ IU/ml) by the immunoradiometric assay (Abbott Lab.). The anti-thyroglobulin (TG) antibody and the antithyroid microsomal (MC) antibody were tested with the tanned sheep erythrocyte (RBC) hemagglutination test kit (Fujirebio Inc., Japan). RAIU values were measured with 131 I. Urinary iodine excretion amounts were measured by a millivolt meter (Orion model 811) and a selective iodine electrode (Orion model 94-53).

Lymphocyte studies

Preparation of lymphocytes. Peripheral blood lymphocytes were isolated from the buffy coat with a Pasteur pipette after gradient centrifugation (40 \times g) for 30 min, using Ficoll-Hypaque solution, in which 9% Ficoll (Sigma Co., U.S.A.) and 33.9% Hypaque (Wintrop Lab., U.S.A.) were mixed in a ratio of 24:10. The isolated lymphocytes were rinsed 3 times and suspended in McCoy's medium containing 10% fetal calf serum (FCS) (Gibco Co., U.S.A.).

Total T lymphocytes. Twenty-five microliters of sheep RBC suspension, containing 4×10^8 cells/ml were added to 50 μ l of lymphocyte suspension containing 5×10^6 cells/ml. The mixture was centrifuged for 5 min at 50 \times g, and then rinsed and incubated for 60 min at room temperature (25 \pm 5 $^\circ$ C). The mixture was suspended for microscopic examination after incubation for 18 hr at 4 $^\circ$ C. Total T lymphocytes were identified by the formation of non-immune (E) rosettes.

B lymphocyte count. Five hundred microliters of phosphate buffer solution (PBS) without calcium or magnesium (Gibco) was added to 20 μ l of heat-inactivated rabbit anti-human O RBC antiserum. The mixture was incubated for 30 min at 37 $^\circ$ C after the addition of 500 μ l of 2.5% human O Rh $^+$ RBC, and then incubated again under the same conditions after the

addition of 100 μ l of complement of guinea pig (Difco Co., U.S.A.). The sediment, after centrifugation for 5 min at 200 \times g, was diluted with 1ml of PBS for the preparation of 1% O cell suspension. Fifty microliters of 1% O cell suspension was added to 50 μ l of lymphocyte suspension containing 2×10^6 cells/ml, and the mixture was incubated for 20 min at 37 $^\circ$ C. The sediment, after centrifugation for 20 min at 200 \times g, was suspended for microscopic examination.

For both T and B cell determinations, 100 cells were counted. Lymphocytes attached to more than 3 RBC were assumed to be positive. Readings were duplicated with, in most cases, ± 5 percent variation; the mean values were recorded.

T lymphocyte subsets. Ten microliters of isothianate fluorescein-labeled OKT $_4$ or OKT $_8$ (Ortho-mune Monoclonal Antibody, Ortho Diagnostic System, U.S.A.) was added to the mixture of 5 μ l of PBS and 100 μ l of lymphocyte suspension, containing 1×10^7 cells/ml. The mixture was incubated for 30 min at 4 $^\circ$ C and then centrifuged for 5 min at 2 $^\circ$ -8 $^\circ$ C at 300 \times g. The sediment was suspended with 1ml of PBS and examined for OKT $_4$ or OKT $_8$ positive cells under a fluorescence microscope.

Phytohemagglutinin (PHA) and concanavalin A (Con-A) responses. The lymphocyte suspension (1×10^6 viable cells/ml), diluted with McCoy's medium supplemented with glutamine (Gibco) and 10% FCS were incubated in wells of a microculture plate. Ten microliters of PHA (Difco) or Con-A (Difco) were then added to 200 μ l of lymphocyte suspension in each well. One microcurie of 3 H-thymidine (New England Nuclear, U.S.A.) was added and cultured for 3 days at 37 $^\circ$ C in a humidified 5% CO $_2$ atmosphere. The amount of tritiated thymidine incorporated by the cells was evaluated with a beta counter (Packard, U.S.A.), using 2-5ml of Tri-Carb liquid scintillation cocktail.

ADCC. One hundred microliters of target 51 Cr-chicken RBC, containing 2×10^6 cells, and 100 μ l of effector cells, containing 1×10^7 viable lymphocytes/ml, were mixed in each well, and then 50 μ l of heat-inactivated rabbit anti-chicken RBC antiserum (1:1,000) were added to each well. Each well was adjusted with RPMI 1640 to contain 250 μ l of total volume. Control wells for all experiments included those without effector cells (Triton X 100 for total releasable cpm) and those without antiserum (spontaneous releasable cpm). The plates were incubated for 4 hr at 37 $^\circ$ C in a humidified 5% CO $_2$ atmosphere. After carefully removing 100 μ l from each of the wells with an Eppendorf pipette with disposable tips (Brinkmann Instruments, Inc., Westburg, N.Y.), the supernatant

radioactivity was determined with a gamma counter (Packard). The counts per minute for each well were multiplied by 2.5 to obtain the total release. The mean counts per minute and the standard deviation were determined for each triplicate set and the percentage of specifically released ⁵¹Cr was calculated as follows:

$$\text{Cytotoxic index} = \frac{\text{Experimental release (cpm)} - \text{spontaneous release (cpm)}}{\text{Total release (cpm)} - \text{spontaneous release (cpm)}}$$

Statistical analysis was performed by using a two-tailed t-test. The significance was set at the .05 level. Values were expressed as mean±SD in the text, in tables and in figures.

RESULTS

Thyroid function test

The FT₄ and TSH levels of group II and group III were 1.27±0.16ng/ml compared with 1.24±0.19ng/ml, and 1.59±0.45uIU/ml compared with 1.63±0.36uIU/ml, respectively. They had no thyroid autoantibodies.

All patients in group I were hypothyroid and diagnosed at the 3rd to 8th month (5.0±1.5) postpartum. The mean T₃ (93.2±28.8ng/dl), T₄ (3.4±1.3µg/dl) and FT₄ (0.45±0.27ng/ml) levels were decreased, and their TSH levels were greater than 14uIU/ml. The mean amount of the iodine excreted in their urine (2.52±2.72mg/day) was slightly decreased without statistical significance (age-matched normal value 3.47±2.49mg/day, Kim *et al.* 1985). Tests for TG antibody and MC antibody were positive in 8 cases (32%) and 22 cases (88%), respectively. Their 2-hr (31.0%) and 24-hr (43.3%) RAIU values were increased significantly (Table 1).

There was no significant correlation between the postpartum period and thyroid function. There were negative correlations between MC antibody titers and serum T₃ levels (r=-.5594) or T₄ levels (r=-.5551) (Table 2).

Peripheral blood T lymphocyte

The circulating total T lymphocytes population were not significantly different among group I (68.0±9.0%), group II (71.7±5.1%), and group III (73.4±4.9%). The mean proportion of OKT₄ lymphocytes (Th) in group I (40.0±13.1%) were significantly fewer than those in group II (54.4±13.0%) and group

Table 1. Thyroid function in patients with postpartum thyroiditis

Study	Mean±S.D.	No. of Cases
T ₃ (ng/dl)	93.2±28.8	13
T ₄ (µg/dl)	3.4± 1.3	21
FT ₄ (ng/ml)	0.45±0.27	25
T ₃ /T ₄	27.1± 6.2	12
TSH (µIU/ml)	>14.0*	25
Anti-TG(+) (%)	32.0**	25
Anti-MC(+) (%)	88.0**	25
U-iod (mg/day)	2.52±2.72	25
RAIU 2-hr (%)	31.0±13.5	17
RAIU 24-hr (%)	43.8±20.7	17

*: Above 14µIU/ml in all cases

**: Per cent of positive autoantibody

Table 2. Correlation (r value) between antithyroid antibody titer and thyroid function in patients with postpartum thyroiditis

	Antithyroglobulin Antibody	Antimicrosomal Antibody	No. of Cases
Age	.1784	.1325	25
Post. P	.1015	-.1151	25
T ₃	-.0822	-.5594	13
T ₄	-.1981	-.5551	21
FT ₄	.1273	-.3431	25
TSH	-.3077	.3152	25
TG		.3283	25
MC	.3283		25
U-iod	-.1958	-.3702	25
RAIU 2-hr	.0737	.2276	17
RAIU 24-hr	.1830	.3317	17

Table 3. Immunological study

	Group I	Group II	Group III
Age (Yr)	28.0 ± 2.7	27.8 ± 3.0	27.7±2.6
Post.P (Mo)	5.0 ± 1.5	4.7 ± 1.4	
Total T (%)	68.0 ± 9.0	71.7 ± 5.1	73.4±4.9
Th (%)	40.0 ±13.1†#	54.5 ±13.0	59.6±7.5
Ts (%)	26.0 ±10.3	31.0 ±11.9	25.8±6.3
Th/Ts	1.97±1.81	1.86±0.48*	2.43±0.63
B cell (%)	19.9 ±7.8*	18.3 ±4.8*	13.3±5.9
ADCC	.41±.13*	.42±.11#	.29±.07

† p<.01, as compared with that of group II

p<.01, as compared with that of group III

* p<.05, as compared with that of group III

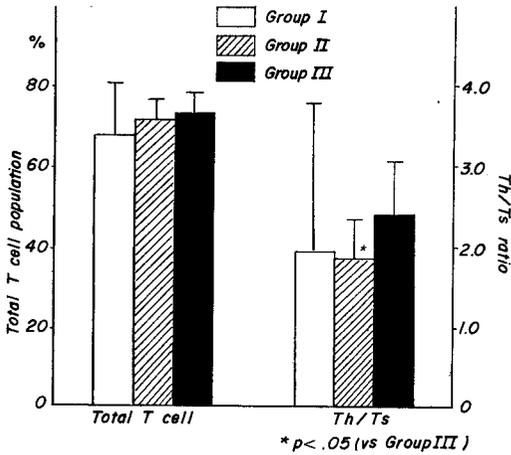


Fig. 1. Circulatory total T cell populations and Th/Ts ratio.

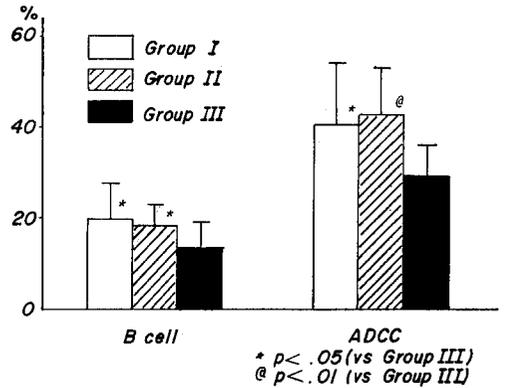


Fig. 2. Circulatory B cell populations and ADCC activities.

III ($59.6 \pm 7.5\%$), but as for the OKT₈ lymphocytes (Ts), there was no significant difference among the three groups. The Th/Ts ratios in group I (1.97 ± 1.81) were not significantly different from those in group II (1.86 ± 0.48) and from those in group III (2.43 ± 0.63), but between the latter two groups, there was a significant difference (Table 3, Fig. 1).

When compared with PHA and Con-A responses in group III, those in group I were slightly reduced, but not to a statistically significant extent (Table 4).

Table 4. PHA and Con-A response

	Postpartum Thyroiditis (n=6)	Normal Control (n=6)
PHA	16.5 ± 12.5	25.6 ± 16.5
Con-A	13.3 ± 9.9	16.5 ± 8.4

Peripheral B lymphocytes

The mean B lymphocyte population in group I ($19.9 \pm 7.8\%$) and that in group II ($18.3 \pm 4.8\%$) were significantly higher than that in group III ($13.3 \pm 5.9\%$, p < .05) (Table 3, Fig. 2).

ADCC

When compared with the mean ADCC in group III ($.29 \pm 0.07$), those in group I ($.41 \pm .13$, p < .05) and group II ($.42 \pm .11$, p < .01) were significantly increased (Table 3, Fig. 2).

The relationship of the postpartum period to anti-thyroid antibody titer, T lymphocyte count, B lymphocyte count and ADCC, in group I

In group I, there was no significant correlation between the postpartum period and the titer of anti-thyroid antibody, T lymphocyte count, B lymphocyte count or ADCC.

DISCUSSION

From the viewpoint of transplantation immunology, pregnancy has been described as a successful allograft of foreign tissue, since it involves intimate association of the histocompatible sperm and ovum. Recently, data have been accumulating on the depression of cell-mediated immunity during pregnancy as a cause of maternal immunological inertness (Scott and Rote 1985). Therefore, autoimmune diseases such as Graves' disease (Amino *et al.* 1982c), autoimmune thyroiditis (Nelson *et al.* 1974), systemic lupus erythematosus, rheumatoid arthritis, may ameliorate in late pregnancy, and the immune response to some viruses such as herpes virus, cytomegalovirus and rubella virus seems to be impaired during pregnancy.

It has been reported that autoimmune diseases have ameliorated during pregnancy, and that the patients have suffered relapses following delivery. It has been suggested that the immune activity during the postpartum period is transiently enhanced, resembling the "rebound phenomenon" observed after withdrawal of immunosuppressive glucocorticoid therapy.

In this study, we have found that the circulating B lymphocyte population and the level of ADCC of normal postpartum women were greater than those of normal non-pregnant and non-postpartum women. However, it has not been revealed whether there are any changes in the proportions of either T or B lymphocytes, or the level of ADCC according to the length of time after delivery (month postpartum), in normal postpartum women.

Thyroid dysfunction occurring soon after delivery represents a syndrome unique from the usual types of thyroid diseases with a different presentation and prognosis. Previously, postpartum hypothyroidism was thought to result from hypopituitarism (Sheehan 1939). In general, however, it is believed that these postpartum abnormalities develop in conjunction with transient enhancement of immune activity and are induced by the aggravation of subclinical autoimmune diseases (Ginsberg and Walfish 1977; Amino *et al.* 1982b; Dahlberg and Jansson 1983). Persistent rather than transiently elevated titers of antithyroid autoantibodies, as well as needle biopsy findings in these patients, may indicate underlying chronic thyroiditis and the associated risk of progression to permanent hypothyroidism (Ginsberg and Walfish 1977; Kim *et al.* 1986). All patients in this study had characteristic laboratory features of the hypothyroid phase of subacute thyroiditis, with decreased serum T_4 , T_3 and FT_4 levels, an increased serum TSH level and increased RAIU. The MC antibody was detected in 88% of the patients, and the TG antibody in 32% of the patients. There were negative correlations between titers of the MC antibody and the serum T_3 or T_4 levels, which was similar to the result of a study by Jansson *et al.* (1984a). However, it is not clear what brings about the production of MC and TG antibodies or what's the role of them. Mori *et al.* (1985) had suggested that thyroglobulin-specific suppressor T cells were related to the regulation of the production. It was also suggested that the MC and TG antigens which existed on thyroid cell surfaces would be presented to the helper-inducer T cells in conjunction with HLA-DR antigens (Volpé *et al.* 1984).

There are many reports on cellular immunity in autoimmune thyroiditis, and it has been frequently suggested that suppressor T lymphocytes play an important role. Jansson *et al.* (1984b) mentioned that the intrathyroidal production of antithyroid autoantibodies had a major role in the pathogenesis of PPT, since in their study on PPT patients, they found that intrathyroid suppressor T lymphocytes were significantly decreased, but circulating T lymphocytes were not. In this study, the circulating suppressor T lymphocyte subsets in PPT patients were slightly decreased over those in normal postpartum women or those in normal non-pregnant women, but the difference was not statistically significant.

Thielemans *et al.* (1981) and Sridama *et al.* (1982) reported that a relatively increased ratio of Th/Ts and increased numbers of B lymphocytes might play a role in the production of antithyroid autoantibodies. However, there are many controversial data about suppressor T lymphocytes, such as functional impairment (Okita *et al.* 1981), or no significant changes in their number (Jansson *et al.* 1983; Wall *et al.* 1983) or in function (Aoki *et al.* 1979) in patients with autoimmune thyroiditis. Bonnyns *et al.* (1983) reported that the thyroid functional state might play a role in the functional regulation of immunomodulatory T lymphocytes, but the question awaits further investigation.

Jansson *et al.* (1984b) reported that they found in their study that there was no significant difference in the circulating total T lymphocyte population, helper T lymphocytes, and B lymphocytes between PPT patients and normal non-pregnant women, and that they observed a significant increase in intrathyroidal B lymphocytes in PPT patients. In our PPT patients, the circulating total T lymphocyte population and the Th/Ts ratios were not significantly different from those of normal non-pregnant women, and helper T lymphocytes were decreased significantly and B lymphocytes increased significantly compared to those of normal non-pregnant women. It is not clear what the decrease of helper T lymphocytes in our PPT patients means, but similar results have been reported by Thielemans *et al.* (1981) and Chan and Walfish (1986). The latter, especially, studied PPT patients in the hyperthyroid phase, and the study revealed that the activated helper T lymphocyte subset was significantly decreased, and the activated suppressor T lymphocyte subset was increased. However, many studies had previously revealed that the helper T lymphocyte population was not significantly different in autoimmune thyroiditis (Sridama 1982; Jansson *et al.* 1984b). This discrepancy may be attributable to the fact that OKT₄ and OKT₈ monoclonal antibody specificities do not represent truly the functional characteristics of the phenotypically identified cells and that alterations of lymphocyte subsets may not necessarily parallel with those of antigen specific T lymphocytes. Wall *et al.* (1983) have reported that B lymphocyte population in patients with autoimmune thyroiditis were increased when compared with those of the normal control. The increase in B lymphocytes has been suggested to induce the production of suppressor T lymphocyte-specific autoantibodies (Sakane *et al.* 1979). Delfraisy

et al. (1980) blamed the cause of autoimmune thyroiditis on the impairment of helper T lymphocytes. Recently, Tao et al. (1985) have suggested that the production of antithyroid autoantibodies results from the functional impairment of thyroglobulin-specific suppressor T lymphocytes and the functional enhancement of helper T lymphocytes.

Calder et al. (1976) and Amino et al. (1982a) claimed that the elevated ADCC in patients with autoimmune thyroiditis might be the cause of the disease. Our PPT patients had an increased ADCC over that of normal non-pregnant women, but the degree of increase in ADCC was similar to that in normal postpartum women.

In summary, this investigation demonstrated that immune activities in normal postpartum women were enhanced to a degree comparable to those of PPT patients. These data suggested that enhanced immune activities might be a condition required for the disease to develop, but not a direct causative factor, and some other causative or triggering factors such as genetic predisposition, viral infection, iodine intake (Yoshinari et al. 1983; Bagchi et al. 1985; Jansson et al. 1985; Lee et al. 1985), and/or some unknown factors might be responsible for the occurrence of the disease. Further studies on intrathyroidal lymphocytes and/or activated lymphocytes in PPT patients during the earlier postpartum period compared with those in normal postpartum women may define the precise role of immune activities in the clinical expression of PPT.

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