Endocrine, *vol. 27, no. 3, 279–282, August 2005* 0969–711X/05/27:279–282/$30.00

Follow Up of Patients with Postpartum Thyroiditis

A Population-Based Study

Farzaneh Sarvghadi, Mehdi Hedayati, Yadollah Mehrabi, and Fereidoun Azizi

Endocrine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, I.R. Iran

In this survey we studied the prevalence of permanent hypothyroidism and prognostic factors for its occurrence 3–5 yr after postpartum thyroiditis (PPT); 54 of 120 women with PPT and 50 of 920 healthy women from among 1040 women followed 4–5 yr earlier for PPT were recalled. Demographic information, signs, and symptoms of thyroid disorders and results of physical exams were documented. Serum T_3, T_4, RT_3U, TSH, and antithyroperoxidase (antiTPO ab) and antithyroglubolin (antiTg ab) antibodies were measured. Twenty-two percent of the cases and four percent of the control group had permanent hypothyroidism, $p < 0.01$. Based on the TSH level we divided the case group into two subgroups: PPT-Hypothyroidism (PPT-Hypo) and PPT-Eutyhroidism (PPT-EU); PPT-Hypo had greater titer of antiTPO ab than PPT-Eu (437 ± 283 vs 126 ± 221 IU/mL, $p < 0.001$). Comparison of mean peak serum TSH level and antiTPO ab during the postpartum thyroiditis phase between PPT-Hypo and PPT-Eu in the case group was significant (56 ± 24 vs 23 ± 28 mU/L, $p < 0.001$, and 1960 ± 1270 vs 640 ± 959 IU/L, $p < 0.001$, respectively). Results of this survey show a high prevalence of permanent hypothyroidism following PPT in Tehran. High titers of antiTPOAb and TSH levels at postpartum period are prognostic factors for occurrence of permanent hypothyroidism.

Key Words: Postpartum thyroiditis; hypothyroidism; thyrotropin; antithyroid antibodies.

Introduction

Postpartum thyroiditis (PPT) is an autoimmune process that occurs during the first year after delivery *(1–4)* with a prevalence rate ranging between 1.1% and 16.7% *(5–7)*. The main pathogenesis is autoimmunity, which is presented by elevated titers of thyroid autoantibodies (antiTPO antibody and antiTg antibody) in serum and T-cell infiltration in thyroid tissue *(8,9)*.

Received May 15, 2005; Revised June 15, 2005; Accepted June 16, 2005.
Author to whom all correspondence and reprint requests should be addressed: Fereidoun Azizi, MD, Endocrine Research Center, P.O. Box: 19395-4763, Tehran I.R. Iran. E-mail: Azizi@erc.ac.ir

Although there is usually a transient period of thyrotoxicosis, hypothyroidism, or both, based on the autoimmune pathogenesis, long-term follow ups reveal permanent hypothyroidism in 20–30% of patients *(10–12)*. Recent studies have demonstrated a positive relationship between severity of hypothyroidism and high titer of antiTPO antibody during the PPT phase and occurrence of permanent hypothyroidism on long-term follow up *(13)*, but the relationship between permanent postpartum hypothyroidism and other factors like specific HLA types, multiparity, and previous history of abortion are still controversial issues in different studies *(14,15)*.

Considering the paucity of information regarding the follow up of patients with PPT diagnosed during an epidemiological survey of PPT, this investigation was conducted to follow the outcome of patients with PPT in a population based study.

Results

Mean ± SD for age of women with PPT and the control groups were 30 ± 5 and 32 ± 4.5 yr, respectively, and the mean durations from previous episodes of PPT were 4.2 ± 0.8 and 4.5 ± 0.6 yr in the case and control women (no significant differences).

Twelve women in the case group had abnormal thyroid function tests; 9 women had overt hypothyroidism and 3 women had subclinical hypothyroidism, so the prevalence rate of permanent hypothyroidism was 22.2%; there was no case of thyrotoxicosis. In the control group, two women (4%) had subclinical hypothyroidism, none had overt hypothyroidism or thyrotoxicosis, and the occurrence of permanent hypothyroidism was significantly higher in the case as compared to the control group (22.2% vs 4%, $p < 0.01$) (Table 1). Comparison for clinical manifestations between the case and control groups was not significant.

Serum concentrations of T_4, T_3, RT_3U, TSH, and thyroid autoantibodies were compared between case and control groups (Fig. 1). Mean serum TSH in the case group was significantly greater than in the controls (7.3 ± 13 vs 2.0 ± 0.2 mU/L, $p < 0.001$) but mean serum T_4-T_3 and RT_3U was the same between these two groups. Mean titer of antiTg ab was greater in the case than in the control group (360 ± 571 vs 41.2 ± 34 IU/mL, $p < 0.001$). However, the differences

Table 1
Occurrence of Thyroid Dysfunction
in Patients with Postpartum Thyroiditis and the Controls

Thyroid dysfunction	Case* ($n = 54$)	Control ($n = 50$)
Hypothyroidism overt	9	0
Subclinical	3	2
Thyrotoxicosis	0	0
Total	12†	2
	(22.2%)	(4%)

*Women with history of PPT, 5 yr prior to this study.
†$p < 0.01$.

in serum titer of antiTPO were not statistically significant between the two groups (196 ± 267 vs 74.2 ± 160, p = NS). Based on the TSH level, patients with history of PPT (case group) were divided into two groups: hypothyroid (PPT-Hypo) and euthyroid (PPT-Eu) 5 yr after the original survey of PPT. Mean serum TSH and T_4 were 22 ± 25 mU/L and 4.3 ± 2.5 µg/dL in PPT-Hypo, and 2.4 ± 1.4 mU/L and 7.2 ± 0.2 µg/dL in PPT-Eu women, but there was not significant difference for mean serum T_3 or RT_3U. Mean titer of antiTPO ab was significantly greater in PPT-Hypo than PPT-Eu women (437 ± 283 vs 126 ± 221 IU/mL, $p < 0.001$) (Fig. 2). We also compared mean serum concentrations of TSH-T_3-RT_3U and T_4 between PPT-Eu women and the control group and no significant differences were observed; however, comparison of these two groups for mean serum autoantibodies revealed significant differences, mean serum antiTPO ab was greater in the PPT-Eu as compared to the control group (126 ± 221 vs 74 ± 160, $p < 0.05$), and mean serum anti-Tgab was also greater in PPT-Eu when compared to that of the control group (379 ± 629 vs 41.2 ± 34, $p < 0.001$).

During the previous PPT phase, mean peak of serum TSH in PPT-Hypo was greater than among PPT-Eu women (55.8 ± 24 vs 23.1 ± 28 mU/L, $p < 0.05$); indeed more than 83% of PPT-Hypo women and 25% of PPT-Eu women had peak serum TSH concentrations over 45 mU/L ($p < 0.001$). The mean peak of antiTPO ab was also greater during PPT, in the PPT-Hypo compared to the PPT-Eu women (1960 ± 1270 vs 640 ± 959 IU/mL, $p < 0.001$). Values for antiTg ab levels were not significant between the two groups (977 ± 153 vs 1048 ± 770 IU/mL).

Discussion

Postpartum thyroiditis as an autoimmune process has been known for more than 25 yr and, based on its pathogenesis, long-term follow ups have revealed the occurrence of permanent hypothyroidism several years after recovery *(11, 14,16)*. In the present survey, a population-based study, we followed our patients 4–5 yr after occurrence of PPT, and observed that more than 22% of them were hypothyroid, a finding in agreement with results of the other population-based studies; we believe that longer durations of follow-up will reveal a higher rate of permanent hypothyroidism. Nikolai et al. followed 25 women for 3 yr after PPT and 12% of them had permanent hypothyroidism *(11)*. Tachi and coworkers observed 44 women with PPT for about 8.7 yr following delivery and permanent hypothyroidism was detected in 23% of them *(15)*. In Sweden, a follow up of 47 patient with PPT revealed a prevalence rate of 30% *(12)* and from UK, a prevalence rate of 23% was reported after a 3.5 yr follow up of 40 women with PPT *(14)*. Lucas et al. reported a prevalence rate of 11.1% for permanent hypothyroidism after 3.5 yr of follow up of 42 women with PPT *(16)*; Premawardhana et al. also followed 48 antiTPO-positive women with PPT (group 1), 50 antiTPO-positive without PPT (group 2), and 70 antiTPO-negative women (group 3) for a mean duration of 77 mo postpartum and observed hypothyroidism in 46% of group 1 vs 4% of group 2 and 1.4% of group 3 ($p < 0.001$) *(13)*. The present study reveals that comparison for clinical presentation between case and control groups and also hypothyroid and euthyroid subgroups was not significant; in other words, none of the clinical manifestations were specific for diagnosis; Lucas et al. from Spain reported that clinical presentations of their patients were not diagnostic for hypothyroidism *(16)*.

Comparison between the case and control groups for mean thyroid function tests and autoantibodies revealed significant results for mean serum TSH and antiTg antibodies; the greater mean serum TSH in the case group was acceptable, because over 20% of women in the case group had hypothyroidism, but elevated mean titer of antiTg antibody in the case group showed that there is probably a subclinical process of autoimmunity in this group as compared to the control group. Analyses of these data in the case group between hypothyroid and euthyroid women for mean serum TSH and T4 were significant; the high mean serum TSH and low mean of T4 in hypothyroid women were predictable, but an interesting observation we made was the significantly greater mean titer of antiTPO ab (but not antiTg antibody) in the PPT-Hypo group in comparison to the PPT-Eu women. It is suggested that elevated mean titers of this antibody are evidence of an acute autoimmune disorder and may be a clue for recurrence of hypothyroidism; it is a documented fact today that antiTPO ab is a more specific factor than antiTg antibody for detection of acute autoimmunity in thyroid disease and plays an important role in tissue destruction due to Hashimoto's hypothyroidism and atrophic thyroiditis *(17–20)*.

In this study we observed that the mean peak of serum TSH of the case group, during the previous PPT phase, was significantly greater in the hypothyroid as compared to the euthyroid women of this group, demonstrating that the significantly higher TSH previously was found in the women who developed hypothyroidism later. Furthermore, 83%

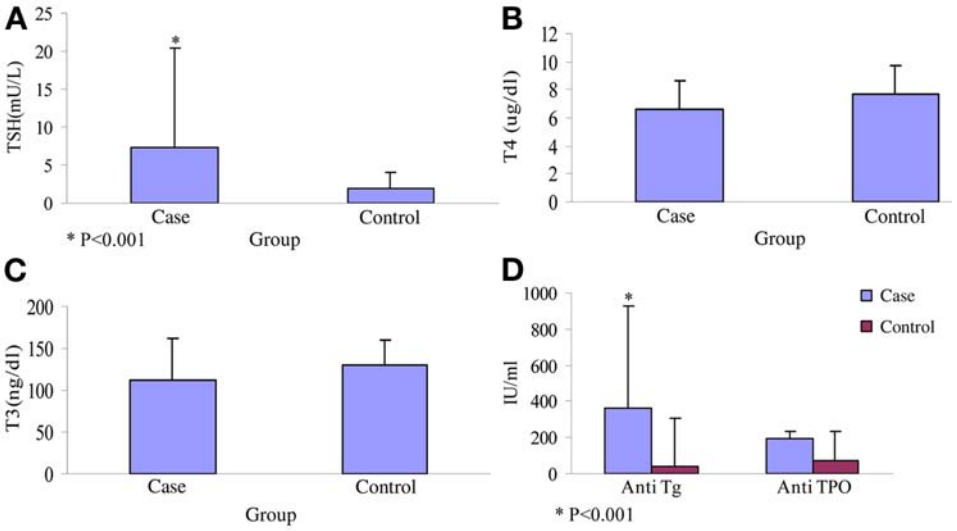

Fig. 1. Comparison of thyroid function tests and serum auto antibodies concentration between case (women with history of PPT, $n = 54$) and control ($n = 50$) subjects. The bars represent mean ± SD. Values in **A**, **B**, **C**, and **D** represent TSH, T_4, T_3, and antibodies.

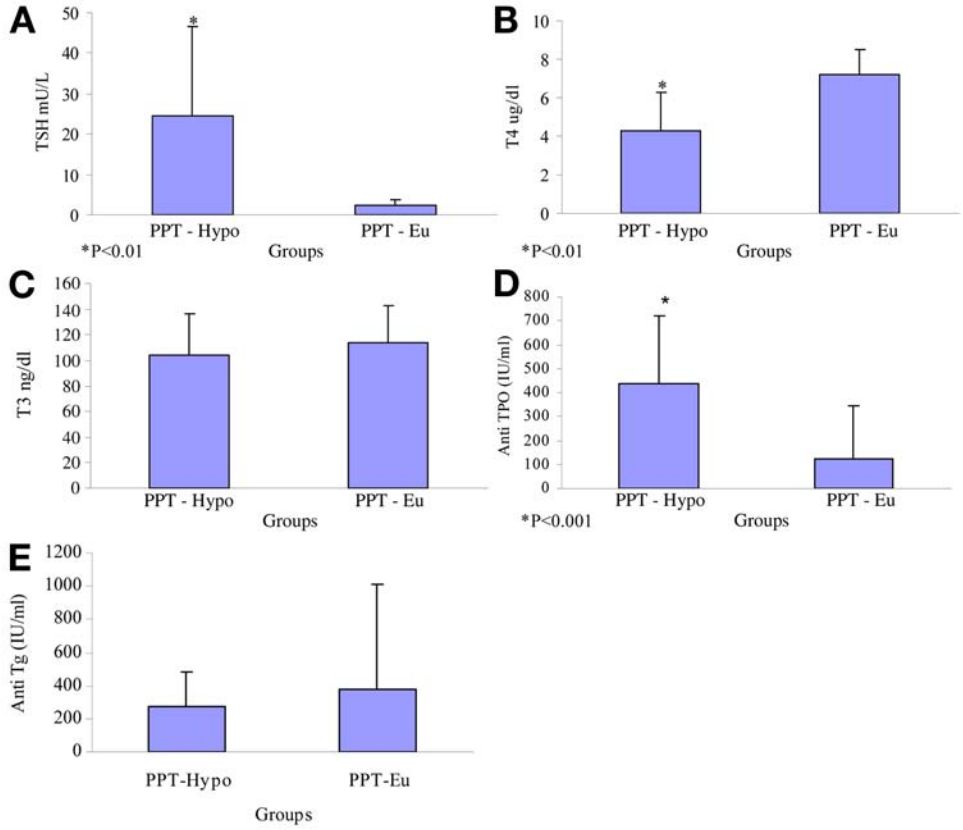

Fig. 2. Thyroid function tests and serum autoantibodies concentration in women with history of PPT: Comparison between hypothyroid (PPT-Hypo) and euthyroid (PPT-Eu) women, 5 yr after occurrence of PPT. The bars represent mean ± SD. Values in **A**, **B**, **C**, **D**, and **E** represent TSH, T4, T3, antiTPO ab, and antiTg ab.

of the hypothyroid women and less than 25% of the euthyroid women had a peak TSH more than 45 mU/L during the previous PPT ($p < 0.001$). This was also true for mean peak antiTPO ab; women with larger titers of antiTPO ab during PPT had higher risk for occurrence of permanent hypothyroidism. This is in agreement with other studies; a recent study conducted by Premawardhana et al. shows similar results; they followed 48 women for 6.5 yr after PPT and observed a positive relationship between peak titer of antiTPO ab during PPT and occurrence of permanent hypothyroidism. More than 70% of their hypothyroid women at follow up had TSH over 20 mU/L during the PPT phase that was significantly greater than that of euthyroid women *(13)*. Lucas and co-workers also reported a positive relationship

between mean peak of serum TSH and antiTPO ab and permanent hypothyroidism on follow up of PPT *(16)*. We conclude therefore that severity of the hypothyroid phase (based on serum TSH) and high titers of antiTPO antibody during PPT period are two strong predicting factors for further occurrence of permanent hypothyroidism. The main limitation of this survey was the number of patients who responded to our invitation, which was 48% of the total women having a previous history of postpartum thyroiditis.

Based on the results of the present study and the autoimmune pathogenesis of PPT, we recommend long-term follow up for all women with PPT for earlier diagnosis and treatment of permanent hypothyroidism, especially if they have had a severe hypothyroid episode or high titer of antiTPO ab.

Materials and Methods

In our previous study on the prevalence of postpartum thyroid dysfunction conducted in Tehran (1998–1999) *(7)*, 1040 women were evaluated monthly for occurrence of PPT during the first year after delivery. At the end of 1 yr, 120 women had PPT (patient group) and 920 women remained euthyroid (normal group). In this study, all patients with a history of PPT were recalled and 54 women responded. Of the previous normal group, 50 women were selected randomly as the control group. A questionnaire was completed for symptoms of thyroid disorders including hair loss, fatigue, palpitation, weight changes, appetite, sleep changes, dry or wet skin, preorbital edema, puffiness, tremor, and menstruation changes. An endocrinologist performed a complete physical examination. A venous sample was obtained for thyroid function tests and serum thyroid autoantibody concentrations at present study and also original survey. Fifty-one women of the case group had transient hypothyroidism during previous PPT who used levothyroxin only for several months but three women had permanent hypothyroidism; for three women in the case group who had used levothyroxine for hypothyroidism after the previous PPT episode until present study, information and blood samples were obtained 8 wk after discontinuation of levothyroxine.

Serum T_3, T_4, and RT_3U concentrations were measured by RIA, TSH by IMA (Isotope Co., Hungary) and antithyroperoxidase antibody (antiTPO ab)–antithyroglubolin antibody (AntiTg Ab) evaluated using ELISA (Labodia, Switzerland); the normal (reference) ranges are: T_3: 60–200 ng/dL; T_4: 4.5–12.7 μg/dL; RT_3U: 25–35%; TSH: 0.3–6 mU/L, AntiTPO antibody up to 100 IU/mL, and antiTg antibody up to 150 IU/mL.

Hypothyroidism was diagnosed in patients with $T_4 < 4.5$ μg/dL and TSH > 6 mU/L; those with a normal T_4 but TSH > 6 mU/L were considered to have subclinical hypothyroidism. Positive autoantibody was defined as titer greater than 100 IU/mL and 150 IU/mL for antiTPO Ab and antiTg Ab, respectively.

Statistical Analysis

Initially we collected data of both the case and control groups, then on the bases of serum TSH concentration, we divided women in the case group into two subgroups: PPT-Hypothyroid (PPT-Hypo) with previous history of postpartum thyroiditis 5 yr previously who were currently hypothyroid and PPT-Euthyroid (PPT-Eu) with history of postpartum thyroiditis who were presently euthyroid. We compared the variables of these subgroups, as we did the PPT-Eu with the control group; eventually the new data of the present study were compared with that of the earlier PPT phase. We compared quantitative variables using Student's *t*-test and autoantibodies with Mann–Whitney, SPSS version 10 software. A p value below 0.05 was considered significant.

References

1. Amino, N., Tada, H., and Hidaka, Y. (1999). *Thyroid* **9,** 705–713.
2. Lazarus, J. H. and Kokandi, A. (2000). *Clin. Endocrinol.* **53,** 265–278.
3. Lazarus, J. H., Parkes, A. B., and Premawardhana, L. D. (2002). *Autoimmunity* **35,** 169–173.
4. Muller, A. F., Drexhage, H. A., and Berghout, A. (2001). *Endocr. Rev.* **22,** 605–630.
5. Stagnaro-Green, A. (2000). *Endocrinol. Metab. Clin. North Am.* **29,** 417–430.
6. Barca, M. F., Knobel, M., Tomimori, E., Cardia, M. S., and Medeiros-Neto, G. (2000). *Clin. Endocrinol.* **53,** 21–31.
7. Shahbazian, H. B., Sarvghadi, F., and Azizi, F. (2001). *Eur. J. Endocrinol*. **145,** 397–401.
8. Kita, M., Goulis, D. G., and Avramides, A. (2002). *J. Endocrinol. Invest*. **25,** 513–519.
9. Giltay, E. J., Fonk, J. C., von Blomberg, B. M., Drexhage, H. A., Schalkwijk, C., and Gooren, L. J. (2000). *J. Clin. Endocrinol. Metab*. **85,** 1648–1657.
10. Lazarus, J. H., Ammari, F., Oretti, R., Parkes, A. B., Richards, C. J., and Harris, B. (1997). *Br. J. Gen. Pract*. **47,** 305–308.
11. Nikolai, T. F., Turney, S. L., and Roberts, R. C. (1987). *Arch. Intern. Med*. **147,** 221–224.
12. Jansson, R., Bernander, S., Karlsson, A., Levin, K., and Nilsson, G. (1984). *J. Clin. Endocrinol. Metab*. **58,** 681–687.
13. Premawardhana, L. D., Parkes, A. B., Ammari, F., et al. (2000). *J. Clin. Endocrinol. Metab*. **85,** 71–75.
14. Othman, S., Phillips, D. I., Parkesm, A. B., et al. (1990). *Clin. Endocrinol*. **32,** 559–564.
15. Tachi, J., Amino, N., Tamaki, H., et al. (1988). *J. Clin. Endocrinol. Metab*. **66,** 480–484.
16. Lucas, A., Pizarro, E., and Granada, M. L. (2000). *Thyroid* **10,** 71–77.
17. Chiovato, L., Bassi, P., Santini, F., et al. (1993). *J. Clin. Endocrinol. Metab*. **77,** 1700–1705.
18. Guo, J., Jaume, J. C., Rapoport, B., and McLachlan, S. M. (1997). *J. Clin. Endocrinol. Metab.* **82,** 925–931.
19. Toldy, E., Locsei, Z., Kalmar, I., Varga, L., and Kovacs, L. G. (1996). *Orv. Hetil.* **137,** 2075–2080.
20. Hollowell, J. G., Staehling, N. W., Flanders, W. D., et al. (2002). *J. Clin. Endocrinol. Metab*. **87,** 489–499.