Prevalence and characteristics of postpartum thyroid dysfunction in Tehran

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Abstract
Objective: To determine the prevalence of postpartum thyroiditis (PPT), one of the autoimmune disorders of the thyroid which usually occurs in women in the first year after parturition. PPT presents with periods of transient thyrotoxicosis and hypothyroidism, in many cases resulting in permanent hypothyroidism.

Design: The study involved 1040 mothers who had contacted five health centers in Tehran for vaccination of their children.

Methods: Signs and symptoms of hypothyroidism and thyrotoxicosis, and the presence of goiter (using the World Health Organization classification), were sought. Serum T3, T4, TSH, anti-TPO and anti-Tg antibodies were measured at 3, 4.5, 6 and 9 months after parturition. In those with hypothyroidism or thyrotoxicosis and a matched group of normal women, thyroid sonography was performed.

Results: The prevalence of thyroiditis was 11.4%. Hypothyroidism and thyrotoxicosis occurred in 68 and 42 mothers respectively. Nine had thyrotoxicosis followed by hypothyroidism. There was one case of Graves’ disease. Out of 68 hypothyroid patients, 33 women underwent treatment with levothyroxine (because of the severity of symptoms) for 12 months. Six women showed increased TSH at 6 weeks after discontinuation of thyroxine. Stage II goiter (World Health Organization classification) were observed in 21.8% of patients and in 6.7% of postpartum euthyroid women (P < 0.001). Positive anti-TPO was found in 61.5% of patients and in 19% of the control group; positive anti-Tg was found in 58% of patients and in 6% of the control group (P < 0.001). Sonographic changes were observed in 96% of the patients and in 7% of the control group (P < 0.001). There was no significant correlation between the occurrence of thyroiditis and parity, the age of the mother, a previous history of thyroid disease in the patient or family, breast-feeding, or the gender of the child.

Conclusion: The results of this study show a high prevalence of PPT in Tehranian women. This may be due to the length and frequency of follow-up and/or the transition from low to adequate iodine intake. The major difference with respect to other studies is the low frequency of the biphasic form of PPT.

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Introduction
Postpartum thyroiditis (PPT) consists of a group of autoimmune thyroid disorders, occurring in the first year after delivery (1, 2). It presents as transient periods of thyrotoxicosis, hypothyroidism or both (3), and results in permanent hypothyroidism in some patients. PPT was first described in 1948 by Robertson (4) and further characterized by Amino et al. in 1976 (3). During the last 20 years, several epidemiological studies from different parts of the world have reported a prevalence of PPT ranging from 1.1 to 16.7% (5–18). This wide range may be due to differences in ethnic group, geographical area, methodology, or the rate of follow-up visits for patients in the first year after parturition.

The aim of the present study was to assess the prevalence of PPT in a group of Tehranian women, and to describe the clinical and laboratory characteristics together with factors associated with its development and evolution.

Subjects and methods
Patient population
All of the healthy Tehranian women who brought their children for vaccination to five health centers in Tehran in the third month postpartum were requested to participate in this study. From October 1998 to July 1999, 1040 women agreed to participate in this
survey. Every woman underwent clinical and paraclinical evaluation at 3, 4.5, 6 and 9 months after delivery.

**Study protocol and methods**

Initial clinical evaluation included family and personal history of thyroid disorders, the number of pregnancies, the gender of the infant, and information relating to breast-feeding, drug use, and iodized-salt intake. Each patient was asked to complete a specific thyroid-symptom questionnaire by answering yes or no to a set of 45 questions regarding hypo- and hyperthyroidism. Physical examination for signs of thyroid dysfunction, and estimation of thyroid size by using palpation, were then performed; thyroid size was classified—according to the World Health Organization classification—into the following grades: 0, not palpable; 1, palpable but not visible; 2, visible goiter.

**Follow-up clinical evaluation** At each postpartum visit, women were asked about breast-feeding and drug consumption. Symptoms and signs of thyroid dysfunction and the size of the thyroid were assessed. Blood samples were drawn at each visit, to determine the serum tri-iodothyronine (T₃), thyroxine (T₄) and thyrotrropin (TSH) concentrations. T₃ resin uptake and antibody titers. A random urine sample was obtained, to determine urinary iodine excretion.

**Laboratory measurements** Urinary iodine content was measured by the digestion method (Sandell-Kolthoff), and commercially available kits were used to measure serum concentrations of T₃, T₄ and T₃ resin uptake (by RIA), TSH (by immunoradiometric assay; Spectra, Fenzia, Finland), and anti-Tg and anti-TPO by enzyme-linked immunosorbent assay (Radim, Rome, Italy). The normal (reference) ranges are as follows: T₃, 80–220 ng/dl; T₄, 4.5–12.7 μg/dl; T₃RU 25–35%; TSH, 0.3–4.5 mU/l, anti-TPO, up to 100 IU/ml; anti-Tg, up to 150 IU/ml.

**Diagnosis of PPT** Transient thyrotoxicosis was diagnosed in patients with T₄ values >12.7 μg/dl and/or T₃ > 220 ng/dl and TSH <0.3 mU/L with high free T₄ index (FT₄I) that lasted less than 8–12 weeks. Hypothyroidism was diagnosed in women with T₄ values <4.5 μg/dl and TSH values >10 mU/L. A TRH test was used for definite diagnosis in those subjects with borderline results in thyroid function tests, and in subjects with 4.5 < TSH < 10; if the TSH response was above 22 mU/l 30 min after TRH injection, the subject was included in the hypothyroid group.

Because of the difficulties associated with interruption of breast-feeding, we did not use radiiodine uptake of the thyroid to differentiate PPT from Graves’ disease and other causes of hyperthyroidism. Instead, judgment was based on the clinical course of the disease. The erythrocyte sedimentation rate was assessed in hyperthyroid patients, to rule out subacute thyroiditis.

One hundred and twenty postpartum women without hormone abnormalities were selected randomly as the control group. None of the subjects in the PPT and control groups was diabetic. All of the patients and control subjects underwent ultrasonography by using 7.5 MHz portable equipment (Model SSD 210 DxII; Aloka, Tokyo, Japan).

All PPT patients were followed monthly for up to 12 months postpartum. For each woman, ultrasonography and laboratory evaluation of serum T₃, T₄, T₃RU and TSH were performed at each follow-up visit. Anti-Tg and anti-TPO antibodies were measured in 97 out of 119 patients at each visit.

**Statistical analysis**

We compared variables by using the Student’s t-test and chi squared, and employed the Pearson test to evaluate correlations between variables.

**Results**

One thousand and forty women were initially included in the study at 3 months postpartum: 930 (89%), 834 (80%), and 760 (73%) were followed at 4.5, 6 and 9 months postpartum respectively. One hundred and nineteen women developed PPT, the prevalence being 11.4%. We detected only one permanent, diffuse, toxic goiter.

All patients were diagnosed in the first 6 months after delivery and there were no new cases thereafter. The prevalence and incidence of PPT at 3, 4.5, 6 and 9 months postpartum are shown in Table 1.

Of 119 PPT patients, 68 (57%) presented only with hypothyroidism, 42 (35%) presented with transient hyperthyroidism, and nine (8%) presented with transient hyperthyroidism followed by hypothyroidism. Figure 1 shows the occurrence and times of onset of several types of thyroid derangement in postpartum women: 37 out of 119 patients developed PPT at 3 months after delivery (seven were hypothyroid, 22 were thyrotoxic, and eight were thyrotoxic then hypothyroid), 49 patients developed PPT at 4.5 months after delivery (38 were hypothyroid, 10 were thyrotoxic, and one was thyrotoxic then hypothyroid), and 33 patients developed PPT at 6 months after delivery (23 were hypothyroid and 10 were thyrotoxic).

The thyrotoxic patients had a few mild signs and symptoms, such as tremor, tachycardia and nervousness, and none of them required treatment. Thirty-three (48%) of the hypothyroid patients had moderate to severe signs and symptoms of hypothyroidism and required treatment with 75 to 100 μg levothyroxine dialy. After 6–9 months of treatment, levothyroxine was discontinued for 6 weeks and the thyroid-function
tests re-evaluated: six patients (8%) had permanent hypothyroidism. All of the untreated hypothyroid patients had become euthyroid by 12 months postpartum.

Visible goiter was found in 21.8% of the patients and in 6.7% of the control group \(P < 0.001\). Ultrasonographic evaluation detected hypoechogenicity in 96% of PPT patients; this contrasts with the detection (7%) in the control group \(P < 0.001\).

Anti-Tg and anti-TPO antibodies were found in 58 and 61.5% of PPT patients respectively. The corresponding detection rates in the control group were 7 and 19%. Normal titers of both antibodies were found in 76% of controls and in 21% of patients. Table 2 shows the rate of positive results for antibodies in hyperthyroid and hypothyroid patients. Tests for antithyroid antibodies were positive in 40% of thyrotoxic patients and in 92% of hypothyroid patients \(P < 0.001\). There was no significant difference in median urinary iodine excretion for PPT patients and controls (22 versus 20 \(\mu\)g/dl respectively). There was no significant correlation between the prevalence of PPT and the severity of disease, breast-feeding, the gender of the infant, age at pregnancy, or the personal or family history of thyroid disorders.

### Discussion

In this survey of 1040 unselected postpartum women in Tehran, PPT occurred in 11.4%. This is a relatively high prevalence in relation to other studies in different countries (Table 3). Although the reported prevalence of PPT has been between 1.1 and 16.7% (5–18), only one study has found a higher prevalence than that reported here (10). The wide range of prevalences in various reports may be due to differences in ethnic groups, geographical area, iodine intake, methodology, population size, and length of follow-up. A methodological overview of the literature shows that PPT affects between 3.7 and 5.9% of women during the first postpartum year (19).

In the present study, the number of women studied is the highest of all the PPT studies, though a larger number have been screened antenatally. In addition, the population studied consisted of unselected postpartum women, of which three-quarters had four full clinical and paraclinical evaluations between 3 and 9 months after delivery. Most of the studies reported previously were confined to a few hundred patients, and thyroid-function tests were performed only on one or two occasions, mainly during the first 5 months.
following delivery; in our study, the prevalence rate was 4 and 5.9% at 3 and 4.5 months after delivery respectively, and it reached 11.4% by the ninth month postpartum. Therefore, we would have reported a prevalence of 5.9% had we not continued the study for longer. In the study of Fung et al. (12 months of follow-up), a prevalence of 16.7% was found (8). Another explanation of the high prevalence of PPT in Tehran is the endemic goiter found here prior to 1990 (20): the problem was resolved by universal salt iodization (21). The rate of PPT in countries with iodine deficiency has been reported to be low (6). It is conceivable that an increase in PPT, such as that reported for thyrotoxicosis, may have occurred in Iranian women following consumption of iodized salt used to control iodine-deficiency disorders. However, it should be noted that in the USA and Japan – where iodine intake is more than adequate – and in other countries with normal iodine intake, the prevalence of PPT is variable (7, 11–18).

In this study, 35% of PPT patients presented with thyrotoxicosis, 57% with hypothyroidism, and 8% with thyrotoxicosis followed by hypothyroidism. In most of the other studies, more than one-third of patients had thyrotoxicosis with subsequent hypothyroidism (19, 22–26, 31). This difference may be due to the fact that we began the evaluation of postpartum women at the third month after delivery. It may be that few patients would have developed thyrotoxicosis before the third month, and, since the thyrotoxicosis might have subsided by weeks 4–8, it might have been resolved by the time of this evaluation.

The occurrence of goiter in the present study is similar to that described in other reports (5, 22). Ultrasonographic evaluation showed hypoechogenicity in 96% of PPT patients in the inflammatory phase of the disease. This is in agreement with a previous report (25). The change in thyroid echogenicity may be due to abnormal morphology and lymphocytic infiltration. In the present study, there is no significant difference in the urinary iodine excretion of PPT patients and controls. This is in contrast with the findings of one study which detected a higher rate of urinary iodine excretion in PPT patients (27). The discrepancy may be due to different iodine intake in various geographical areas. A positive titer of anti-Tg and or anti-TPO antibodies was found in 79% of PPT patients; this percentage similar to that reported by other authors (5, 26, 29). We failed to show any significant correlation between PPT and age, the gender of the infant, breastfeeding, parity, or a personal or family history of thyroid disorders. These findings are similar to those of the majority of previous reports; however, a positive correlation between PPT and a family history of thyroid disease and the gender of the infant has been found in two studies. (2, 7). A correlation between the gender of the infant and PPT was not found by Roti et al. (15).

Thirty-three of the hypothyroid patients required treatment with levothyroxine because of the severity of the signs and symptoms, and six patients (8%) had permanent hypothyroidism when T4 therapy was discontinued after 1 year. Nicolai et al. followed their patients for 3 years and found a recurrence of hypothyroidism in 48% of the patients with PPT (5). Vargas et al. reported 19% permanent hypothyroidism after 1 year (2), and Lucas et al. (28) reported 15.6% permanent hypothyroidism after 40 months of follow-up. Therefore, long-term follow-up is needed for an accurate determination of the prevalence of permanent hypothyroidism and its rate of recurrence.

We conclude that the actual prevalence of PPT may be higher than previously reported. To avoid such underestimation in surveys of PPT, it is necessary to follow-up each case several times at least in the first 6 months postpartum.

### Table 2 Positive antithyroid antibodies in hypothyroid and hyperthyroid patients with PPT.

<table>
<thead>
<tr>
<th>Positive antithyroid antibodies*</th>
<th>Hypothyroid patients (n = 62)</th>
<th>Thyrotoxic patients (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both anti-Tpo and anti-Tg</td>
<td>34</td>
<td>8</td>
</tr>
<tr>
<td>Only anti-Tpo</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Only anti-Tpo</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>57 (92%)</td>
<td>14 (40%)</td>
</tr>
</tbody>
</table>

*Positive anti-Tg, more than 150 IU/ml; positive anti-TPO, more than 100 IU/ml.

### Table 3 Prevalence of PPT in different studies.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author (reference No.)</th>
<th>Country</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1982</td>
<td>Amino (7)</td>
<td>Japan</td>
<td>5.5</td>
</tr>
<tr>
<td>1985</td>
<td>Wallfish (11)</td>
<td>Canada</td>
<td>7.1</td>
</tr>
<tr>
<td>1986</td>
<td>Freeman (12)</td>
<td>USA</td>
<td>1.9</td>
</tr>
<tr>
<td>1987</td>
<td>Nicolai (5)</td>
<td>USA</td>
<td>6.7</td>
</tr>
<tr>
<td>1987</td>
<td>Lervange (13)</td>
<td>Denmark</td>
<td>3.9</td>
</tr>
<tr>
<td>1988</td>
<td>Fung (8)</td>
<td>Britain</td>
<td>16.7</td>
</tr>
<tr>
<td>1990</td>
<td>Rasmussen (14)</td>
<td>Denmark</td>
<td>3.3</td>
</tr>
<tr>
<td>1990</td>
<td>Rajatanavin (6)</td>
<td>Thailand</td>
<td>1.1</td>
</tr>
<tr>
<td>1991</td>
<td>Roti (15)</td>
<td>Italy</td>
<td>8.7</td>
</tr>
<tr>
<td>1991</td>
<td>Lobig (16)</td>
<td>Germany</td>
<td>2.0</td>
</tr>
<tr>
<td>1992</td>
<td>Wallfish (17)</td>
<td>Canada</td>
<td>6.0</td>
</tr>
<tr>
<td>1992</td>
<td>Stagnaro-Green (18)</td>
<td>USA</td>
<td>8.8</td>
</tr>
<tr>
<td>2000</td>
<td>Lucas (28)</td>
<td>Spain</td>
<td>7.8</td>
</tr>
<tr>
<td>2000</td>
<td>Furlanetto (30)</td>
<td>Brazil</td>
<td>5.3</td>
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<tr>
<td>2000</td>
<td>Present paper</td>
<td>Iran</td>
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