High Rate of Persistent Hypothyroidism in a Large-Scale Prospective Study of Postpartum Thyroiditis in Southern Italy

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Context: The incidence of postpartum thyroiditis (PPT) varies widely in the literature. Limited data exist concerning the hormonal status of women with PPT at the end of the first postpartum year.

Objective: Our aim was to conduct a large prospective study of the incidence and clinical course of PPT.

Design: A total of 4394 women were screened for thyroid function and thyroid autoantibodies at 6 and 12 months postpartum. Women were classified as being at high or low risk of having thyroid disease before any thyroid testing.

Setting: The study was conducted at two ambulatory clinics in southern Italy, an area of mild iodine deficiency.

Patients: A total of 4394 pregnant women were studied.

Intervention: There was no intervention.

Main Outcome Measures: We measured incidence, clinical presentation, and course of postpartum thyroiditis.

Results: The incidence of postpartum thyroiditis was 3.9% (169 of 4384). Women classified as being at high risk for thyroid disease had a higher incidence of PPT than women classified as low risk (11.1 *vs.* 1.9%; odds ratio, 6.69; 95% confidence interval, 4.63, 9.68). Eighty-two percent of the 169 women with PPT had a hypothyroid phase during the first postpartum year. At the end of the first postpartum year, 54% of the 169 women had persistent hypothyroidism.

Conclusions: One of every 25 women in southern Italy developed PPT. Women at high risk for thyroid disease have an increased rate of PPT. The high rate of permanent hypothyroidism at 1 yr should result in a reevaluation of the widely held belief that most women with PPT are euthyroid at the end of the first postpartum year. **(*J Clin Endocrinol Metab* 96: 652–657, 2011)**

Postpartum thyroiditis (PPT) is the occurrence of transient thyroid hormonal abnormalities in the first year after delivery in women who were euthyroid before pregnancy. In its classic form, hyperthyroidism occurs within the first 3 to 6 months, followed by hypothyroidism, with a return to the euthyroid state (in the majority of women) before the conclusion of the first postpartum year. Women at risk for developing PPT are typically thyroid antibody positive and frequently human leukocyte antigen DR 3, 4, or 5 (1). Although treatment is infrequently required for the hyperthyroid state, it is not uncommon for levothyroxine treatment to be initiated for symptoms of hypo-

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Abbreviations: FT4, Free T_4; PPT, postpartum thyroiditis.

thyroidism or if the woman is attempting to conceive. Recurrent PPT is seen in two thirds of all pregnancies (2), and long-term follow-up of women who had an episode of PPT reveals that 20–60% of women develop permanent primary hypothyroidism within 5 to 10 yr of the initial event (3, 4).

The incidence of PPT varies between 1.1 and 16.7%, with a quantitative review estimating that the incidence of PPT is one in every 12 women worldwide (5). It has been postulated that the broad incidence range is secondary to multiple factors, including the frequency and duration of sampling in the postpartum year, geographical variations, and ethnic differences. Another potential cause is that the majority of studies on PPT did not screen women during pregnancy and therefore may have included the 2–3% of women with preexisting, but undiagnosed, hypothyroidism (Available at: http://thyroid.org/professionals/publications/clinthy/volume21/issue6/clinthy_v216_3_7.pdf). Finally, most studies screened a population of women, but then selected a limited cohort of antibody positive and antibody negative women to follow prospectively. At the conclusion of the study, the incidence of PPT for the entire population was mathematically derived, providing yet another potential source of inaccuracy. In light of all of these factors, it is not surprising that published incidence rates of PPT vary dramatically.

We recently completed a large-scale prospective trial (n = 4562) evaluating the efficacy of screening for thyroid disease in the first trimester of pregnancy and studying the impact of treatment on maternal and neonatal outcomes. Half of the women in the study were immediately screened with a TSH and thyroid peroxidase antibody (universal screening group). The other women were immediately screened if the woman had risk factors for thyroid disease (case finding group). Women in the Case Finding Group who were at low risk for thyroid disease had their sera frozen, with testing performed in the postpartum period. Women diagnosed with thyroid disease during pregnancy received the appropriate treatment (levothyroxine for hypothyroidism and antithyroid drugs for hyperthyroidism). The major finding was that treating unsuspected thyroid disease during pregnancy decreased maternal and neonatal adverse events (6). The trial also demonstrated that thyroid antibody-negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy have a significant increase in miscarriage when compared with first trimester antibody-negative women with TSH levels below 2.5 (6). In the present manuscript, we report the prevalence, clinical presentation, and course of PPT in our prospective cohort.

Subjects and Methods

The present study is the continuation of a prospective trial that evaluated screening for thyroid disease during pregnancy and the impact of treating thyroid disease on neonatal and maternal adverse outcomes (6). Inclusion criteria included a singleton pregnancy within the first 11 wk of pregnancy in women with no known thyroid disease. A total of 4562 women in the first trimester of pregnancy were recruited from two hospitals in southern Italy, the Vito Fazzi Hospital (Lecce, Italy) and the Casa di Cura Salas (Brindisi, Italy). Women were randomly assigned to a universal screening or case finding group. All women were evaluated for their risk for thyroid disease. Women were classified as high risk for thyroid disease if they had any of the following risk factors: family history of autoimmune thyroid disease, presence of goiter, signs or symptoms of thyroid dysfunction, personal history of autoimmune disease, neck irradiation, and prior preterm delivery or miscarriage. All women in the universal screening group and women classified as high risk for thyroid disease in the case finding group were immediately screened for TSH and thyroid peroxidase antibody. Women found to be either hypothyroid or hyperthyroid were referred to an endocrinologist by the 12th gestational week for appropriate management. Women in the case finding group who were classified as low risk for thyroid disease had their sera frozen and assayed postpartum. Thyroglobulin antibody was not assayed in any of the women. A complete description of the study protocol along with results of the screening trial and treatment impact on maternal and neonatal adverse events have been previously published (6).

The present study includes the following groups of women from the initial cohort of 4562: 1) all women in the universal screening group and case finding group who were euthyroid when initially screened in the first trimester of pregnancy, irrespective of whether their blood was assayed immediately or postpartum; and 2) women in the universal screening or case-finding high-risk group who were euthyroid at initial screen (TSH <2.5 mIU/liter), but who, when further evaluated in the second and third trimesters (due to the presence of thyroid antibodies; n = 157), were found to be hypothyroid (n = 16) and were placed on levothyroxine. This subgroup had levothyroxine discontinued postpartum (seven of these women went on to develop PPT). Excluded from the study where all women who had thyroid dysfunction at initial screening (n = 133) and women lost to follow-up (n = 45).

All women had a TSH and thyroid peroxidase antibody performed at 6 and 12 months postpartum. Thyroid function tests were also performed at any time point during the first postpartum year if the woman presented with signs or symptoms of hypothyroidism or hyperthyroidism. PPT was defined as follows: hyperthyroid phase, TSH less than 0.27 mIU/liter; and hypothyroid phase, TSH greater than 4.2 mIU/liter. Patients were started on levothyroxine if the TSH exceeded 10.0 mIU/liter or if the TSH was between 4.2 and 10.0 mIU/liter and the woman had symptoms of hypothyroidism. Women in the hyperthyroid phase of PPT were treated with beta-blockers when symptomatic and/or free T_4 (FT4) values were 1.5-fold above the upper range. Serum TSH and FT4 were measured using a third-generation electrochemiluminescence immunoassay (Roche, Basel, Switzerland). The reference values were 0.27–4.2 mIU/liter for TSH and 9.3–18.0 ng/liter (12–33.5 pmol/liter) for FT4. Thyroid peroxidase antibody titers were determined using a RIA kit [DiaSorin, Saluggia (Vercelly), Italy]. The reference range was 0–16 IU/ml (positive >16 IU/ml).

TABLE 1. Incidence of PPT by risk group and thyroid antibody status in first trimester

	TPO-Ab+ (n = 261)	TPO-Ab− (n = 4123)	Total (n = 4384)
High risk (n = 943)	58/92 (63.0%)	47/851 (5.5%)	105/943 (11.1%)
Low risk (n = 3441)	39/169 (23.1%)	25/3272 (0.8%)	64/3441 (1.9%)
Total (n = 4384)	97/261 (37.2%)	72/4123 (1.7%)	169/4384 (3.9%)

Fractions and percentages in cells display the number of women with PPT divided by total number of women in the cell. High-risk and positive antibody status are significantly associated with increased incidence of PPT. TPO-Ab, Thyroid peroxidase antibody.

Statistical analyses

The probability of PPT was modeled using logistic regression. Age, smoking history, previous pregnancy, week of first obstetrical visit, thyroid antibody positivity at inception of pregnancy, and risk group were introduced as potential predictors. All analyses were conducted with $\alpha = 0.05$ (*i.e.* 95% confidence). Among women with PPT, variations in the course of PPT were described, and thyroid function test values at 6 and 12 months postpartum were compared between progressions using ANOVA with Scheffé tests for paired comparisons. Analyses were conducted using SPSS, version 15 (SPSS Inc., Chicago, IL).

The study was approved by the ethical committees of both institutions, and written informed consent was obtained.

Results

Incidence and predictors of PPT

A total of 4384 patients participated in the study. One hundred sixty-nine women developed PPT, comprising 3.9% of the entire cohort. Table 1 shows the unadjusted incidence of PPT for women by risk group and thyroid antibody status. The regression found that women were more likely to develop PPT if they were in the high-risk group *vs.* the low-risk group overall (odds ratio = 6.69; 95% confidence interval = 4.63, 9.68) and if they were thyroid antibody positive (odds ratio = 34.1; 95% confidence interval = 23.5, 49.6). Previous pregnancy, age, smoking status, and week of first obstetrical visit were not significantly associated with PPT.

Clinical progressions of PPT

There were six distinct clinical progressions of PPT in the 169 women. The presentations, which reflect the thyroid function test results at 6 and 12 months postpartum, were as follows: 1) hypothyroidism followed by euthyroidism (27.2%); 2) euthyroidism followed by hypothyroidism (22.5%); 3) hypothyroidism followed by persistent hypothyroidism (18.3%); 4) hyperthyroidism followed by euthyroidism (16%); 5) hyperthyroidism followed by hypothyroidism (13.6%); and 6) euthyroidism followed by hyperthyroidism (2.4%). Overall, 82% of the 169 women who developed PPT had a hypothyroid phase at some point in the first year postpartum, and 32% of the 169 women had a hyperthyroid phase. Thyroid antibody titers in the six groups with PPT were not significantly different (data not shown).

At the end of the first postpartum year, 54% (n = 92) of the 169 women remained hypothyroid. Of the 261 women who were thyroid antibody positive in the first trimester of pregnancy, 20% (52 of 261) were hypothyroid at the conclusion of the first year postpartum compared with only 1% (40 of 4123) of women who were thyroid antibody negative in the first trimester ($\chi^2 = 429$ on 1 *df*; $P < 0.001$). Of the 97 women who were thyroid peroxidase positive and who developed PPT, there was no difference between the antibody titer in the first trimester of pregnancy in women who were hypothyroid at 1 yr postpartum (median = 429; n = 52) compared with the mean antibody titer in women who were euthyroid at 1 yr postpartum (median = 532; n = 45, Wilcoxon rank-sum W = 2428; $P = 0.383$).

Table 2 presents the thyroid function tests at both 6 and 12 months postpartum of the 169 women who developed PPT. Women with hypothyroidism at 6 months who had persistent hypothyroidism at 12 months had higher median 6-month TSH levels than women who were hypothyroid at 6 months and euthyroid at 12 months (6.7 *vs.* 5.2 mIU/liter; $P < 0.001$). In other progressions, 6-month thyroid function tests were not associated with thyroid hormonal status at 12 months.

Discussion

The present study is the largest prospective cohort to evaluate the incidence, clinical presentation and course of PPT. The major findings of the study are as follows: 1) the incidence of PPT in southern Italy, an area of mild iodine insufficiency, is 3.9%; 2) women classified as high risk for thyroid disease had a 6-fold increase in the incidence of PPT; 3) the vast majority (82%) of women who developed PPT had a hypothyroid phase; 4) women who were euthyroid and thyroid peroxidase antibody-positive in the first trimester have a greater then 37% chance of developing PPT; and 5) over 50% of the women who developed PPT remained hypothyroid at the conclusion of the first postpartum year.

TABLE 2. Clinical progressions of PPT and associated thyroid function test values at 6 and 12 months

	Euthyroid at 6 months		Hyperthyroid at 6 months		Hypothyroid at 6 months	
	Hypothyroid at 12 months	Hyperthyroid at 12 months	Hypothyroid at 12 months	Euthyroid at 12 months	Hypothyroid at 12 months	Euthyroid at 12 months
TSH at 6 months (median, IQR)	2.15 (1.58)	1.35 (1.88)	0.02 (0.04)	0.03 (0.05)	6.7 (1.8)[a]	5.2 (0.77)[a]
TSH at 12 months (median, IQR)	7.25 (5.5)[a]	0.04 (0.10)[a]	7.4 (6.0)[a]	2.0 (1.3)[a]	7.9 (3.8)[a]	3.05 (1.2)[a]
FT4 at 6 months	11.5 (2.3)	13.0 (1.8)	27.3 (6.3)	23.7 (4.9)	8.3 (0.69)	9.1 (0.65)
FT4 at 12 months	8.4 (0.85)[a]	17.8 (10.2)[a]	8.0 (0.93)[a]	12.8 (1.4)[a]	8.2 (0.82)[a]	10.9 (1.7)[a]
No. (%) of women with PPT with this progression	38 (22.5%)	4 (2.4%)	23 (13.6%)	27 (16.0%)	31 (18.3%)	46 (27.2%)

Values of thyroid function tests are given as means (SD), except where noted. IQR, Interquartile range.

[a] Values significantly different in paired comparisons between clinical progressions with a common 6-month thyroid status, based on Scheffé tests (for FT4) or Mann-Whitney *U* tests (for TSH).

The incidence of PPT varies widely in the literature, with the present study reporting an incidence of 3.9%. Although there are methodological, geographical, and genetic reasons for the disparity in reported incidence of PPT, an important issue is the lack of exclusion of women with preexisting thyroid dysfunction in many of the previously published reports. Two large-scale published studies demonstrated an incidence of PPT of 11.4% in Iran and 11.5% in Australia (7, 8). In both of these studies, the initial screen for thyroid disease occurred postpartum. The present study screened all women in the first trimester of pregnancy and discovered 133 with thyroid dysfunction who were excluded from the study. If screening had not occurred during pregnancy, those 133 women would have been classified as having developed PPT and would have erroneously increased the rate of PPT to 6.7%. However, a limitation of the present study is that the incidence of 3.9% represents an underestimation of the true incidence of PPT because screening was performed only twice postpartum and undoubtedly missed transient cases of both hyperthyroidism and hypothyroidism. There are no data demonstrating a genetic explanation for the lower incidence of PPT reported in the present study of women from southern Italy.

The best predictor of PPT is the presence of thyroid antibodies in the first trimester of pregnancy. Previous studies have demonstrated that women who are antibody positive in the first trimester have a 21–46% incidence of PPT (9–14). Similar to prior studies, 37% of the women who were thyroid peroxidase antibody positive in the first trimester of pregnancy in the present study developed PPT. Unique to this study was the correlation of risk factors for thyroid disease as determined early in pregnancy with the development of PPT. Women classified as high risk for thyroid disease were over five times more likely to develop PPT than women not classified as high risk.

The present study illustrates the numerous clinical presentations of PPT. Although hypothyroidism at 6 months with a return to the euthyroid state by 12 months was the most common clinical course, it represents just 23% of all women, demonstrating the marked heterogeneity of the clinical presentation of PPT. Nevertheless, a unifying feature of almost all cases (82%) was the presence of a hypothyroid phase. In contrast, only 32% of women developed a hyperthyroid phase, with 93% of the hyperthyroid episodes occurring at 6 months postpartum. Interestingly, in a study of 73 women who developed PPT, Lazarus *et al.* (15) reported nearly identical results, with 81% of women experiencing a hypothyroid phase of PPT and 32% of women experiencing a hyperthyroid phase of PPT.

The most unexpected finding in the present study was that slightly over 50% of all women who developed PPT remained hypothyroid at the end of the first postpartum year. Thyroid peroxidase titer in the first trimester of pregnancy in women who developed PPT was not predictive of persistent hypothyroidism at 1 yr. Similar findings were noted by Tachi *et al.* (16), who reported that the mean thyroid antibody titer in women who developed PPT and remained hypothyroid at 1 yr was no different than the mean antibody titer in women with PPT who were euthyroid at the conclusion of the first year postpartum. It is well documented that the prevalence of permanent hypothyroidism 5–10 yr after an episode of PPT is between 20 and 60%. Similarly, it is generally accepted that the vast majority of women with PPT are euthyroid at the end of the first postpartum year. Although there are limited data on this subject (because most PPT studies did not follow patients until 1 yr postpartum), the present data do not support this contention. Analysis of six studies with data available at the 1-yr mark reveals that 2–21% of women are hypothyroid at 1 yr [Tachi *et al.* (16), −11% (5 of 44); Fung *et al.* (17), −2.0% (1 of 49); Vargas *et al.* (18), −19%

(8 of 42); Rasmussen *et al.* (19), −8.3% (3 of 36); Walfish *et al.* (20) −24% (10 of 42); and Kita *et al.* (21) 21% (8 of 39)]. It is in this context that the prevalence of hypothyroidism of 54% at 1 yr should be interpreted. It should be noted that the present report evaluated almost four times as many women with PPT at 1 yr than any of the previous studies. However, it is feasible that the 54% rate of persistent hypothyroidism is an overestimation because theoretically only the more severe cases of PPT were detected due to limited sampling postpartum. Nevertheless, even if 50% of the cases of PPT were missed (which is highly unlikely), the rate of persistent hypothyroidism would still have been 36%, a rate appreciably higher than prior studies. Finally, the median TSH at 12 months in the 54% of women with hypothyroidism at 1 yr was 7.4 IU/ml, a level often associated with symptoms of hypothyroidism as well as negative consequences if the woman becomes pregnant.

The degree of hypothyroidism at 6 months postpartum was significantly correlated with the clinical course at the end of the first year postpartum. Women with more severe hypothyroidism initially were more likely to be hypothyroid at 12 months when compared with women with more mild hypothyroidism at 6 months who were more likely to be euthyroid at the conclusion of the first postpartum year. Although there was much overlap of the TSH levels at 6 months in the two groups, it can be concluded that the higher the TSH at 6 months, the more likely that the patient will remain hypothyroid at 12 months postpartum. Similar findings were reported by Sarvghadi *et al.* (22).

In conclusion, the present study demonstrated a 3.9% incidence of PPT in southern Italy, an area of mild iodine insufficiency. The size of the present study and the exclusion of women who had thyroid disease in the first trimester of pregnancy are methodological strengths of the current research. Nevertheless, the prevalence rate of 3.9% probably represents an underestimation due to limited sampling during the postpartum period. Women who have increased risk factors for thyroid disease were shown to have a marked increased prevalence of PPT. The high prevalence of hypothyroidism at the end of the first postpartum year is noteworthy because it is a novel finding with significant clinical implications. Specifically, it will be important to evaluate thyroid function tests at 1 yr postpartum in all women with PPT to identify individuals with ongoing hypothyroidism who require levothyroxine treatment.

Acknowledgments

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Trial Registration Registry—www.ClinicalTrials.gov, registry no. NCT00846755.

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