Editorial

The Continuing Saga of Postpartum Thyroiditis

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Postpartum thyroiditis (PPT) is characterized by the development of postpartum thyroid dysfunction (PPTD), which may occur up to 12 months after delivery. Usually the syndrome presents as transient hyperthyroidism (median time of onset, 13 wk) followed by transient hypothyroidism (median time of onset, 19 wk). Clinically, women are relatively asymptomatic during the hyperthyroid phase, although some may notice palpitations requiring treatment with β-adrenergic blocking agents. In contrast, patients experience persistent and troublesome symptoms related to the hypothyroid period, which usually must be treated with levothyroxine, normally for up to 1 yr (1, 2). Several studies from different countries have shown that about 12–61% of women who develop postpartum hypothyroidism go on to a permanent hypothyroid state when assessed 1 yr or more after delivery (2–4); these women then require lifelong levothyroxine replacement therapy. In those women who do not develop permanent hypothyroidism, the chance of experiencing a recurrence of PPTD after a previous episode is around 70% (5). The incidence of PPTD has been the subject of much debate. Although most reviews cite a range from 4–9% (6), there is considerable variation in these figures due to sample bias, frequency of blood sampling, and definition of the syndrome. For example, an incidence of 16.7% quoted by Fung *et al.* (2) was later shown to be erroneous due to the inclusion of the large denominator of thyroid peroxidase (TPO) antibody-negative persons used in the calculation. Nevertheless, the wider incidence has ranges from 1.1 to 21.1%.

PPTD is an immunological disorder occurring more frequently in women with certain human leukocyte antigen haplotypes and being usually characterized by the presence of circulating TPO antibodies (7). Indeed, the condition occurs in up to 50% of women found to be TPO antibody positive at the end of the first trimester of gestation (*i.e.* before the titers start to decline during pregnancy). The other 50% of TPO antibody-positive women who have no thyroid dysfunction are considered to have PPT but not PPTD. Furthermore, there is evidence that the TPO antibody titer at 16 wk gestation is related to the severity of the PPTD (8).

The prospective study of PPT by Stagnaro-Green *et al.* (9) is an important contribution to the epidemiology of postpartum thyroid disease and adds to the debate in several ways. They took advantage of a previously reported study of screening for thyroid function in pregnancy that examined 4562 pregnant women from southern Italy (Puglia) in the first trimester (10). In that study, women were randomly assigned to a universal screening group or a case-finding group. In addition, women in both groups were grouped as high risk if they had one of the following: family history of autoimmune thyroid disease, presence of goiter, signs and symptoms suggestive for thyroid dysfunction, personal history for type 1 diabetes or other autoimmune disease, and history of neck irradiation, previous miscarriages, or preterm deliveries. A total of 4384 women were tested at 6 and 12 months postpartum for thyroid function (TSH and TPO antibodies), with free T_4 being measured if hyperthyroidism was suspected. They were also screened in the first trimester, and those with thyroid dysfunction at that time were not studied further for this analysis. PPTD was defined by the usual criteria (2). The incidence of PPT was low at 3.9%. This figure should be compared with two studies from northern Italy that reported incidences of 8.7 and 18%, respectively (11, 12). However the base population in both studies did not exceed 400. Although women who were TPO antibody positive or women in the high-risk groups reported by Stagnaro-Green *et al.* (9) were significantly more likely to

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2011-0091 Received January 12, 2011. Accepted January 21, 2011.

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Abbreviations: PPT, Postpartum thyroiditis; PPTD, postpartum thyroid dysfunction; TPO, thyroid peroxidase.

develop PPTD (odds ratio, 34.1 and 6.9 respectively), 72 (42.6%) of the PPTD patients were TPO antibody negative. In other reports, the incidence of PPTD in TPO antibody-negative women is close to zero, and the incidence in TPO antibody-positive women is 50% (13). Some apparent TPO antibody-negative women may have antithyroglobulin antibodies as their only expression of thyroid autoimmunity (approximately 4% in our series). The southern Italian Puglian PPT women (9) seem to have a relatively low prevalence of TPO antibodies and a high prevalence of TPO antibody negativity. There are no data on the iodine status of this population, but it is unlikely to be severely deficient, and iodine status is not thought to influence the incidence of PPTD (14). It should also be noted that thyroid function was only measured twice in the postpartum period; there are studies where it is clear that the reported incidence of PPT is higher with more frequent postpartum sampling due to the transience of the thyroid dysfunction (15).

The main finding from the study by Stagnaro-Green *et al.* (9) is the high rate of persistent hypothyroidism (54%) recorded at the end of the first postpartum year in the 169 women with PPT. The wide range of permanent hypothyroidism already referred to may be due to differences in definition and variable ascertainment of follow-up. The highest rate of 61% was observed 2 yr postpartum. Hence, the figure documented by Stagnaro-Green *et al.* (9) is an outlier and must be explained. Although a large number of women were screened for PPT, the total number discovered (169) was only slightly greater than previous studies. The difference between this series and other studies is that only two thyroid tests were performed in the postpartum period; therefore, a considerable number of PPT patients may have been missed. If, for example, the real incidence of PPT in the population is 8% [as in the report by Roti *et al.* (11), who sampled women four times postpartum], then 350 women would have been expected to have developed PPT. The patients with hypothyroidism at the end of 1 yr might be the same as reported (the most severe cases), giving a 1-yr hypothyroid rate of approximately 26% (92 of 350) in line with other reports. The authors acknowledge this possibility but claim that it is very unlikely that 50% of PPT cases would have been missed and that the calculated rate of hypothyroidism would have been 36%, still much higher than in previous studies. At present, it is suggested that women with hypothyroid PPT receiving levothyroxine during the first year should stop this drug at 1 yr for 4 wk and have a thyroid function test (16). The data from Stagnaro-Green *et al.* (9) confirm the clinical importance of evaluating thyroid function at 1 yr postpartum in those women who appear to have had transient PPT and are not receiving thyroid hormone therapy. Ideally, such women should have annual thyroid function testing (8) to detect the onset of permanent hypothyroidism.

The strength of this Italian study, in addition to the large study sample and risk group stratification, is the illustration of the different clinical presentations and course of PPT. It is interesting that as many as 32% of women were found to have had a hyperthyroid phase of the syndrome at 6 months postpartum. This usually occurs at about 13 wk postpartum and may be missed due to infrequent sampling. The demonstration that more than 60% of PPT women were derived from the high-risk screening group is unique to studies of PPT, although there was no relation of severity of the illness to early pregnancy TPO antibody titer as previously shown. Currently there is no universal screening performed for the detection of PPT, despite evidence of positive cost benefit (17). If PPT screening were to be advocated in a high-risk group, at least it would detect two thirds of the patients and could be combined with the high-risk screening strategy for thyroid dysfunction in pregnancy as suggested by Endocrine Society guidelines (18). However, this strategy would miss the diagnosis in up to 40% of women; this is similar to the number of women with thyroid dysfunction not detected during gestation using a parallel screening strategy (19). PPT has been shown to be a common condition with significant patient morbidity. Debate about the epidemiology of PPT and PPTD will no doubt continue, but the present study confirms the clinical picture and emphasizes the need for continuing vigilance of these patients when their children are aged 1 yr or more.

Acknowledgments

I thank Dr. L. K. D. E. Premawardhana for advice.

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Disclosure Summary: J.H.L. has nothing to declare.

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