# OVER HALF OF WOMEN WITH POSTPARTUM THYROIDITIS REMAIN HYPOTHYROID ONE YEAR LATER

Stagnaro-Green A, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Negro R. **High rate of persistent hypothyroidism in a large-scale prospective study of postpartum thyroiditis in Southern Italy.** J Clin Endocrinol Metab. December 29, 2010 [Epub ahead of print]. DOI: 10.1210/jc.2010-1980

### SUMMARY . . . . . . . . .

# **BACKGROUND**

Postpartum thyroiditis (PPT) is a relatively common thyroid autoimmune disorder affecting women in the first 12 months following delivery, both full-term births and miscarriages. In a review of 21 publications (8000 women) from different countries the prevalence was 8.1% (range, 1.6 to 19) (1). The variability in the reported cases depends on patient selection, geographic and ethnic differences, diagnostic criteria, frequency and timing of blood samples, and perhaps iodine consumption in the population studied. PPT is defined as a syndrome of thyroid dysfunction occurring in women during the first year after parturition. In the present reviews, patient selection was limited to euthyroid thyroid peroxidase antibody (TPOAb)-positive women in the first trimester of pregnancy. Women with known chronic thyroiditis are at risk of developing the syndrome, particularly those with high TPOAb titers in the first trimester of pregnancy; in some studies, women expressing human leukocyte antigen haplotype DR 3, 4, or 5 are at higher risk (2). However, PPT has been reported in a small percentage of women without evidence of autoimmune thyroid disease (3). Patients with Graves' disease whose disease is in remission before conception are at higher risk of recurrence of hyperthyroidism in the year following delivery (4). There are controversies concerning whether the onset of Graves' hyperthyroidism is more common in the year following delivery. In its classical description, a sequence of three phases has been described, a bout of hyperthyroidism occurring within the first 2 to 4 months after delivery, followed by a hypothyroid phase lasting between 3 and 8 months, with a recovery phase of 6 to 12 months. In most published series, the vast majority of women returned to euthyroidism, and only 5 to 20% of them remain hypothyroid permanently (5). Not every patient goes through the three phases; one third suffered only the initial hyperthyroid phase,

another third only the hypothyroid phase, and the rest go through the hyperthyroid, hypothyroid, and euthyroid phases. It is also reported that permanent hypothyroidism will develop in 30 to 50% of women within 5 years after the original episode. Stagnaro-Green et al., studied a population in Southern Italy with mild iodine deficiency, comprising 4562 women with a singleton pregnancy who were screened in the first 11 weeks of pregnancy. The aim "was to conduct a large prospective study of the incidence and clinical course of PPT." This group of women is part of a large-scale prospective trial evaluating the efficacy of screening for thyroid disease early in gestation and studying the impact of treatment on maternal and neonatal outcomes (6).

### **METHODS**

A total of 4562 women who were within the first 11 weeks of pregnancy and had no known thyroid disease were recruited. All of them had serum thyrotropin (TSH), free thyroxine, and thyroid peroxidase antibody (TPOAb) levels measured at study entry. The authors excluded from the initial group 113 women with thyroid dysfunction and 45 women were lost to follow-up. All 4384 remaining women were euthyroid (serum TSH, <2.5 mIU/L) and most of them remained euthyroid through pregnancy. Serum TSH and TPOAb measurements were repeated 6 and 12 months postpartum, or at any time in the presence of symptoms or signs of thyroid dysfunction. Postpartum hyperthyroidism was defined as a serum TSH <0.27 mIU/L and postpartum hypothyroidism as a serum TSH of >4.2 mIU/L. The probability of PPT was modeled using logistic regression, with age, smoking history, previous pregnancies, week of first obstetrical visits, TPOAb positivity on study entry, and risk group (low or high) as potential predictors. Test results at 6 and 12 months postpartum were compared between progressions using analysis of variance with Scheffé tests for paired comparisons.

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### **RESULTS**

A total of 4383 women participated in the study; PPT developed in 169 (3.9%). Women were divided at the time of study entry, into two groups according to their risk for thyroid disease, based on a personal questionnaire and physical examination; there were 943 women in the high-risk group (21.5%) and 3441 (78.5%) in the low-risk group.

Of the 4384 women recruited, 261 were TPOAbpositive (5.9%), of whom 92 (35.2%) belonged to the high-risk group. The incidence of PPT was 58 of 92 (63.0%). Of the 261 women who were TPOAbpositive, 169 (64.8%) were part of the low-risk group. The incidence of PPT was 39 of 169 (23.1%). The total incidence of PPT in the TPOAb-positive group was 97 of 261 (37.2%).

Of the 4123 TPOAb-negative women, 851 were in the high-risk group and 47 of them had PPT (5.5%). Of the 3272 women in the low-risk group who were TPOAb-negative, 25 (0.8%) had PPT. The total incidence of PPT in TPOAb-negative women was 72 of 4123 (1.7%). The figure summarizes these data.

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

4383 Euthyroid Women before 11 Weeks of Gestation (serum TSH <2.5 mIU/L and TPOAb status)

High risk 943 (21.5)

TPOAb+ 851 (90.3%)

PPT 105/943 (11.1%)

PPT 169/4383 (3.9%)

PPT 169/4383 (3.9%)

Logistic-regression analysis found that PPT was more likely to develop if the women were in the high-risk group versus the low-risk group (odds ratio [OR], 6.69; 95% confidence interval [CI], 4.63 to 9.68) and if they were TPOAb-positive (OR, 34.1; 95% CI, 3.5 to 49.6); all the other factors included in the logistic-regression analysis were not significantly associated with PPT.

The authors described six distinct clinical progressions of PPT in the 169 women: hypothyroidism at 6 months followed by euthyroidism at 12 months (27.2%), euthyroidism followed by hypothyroidism (22.5%), hypothyroidism followed by persistent hypothyroidism (18.3%), hyperthyroidism followed by hypothyroidism (13.6%), hyperthyroidism followed by euthyroidism (16.0%) and euthyroidism followed by hyperthyroidism (2.4%). A total of 54.4% had hypothyroidism at 12 months.

Overall, 82% of the 169 women in whom PPT developed had a hypothyroid phase, and 32% had a hyperthyroid phase. Thyroid antibody titers were not significantly different among patients who had the hyperthyroid phase as compared with the hypothyroid phase.

There was no difference in antibody titer at study entry between hypothyroid and euthyroid women at 12 months postpartum.

The median serum TSH at 6 months was significantly different (6.7 vs. 5.2 mIU/L; P<0.001) between women with persistent hypothyroidism and those who were euthyroid.

# **CONCLUSIONS**

Of the 261 TPOAb-positive women, 97 (37.2%) had PPT, versus 72 (1.7%) of the 4123 TPOAb-negative women. Of the 169 women in whom PPT developed, 92 (54%) remained hypothyroid at the end of the first postpartum year. Of the 261 TPOAb-positive women, 52 (20%) were hypothyroid 1 year after delivery, versus 40 (1%) of 4123 TPOAb-negative women (P<0.001).

### COMMENTARY • • • • • •

This study is the largest prospective cohort to evaluate the incidence, clinical presentation, and course of PPT. The author's findings differed from previous published reports: (1) The incidence of PPT was 3.9%. If 133 women with thyroid dysfunction at study entry (originally excluded) were included, the incidence of PPT would have increased to 6.7%. (2) Women classified as high risk for thyroid disease had a sixfold increase in the incidence of PPT. (3) The vast majority (82%) went through a hypothyroid phase. (4) Euthyroid TPOAb-positive women in the first trimester of pregnancy have a greater than 37% chance of PPT developing. (5) Fifty-four percent of the women in whom PPT developed remained hypothyroid at the conclusion of the first postpartum year.

This study supports the high incidence of a hypothyroid phase in the course of PPT. The most unexpected finding, as stated by the authors is the high incidence of permanent hypothyroidism, over 50% of their patients. The literature mentioned a 5 to 20% incidence of permanent hypothyroidism at 12 months postpartum and a 20 to 60% incidence of permanent hypothyroidism after 5 to 10 years. The authors speculated that the low incidence of PPT in their study represents an underestimation due to limited sampling only at 6 and 12 months postpartum.

The clinical diagnosis of PTT is a challenge for the physician; symptoms of hypothyroidism or hyperthyroidism are mild and nonspecific, and many patients remain undiagnosed. Some symptoms, such as fatigue and irritability may be attributed to the postpartum situation itself. Fatigue is a common symptom. Whether postpartum depression can be attributed to PPT is controversial, since it has been reported in euthyroid women who are TPOAb-positive. In clinical practice, some women

may have severe symptoms of thyroid dysfunction and benefit from therapy. In the present study, there are no indications of the clinical severity of symptoms or the incidence of goiter. An important observation is the sixfold increase in the incidence of PPT in women classified as high risk, supporting the clinical value of a careful medical history and physical examination. Although not mentioned by the authors, the presence of an enlarged thyroid gland in the postpartum period should alert the physician to perform proper thyroid tests. The high incidence of permanent hypothyroidism at the end of the first year postpartum is a novel finding, and it suggests the importance of following women closely after the first year postpartum, particularly those who are planning future pregnancies. I hope the authors will continue to follow these patients to assess how many of them with mild subclinical hypothyroidism may return spontaneously to the euthyroid state.

The incidence of PPT in this study was lower than in other reports. It could be attributable to several reasons, as indicated by the authors, including the selection of patients: All their patients were euthyroid in the first trimester of pregnancy, and the thyroid tests were done routinely at 6 and 12 months postpartum. In other studies thyroid tests were performed every 3 months for 12 months, and this could have yielded a higher incidence of women with PPT. Graves' hyperthyroidism may present or recur in the postpartum period or 6 to 8 months after delivery. The authors reported that 2.4% of their patients were hyperthyroid at 12 months but euthyroid at 6 months, possibly representing the new onset of Graves' hyperthyroidism. Finally, the authors confirm previous studies reporting a typical course of PPT in women with negative antibodies, although only 1% of them were hypothyroid at 12 months, as compared with 20% of those with positive antibodies in the first trimester.

— Jorge Mestman, MD

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