Usefulness of Antimicrosomal Antibody Titers in the Diagnosis and Treatment of Postpartum Thyroiditis

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Background. Postpartum thyroiditis is a common but frequently unrecognized disorder, affecting approximately 5% of women during the first 12 months after delivery. We investigated whether the antimicrosomal antibody titer could be used to determine which women with positive titers postpartum (1) might develop symptomatic or biochemical abnormalities within the first postpartum year (early disease), (2) might require therapy with thyroid hormone, and (3) might have persistent abnormalities (late disease).

Methods. Women (n = 55) who had positive antimicrosomal antibody titers at delivery were prospectively followed for 11 to 45 months. Titers were evaluated again at 6 to 10 weeks postpartum and approximately every 8 weeks for the first year.

Results. Early disease occurred in 40 of 55 (73%) women, late disease occurred in 29 of 55 (53%) women, and treatment was required by 21 of 55 (38%) women. The occurrence of early disease was associated with the occurrence of late disease ($P < .05$). The chances of developing early disease were 6 to 1 ($P = .01$) when serum titers of antimicrosomal antibodies were ≥400 at delivery, and 5 to 1 ($P = .02$) when titers were ≥1600 at 6 to 10 weeks postpartum. The chances of being given thyroid hormone therapy were 23 to 1 ($P = .006$) when titers at delivery were ≥6400, and 6 to 1 when titers at 6 to 10 weeks postpartum were ≥6400 ($P = .004$). Titers were not useful in estimating who would have late disease.

Conclusions. Screening for postpartum thyroid dysfunction after delivery using antimicrosomal antibody titers is highly useful. The titer value can help guide the physician in the care of patients with postpartum thyroiditis whose disease may not be self-limiting and who will probably require thyroid hormone therapy.

Key words. Puerperium; thyroiditis; autoantibodies.
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Postpartum thyroiditis has been described as part of the spectrum of autoimmune thyroid disorders.[1,2] It is marked by a stereotypic time course of thyroid dysfunction. Transient thyrotoxicosis usually occurs 1 to 3 months after delivery, and is caused by the release of stored hormones from the inflammatory destruction of the thyroid follicles. This phase is often followed by hypothyroidism that occurs 4 to 8 months postpartum. Goiter is often noted, but the thyroid gland is not tender, which differentiates this disorder from subacute thyroiditis, in which the thyroid gland is painfully enlarged. Some women with postpartum thyroiditis have only one phase of thyroid dysfunction. Originally thought to be self-limiting, postpartum thyroiditis is a cause of significant morbidity that often goes unrecognized as a treatable disease.

In a previous paper,[3] we described the occurrence and morbidity of thyroid disease in 72 patients with positive antimicrosomal antibodies followed prospectively for 6 months. We found that patients with the highest antibody titers had the highest occurrence of postpartum thyroid dysfunction, and that these women frequently required treatment with L-thyroxine, whereas those women with low titers rarely had biochemical abnormalities or symptoms. These results led us to pose the following questions concerning women with positive antithyroid antibodies: (1) how well do the titers determine who will develop either biochemical or symptomatic thyroid dysfunction within the first year postpartum? (2) who may develop persistent thyroid disease? and (3)

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who may require thyroid hormone therapy either within or after the first postpartum year?

Methods

A postpartum thyroiditis screening program was begun at Walter Reed Army Medical Center in March 1985. Serum thyroid antibodies were measured on the second postpartum day. Patients with positive results were contacted and asked to participate in a longitudinal study that was approved by the medical center's Human Use Committee and Institutional Review Board. Eligible patients signed an informed consent before participation; patients who had a known thyroid disorder and were taking L-thyroxine were excluded from this study. Subjects were first seen in the endocrinology clinic 6 to 10 weeks postpartum and followed prospectively every 4 to 12 weeks for the first year and 6 to 12 months thereafter.

At each clinic visit, the patients were seen by a physician who performed a clinical evaluation and estimated thyroid gland size by palpation. Serum antimicrosomal and antithyroglobulin antibodies were measured at each visit, with levels determined by tanned red blood cell hemagglutination assay (Sera-Tek, Miles Laboratories, Elkhart, Ind). The lowest positive titer was 1:100. Thyroid function tests were also measured at each visit and included serum thyroxine (T_4), triiodothyronine resin uptake (RT_3U), free thyroxine index (FTI), and triiodothyronine (T_3) (Micromedic, Horsham, Pa), and thyrotropin (thyroid-stimulating hormone [TSH]) by immunoradiometric assay (IRMA) (normal range: 0.30–4.0 μU/mL) (Diagnostic Products, Los Angeles, Calif). At 1 year postpartum, patients underwent a protirelin (thyrotropin-releasing hormone [TRH]) stimulation test (500 μg intravenously) with measurement of TSH at 0, 15, and 30 minutes after infusion.

Definition of Terms

For the purposes of this study the following definitions were used: (1) *goiter*: a thyroid gland estimated as being >20 g by palpation; (2) *thyrotoxicosis*: an elevated serum T_4 or serum T_3 with a basal TSH <0.3 μU/mL; (3) *hypothyroidism*: a decreased serum T_4 with a basal TSH >4.0 μU/mL or a normal serum T_4 but with a basal TSH >10 μU/mL; (4) *early disease*: the occurrence of a goiter, thyrotoxicosis, or hypothyroidism alone, or thyrotoxicosis followed by hypothyroidism within the first 11 months (hereafter referred to as *first year*) postpartum; (5) *late disease*: (after completion of a TRH stimulation test 11 to 15 months postpartum, hereafter referred to as *after the first year*) the occurrence of goiter alone, thyrotoxicosis, a basal TSH <4.0 μU/mL with TSH >35 μU/mL in response to TRH, or a basal TSH >10 μU/mL; and (6) *treatment*: L-thyroxine was prescribed when symptomatic hypothyroidism was present. The symptoms that prompted therapy included fatigue, an inability to lose weight, and impaired cognitive performance. β-Blockers alone were prescribed for early transient thyrotoxicosis and β-blockers with antithyroid drugs were given for persistent thyrotoxicosis. In patients receiving thyroid hormone, L-thyroxine was stopped for 6 to 8 weeks before the performance of a TRH stimulation test.

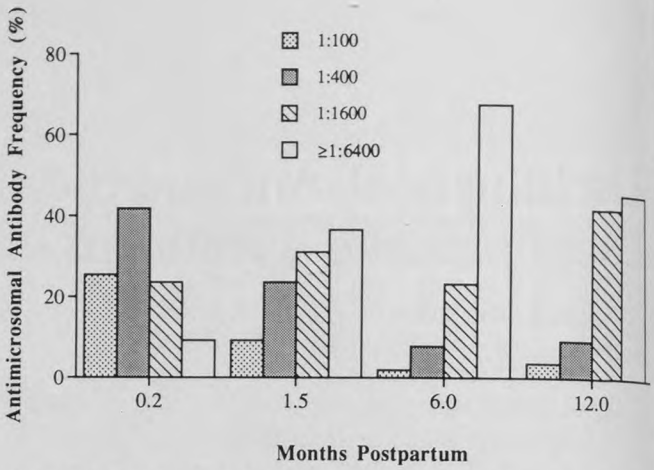

Figure 1. Frequency of titers of serum antimicrosomal antibodies in 55 women who had positive antimicrosomal antibodies at delivery and who were followed for 1 year postpartum. Each group of bars shows the percentages of women who had the indicated titers at selected times postpartum. The highest antibody titers were seen at 6 months postpartum.

Data Analyses

The degree of association among antibody titers, clinical or biochemical course, and treatment were analyzed using descriptive, chi-square (χ^2), or two-tailed Fisher's exact test (for small cell size) statistical techniques.[4,5] Our primary questions of association were investigated using relative risk odds ratio techniques, with the confidence interval (CI) calculated according to Fleiss.[6] Analyses were performed using SPSS-PC[4] and Statistix 3.1[5] with significance set at $P < .05$.

Results

Descriptive Analysis

Figure 1 shows the frequency of antimicrosomal antibody titers at delivery and at other selected times during

the first year postpartum. Antimicrosomal titers increased from delivery to the first visit (6 to 10 weeks). The highest titers occurred at 6 months, with two thirds of the 55 women having titers ≥1:6400.

The distribution of diagnoses during the period of early disease was as follows: of the 55 women, 15 women were normal, 10 had goiter only, 8 were thyrotoxic, 7 had thyrotoxicosis preceding hypothyroidism, and 15 had only hypothyroidism. Five of the 10 women with goiter alone had documented normal-sized thyroid glands found on their initial postpartum examinations. It is possible that the remaining 5 women had antecedent goiter, as they were not examined during pregnancy. Subsequent resolution of goiters in 3 of the latter 5 women, however, suggests that development of euthyroid goiter was a postpartum occurrence in most cases.

Our study of the relationship between early and late disease revealed the following results: Four of the 15 women who had a normal early course had an abnormal TRH stimulation test after the first year postpartum. We cannot exclude the presence of this mild abnormality before 1 year, as stimulation tests were not performed at earlier times. Ten women initially had goiter alone. After 1 year, 4 were normal, 2 had abnormal TRH tests, and 4 had persistent goiter. In 4 of the 8 women with thyrotoxicosis, the condition resolved spontaneously, presumably because of thyroiditis, although radioactive iodine uptake (RAIU) tests were not performed. The thyrotoxicosis persisted in the other 4 women and was diagnosed as Graves' disease with an increased RAIU. Of the 7 women who went through sequential thyrotoxic and hypothyroid phases, 3 were normal after one year and 4 had abnormal TRH tests. Fifteen women had only hypothyroidism in the first year. After 12 months, 4 of these women were normal, 1 had a goiter, 4 had abnormal TRH tests, and 6 had baseline TSH levels >10 μU/mL. Thus, 15 of the 40 women (38%) with early disease were normal after the first year, whereas 25 (63%) had both early and late disease. If a woman experienced biochemical or symptomatic dysfunction within the first year, there was an association ($\chi^2 = 4.18$, $P < .05$) with having thyroid dysfunction after 1 year.

Next, we examined the frequency of disease occurrence (both early and late) in relation to the frequency and time required for therapy. During the first year postpartum, 15 of the 55 subjects had no disease and 10 additional women had only a goiter. None of these women required treatment at any time. Four of the 8 women with thyrotoxicosis alone had transient disease and 4 had Graves' disease. Seven women became spontaneously hypothyroid shortly after a period of thyrotoxicosis in the first year. Five of these women required early therapy with resolution of the hypothyroidism by 11 to 15 months, one never received treatment, and one had persistent disease that required long-term therapy. Nine of the 15 patients who became hypothyroid without thyrotoxicosis required long-term therapy. Of note, 82% (18 of 22) of the chemically hypothyroid patients were symptomatic and required therapy during the first postpartum year. Furthermore, 10 of these 22 women received long-term therapy for persistent disease.

It is interesting that 22 of 26 patients with a normal TRH test after the first year never required therapy. Four of the 5 women with persistent goiter alone never received therapy. The fifth patient was treated early in the disease but not after the first year. Both the thyrotoxic patients and those with overt biochemical hypothyroidism had persistent disease requiring therapy. The most diverse patient group was 14 women with normal basal TSH and hyperstimulated TRH tests. Seven never required therapy, 3 were treated early for transient hypothyroidism, and 4 were treated both early and late because of symptoms.

Relative Risk Analyses

Our primary questions centered on how useful antimicrosomal antibody titers would be in determining which women would develop symptomatic or biochemical thyroid dysfunction either within or after the first postpartum year, and of the women with disease, who would require treatment. Figure 2 shows the frequency distribution of antimicrosomal antibody titers 2 days after delivery in relation to the presence or absence of disease and treatment. Odds ratio analyses revealed that postpartum women with positive antimicrosomal antibodies had a 6.5-to-1 (95% CI = 1.4 to 31.1, $P = .01$) risk for early disease when titers at delivery were ≥400. Patients who required treatment had an odds ratio of 23-to-1 (95% CI = 1.22 to 412, $P = .006$) when titers at delivery were ≥6400. The occurrence of late disease showed a 3.4-to-1 trend when titers at delivery were ≥1600, but the 95% CI (.98 to 13.9, $P = .051$) precluded accepting the significance.

The frequency distribution of antimicrosomal antibody titers determined 6 to 10 weeks (first visit) after delivery are presented in Figure 3. Odds ratio analyses indicated a 5-to-1 (95% CI = 1.2 to 22.7, $P = .02$) chance of early disease occurring when the first visit titers were ≥1600, and a 6-to-1 (95% CI = 1.6 to 25.7, $P = .004$) chance of needing treatment when the titers were ≥6400. Antimicrosomal antibody titers were not useful in estimating who might have permanent thyroid dysfunction. As presented in Figure 1, there was a natural increase in titers from delivery to the first visit, so the

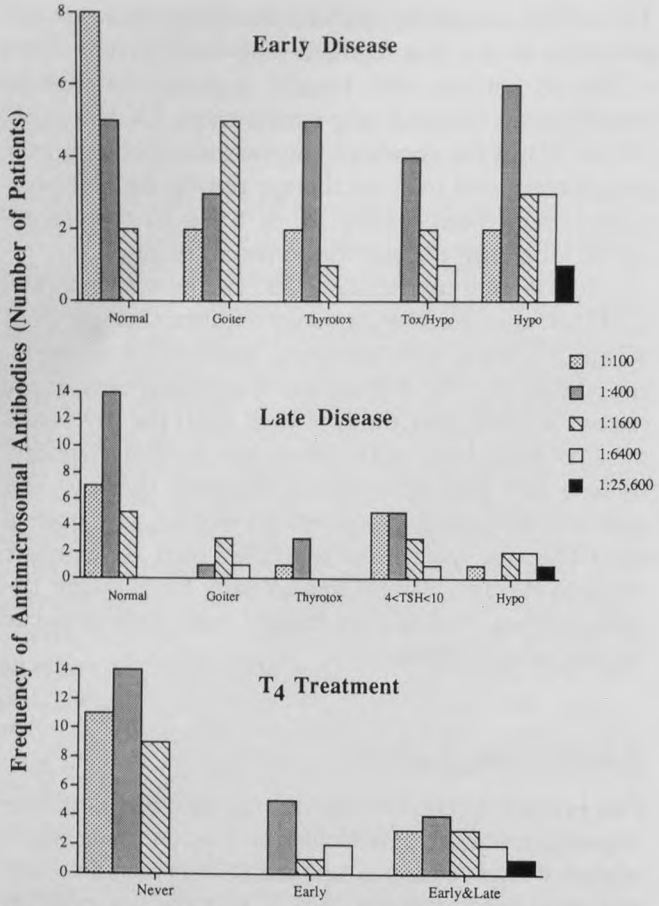

Figure 2. Frequency of titers of serum antimicrosomal antibodies at delivery in 55 women. The top panel shows the frequency of titers vs thyroid status during the first year postpartum (early disease). The middle panel shows the frequency of titers vs thyroid status after 1 year postpartum (late disease). The bottom panel shows the frequency of titers vs T_4 treatment. (Thyrotox denotes thyrotoxic only; Tox/Hypo, thyrotoxicosis followed by hypothyroidism; Hypo, hypothyroid only; Early, T_4 treatment during first year; Early & Late, T_4 treatment during the first year and thereafter.)

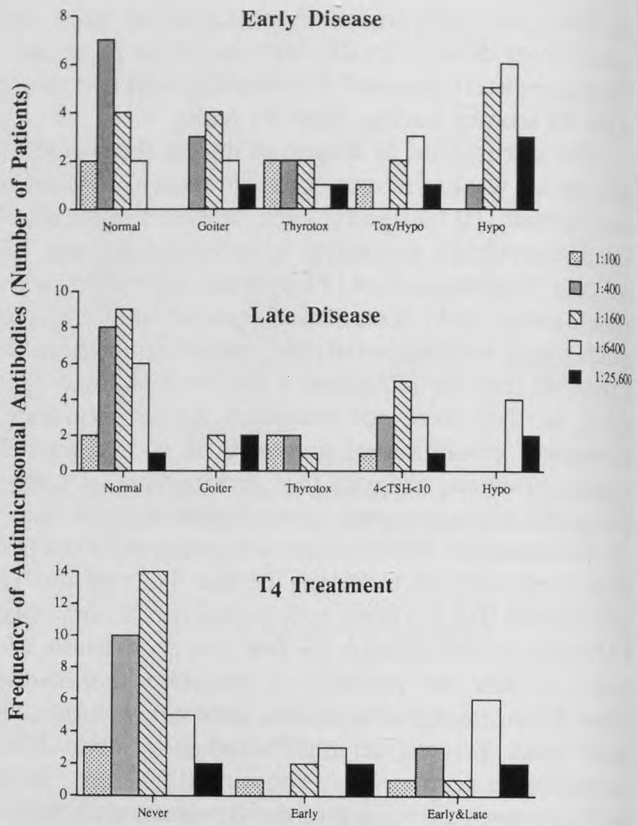

Figure 3. Frequency of titers of serum antimicrosomal antibodies at 6 to 10 weeks postpartum in 55 women. The top panel shows the frequency of titers vs thyroid status during the first year postpartum (Early Disease). The middle panel shows the frequency of titers vs thyroid status after 1 year postpartum (Late Disease). The bottom panel shows the frequency of titers vs T_4 treatment. (Thyrotox denotes thyrotoxic only; Tox/Hypo, thyrotoxicosis followed by hypothyroidism; Hypo, hypothyroid only; Early, T_4 treatment during first year; Early & Late, T_4 treatment during the first year and thereafter.)

higher titers required for early disease occurrence and treatment are not surprising.

Discussion

Postpartum thyroiditis is common, yet its presence frequently goes unrecognized. Despite its significant morbidity,[3] few physicians screen for this disease, either at term or throughout the postpartum period. This study demonstrates that measuring serum antimicrosomal antibodies at delivery is a convenient mechanism for identifying women who have positive antithyroid antibodies, and that antimicrosomal antibody titers are highly useful in determining who is at risk for the occurrence of postpartum thyroiditis.

Our results would further indicate that a rise in titers from delivery to 6 to 10 weeks after delivery increases the risk of disease occurrence. A single time of assessment, however, is more practical than using two time points. We recommend that titers be obtained at delivery to provide the most useful information about future disease occurrence. In our study, there was a strong suggestion for the occurrence of late disease when delivery titers were $\geq$1600, but there was no association between late disease and first visit titers. This finding differs from Swedish,[7,8] Japanese,[9] and Welsh[10] groups, who have recommended testing either in the first trimester or at 2 months or later postpartum, and with a Canadian study[2] that found the greatest sensitivity of antibody titers at 5 to 7 months postpartum. In addition to identifying which time of assessment is beneficial in determining the

chance of developing disease during the first year postpartum, we have identified the titers (≥400 at delivery, ≥1600 at first visit) that indicate the greatest probability for early dysfunction. It is not necessary to wait until peak titer levels occur at 6 months postpartum to identify those patients who have the greatest chance for disease occurrence, as previously recommended.[8,10]

Based on our results, 73% of our screened group developed early disease if goiter was included, whereas the incidence was 55% when euthyroid goiter was excluded. All of our patients with euthyroid goiter had lower antibody titers, and none required therapy. Several previous reports[3,11] have included this category of patients in the disease group when reporting on the frequency or prevalence of postpartum thyroiditis. Perhaps these women should not be included in disease statistics. Nevertheless, our observations indicate that a euthyroid goiter may represent one end of the spectrum of postpartum thyroiditis.

The occurrence of late disease in this study appears to be comparable to that reported by others. Nikolai et al[11] found that 12 of 25 women (48%) who developed postpartum thyroiditis and were recalled 3 years later had permanent thyroid disease, including euthyroid goiter, an augmented TSH response to protirelin, and biochemical hypothyroidism. Tachi et al[12] recalled 44 women 5 years after an episode of postpartum thyroiditis and found that 23% were hypothyroid; however, neither the presence of euthyroid goiter nor response to protirelin testing was reported. Othman et al[13] also reported a 23% occurrence of permanent hypothyroidism (10 of 43 women), but again there was no mention of euthyroid goiter. Thus, there is increasing evidence of substantial numbers of patients with longstanding morbidity from a disease that heretofore was considered transient.

The best indicator for late disease was disease within the first year postpartum, and the women who were most likely to have late disease were those who developed hypothyroidism without a thyrotoxic phase. Hypothyroidism without thyrotoxicosis, and high antimicrosomal antibody titers at 16 weeks postpartum, have both been described[13] as suggestive of late disease; however, we were unable to confirm the direct association between these titers and the occurrence of late disease. Antithyroglobulin antibodies have also been reported to be predictive of permanent disease,[12] but we were also unable to confirm this association.

Finally, postpartum thyroiditis has been termed transient or self-limiting.[7,11] However, even with the exclusion of goiter, 44% of our patients had late disease, and 38% required treatment either temporarily or permanently. A 6-to-1 chance of having symptomatic and/or biochemical thyroid dysfunction within 11 months postpartum, along with a 23-to-1 chance of needing treatment, cannot be ignored. We further found that, unlike the classic symptoms of hypothyroidism, generalized fatigue, loss of attention span, difficulty in providing new baby care, and a variety of cognitive difficulties predominated in postpartum thyroiditis.[3] It was also our impression that the biochemical abnormalities preceded these symptoms by one clinic visit, and we were therefore able to anticipate which women might need therapy. We agree with others that age, parity, and personal or family history of other autoimmune disorders are not helpful in determining either the occurrence of postpartum thyroiditis or the need for treatment.

In conclusion, we believe that antimicrosomal antibody titers obtained at delivery provide highly useful information about the likelihood of postpartum thyroiditis developing and indicate who will most likely require medical therapy. However, the financial impact of screening such a large population must be considered. We previously reported[3] that, when the absolute costs for reagents and technician time are considered, the expense of screening is cost-effective. Nevertheless, prospective longitudinal studies delineating the precise predictive accuracy of these titers and cost-benefit analyses under a variety of practice scenarios are required to further address these issues. In the meantime, wider recognition of postpartum thyroiditis by primary care physicians should increase the likelihood of prompt diagnosis and therapy.

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