The clinical spectrum of postpartum thyroid disease

J.H. LAZARUS, R. HALL*, S. OTHMAN, A.B. PARKES, C.J. RICHARDS2, B. McCULLOCH and B. HARRIS1

From the Departments of Medicine and 1Psychological Medicine, University of Wales College of Medicine, Cardiff, and 2Caerphilly District Miners Hospital, Mid Glamorgan, UK

Received 15 January 1996 and in revised form 22 February 1996

Summary

The clinical and biochemical features of postpartum thyroid disease were analysed in 152 antithyroid peroxidase antibody-positive (anti-TPO+ve) women and compared with 239 anti-TPO-ve age-matched control postpartum women. All were assessed monthly for up to 12 months postpartum. Seventy three anti-TPO+ve women developed postpartum thyroiditis (PPT): 19.2% hyperthyroid alone, 49.3% hypothyroid alone, and 31.5% characterized by hyper- followed by hypothyroidism. None of the antibody-negative women developed any thyroid dysfunction. A significant increase in many of eleven symptoms of hypothyroidism and some of eight symptoms of hyperthyroidism compared to control women was observed in all anti-TPO+ve women, independent of thyroid status. This was particularly seen in women who later developed PPT when they were euthyroid, but was also observed in euthyroid anti-TPO+ve women who showed no decline of thyroid function during the postpartum period. Although PPT is usually transient, this condition, and the euthyroid antibody-positive state, may be associated with significant symptomatology, including an increased incidence of minor to moderate depression. Early recognition of this syndrome by antenatal screening of thyroid antibodies may contribute to improved management of women during the postpartum period.

Introduction

Postpartum thyroid dysfunction is characterized by transient hyperthyroidism occurring about 14 weeks postpartum followed by transient hypothyroidism which presents at 19 weeks. The condition, a destructive thyroiditis, predominantly occurs in patients with positive titres of thyroid peroxidase (TPO) auto-antibody (Ab), (the microsomal antibody) seen in 10% of women at approximately 16 weeks gestation. Although the clinical manifestations of the hyperthyroid state are not usually severe, the same cannot be said for the hypothyroid condition. Moreover we and others have found an increased incidence of depressive symptomatology in thyroid antibody-positive women compared to thyroid antibody-negative control postpartum women. In addition, there is evidence that in 25–30% of hypothyroid postpartum women the hypothyroidism becomes permanent. Despite these facts, postpartum thyroid disease has not been widely recognized, and the clinical symptomatology has been thought to be mild. The condition has been described in many countries and has been reviewed. Most reports have described relatively small numbers of patients followed over short periods of time. This has created a problem in defining the incidence of the condition, although it is now accepted that it occurs in 5–9% of women during the first year postpartum. We have recently identified 158 thyroid antibody-positive women in early gestation and have assessed them together with control thyroid antibody-negative women at monthly intervals postpartum for up to one year. We now describe the clinical spectrum of their thyroid dysfunction and associated features.

Address correspondence to Dr J.H. Lazarus, Senior Lecturer in Medicine, Department of Medicine, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN

*Deceased

© Oxford University Press 1996
Methods

Patients

Over a two-year period, patients were screened for antithyroid antibodies at the Booking Clinic (16 weeks gestation) of a district hospital in South Wales and those that were positive were invited to attend the postpartum clinic at monthly intervals starting at one month postpartum. They, and thyroid antibody age-matched ‘control’ postpartum women, each gave written informed consent to the study which was approved by the local Ethical Committee. While most women were recruited as stated, a small number were screened at delivery prior to recruitment. At the postpartum clinic, patients were assessed clinically for thyroid status at monthly intervals on at least nine occasions; in 20 extra patients, weekly review was performed for 20 weeks postpartum, blood samples being obtained every week. A symptom questionnaire which assessed eight symptoms of hyperthyroidism (lack of energy, irritability, nervousness, weight loss, sweating, shaking hands, palpitations and heat intolerance) and eleven of hypothyroidism (lack of energy, puffy face, dry hair, dry skin, constipation, aches and pains, parasthesiae, cold intolerance, poor memory, lack of concentration and depression) was completed on each occasion by one of three endocrine physicians (JHL, RH, SO). These symptoms have previously been well validated for altered thyroid function. The physicians were not aware of the antibody status or thyroid function test result at the time of the patient interview. The patients were not aware of their thyroid antibody status at the time of examination. Goitre size was recorded as: 0, not palpable; 1, palpable but not visible; 2, palpable and visible; 3, very obvious. Patients were weighed and blood drawn for measurement of FT4, FT3, TSH and thyroid antibodies. Blood samples were collected at booking, at delivery, and monthly for 12 months postpartum, and the serum was stored in aliquots at —20 °C. On four occasions during the study, patients underwent extensive psychiatric testing by a psychiatrist. FT3 and FT4 were measured by the Amerlex M method (Amer sham) and TSH by the Amerlite RIST. Microtitre plates were coated overnight with sodium-deoxycholate-solubilized Graves’ thyroid microsomal protein (Graves’ thyroid microsomes were prepared from snap-frozen tissue by differential centrifugation). After washing, the coated wells were filled with 1:100 dilutions of patient serum (or standard dilutions) and incubated at room temperature for 2 h. This was followed by dilute peroxidase-conjugated sheep anti-human IgG. The bound peroxidase activity, seen as a green colour after the addition of ABST (Sigma) and hydrogen peroxide as substrates, was measured at 550 nm in a Flow Multiscan spectrophotometer.

Data was analysed using the SPSS statistical package. The statistical test used was the \( \chi^2 \) test. If necessary, log transformation was used to normalize the data.

Results

Of 1996 women screened for anti-TPO antibody, 152/235 positives were recruited to the study together with 239 antibody-negative control women. None of the control women developed clinical or biochemical features associated with thyroid dysfunction during the postpartum year. Seventy-five of the positive women remained euthyroid during the postpartum year, and a further four were excluded from the study because of pre-existing thyroid disease. The remaining 73 women developed postpartum thyroid dysfunction, 14 characterized by transient hyperthyroidism alone, 36 hypothyroidism alone, and 23 hyper-followed by hypothyroidism. Typical progression of thyroid function during the first 20 weeks postpartum is shown for three patients followed weekly during this period (Figure 1). At the end of 12 months’ follow-up, 20% of patients who had presented with hypothyroidism were still requiring T4 replacement therapy. There were more Ab+ve patients (34%) with a positive family history of thyroid disease than in the Ab−ve group (22%) \( (p<0.01) \). There was a slight but significant difference between the mean age of the two groups (Ab+ve 27.7 years, Ab−ve 25.9 years, \( p<0.002 \)).

Sixty-eight (45.9%) of Ab+ve women had taken the oral contraceptive for a mean of 41.5 months (±29.4 SD) before the current pregnancy; slightly more Ab−ve women (139, 58.2%) had received the pill for the same length of time (39.0±30.1 months).
There was no difference between the two groups in the onset of menarche (approx. 12.8 years). There was no relationship between any of the following factors and thyroid antibody status; sex of the baby, length of gestation, foetal outcome (survival) at birth, thyroid problems in the baby, mode of delivery (e.g. normal or Caesarean section), number of previous pregnancies, incidence of cigarette smokers, regularity of previous menstrual cycles, type of previous thyroid disease, incidence of other autoimmune diseases and previous episodes of depression or nervous breakdown. There were also no differences between the incidence of the above parameters in Ab+ve and —ve groups when the Ab+ve group was divided into those who developed PPT or remained euthyroid.

Symptoms

A significant increase in prevalence of many symptoms of hypothyroidism and a few of hyperthyroidism was seen in the anti-TPO +ve group (i.e. those with thyroid dysfunction and euthyroidism) compared to the control patients at all times studied (Figure 2).

In the PPT group significantly increased hyperthyroid symptomatology compared to the Ab—ve group was noted in lack of energy and irritability from 3 to 9 months. None of the other hyperthyroid symptoms were increased in the PPT group compared to controls. Of the hyperthyroid symptoms, nervousness, weight loss, sweating, shaking hands, palpitations and heat intolerance were not helpful in diagnosing hyperthyroidism in the postpartum period. In contrast, the most frequently occurring hypothyroid symptoms were lack of energy, aches and pains, poor memory, dry skin and cold intolerance, each being observed more commonly than in the Ab—ve group at least on three visits to a maximum of six visits. Although the mean onset of hypothyroidism was not until 18 weeks, several symptoms (dry skin, aches and pains, poor memory and lack of concentration) were seen in this group more frequently than in the control group at 12 weeks or before. Indeed, poor memory was observed at 6 weeks in this group at a time of normal thyroid function. In addition, many other symptoms were observed statistically more often in the PPT group when they had normal thyroid function than in the Ab—ve controls at the same postpartum assessment (Figure 3). The symptoms least helpful in discriminating hypothyroidism were puffy face, constipation, paraesthesiae and cold intolerance.

In the Ab+ve group (euthyroid who did not develop PPT) increased nervousness (compared to the Ab—ve group) was noted at 2, 3, 7 and 8 months as well as a significant increase in the frequency of palpitations, heat intolerance and aches and pains at different times. The contribution of the frequency of symptoms in the euthyroid antibody-positive group to the total symptom prevalence in the antibody-positive (euthyroid and PPT groups) was shown by the fact that a number of symptoms had a significantly increased incidence compared to the Ab—ve group when this was not the case for each antibody-positive group analysed separately. Thus, increased rates of depression were noted at visit 1 and 4 and of lack of concentration at visits 4, 6, 7 and 8. There was also an increased incidence of lack of energy, dry skin, aches and pains, poor memory and depression compared to the Ab—ve group noted at the first visit (4 weeks) postpartum. There was significantly more depression (p<0.007) as elicited by direct questioning at the 4-week postpartum visit in the Ab+ve group. Although the level of probability (p>0.062) was not significant for Ab+ve (PPT+ve) vs. Ab—ve, the Ab+ve PPT—ve group separately had more depression than the control group (p<0.0056).

Discussion

Roberton \(^2\) was the first author to describe symptoms of thyroid dysfunction occurring after pregnancy and alluded to irritability and fatigue associated with depression. In fact he described hypothyroid symptoms in 53% of 219 patients with 483 pregnancies. Other notable symptoms were cold and heat intolerance, hair loss, palpitation and weight loss. Thyrotoxic symptoms were also commented upon by subsequent groups.\(^3\)-\(^5\) Other hyperthyroid symptoms including palpitations, heat intolerance, tremulousness and nervousness have also been noted.\(^6\) Jansson et al.\(^7\) noted that fatigue, loss of initiative, weight gain and ‘mild psychic discomfort’ were the most frequent symptoms. None of the above authors, however, have addressed the specific incidence of symptomatology compared to euthyroid controls during the postpartum period in substantial numbers of women. Hayslip et al.\(^8\) did compare hypothyroid symptoms in 17 hypothyroid and 18 euthyroid postpartum women. They found significantly more depression, impairment of concentration, memory and carelessness in the hypothyroid group. In addition the patients with hypothyroidism had three times as many complaints as the euthyroid women at 3–5 months postpartum. The present data relate to a large number of patients and indicate for the first time that women with positive anti-TPO antibodies have more symptoms than control women even as early as 4 weeks postpartum. This occurred both in women who subsequently developed PPT as well as in women who remained euthyroid and who were all clinically and biochemically euthyroid at this
Figure 1. Postpartum thyroid dysfunction in three patients. In patient 3004 (a) hyperthyroidism occurred transiently at 8–9 weeks postpartum. Hyperthyroidism also occurred transiently in patient 2970 (b) but much later (22–24 weeks postpartum). In patient 3010 (c) modest transient hyperthyroidism was followed by severe transient hypothyroidism. In all those patients blood samples were obtained weekly postpartum. Note the significant postpartum rise in anti-TPO antibody.
time. Although PPT + ve women had greater frequencies of thyroid related symptoms at the time of onset of hyper- and hypothyroidism, some hyperthyroid symptoms persisted at high frequencies till the later months (e.g. lack of energy and irritability). Conversely, many hypothyroid symptoms (lack of energy, dry skin, aches and pains, cold intolerance and poor memory) were observed in greater frequencies in the PPT group many weeks before the onset of postpartum hypothyroidism. Interestingly, there was more depression noted at one month postpartum (p<0.007) in the women who were to develop PPT as well as at later times. We have previously reported that there is an increase in depressive symptomatology, assessed by validated questionnaires, in anti-TPO + ve postpartum women independent of thyroid dysfunction during this time. The relationship between thyroid antibodies and psychiatric symptomatology is not clear. Whether antibodies could modulate neurotransmitter function through alterations in cytokine concentration is yet to be established. There are cytokine receptors in the brain. The possibility that thyroid antibodies are a marker for a specific genotype related to depression also requires investigation. Certainly in the Ab + ve PPT—ve group there was no evidence that thyroid function, as judged by FT4, FT3 and T4/T3 ratio was declining through the postpartum period which might have accounted for mood changes or other symptoms.

These data suggest that symptoms of hyperthyroidism and hypothyroidism may occur well before the biochemical abnormalities are observed. In addition many of these symptoms remain well after return to biochemical euthyroidism. Crooks et al. were the first to describe detailed weighting to individual symptoms in the diagnosis of hyperthyroidism and also to use a score of hypothyroid symptoms for follow-up. Subsequent analysis has shown that there is not a close correlation between the biochemical severity and the extent of clinical disability from thyrotoxicosis. With regard to hypothyroidism, while it is true that patients who develop it rapidly have more symptoms than those whose onset is gradual, there are no data on the incidence of symptoms in euthyroid patients with antibodies. In contrast, there are a number of studies documenting the association of depression and other neuropsychiatric features with subclinical hypothyroidism.

In addition to the well-documented biochemical and immunological features of PPT, this study has demonstrated the wide clinical spectrum of the condition. Patients with positive thyroid antibodies are more symptomatic than control women and these symptoms occur before, during and after thyroid dysfunction as well as in thyroid antibody-positive
Figure 2. Mean prevalence of symptoms of hyperthyroidism and hypothyroidism (see text) in all anti-TPO Ab-positive patients compared to euthyroid postpartum control women. a 1 month postpartum; b 7 months postpartum; c 9 months postpartum.

Figure 3. Frequency of symptoms in PPT patients when they were euthyroid. Data show the number of symptoms occurring statistically more frequently in the PPT group than in euthyroid antibody-negative control postpartum women.

women with no thyroid hormone abnormalities. Symptomatic recovery from hyper- or hypothyroidism is not complete even when thyroid function has returned to normal. These clinical data reinforce the view that screening for postpartum thyroiditis, for example, by measuring thyroid antibodies in early pregnancy, should be evaluated as a possible health gain strategy.

Acknowledgements
We would like to thank Dr R. John, Department of Medical Biochemistry, for thyroid function tests and Mrs L. Taylor for technical assistance.

References


