

Clinical aspects of recurrent postpartum thyroiditis

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SUMMARY

Background. Postpartum thyroiditis (PPT), characterized by transient hyperthyroidism and transient hypothyroidism, occurs in 5–9% of women. It is accompanied by the presence of circulating antithyroid peroxidase antibodies (TPOAb) which have been associated with an increase in depressive symptomatology compared with TPOAb-negative women.

Aim. To assess the frequency and nature of the syndrome in patients studied in detail after more than one pregnancy, as there are only sparse data on recurrence of PPT.

Method. Fifty-four patients were identified who had participated in at least two of three detailed postpartum studies of thyroid and psychiatric function during the past 12 years in the Caerphilly and Cardiff regions of South Wales. They included two women who had had three pregnancies. All patients had been followed monthly postpartum for at least six months, and 44 had been followed for 12 months.

Results. Of the 13 patients who developed PPT after their first pregnancy, nine had a recurrence of dysfunction after a further pregnancy and four remained TPOAb positive. Of the 24 women who were euthyroid anti-TPO positive after the first pregnancy, six developed thyroid dysfunction after a subsequent delivery, 14 remained antibody positive and euthyroid, while four underwent seroconversion and were antibody negative. The control group of 17 women were antibody negative after the first pregnancy; 16 remained negative after a further pregnancy and one became anti-TPO positive. The severity of PPT was slightly, but not significantly worse after the second recorded pregnancy (67% hypothyroid versus 44% hypothyroid). Neither the maximum anti-TPO titre following the first pregnancy, nor the rise in titre during this period were predictive of outcome after a subsequent pregnancy. Data from 26 women showed that recurrent depression was seen in 15.4%; a further six were depressed after the first pregnancy only, and two during a further postpartum period.

Conclusion. There was a 70% chance of developing recurrent PPT after a first attack, and a 25% risk even in women who were only anti-TPO positive without thyroid dysfunction during the first postpartum period. The recurrence of postpartum depression was not related to thyroid function. Patients noted to have thyroid dysfunction or just to be euthyroid but anti-TPO positive after pregnancy should be assessed carefully after a subsequent pregnancy.

Introduction

POSTPARTUM thyroiditis (PPT) is characterized by the development of transient hyperthyroidism and transient hypothyroidism from three to six months after delivery.^{1,2} Up to 30% of women who develop hypothyroidism proceed to permanent hypothyroidism and require lifelong thyroxine therapy.³ The condition is associated with the presence of circulating antithyroid peroxidase antibodies (TPOAb) in the great majority of cases, and a pathogenetic similarity to Hashimoto's autoimmune thyroiditis has been suggested. Only half the women identified as anti-TPO positive at around 12 to 16 weeks gestation will develop PPT. The other 50% will be euthyroid anti-TPO positive in the postpartum period.⁴ As the condition is almost always diagnosed later than six weeks postpartum, the care of mother and child is very much in the province of the general practitioner rather than the obstetrician.

The incidence of PPT varies from 5–9%. This variation is due to the frequency of postpartum assessment, especially with regard to the recognition of postpartum hyperthyroidism, which may last only a few weeks. Although it is recognized that PPT can recur in subsequent pregnancies, data on the risk of recurrence are sparse, perhaps in part because of difficulty in ascertainment. During the past 10 years we have performed three detailed studies of PPT to evaluate the clinical, immunological and psychiatric features of the syndrome. In each of these studies, patients were assessed postpartum approximately each month for at least six months, and in most cases for up to one year. In order to assess the frequency of recurrent PPT and to evaluate the effect of anti-TPO antibodies on subsequent postpartum thyroid function, we examined the course of women who had been documented in the three studies mentioned. As postnatal depression is known to recur,⁵ psychiatric status was reviewed where possible.

Methods

Patients

A retrospective search was conducted of three surveys of postpartum thyroid disease carried out between 1983 and 1994. These studies defined the clinical features and prevalence of PPT,⁶ the association of psychiatric symptomatology with positive thyroid antibodies,⁷ and our current attempt to prevent postpartum psychiatric symptomatology in thyroid antibody positive women by administering thyroxine.⁸ The anti-TPOAb titre (measured at booking) for entry to studies 1 and 2 included any woman with a titre >2 SD above the upper limit of normal. Ab titre requirement for entry to study 3 was more stringent (>3 SD above the upper limit of normal).

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Fifty-four women were identified as having had two or more documented pregnancies in two of the three studies between 1983 and 1995. Two of the women had had three pregnancies but only the events following the first and second pregnancies are analysed in this report. Blood samples had been collected at booking (about 16 weeks gestation) and monthly after delivery for 12 months in the first two studies and for six months in the third.

Laboratory investigations

Study 1.

Blood samples were collected at around 16 weeks gestation and at monthly intervals for one year postpartum. Free triiodothyronine (FT3) and free thyroxine (FT4) were measured using the 'Amerlex' assay (Amersham) and Thyroid Stimulating Hormone (TSH) was measured by a two-site immunoradiometric assay with a limit of detection of 0.1 mU/l.⁹ Thyroid autoantibodies were measured by enzyme-linked immunosorbent assay (ELISA).¹⁰

Studies 2 and 3.

Blood samples were obtained at 16 weeks gestation and monthly for 12 months postpartum (study 2), and at 6, 12, 16, 20 and 24 weeks postpartum (study 3). FT3 and FT4 were measured by the Amerlex M methods (Amersham), and TSH was measured by the Amerlite TSH method (Amersham International plc, Chalfont, Bucks, UK) with a limit of sensitivity of 0.04 mU/l.¹¹ The reference ranges for thyroid function tests used in these studies (FT4 8–19 pmol/l; FT3 4.2–7.7 pmol/l and TSH 0.5–3.6 mU/l) were derived from the analysis of serum samples from antibody negative subjects included in the second trial.⁷ An episode of thyroid dysfunction was defined as follows:

- Hyperthyroidism: either suppressed TSH together with FT4 >19 pmol/l or FT3 >7.7 pmol/l, or elevated FT3 and FT4, with either set of criteria occurring on one or more occasions.
- Hypothyroidism: either TSH >3.6 mU/l together with FT4 <8 pmol/l or FT3 <4.2 pmol/l, or TSH >10 mU/l on one or more occasions.

Thyroid antibodies were measured by ELISA.¹² In order to be able to make comparisons of 'microsomal' antibody activities between study 1 and the later studies, antibody data from this time was corrected by applying the equation:

$$\text{Antibody activity (U/ml)} = [(\text{OD} \times 52.7) + 15.7]^2; \\ (r = 0.80, P < 0.001)$$

as described previously.³ Goitre size was assessed clinically.⁶

Results

Postpartum thyroid disease

The relationship between thyroid status during the first postpartum period and outcome after the second pregnancy is shown in Table 1.

Seventeen of the 54 women were anti-TPO negative during gestation and after the first pregnancy. Sixteen (94%) of these remained anti-TPO negative after the second observed pregnancy, while one patient became antibody positive at this time. Thirteen of the remaining 37 anti-TPO positive women developed PPT after the first pregnancy, and the syndrome recurred in nine (69.2%) of these women after the second observed pregnancy. The remaining four were anti-TPO positive after the second pregnancy but did not develop PPT. Of the 24 anti-TPO positive women who remained euthyroid after the first pregnancy, six (25%) developed PPT after the subsequent pregnancy, while four (16.7%) underwent seroconversion to antibody negative status at this time. Fourteen (58.3%) of the 24 anti-TPO positive women remained euthyroid during the second postpartum period. There was no significant difference in the time intervals separating the births between those women who sustained recurrent PPT (mean 40.6 months; range 16–65 months) and those who developed it for the first time after a subsequent pregnancy (mean 40.4 months; range 13–76 months). The severity of the PPT, as judged by the incidence of hypothyroidism, was not significantly different between the two postpartum periods in the nine patients with a recurrence of the syndrome (44% versus 67%; $\chi^2 = 1.8$ [not significant]).

There was no relationship between age at the first pregnancy, or family history of thyroid disease, and eventual outcome after the subsequent pregnancy. Six out of nine (55.5%) women with recurrent PPT had a goitre size greater than 2 on a scale of 1–5, where 3 = palpable and significantly enlarged. This was a significantly greater number ($\chi^2 > 10$, $P < 0.01$) than that seen in the TPOAb-positive women (5/32; 15.6%). Anti-TPO titre after the first pregnancy was examined to determine its possible predictive power for outcome following the second pregnancy. In all anti-TPO positive groups there was no difference between the initial titre (six weeks postpartum) and the maximum titre during the postpartum period in relation to outcome. As an index of the rise of the immune response postpartum, the ratio of the maximum titre postpartum divided by the six week titre was calculated. This was greater than 2.0 in 14 of 37 (37.8%) of the anti-TPO positive women (range 2.07–11.1), but there was no relationship between this ratio and, for example, the development of PPT after the second pregnancy.

Table 1. Progression of relationship between thyroid function and anti-TPO status during the first postpartum period and outcome after subsequent pregnancy.

First postpartum assessment	Thyroid and antibody status	Subsequent postpartum assessment
17 women: TPOAb -ve, euthyroid		16 remained euthyroid, TPOAb -ve 1 became euthyroid, TPOAb +ve
24 women: TPOAb +ve, euthyroid		4 became euthyroid TPOAb -ve 14 remained euthyroid TPOAb +ve 6 became TPOAb +ve with thyroid dysfunction
13 women: TPOAb +ve with thyroid dysfunction		4 became TPOAb +ve, euthyroid 9 remained TPOAb +ve with thyroid dysfunction

Discussion

Postpartum thyroiditis is usually transient, although permanent hypothyroidism may occur in up to 30% of patients.³ Amino *et al*¹⁴ observed a recurrence of transient PPT during two consecutive postpartum periods in two out of 14 patients studied, while Fein *et al*¹⁵ described a definite recurrence in one of their five patients and possibly another recurrent episode in another. Of 14 Swedish women with symptomatic PPT reported by Dahlberg and Jansson,¹⁶ two had experienced similar features after previous pregnancies and another woman was documented to have transient thyrotoxicosis after a second pregnancy. In two long-term follow-up studies it was noted that there was a 40% incidence of recurrence in one,¹⁷ while we found that 30% of women developed PPT for the second time.³ Although these studies have indicated that recurrent PPT does occur, the number of cases in each report has generally been too small to indicate the definitive risk. The present retrospective data, derived from a moderately large number of women who have been extensively studied during the postpartum period on two occasions, suggest that there is about a 70% risk of developing PPT after a subsequent pregnancy if the condition has occurred previously. Ideally, a large prospective study would be the best method to evaluate the risk of recurrent PPT. However, no group has performed such a study, probably because of logistical problems. In a woman who has positive anti-TPO antibodies and who remains euthyroid after a first pregnancy, there is a 25% chance of developing PPT after a subsequent pregnancy. Although the anti-TPOAb titre for entry to the third study was more restrictive than for the first two studies, the wide range of antibody titres observed in patients (independently of which trial they had been in, or the eventual outcome) suggests that these women may be assumed to be representative of women with positive anti-TPO antibodies.

Other groups have suggested that the titre of anti-TPO antibodies is a valid predictor of the severity of PPT and possibly of recurrent disease.^{18,19} While we have found high titres of antibody in women with PPT, there is considerable overlap with those women who have remained euthyroid. Similarly, in the present study we find no relationship between the antibody titre or the rise in titre following the first pregnancy and the development of PPT after a subsequent pregnancy. We have recently suggested that the presence of circulating thyroid autoantibodies able to activate the complement system may correlate more closely with the development of PPT, although even this relationship is not perfect.²⁰ Other immune factors, possibly related to the immunological damage following the first pregnancy, may predict a recurrence, but these remain to be identified. The question arises whether, in view of the risk of thyroid damage after a subsequent pregnancy, long-term development of thyroid failure may occur in these women. To date this has not been shown in previous studies.²¹ Although women with PPT after the first pregnancy had a greater incidence of thyroid enlargement than PPT negative TPOAb positive women, the presence or absence of goitre is not an accurate predictor of subsequent disease. While there are data concerning the morphology of the thyroid²² and serum thyroglobulin²³ levels in postpartum TPOAb positive women, these data were not available in this group.

There has been recent interest in the course and recurrence of postnatal depression,⁵ particularly as it appears that those whose depressive episode arises *de novo* postpartum are at raised risk of having further episodes of postnatal depression. Also, there is evidence that there is an excess of mild to moderate depression in women with circulating thyroid antibodies.⁷

In conclusion, there is a 70% chance of recurrence of PPT following an episode in a previous pregnancy. Even if there had

been no thyroid abnormality apart from positive TPO antibody after a first pregnancy, there is a 25% risk of developing PPT after subsequent delivery. These data reinforce the suggestion that women who are found to have thyroid dysfunction or circulating thyroid antibodies after pregnancy should be carefully assessed after a second birth.

The frequency of postpartum thyroid disease is indicated in the summary points below. In view of the relatively high incidence of this condition we believe that screening for thyroid antibodies of 12–16 weeks gestation should be performed.

- 10% of women have positive thyroid antibodies at 16 weeks gestation
- 50% of the above develop abnormal thyroid function 3–6 months postpartum (PPT)
- Postpartum depression is more common in women with positive thyroid antibodies
- The risk of recurrent PPT after a subsequent pregnancy is 70% (25% if only antibody +ve after first pregnancy)
- Screening for thyroid antibodies in pregnancy should be considered.

A positive result at this time is an indication to check thyroid function at around three months postpartum and to be aware of the higher risk of postpartum psychiatric symptomatology.

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