Randomised trial of thyroxine to prevent postnatal depression in thyroid-antibody-positive women

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Background Women who are positive for thyroid antibodies in early gestation are prone to post-partum depression, apparently independent of thyroid dysfunction, as measured by serum levels of free thyroxine, free triodothyroxine and thyroid-stimulating hormone. This finding may be due to infrequent monitoring of thyroid function, because hyperthyroidism, hypothyroidism and combinations of both may occur post-partum.

Aims To test the hypothesis that stabilising thyroid function post-partum by administering daily thyroxine reduces the rate of occurrence and severity of associated depression.

Method In a randomised double-blind placebo-controlled trial, 100 μg of thyroxine or placebo was given daily to 446 thyroid-antibody-positive women (342 of whom were compliant) from 6 weeks to 6 months post-partum, assessing their psychiatric and thyroid status at 4-weekly intervals.

Results There was no evidence that thyroxine had any effect on the occurrence of depression. The 6-month period prevalence of depression was similar to that reported previously.

Conclusions The excess of depression in thyroid-antibody-positive women in the post-partum period is not corrected by daily administration of thyroxine.

Declaration of interest None. Financial support is detailed in the Acknowledgements.

Women who are positive for thyroid antibodies are prone to post-partum depression. Both the thyroid peroxidase autoantibody (TPOAb) and thyroglobulin antibody (less so) are associated with post-partum thyroid dysfunction (PPTD), and some studies have shown an association of post-partum depression with PPTD (Harris *et al*, 1989; Pop *et al*, 1991, 1993). However, using strict Research Diagnostic Criteria (RDC) for depression (Spitzer *et al*, 1978), it has been shown that there is no excess of post-partum *major* depression but of depression in general, which is related to positive thyroid antibody status rather than to PPTD. The depressed mood may be related to the general malaise associated with an autoimmune condition or to subtle fluctuations in thyroid hormones. If the latter is true, then prophylactic administration of thyroxine would be expected to prevent or diminish development of the post-partum depressed mood.

METHOD

The study was designed to identify thyroid-antibody-positive women during gestation and to administer thyroxine or placebo over the 6-month post-partum period under double-blind conditions.

All women delivering at two district general hospitals over a 3-year period were screened for thyroid antibody status at the antenatal check-in (approximately 16 weeks' gestation): the study was explained to these women and written informed consent was obtained if they agreed to participate. Women who had known thyroid disorder were excluded at this initial screening process. A total of 446 thyroid-antibody-positive women were entered into the study and assessed at weeks 6, 12, 16, 20 and 24 (i.e. until the sixth post-partum month) by attending the out-patient department or, if failing to do so, during a home visit by a nurse trained by the psychiatrists. Of approximately 7500 women screened there were just over 700 who were thyroid antibody positive. The most common reasons for non-involvement in the study were premature delivery, pre-existing thyroid disease and simple refusal because of the requirement to attend the hospital out-patient department frequently.

Psychiatric assessments

Psychiatric assessments were carried out by a trained psychiatrist (B.H. or R.O.) using RDC for depressive disorder, and mood was rated using the Montgomery and Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979). The women also completed the Edinburgh Postnatal Depression Scale (EPDS; Cox *et al*, 1987) and the 30-item General Health Questionnaire (GHQ; Goldberg, 1972). The cut-off points in terms of depression for these questionnaires are 15, 13 and 8, respectively.

Medical assessments

Medical assessments were carried out on each occasion by experienced endocrinologists (J.L. and R.H.) and included neck palpation and checking of radial pulse, a blood sample also being taken for estimation of free thyroxine (fT4), free triodothyronine (fT3), thyroid-stimulating hormone (TSH) and thyroid antibodies. Randomisation was achieved by a computer-generated sequence of numbers, and all of the investigators and the women were blind to therapy at every visit.

Prescribing occurred from the sixth week post-partum, with the women receiving a new supply of 100 μg of thyroxine or placebo tablets daily at every visit; a tablet count was carried out at each subsequent visit to check on compliance of administration.

Assay methods

Thyroid peroxidase autoantibodies (TPOAb) were measured by enzyme-linked immunoabsorbent assay (Groves *et al*, 1991), standardised against NIBSC 66/387, the anti-thyroid microsome serum (National Institute for Biological Standards and Control, Holly Hill, London, UK). Antibody activity was considered to be normal when levels were <19.4 kIU/l. The intra- and interassay variations were 4.9% (at a mean of 155 kIU/l) and 7.6% (at a mean of 149 kIU/l) respectively. The

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levels quoted are the mean of quadruplicate measurements.

Serum levels of fT3, fT4 and TSH were measured on an automated immunoassay analyser, the ACS-180 Plus (Chiron Corp., Halstead, UK). Free T3 and fT4 were measured using competitive labelled antibody assays with an acridinium ester as the label and paramagnetic particles as the solid phase. Measurement of TSH was by a two-site immunochemiluminometric assay. The stated normal ranges for these assays were as follows: fT3, 4–6.8 pmol/l; fT4, 9.8–23 pmol/l; TSH, 0.5–5.2 mU/l. Between-batch precisions for these assays were: fT3, 4.85% at a mean of 5.27 pmol/l; fT4, 4.0% at a mean of 134.6 pmol/l; TSH, 7.56% at a mean of 4.89 mU/l.

Statistical analysis

Statistical methods compared the placebo and active groups using the Mann–Whitney test (it had been shown by power calculation that approximately 400 women were required to be randomised to avoid type 2 error).

RESULTS

Analyses were based on 342 out of 446 subjects judged to have an adequate degree of compliance (i.e. the tablet count indicating 80% or more of expected consumption). The women came mostly from social groups 3–5, with a few exceptions.

Comparison of the compliant group with the non-compliant group indicated a significant difference in age (compliant: median 29 years, range 19–44; non-compliant: median 27 years, range 17–43; Mann–Whitney $P<0.001$). There were no significant differences in parity and gender of offspring between the two groups. A total of 167 women were in the control group and 174 in the active group. There was no significant difference in age (means 29.5 and 29.4 years, ranges 20–42 and 19–44) or parity (median 2, range 1–6) between the active and placebo groups, and there was no significant difference between gender of offspring.

The overall rate at which major depression (RDC definite and probable combined) occurred was 18.5% (i.e. the 6-month prevalence for the whole population), and for depression in general it was 38% (i.e. inclusive of minor depression). Rates of depression occurring at each visit are shown in Table 1 (i.e. both in terms of RDC categories and also the cut-off point of the EPDS). At visit 1 (i.e. before treatment was started) the EPDS score was significantly one point higher in the active group than in the placebo group (unpaired *t*-test) and the analyses at subsequent time points were designed to adjust for this chance baseline imbalance. The Mann–Whitney test failed to provide any substantial evidence of clinical benefit. When the groups were combined, the rates of major depression (definite and probable) varied between 5.1% (visit 5) and 9.1% (visit 2). Results for the MADRS and GHQ were similar (i.e. there were no significant differences between the active and placebo groups for mean scores or 'caseness' at each visit or in terms of the 6-month prevalence).

Thyroid status

No patient was clinically hyperthyroid or hypothyroid before or during the study in the T4-treated or the placebo group. However, unknown to the investigators, a small number of women were biochemically hyperthyroid at 6 weeks post-partum (elevated fT4 and fT3 with suppressed TSH) before randomisation into the trial. During the study, significantly more women in the active group had serum thyroid hormone concentrations consistent with hyperthyroidism than in the placebo group (Table 2), although these women did not show clinical symptoms of hyperthyroidism. Again this was not known to the investigators because they were blind to the thyroid status of the women. The incidence of PPTD in the placebo group was 50.6%, similar to previous reports by our group (Fung *et al*, 1988). In the T4-treated group, the incidence of post-partum hypothyroidism was reduced to 17.2% (Table 2) and some of the non-specific symptoms were ameliorated. Antibody concentrations in the two groups were similar and not significantly different between the two groups over the time course of the study (Mann–Whitney: 91.6 and 98.8 kIU/l at 6 weeks post-partum, rising to 182 and 213 kIU/l at 24 weeks post-partum). In accordance with our previously published data, thyroid function in the placebo group showed that approximately half of the women remained euthyroid and the remainder developed some form of biochemical thyroid dysfunction (Table 2). However, in the active group there was a marked increase in the incidence of biochemical hyperthyroidism, but this was not accompanied by any clinical symptomatology (Table 2).

Table 1 Rates of major depression (% RDC definite and probable combined), all RDC depression and rates according to the EPDS (cut-off point 13)[1]

	Active	Placebo	Combined
6 weeks			
Major	6.5	6.9	6.7
RDC: any	17.4	20.1	18.8
EPDS	18.3	15.0	16.7
12 weeks			
Major	8.4	9.7	9.1
RDC: any	23.5	24.4	24.0
EPDS	21.5	16.2	19.5
16 weeks			
Major	7.2	9.5	8.5
RDC: any	22.8	22.0	22.3
EPDS	21.3	15.0	18.2
20 weeks			
Major	7.2	8.1	7.7
RDC: any	16.9	16.8	16.8
EPDS	15.0	14.5	14.7
24 weeks			
Major	4.8	5.3	5.1
RDC: any	12.7	15.8	14.3
EPDS	11.8	12.1	11.9

RDC, Research Diagnostic Criteria; EPDS, Edinburgh Postnatal Depression Scale.
1. There was no significance in the rates of depression at any time point between the groups receiving active medication and placebo (Mann–Whitney).

DISCUSSION

An association between hyperthyroidism, hypothyroidism and mood has long been known (Hendrick *et al*, 1998). Primary thyroid disease is associated with anxiety and depression, and in conditions of primary mood disorder (major depression) approximately 25% of patients show a disturbance of the hypothalamic–pituitary–thyroid axis (Prange *et al*, 1972), with a blunted response of TSH to an intravenous bolus of thyrotrophin-releasing hormone (TRH).

Thyroid autoantibodies

The relationship between autoimmune thyroid disease and depression remains undecided, but it has been suggested that measurement of thyroid antibody titres may be useful in identifying patients at risk

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Table 2 Number of patients in the two groups according to thyroid status throughout the study[1]

	Euthyroid	Biphasic	Hypothyroid only	Hyperthyroid only
Placebo	82	38	14	32
Active	24	21	8	116

1. The difference between the rates of occurrence of biochemical hyperthyroidism between the placebo and active groups is highly significant ($\chi^2=20.37$, $P<0.0001$); for the reduced rate of hypothyroidism in the active group (biphasic and hypothyroid combined) $\chi^2=9.17$, $P<0.01$.

of developing hypothyroidism when on lithium therapy, and also to identify subclinical thyroiditis as a causative factor in treatment-resistant depression (Hendrick *et al*, 1998).

A further aspect of the association of thyroid function and mood disorder concerns women with positive thyroid antibody status (TPOAb and anti-thyroglobulin), which affects approximately 12% of British women (Prentice *et al*, 1990). Roberton (1948) first reported an excess of women with mild post-partum hypothyroidism, and almost 30 years later Amino *et al* (1976) described a number of women who presented with mild hypothyroidism in the 6-month post-partum period who were positive for thyroid antibodies. In a further study, Amino *et al* (1982) showed that approximately 4% of Japanese women experienced transient thyroid dysfunction (some having 'depressive psychosis') in the post-partum period associated with positive thyroid antibody status (TPOAb and anti-thyroglobulin). However, although the TSH-receptor-stimulating antibody may cause hyperthyroidism in the neonate, it is not associated with PPTD in the mother (Lazarus & Kokandi, 2000).

There have been conflicting reports about the possible relationship between positive thyroid antibody status, PPTD and depression. The rates at which depression occurred in the study reported here were similar to those reported for thyroid-antibody-positive women in a previous study compared with a control group of thyroid-antibody-negative women (Harris *et al*, 1992). Similarly, in a study of perimenopausal women, Pop *et al* (1998) have shown depressed mood to be associated with thyroid antibody status rather than with thyroid dysfunction as assessed by plasma T3, T4 and TSH. Furthermore, the same group, in studying a cohort of 310 unselected pregnant women, conclude that the presence of TPOAb during pregnancy can be regarded as a marker for subsequent post-partum depression (Kuijpens *et al*, 2001). On the other hand, a recent study of point prevalence of PPTD and depression in Australian women at 6 months post-partum (Kent *et al*, 1999) failed to demonstrate an association of depression with either PPTD or thyroid antibody status (although their 6-month point prevalence for depression according to DSM–III–R criteria (American Psychiatric Association, 1987) was higher, at 9.4%, than the 6-month *point* prevalence of 5.1% in the study reported here; Table 1). Clearly, if women are assessed more frequently then a much higher rate of depression is found, particularly as the highest rate of depression occurs at 12 weeks post-partum (Table 2).

Administration of thyroxine

The main objective of this study was to administer thyroxine to stabilise thyroid function over a period when it is known to be fluctuating, with the further objective of preventing the development of post-partum depressed mood that might be associated with covert PPTD. The negative finding makes it more likely that depressed mood in these women is associated with the known risk factors for postnatal depression, including positive thyroid antibody status (Kuijpens *et al*, 2001), rather than with abnormal biochemical thyroid function. This is supported by a further analysis of the data reported in the study of 1992 (Harris *et al*), where post-partum depression in thyroid-antibody-positive and -negative women was associated with the total number of life events, especially negative life events, in the year prior to delivery, whereas PPTD was not (Oretti *et al*, 2002).

General malaise cannot be excluded as a cause for some depressive features, and as far as the latter is concerned a positive correlation has been found between activation of the inflammatory response system (as measured by an increase of serum interleukin-6 and interleukin-1 receptor antagonist) and postnatal depressive and anxiety symptoms, and a causal relationship has been suggested (Bluthe *et al*, 1992; Maier & Watkins, 1998; Maes, 1999; Maes *et al*, 2000). In support of this it has been shown that administration of proinflammatory cytokines with consequent activation of the inflammatory response may result in depressive and anxiety symptoms (Maier & Watkins, 1998). Even more recently it has been reported that administration of an endotoxin in healthy male volunteers is associated with cytokine-related anxiety, depressed mood and decrease in memory performance (Reichenberg *et al*, 2001). On the other hand, our group has shown no elevation of interleukin-6 levels in PPTD patients, independent of thyroid function (Ahmad *et al*, 1998). This suggests that further studies should concentrate on these parameters in thyroid-antibody-positive women.

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CLINICAL IMPLICATIONS

- Positive thyroid antibody status is associated with post-partum depression.
- Administration of thyroxine does not reduce postnatal depression.
- Biochemical (not clinical) hyperthyroidism may result.

LIMITATIONS

- The study was not able to detect significant differences in symptomatology in patients made biochemically hyperthyroid.
- Eighty per cent of the original study group were medication compliant.
- There was no assessment of women refusing to join the study.

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