Prevalence of autoimmune thyroid dysfunction in postpartum psychosis

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Background
Postpartum psychosis is a life-threatening psychiatric emergency, which often occurs without significant premorbid symptoms. Although many studies have postulated an involvement of the immune and endocrine systems in the onset of postpartum psychosis, the specific aetiological factors have remained unknown.

Aims
To examine the hypothesis that autoimmune thyroid dysfunction may be associated with the onset of postpartum psychosis.

Method
Thirty-one consecutive primiparous women with no prior psychiatric history were referred to our in-patient unit for postpartum psychosis. The control group (n = 117) comprised primiparous women with consecutive deliveries at a community practice. Blood samples were obtained from all participants at 4 weeks and 9 months postpartum. Thyroperoxidase antibody levels were quantified as immunological measures of autoimmune thyroid disease (AITD). Thyroid-stimulating hormone and free thyroxine levels were measured to assess clinical thyroid dysfunction.

Results
At 4 weeks postpartum and prior to the initiation of mood stabiliser therapy, 19% of women with postpartum psychosis had AITD compared with only 5% in the control group. Women with both postpartum psychosis and AITD had a dramatically higher risk of progression to clinical thyroid dysfunction (67%) than control participants with AITD (20%).

Conclusions
Women with postpartum psychosis are at higher risk not only of AITD but also of clinical thyroid failure. These data implicate thyroid function as an important clinical outcome in patients with postpartum psychosis. Further, AITD represents a potentially strong aetiiological factor for the development of postpartum psychosis. Therefore, screening for thyroperoxidase antibodies is warranted in patients with postpartum psychosis.

Declaration of interest
W.A.N. has received honoraria, consulting fees or research support from AstraZeneca, Eli Lilly, GlaxoSmithKline, Wyeth, Servier, Pfizer and Cyberonics.

Postpartum psychosis is a severe disorder occurring in 0.1% of childbearing women. The clinical symptoms include fluctuations in mood accompanied by delusions and hallucinations, as well as agitation, insomnia and cognitive impairment. Patients often require urgent hospital admission with thoughts of suicide and infanticide.1–4 Although there are no current treatment guidelines for postpartum psychosis, both antipsychotics and mood stabilisers are recommended and widely used.4,5 Women with bipolar affective disorder are at high risk of developing postpartum psychosis: up to half of women with bipolar disorder relapse in the early postpartum period, often with psychotic symptoms.6–8 However, most patients with a postpartum psychosis have no history of psychiatric disorder.9 During the past century many possible determinants of postpartum psychosis have been proposed. In particular, many studies have focused on neurosteroid pathways, given the dramatic changes in hormone levels throughout pregnancy and the postpartum period. However, no specific mechanism has been conclusively identified as an aetiological factor in postpartum psychosis.

Postpartum autoimmune thyroid disease (AITD) is defined by autoimmune thyroid inflammation and elevated thyroid antibody titres, occurring within the first year after delivery. With a postpartum prevalence of 5–7% in the general population,10 AITD has been identified as a risk factor for postpartum depression.11–15 In contrast to the emerging consensus regarding the link between AITD and postpartum depression, the lower incidence of postpartum psychosis has thus far precluded analogous studies. Although case reports have documented the co-occurrence of postpartum psychosis and AITD,16,17 the only previous systematic study found no evidence for an increase of AITD in patients with a late-onset presentation of postpartum psychosis (> 4 weeks after delivery).18 Importantly, however, no prior study has reported prospective AITD screening in patients with classic early-onset postpartum psychosis (≤ 4 weeks after delivery) before the start of medication. Lithium, frequently used in the treatment of postpartum psychosis, has several deleterious effects on thyroid function.19 Our study was therefore designed to document the prevalence of serological and clinical evidence of autoimmune thyroid dysfunction in patients with early-onset postpartum psychosis during the first 9 months after delivery.

Method
The study protocol was approved by the institutional review board of the Erasmus University Medical Centre, Rotterdam, The Netherlands. After receiving a complete description of the study, all patients and their authorised legal representatives provided written informed consent before participation.

Between August 2005 and November 2008 we examined all patients referred to the mother and baby in-patient unit of the department of psychiatry at the Erasmus Medical Centre for evidence of postpartum psychosis, using the Structural Clinical Interview for DSM–IV (SCID).20 The catchment area for this unit includes the provinces of South Holland, Zeeland and North Brabant. Since ‘postpartum psychosis’ is not described as a separate disease entity in DSM–IV, we selected patients for whom the SCID interview generated the following DSM–IV diagnoses:
psychotic disorder not otherwise specified, brief psychotic disorder or mood disorder (manic, mixed or major depressive episode) with psychotic features, all requiring the specifier ‘with postpartum onset’ (≤ 4 weeks after delivery). Of the 123 patients examined, 53 fulfilled the criteria of postpartum psychosis. Twenty-one patients were excluded because of their psychiatric history (eight patients with bipolar disorder, five patients with psychosis not otherwise specified, five patients with a previous postpartum episode, two patients with schizoaffective disorder and one patient with chronic cannabis misuse). Thirty-four patients reported no previous psychiatric history. A parallel history was obtained to confirm the time course of symptoms for all patients examined. One patient declined to participate. All patients except two were primiparous. As parity is a potential risk factor for thyroid autoimmunity, data analysis was restricted to the 31 primiparous women.

Patients were referred by acute psychiatric services and the majority had been briefly treated with benzodiazepines (lorazepam, temazepam or oxazepam: 23 patients with a treatment duration of 3.5 days, s.d. = 0.6) and/or antipsychotics (haloperidol or olanzapine: 19 patients, treatment duration 4.5 days, s.d. = 1.1). Of the 31 primiparous women with postpartum psychosis, 23 had a presentation of manic psychosis, 5 had a mixed episode and 3 presented with psychotic depression. During admission all 31 patients were treated with benzodiazepine anxiolytic medication and 29 patients required clinical treatment with an antipsychotic. In 25 of these 29 patients a trial of antipsychotic monotherapy provided suboptimal efficacy, with addition of lithium for improved mood stabilisation. Lithium dose was determined by plasma level (0.6–1.0 mmol/l). Importantly, no patient received lithium prior to the plasma sampling at admission. The control group was established by screening 291 women consecutively evaluated during pregnancy between 1994 and 1996 in the North Brabant province. Selection was based exclusively on primiparity, regardless of medical or psychiatric history. Each control group participant (n = 117) was followed during pregnancy and the first year after delivery to determine the incidence of postpartum thyroid dysfunction and postpartum depression. Laboratory thyroid function assays in both the postpartum psychosis and control groups were performed using the same immune assays in the same laboratory (Laboratory of Autoimmune Diseases, Department of Immunology, Erasmus Medical Centre, Rotterdam).

**Laboratory assessments**

Blood samples were obtained from all participants 4 weeks and 9 months after delivery. In addition, patients with postpartum psychosis had blood samples taken at various times over the 9-month study period, as clinically indicated. Thyroperoxidase antibodies were measured using the Immulite human immunoassay (Siemens, Los Angeles, California, USA); values greater than 35 IU/ml were regarded as positive serological evidence of autoimmune thyroid disease. Thyroid-stimulating hormone and free thyroxine levels were measured in the clinical laboratory of the Erasmus Medical Centre using reference ranges (thyroid-stimulating hormone 0.4–4.0 mIU/l; free thyroxine 10–24 pmol/l) defined by the Centre’s validated standards. Clinical thyroid dysfunction was defined as the coexistence of abnormal levels of the two hormones.

**Statistical analysis**

All analyses were performed using SAS version 9 for Windows. For sample characteristics, categorical data were evaluated using Fisher’s exact test and continuous variables using a two-sample t-test. Continuous variables are expressed as the mean (standard error) unless otherwise indicated. Categorical outcomes were examined using odds ratios with corresponding 95% confidence intervals. Time to clinical thyroid dysfunction was evaluated using Kaplan–Meier methodology and the log-rank test. All hypotheses were tested with an alpha of 0.05 (two-sided).

**Results**

Participants with postpartum psychosis were 3.2 years older than the general population cohort (Table 1). Although a similar percentage of patients and controls had ever smoked in the past, a significantly higher percentage of the control group smoked during pregnancy (22%) compared with the patient cohort (3%). No difference was found in the frequency of Caesarean section, rate of primigravidity, birth weight of the child or incidence of preterm birth. None of the patients or controls had a history of thyroid or autoimmune disease.

**Prevalence of AITD in the early postpartum period**

At 4 weeks postpartum, 5% of the control group had AITD, with no case of clinical thyroid dysfunction. In contrast, 19% of the patients with postpartum psychosis met criteria for AITD on admission to the hospital, before the start of antipsychotic or lithium pharmacotherapy (OR = 4.44, 95% CI 1.32–14.92; Table 2). Further, half of the patients with postpartum psychosis and AITD also demonstrated clinical thyroid dysfunction at the time of admission to the hospital.

**Follow-up**

The 9-month prevalence of AITD was significantly higher in women with postpartum psychosis (29%) compared with controls

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Sample characteristics of women with postpartum psychosis and a general population postpartum control group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Postpartum psychosis group</strong></td>
<td><strong>Postpartum control group</strong></td>
</tr>
<tr>
<td>(n = 31)</td>
<td>(n = 117)</td>
</tr>
<tr>
<td>Ethnicity, white: n (%)</td>
<td>29 (94)</td>
</tr>
<tr>
<td>Never smoked, n (%)</td>
<td>20 (65)</td>
</tr>
<tr>
<td>Smoked in pregnancy, n (%)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Primigravida, n (%)</td>
<td>27 (87)</td>
</tr>
<tr>
<td>Caesarean section, n (%)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Preterm birth, n (%)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>History of thyroid disease, n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>History of other autoimmune disease, n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Age, years: mean (s.d.)</td>
<td>31.2 (3.8)</td>
</tr>
<tr>
<td>Birth weight of child, g: mean</td>
<td>3340</td>
</tr>
</tbody>
</table>

a. Fisher’s exact test.
b. Two-sided t-test.
To the best of our knowledge, this is the first observational study of primiparous women with first-onset postpartum psychosis and no previous psychiatric history. Our data show that autoimmune thyroid disease is much more prevalent in women with first-onset postpartum psychosis than in postpartum women from the general population. Further, clinical thyroid failure occurs significantly faster and in a greater percentage of patients with postpartum psychosis. Importantly, these differences appear to be independent of antipsychotic or lithium treatment in the early postpartum period. Taken together, the high prevalence of clinical thyroid dysfunction in patients with postpartum psychosis is an important consideration for both clinical management and pathophysiological understanding.

Although one limitation of the current study is that the control group was not drawn from the identical population within The Netherlands, the 5% point prevalence ofAITD in our control group at 4 weeks postpartum closely matches the mean prevalence of 5–7% determined from a review of over 20 studies on women from the general population. Further, our findings in patients with postpartum psychosis are similar to the increased prevalence ofAITD in women with bipolar disorder. In addition, a twin study of people with bipolar disorder showed thatAITD was related not only to the disorder itself but also to the genetic vulnerability to development of the disorder.

During pregnancy, changes in the maternal immune system are necessary to induce tolerance of the mother towards genetically different fetal tissue. From a clinical point of view, this state of tolerance is reflected by a substantial amelioration of symptoms in patients with certain autoimmune diseases such as rheumatoid arthritis or autoimmune thyroiditis. Consistent with this model, substantial decreases of the relevant serum autoantibody concentrations are frequently observed during pregnancy. After delivery the immunosuppressive state of pregnancy does not simply return to normal but shoots into overreaction (the ‘rebound’ phenomenon). In some women this results in exacerbation of pre-existing autoimmune disease or a first manifestation of an episode of autoimmune disease, reflected by increases in autoantibody concentrations. Postpartum immune activation is postulated to produce the clinical manifestations of both thyroid dysfunction and psychiatric illness (Fig. 2). In one scenario the postpartum psychotic condition per se may exacerbate an underlying postpartum thyroiditis. Conversely, in some cases postpartum thyroiditis may serve as an important aetiological factor leading to either depression or mania, depending on the patient’s neurobiological vulnerability.

Fig. 1  Survival curve of thyroid function during the 9-month study period in patients with postpartum psychosis and controls with autoimmune thyroid disorder.

Table 2  Prevalence of autoimmune thyroid disease and clinical thyroid dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Postpartum psychosis group</th>
<th>Postpartum control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 31)</td>
<td>(n = 117)</td>
</tr>
<tr>
<td></td>
<td>% (n/N)</td>
<td>% (n/N)</td>
</tr>
<tr>
<td>4 weeks postpartum (prior to treatment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune thyroid disease</td>
<td>19 (6/31)</td>
<td>5 (6/117)</td>
</tr>
<tr>
<td>Clinical thyroid dysfunction</td>
<td>10 (3/31)</td>
<td>0 (0/117)</td>
</tr>
<tr>
<td>Clinical thyroid dysfunction per AITD</td>
<td>50 (3/6)</td>
<td>0 (0/6)</td>
</tr>
<tr>
<td>9 months postpartum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune thyroid disease</td>
<td>29 (9/31)</td>
<td>13 (15/117)</td>
</tr>
<tr>
<td>Clinical thyroid dysfunction</td>
<td>19 (6/31)</td>
<td>3 (3/117)</td>
</tr>
<tr>
<td>Clinical thyroid dysfunction per AITD</td>
<td>67 (6/9)</td>
<td>20 (3/15)</td>
</tr>
</tbody>
</table>

AITD, autoimmune thyroid disease; NC, not computed.
a. Odds ratio cannot be computed given the absence of clinical thyroid dysfunction in controls at 4 weeks postpartum.

(13%; OR = 2.78, 95% CI 1.08–7.17; Table 2). Further, clinical thyroid dysfunction occurred in 19% of patients compared with only 3% of controls (OR = 9.12, 95% CI 2.14–38.96). Patients with postpartum psychosis showed a significantly higher rate of progression from subclinical AITD to clinical thyroid dysfunction (log-rank P = 0.017; Fig. 1). Specifically, of the patients with AITD at the 9-month follow-up, 67% had overt thyroid dysfunction compared with only 20% of the control group (OR = 8.00, 95% CI 1.23–52.25). Importantly, as shown in both Fig. 1 and Table 2, the increased rate of clinical thyroid dysfunction in patients with postpartum psychosis was already evident at the time of hospital admission, prior to the administration of antipsychotic or lithium treatment.

At 9 months, 23 patients remained on lithium monotherapy, 2 patients were taking antipsychotics and 2 patients required initiation of antidepressant medication (sertraline and citalopram). Notably, the 3 patients who developed AITD and clinical thyroid dysfunction during treatment with mood stabilisers were all taking lithium. In contrast, none of the 18 lithium-treated patients without AITD developed clinical thyroid dysfunction.

Discussion

To the best of our knowledge, this is the first observational study of primiparous women with first-onset postpartum psychosis and no previous psychiatric history. Our data show that autoimmune thyroid disease is much more prevalent in women with first-onset postpartum psychosis than in postpartum women from the general population. Further, clinical thyroid failure occurs significantly faster and in a greater percentage of patients with postpartum psychosis. Importantly, these differences appear to be independent of antipsychotic or lithium treatment in the early postpartum period. Taken together, the high prevalence of clinical thyroid dysfunction in patients with postpartum psychosis is an important consideration for both clinical management and pathophysiological understanding.

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From a clinical point of view it is evident that postpartum thyroid dysfunction needs to be diagnosed and treated early. Given our findings of a dramatically increased rate of autoimmune thyroid dysfunction in women with postpartum psychosis, we strongly suggest that thyroid function and autoantibody titres should be rigorously monitored in all women.
Autoimmune thyroid dysfunction in postpartum psychosis

presenting with postpartum psychosis. Further, we believe that all women at high risk of developing postpartum psychosis should be screened for thyroperoxidase antibodies prior to delivery. Clinically, a previous history of bipolar affective disorder and/or postpartum psychosis is the only known strong risk factor for developing a subsequent postpartum psychosis. Therefore, we recommend that any woman with a history of bipolar affective disorder and/or postpartum psychosis should have thyroperoxidase antibody testing. Importantly, for effective perinatal screening of this antibody we recommend testing in early gestation or preferably before pregnancy, because levels of this antibody decrease significantly during pregnancy. Further, in these high-risk groups we recommend testing thyroid function and autoantibody titres at both 4 weeks and 6 months postpartum, given the well-documented postpartum rebound of thyroid autoantibodies.

Several studies have documented that in addition to female gender, elevated thyroperoxidase antibody titre and lithium treatment are both independent risk factors for the development of thyroid dysfunction.24–28 However, lithium has widespread clinical support as a highly effective mood stabiliser in postpartum psychosis.29–31 Although our study lacks the statistical power to determine the influence of lithium treatment on thyroid function, the risks and benefits of lithium should be weighed carefully in choosing the most appropriate pharmacological regimen for treatment of postpartum psychosis, particularly for patients with elevated thyroperoxidase antibody titres.

Together, these data demonstrate compelling evidence for autoimmune thyroid dysfunction in patients with postpartum psychosis. Further research is needed to confirm our findings and ascertain whetherAITD is an aetiological factor in postpartum psychosis.

Fig. 2 Pathophysiological model for a shared vulnerability to autoimmune thyroid dysfunction and postpartum psychosis.

Funding

This work was funded by MOODINFLAME (early diagnosis, treatment and prevention of mood disorders targeting the activated inflammatory response system), FP7-Health-2007, Project no: 222963.

Acknowledgements

We greatly appreciate the assistance of Harm J. de Wit, Siska Verploegh, Jeroen Vervoort and Andre Wierdsma.

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**Happiness**

Aarohee B. Desai

Over the rocks
Beside the ocean
Beneath the heaven – Happiness!

The dim-dusk
The mild mist
Darkness all around
And above adorns the heaven –
A gentle brightness
Orangish pink – Happiness!

Wondrous shapes
Displayed by clouds
Against the tender background
Synchronous movements
Of ocean waves beneath
And hither . . .
A dash on the rocks – Happiness!

A melodious tune
Carried by the breeze across the sea
Far – a boat afloat
A chain of light
Like pearls woven
The company of one’s dear – Happiness!

Holding life together
Faith, Hope, Motive . . . – Happiness!

Aarohee B. Desai is ST5 in general adult psychiatry, Highgate Mental Health Centre, London. Another of Dr Desai’s poems was published in the October 2010 issue of the Journal.
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Access the most recent version at DOI: 10.1192/bjp.bp.110.082990

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