Thyroid peroxidase antibodies during gestation are a marker for subsequent depression postpartum

Johannes L Kuijpens, Huib L Vader, Hemmo A Drexhage, Wilmar M Wiersinga, Maarten J van Son and Victor J Pop

Faculty of Social and Behavioural Sciences, University of Tilburg, Tilburg, 1Clinical Laboratories, St Joseph Hospital, Veldhoven, 2Department of Immunology, Erasmus University Rotterdam, Rotterdam, 3Department of Endocrinology AMC, University of Amsterdam, Amsterdam and 4Department of Clinical Psychology, University of Utrecht, Utrecht, The Netherlands

(Correspondence should be addressed to V J Pop, Faculty of Social and Behavioural Sciences, University of Tilburg, PO Box 90153, 5000 LE Tilburg, The Netherlands; Email: V.J.M.Pop@kub.nl)

Abstract

**Objective**: Depression is not adequately diagnosed in many cases. Therefore, the question arises as to whether markers exist for depression. We investigated whether the presence of thyroperoxidase antibodies (TPOAbs) during pregnancy can be regarded as a marker for depression in the first year postpartum, particularly in relation to (overt or subclinical) thyroid dysfunction and other determinants of depression.

**Design**: This work was a prospective observational study.

**Patients**: A cohort of 310 unselected women (residing in the Kempen Region, southeastern Netherlands) were visited at 12 and 32 weeks gestation and at 4, 12, 20, 28 and 36 weeks postpartum.

**Methods**: At each visit, TSH, free thyroxine and TPOAb testing was performed, determinants associated with depression were asked for, and depression was assessed (according to the Research Diagnostic Criteria). Multiple logistic regression was performed to determine independent risk factors (odds ratios, ORs) for depression in gestation and/or postpartum depression.

**Results**: Data for 291 women were available for analysis; 41 women (14.1%) had TPOAbs at one or more time points, and 117 women (40.1%) had depression at one or more time points postpartum. The multiple logistic regression analysis showed that TPOAbs were independently associated with depression at 12 weeks gestation and at 4 and 12 weeks postpartum (OR, 95% confidence interval: 2.4 (1.1–6.0), 3.8 (1.3–7.3) and 3.6 (1.2–7.1) respectively). After the exclusion of women who were depressed at 12 weeks gestation, the presence of TPOAbs during early pregnancy was still associated with the development of postpartum depression (OR, 95% confidence interval: 2.8 (1.7–4.5); after exclusion of women who had had depression in earlier life (n = 51), TPOAb during early gestation was still associated with postpartum depression (OR, 95% confidence interval: 2.9 (1.8–4.3).

**Conclusions**: The presence of TPOAbs during gestation is associated with the occurrence of subsequent depression during the postpartum period and as such can be regarded as a marker for depression.

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Introduction

Depression is a major health problem with a 1 year prevalence of 4–8%, and is associated with increased morbidity, a high risk of death by suicide, a threefold-increased risk of overall mortality, and considerable health-care costs (1–5). A major problem of depression is its social and psychological burden: it is estimated that more than half of the subjects with depression do not seek professional care. Moreover, in subjects who visit their general practitioner, the diagnosis is missed in up to 50% (6). Therefore, it would be helpful to have reliable and objective markers that allow detection of the disease at an early stage. Women are particularly at risk of developing depression (having a 1 year prevalence, in general, of 8–12%, which rises to 15% during the postpartum period (1, 3, 4, 7, 8).

The aetiology of depression is thought to be multifactorial: biological, genetic and psychosocial factors interact in order to provoke depression (5). One biological factor for which an association with depression has often been described is thyroid dysfunction, which is mostly caused by thyroid autoimmunity. Around 10% of women over 20 years of age have elevated concentrations of thyroperoxidase antibodies (TPOAbs), an early sign of thyroid autoimmunity.
(9–11) and a major risk factor for the development of overt thyroid dysfunction, both during the postpartum period and in general (12–15). At a univariate level and in cross-sectional models, a relationship (independent of overt thyroid dysfunction) between the presence of TPOAbs and depression has been reported (9, 16, 17).

Using a prospective observational study design, we questioned, within a multivariate model, whether the presence of TPOAbs (as a sign of thyroid autoimmunity) during pregnancy is associated with the subsequent occurrence of depression after delivery.

**Subjects and methods**

**Subjects**

Permission for the study was obtained from the Medical Ethics Committee of the Academic Medical Centre, University of Amsterdam, the Netherlands.

The study was performed in the Kempenland Region, a semi-rural area in southeastern Netherlands in which the population has a low-to-normal iodine intake (mean daily urinary iodide excretion 111 μg) (18). All of the women (n = 448) consecutively booking in for antenatal checks by the local midwives or at the Obstetrics Department of the St Joseph Hospital, Veldhoven, were invited to participate in a prospective study. Before being included in the study, all participants provided written informed consent. In total, 310 women (69%) agreed to participate. The mean age and parity of the non-participants (n = 138) were similar to those of the participants. All participating women were visited at home at 12 and 32 weeks gestation and at 4, 12, 20, 28 and 36 weeks postpartum. None of the women used thyroid medication. Nineteen (6.1%) women were excluded from the analysis: seven women refused to continue participating after experiencing spontaneous miscarriage or stillbirth, one suffered from puerperal psychosis, nine were pregnant again within 6 months after delivery (and therefore it was impossible to evaluate postpartum depression), and two women moved out of the region. The data analysis relates to the remaining 291 women. During the baseline visit, a family and personal history of autoimmune thyroid disease and previous episodes of depression was taken; in addition, lifestyle habits (such as alcohol consumption and smoking) and social-economic status were noted. Determinants relating to depression (such as educational level, marital state, employment status, and the occurrence of major life events) were carefully assessed during an interview. The occurrence of major life events (such as bereavement, divorce, serious illness of relatives, financial problems, and unemployment) was investigated during every visit by using an adapted version of a Dutch survey of recently experienced life events (19, 20).

During all visits, venous blood samples were collected for the assessment of thyroid function and TPOAbs.

**Methods**

**Thyroid-function tests** The concentration of thyroid-stimulating hormone (TSH) was measured (Kodak Amerlite TSH-30, Kodak Clinical Diagnostics Ltd, Amersham, Buckinghamshire, UK), with a reference interval of 0.15–2.0 μU/ml, as defined for 225 non-pregnant women in the 20–40-year age group and living in the same region. The interassay coefficients of variation were 20, 4.8, 6.3 and 5.1% at concentrations of 0.04, 0.68, 8.2 and 29.2 μU/ml, respectively. Free thyroxine (fT4) was determined by using the Kodak Amerlite MAB FT4 assay, using a reference interval of 8.7–19.6 pmol/l, and was defined as described above. The interassay coefficients of variation were 11.1, 11.3 and 12.2% at concentrations of 6.1, 19.3 and 27.7 pmol/l, respectively.

Clinical thyroid dysfunction was defined as abnormal TSH in combination with abnormal fT4, and subclinical thyroid dysfunction was defined as abnormal TSH with normal fT4. TPOAbs were measured by using the Immunometric Enzyme Combikit (Orgentec GmbH, Mainz, Germany); a concentration of >50 U/ml was defined as ‘positive’ (TPOAb+). The interassay coefficients of variation were 18, 12 and 8.5% at concentrations of 18, 50 and 1000 U/ml, respectively.

**Depression** Depression was defined according to the Research Diagnostic Criteria, which discriminate between major and minor depression (21). During a semi-structured interview, one investigator, who was unaware of the thyroid function, established syndromal diagnosis of depression.

**Statistical analysis** Statistical analyses were performed using SPSS-7 (SpSS, Evanston, IL, USA). Multiple logistic regression analysis was used to determine factors independently associated with depression. Factors found to be associated with depression in the univariate analysis were introduced into the model. ORs with 95% confidence intervals (95% CI) were calculated.

**Results** In total, 41 women (14.1%) were found to be TPOAb+ at one or more time point(s) during gestation and/or in the postpartum period. During the study, 232 (80%) women remained euthyroid, seven (2.4%) women showed clinical thyroid dysfunction, and 30 (10.4%) showed subclinical thyroid dysfunction during pregnancy; 15 women (5.2%) developed clinical thyroid dysfunction and 21 (7.2%) developed subclinical thyroid dysfunction during the postpartum period. The demographic and psychosocial features and obstetric complications of the TPOAb+ women did not
differ from those of the women without TPOAbs (Table 1). One hundred and fifty-eight women (54.3%) presented with at least one episode of depression (minor and major), and 117 women (40.1%) had had depression at one or more time point(s) in the postpartum period. The peak prevalence of depression varied from 13% to 24%, the highest prevalence being at 32 weeks gestation. During pregnancy and in the early postpartum period (up until 12 weeks postpartum), women with depression presented more often with elevated TPOAb concentrations. Both (sub-)clinical thyroid dysfunction and depression were significantly more prevalent in TPOAb+ women (Table 1). The results of the multiple logistic regression analysis at each assessment, with depression (minor and major) as the dependent variable, are presented in Table 2. The occurrence of a major life event was significantly associated with depression at each assessment. The presence of TPOAbs was associated with depression at 12 weeks gestation (OR = 2.4; 95% CI 1.1–6.0) and during the first 3 months postpartum (4 weeks postpartum: OR = 8 (95% CI 1.3–8.9) and 12 weeks postpartum: OR = 6 (95% CI 1.3–7.3). Complications during labour were

**Table 1** Characteristics of 41 women tested positive for TPO antibodies at one or more time points during pregnancy and/or postpartum (TPOAb+), and 250 women negative for TPO antibodies (TPOAb−).

<table>
<thead>
<tr>
<th>Variable</th>
<th>TPOAb+</th>
<th>TPOAb−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) (± s.d.)</td>
<td>30.8 (±2.7)</td>
<td>29.5 (±3.2)</td>
</tr>
<tr>
<td>Educational level (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary/secondary school</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>poor college degree</td>
<td>51</td>
<td>53</td>
</tr>
<tr>
<td>good college/academic degree</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>Smoking habits (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>never smoked</td>
<td>56</td>
<td>57</td>
</tr>
<tr>
<td>stopped</td>
<td>33</td>
<td>27</td>
</tr>
<tr>
<td>currently smoking</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Parity (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>33</td>
<td>42</td>
</tr>
<tr>
<td>≥1</td>
<td>67</td>
<td>59</td>
</tr>
<tr>
<td>Complications during pregnancy (%)</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Complications during labour (%)</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Male child (%)</td>
<td>54</td>
<td>56</td>
</tr>
<tr>
<td>Breastfeeding (%)</td>
<td>23</td>
<td>33</td>
</tr>
<tr>
<td>Previous episode of depression (%)</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Major life events (%)</td>
<td>54</td>
<td>61</td>
</tr>
<tr>
<td>Postpartum depression* (%)</td>
<td>59</td>
<td>38 (P = 0.03)</td>
</tr>
<tr>
<td>Subclinical thyroid dysfunction** (%)</td>
<td>44</td>
<td>18 (P = 0.0001)</td>
</tr>
<tr>
<td>Clinical thyroid dysfunction** (%)</td>
<td>26</td>
<td>4 (P &lt; 0.00001)</td>
</tr>
</tbody>
</table>

*At one or more time points after delivery.
**At one or more time points during pregnancy and/or postpartum.

**Table 2** Multiple regression analysis of 291 women at seven separate time points during pregnancy and postpartum. Dependent variable: depression according to Research Diagnostic Criteria. Odds ratios have 95% confidence intervals.

<table>
<thead>
<tr>
<th>Variable</th>
<th>12 weeks gestation</th>
<th>32 weeks gestation</th>
<th>4 weeks postpartum</th>
<th>12 weeks postpartum</th>
<th>20 weeks postpartum</th>
<th>28 weeks postpartum</th>
<th>36 weeks postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor education</td>
<td>1.5 (0.9–2.4)</td>
<td>1.6 (1.1–2.6)</td>
<td>1.3 (0.8–2.5)</td>
<td>1.4 (0.8–2.5)</td>
<td>1.8 (1.1–3.2)</td>
<td>1.4 (0.8–2.1)</td>
<td>1.3 (0.7–2.2)</td>
</tr>
<tr>
<td>Higher age</td>
<td>1.2 (0.9–2.1)</td>
<td>1.3 (0.5–1.9)</td>
<td>1.2 (0.7–2.4)</td>
<td>1.5 (0.8–2.2)</td>
<td>1.5 (0.7–2.1)</td>
<td>1.2 (0.6–2.1)</td>
<td>1.3 (0.5–1.8)</td>
</tr>
<tr>
<td>Multiparity</td>
<td>1.3 (0.9–2.1)</td>
<td>1.0 (0.7–2.5)</td>
<td>1.2 (0.6–1.9)</td>
<td>1.1 (0.7–1.8)</td>
<td>1.1 (0.7–1.9)</td>
<td>1.3 (0.5–1.8)</td>
<td>1.4 (0.8–2.4)</td>
</tr>
<tr>
<td>Occurrence of major life events</td>
<td>3.0 (1.5–5.8)</td>
<td>2.6 (1.4–5.8)</td>
<td>2.2 (1.1–4.6)</td>
<td>2.5 (1.2–5.8)</td>
<td>4.7 (1.4–6.8)</td>
<td>4.3 (2.0–7.1)</td>
<td>2.7 (1.1–4.3)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.1 (0.7–1.7)</td>
<td>1.2 (0.8–1.9)</td>
<td>1.2 (0.8–2.0)</td>
<td>1.4 (0.9–2.4)</td>
<td>1.5 (0.9–2.4)</td>
<td>1.1 (0.7–1.8)</td>
<td>1.1 (0.7–1.9)</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>1.5 (0.8–2.1)</td>
<td>1.2 (0.9–2.0)</td>
<td>1.4 (0.7–2.1)</td>
<td>1.3 (0.7–2.2)</td>
<td>1.1 (0.7–1.9)</td>
<td>1.0 (0.6–1.7)</td>
<td>2.0 (0.5–2.3)</td>
</tr>
<tr>
<td>Previous depression</td>
<td>4.5 (2.0–7.9)</td>
<td>3.0 (1.5–5.8)</td>
<td>1.2 (0.6–2.5)</td>
<td>1.5 (0.6–3.7)</td>
<td>1.1 (0.4–2.7)</td>
<td>1.4 (0.6–3.9)</td>
<td>3.5 (1.2–4.2)</td>
</tr>
<tr>
<td>Subclinical thyroid dysfunction</td>
<td>1.5 (0.6–8.1)</td>
<td>1.9 (0.3–24)</td>
<td>1.8 (0.5–16)</td>
<td>1.8 (0.4–19)</td>
<td>1.1 (0.3–17)</td>
<td>1.4 (0.6–14)</td>
<td>2.0 (0.3–21)</td>
</tr>
<tr>
<td>Clinical thyroid dysfunction</td>
<td>7.6 (0.6–65.3)</td>
<td>9.4 (0.3–35)</td>
<td>2.2 (0.2–43)</td>
<td>9.8 (0.3–62)</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPOAb &gt;50 U/ml</td>
<td>2.4 (1.1–6.0)</td>
<td>2.4 (0.7–8.9)</td>
<td>3.8 (1.3–7.3)</td>
<td>3.6 (1.2–7.1)</td>
<td>2.8 (0.8–7.4)</td>
<td>1.5 (0.4–6.6)</td>
<td>1.0 (0.3–6.1)</td>
</tr>
<tr>
<td>Complications during pregnancy</td>
<td>1.4 (0.8–4.2)</td>
<td>2.1 (0.6–7.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications during labour</td>
<td>–</td>
<td>–</td>
<td>3.7 (1.3–5.7)</td>
<td>2.6 (1.2–6.1)</td>
<td>2.1 (0.9–4.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>–</td>
<td>–</td>
<td>1.2 (0.7–2.2)</td>
<td>1.5 (0.8–1.9)</td>
<td>1.3 (0.8–1.9)</td>
<td>1.1 (0.7–2.1)</td>
<td>1.1 (0.6–2.1)</td>
</tr>
</tbody>
</table>

*Too few cases.
–, Not relevant; bold, statistically significant.

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also significantly associated with the occurrence of depression within the first 3 months after delivery \((OR = 3.7; 95\% CI 1.3–5.7)\). Neither clinical thyroid dysfunction nor subclinical thyroid dysfunction was significantly associated with depression, probably because of the low numbers (Table 2). In a second analysis, the question as to whether TPOAb+ status precedes the development of an episode of depression was investigated. Therefore, all women with a previous episode of depression before 12 weeks gestation and/or at 12 weeks gestation were excluded \(n = 70\). Of these, nine women \(12\%\) were TPOAb+ at 12 weeks gestation. In the remaining 221 women, the presence of TPOAbs at 12 weeks gestation was significantly associated with the occurrence of postpartum depression \((OR = 2.8; 95\% CI 1.7–4.5); this was not the case for the occurrence of depression at 32 weeks gestation (data not shown). Subsequently, in order to exclude the possibility that a previous episode of depression in a woman’s life might interfere with the occurrence of TPOAbs, these women \(51; 5 (10\%)\) TPOAb+ and 21 \(41\%\) depressed at 12 weeks gestation were also excluded from the analysis. In the remaining 191 women, again the presence of TPOAbs at 12 weeks gestation was significantly associated with postpartum depression \((OR = 2.9; 95\% CI 1.8–4.3); this was not the case for TPOAb+ women at 32 weeks gestation \(OR = 2.3; 95\% CI 0.5–7.1\).

**Discussion**

This is the first study with a prospective design, using a multivariate model (taking into account other well-known determinants of depression), which shows a relationship between the presence of TPOAbs during gestation and the subsequent development of a depressive episode after delivery.

So far, an association between thyroid autoimmunity and depression has been described only with a univariate model and a cross-sectional design in which higher prevalence rates of depression and/or more severe complaints of depression were reported in TPOAb+ women \(9, 10, 16, 17\), while others could not demonstrate such an association \(22\). However, depression is thought to have a multifactorial origin, which implies that when investigating the effect of thyroid disease on depression other independent factors should also be taken into account \(5\). Within this model, the often-reported determinants of depression (such as the occurrence of a major life event) were also significantly associated with depression in the present study; they were independently associated with depression at all assessment points \(ORs\) varied from 2.2 to 4.7) and with a previous episode of depression at several assessment points \(ORs\) varied from 3.0 to 4.5; Table 2). It is noteworthy that another cross-sectional survey (using a similar multivariate model) of perimenopausal women originating from the same region also found an independent relationship between TPOAb positivity and depression \(11\). In the study of Kent et al., no association was found between the presence of TPOAbs and actual depression \(22\). However, in this (cross-sectional) study, subclinical thyroid dysfunction was included in the definition of postpartum thyroid dysfunction, and TPOAbs were not studied in relation to future depression. In our study (Table 2), subclinical thyroid dysfunction was not significantly associated with depression either.

Depression is a common disorder, especially in women: various studies originating from The Netherlands and other Western societies found high prevalence rates of depression in women of different ages (and assessed using different methods) \(23–28\). We confirmed that the cumulative incidence and prevalence rates of depression were high. Comparable prevalence rates were found by Harris et al. \(16\); others found lower rates for depression during pregnancy and in the postpartum period \(7–8\% of the women were depressed in the second half of pregnancy and 10–14\% were depressed at different time points after delivery \(8, 20\).

There is still no explanation for the relationship between early forms of autoimmune thyroid disease (with normal TSH and \(\Gamma^4\) or free tri-iodothyronine) and depression. In psychoneuroimmunological studies (which have been reviewed elsewhere), the relationship between depression and alterations in the immune system has been studied, and rather speculative conclusions are presented \(29, 30\). However, the question as to whether depression precipitates immune alterations or whether immune dysfunction precedes depression is far from being resolved. In this context, we excluded women who had been suffering from a previous episode of depression (in earlier life and/or at 12 weeks gestation) in order to investigate whether women with TPOAbs are at risk of developing subsequent (postpartum) depression. An OR of 2.9 \(95\% CI 1.8–4.3\) tends to support the assumption that women with an already existing autoimmune thyroid disorder – without a history of previous depression – are at risk of a first episode of depression (in the postpartum period).

As mentioned earlier, one major problem of depression in general (which is a very common, serious, but treatable, disease) is its hidden course: a substantial proportion of patients suffering from depression do not seek medical help, and, once the patient contacts a physician, often a proper diagnosis is not made \(1, 3, 4–6\). It is well known that TPOAbs are an important risk factor or a marker for the development of future overt thyroid dysfunction, which also often presents with atypical complaints. This study does suggest that TPOAbs could be regarded as a marker for the occurrence of future depression in this particular at-risk group of patients.

Several limitations of the study should be mentioned. The numbers are rather small, and other putative...
biological determinants of depression were not included in the analysis, which means that the association between thyroid autoimmunity (TPOAbs) and depression should be interpreted with caution.

What are the clinical implications of this study? Testing for TPOAbs is not yet suitable for the detection of an actual episode of depression: the sensitivity of the test is rather low (0.1–0.2 at the various time points) and the positive predictive value is limited (0.26–0.39). Consequently, TPOAb testing is not a diagnostic tool for detecting depression, but it helps the clinician to identify women at risk for depression (in the context of other risk factors).

It has been suggested previously that screening of women for TPOAbs in the first trimester of pregnancy might be worthwhile, since these antibodies are markers for the later development of postpartum thyroid dysfunction (14, 17, 31–33). Also, women with TPOAbs during pregnancy have an increased risk for impaired development of their offspring (34, 35). Others, however, have stated that screening is not justified, because of the low predictive value of TPOAb testing and the absence of severe clinical symptoms (36, 37). The present study appears to provide an argument for TPOAb screening: women with TPOAbs during early pregnancy in the absence of a present or previous episode of depression have a threefold-increased risk of developing subsequent depression. Because of the high incidence (10–15%) of depression, coupled with its hidden nature, knowledge of the TPOAb status of a woman might help the clinician to detect those at risk of depression at an early stage after parturition. Subsequent adequate treatment might prevent symptoms from occurring in the postpartum period.

An analysis of the cost-effectiveness of screening for TPOAbs is still lacking (33, 37). The results of our study strengthen the necessity for performing such a study.

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