Depressive disorder and thyroid axis functioning during pregnancy

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Depressive disorder and thyroid axis functioning during pregnancy

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Abstract

Background. Depression and thyroid dysfunction are prevalent in women, including pregnant women. The aim of this study was to assess the relationship between depression and thyroid function during pregnancy.

Methods. One hundred and ninety-nine pregnant women three times during pregnancy were assessed for depressive disorder and for thyroid stimulating hormone (TSH) and free thyroxine (FT4) concentrations.

Results. Prevalence of depressive disorder was 6.5% in early pregnancy, 3.0% in middle pregnancy and 3.5% in late pregnancy. There were no women with overt thyroid dysfunction. Subclinical hyperthyroidism was found in 23% of women in early pregnancy, in 5% of women in middle pregnancy and in 6% of women in late of pregnancy. In late pregnancy depressed women compared to non-depressed women had significantly higher FT4 concentrations and a strong trend towards lower TSH concentrations as well as higher prevalence of subclinical hyperthyroidism.

Conclusions. These findings show an association between thyroid dysfunction and depression in late pregnancy. Because gestational depression might interfere with pregnancy outcome, evaluation of thyroid function during gestation is warranted.

Key words: Depressive disorder, gestation, thyroxine, thyroid stimulating hormone, thyroid auto-immunity

Introduction

The life-time prevalence of depression in women has been reported to be twice that of men (Kessler et al. 2003). Based on meta-analysis, it is estimated that the prevalence of syndromal depression is approximately 14% during pregnancy and also during the first 3 months postpartum (Gaynes et al. 2005; Gavin et al. 2005). Depression during pregnancy is a major risk factor for maternal depression after childbirth (Austin and Lumley 2003; Kitamura et al. 2006). Depressive disorders during pregnancy are associated with conflicts in the family (Felice et al. 2004), substance abuse (Zhu and Valbo 2002), diminished foetal well-being (Allister et al. 2001; Felice et al. 2004), poor obstetric outcomes, including low infant birth weight and prematurity (Dayan et al. 2002; Orr et al. 2002).

Depressed women have a higher prevalence of concomitant thyroid disease (O’Keane 2000). Relationships between depression and thyroid dysfunction or thyroid auto-immunity has been well documented in psychiatric (Bauer et al. 2008; Bunevicius 2009) and primary care patients (Bunevicius et al. 2007) as well as in general population (Carta et al. 2004; Fountoulakis et al. 2004) including postpartum women (Harris et al. 1992; Kuipjens et al. 2001). It was demonstrated that subclinical hyperthyroidism increases risk of depression in early pregnancy (Pop et al. 2006). On the other hand, low antenatal thyroid functioning in late pregnancy is related with postpartum depression (Pedersen et al. 2007).

Up to 10% of women have an elevated thyroid peroxidase (TPO) antibody concentration in early gestation (Lazarus 2002), a reflection of thyroid autoimmune problems. However, the relationship between thyroid dysfunction or thyroid autoimmune and depression during pregnancy has hardly been investigated. Furthermore, the only two published studies in this area obtained conflicting results (Oretti et al. 1997; Pop et al. 2006).
Therefore, the aim of this study was to assess the relationship between depression and thyroid function or thyroid auto-immunity during pregnancy.

Methods

Subjects

Women who obtained antenatal care at two clinics in Kaunas, Lithuania during one calendar year (2005) were invited to participate in a study investigating the relationship between psychosocial and biological factors and depression during pregnancy. The study and its consent procedures were approved by the Regional Committee of Ethics in Biomedical Research at the Kaunas University of Medicine, Kaunas, Lithuania. Antenatal care for all invited women was provided by midwives and family doctors. There was an obligatory consultation with an obstetrician twice during pregnancy. Three hundred and seven consecutive pregnant women gave written informed consent for participation in the study, but only 230 women attended all three assessments (Bunevicius et al. 2009). Thyroid measures were not obtained at one or more time points in 28 of these women. In addition, two women had exclusionary medical conditions (diabetes mellitus, multiple sclerosis) and one woman was taking thyroid hormone. Our final analyses were conducted on data from the remaining 199 women. Demographic and clinical data on women who completed the study are provided in Table I. All subjects were Caucasians and fluent in Lithuanian.

Procedures

Subjects were assessed during three time periods: 12–16 weeks (early gestation), 22–26 weeks (mid gestation) and 32–36 weeks (late gestation) of pregnancy. Two diagnostic interviews were used to evaluate mental status of women (Möller 2009). During each assessment period, women were screened for depressive symptoms using the World Health Organization’s Composite International Diagnostic Interview Short Form (CIDI-SF) (WHO 1993). The CIDI-SF was developed by the World Health Organization from the full version of the CIDI to screen for the most commonly occurring psychiatric diagnoses. Women who reported one or more depressive symptom were interviewed in more detail using the mood disorders modules of the Structured Clinical Interview for DSM-III-R (SCID-NP) (Spitzer et al. 1990) to determine if they met criteria for major depressive disorder or dysthymia. The validated Lithuanian translation of the SCID-NP was employed (Bunevicius 1995). Subjects who met criteria for major depressive disorder or dysthymia classified as cases of depressive disorder.

A semi-structured interview was administered during the first assessment (early pregnancy) to collect data on age, level of education, work outside the home, smoking during pregnancy, drinking during pregnancy, personal and family history of depression, obstetrical history as well as how much women wanted to be pregnant.

Assays

Blood was drawn at each assessment time point for assay of thyroid stimulating hormone (TSH) and free thyroxine (FT₄) concentrations and at first assessment time for assay of thyroid peroxidase (TPO) antibodies concentration. All blood samples were centrifuged, serum samples were frozen at −70°C and each assay was performed on all samples using the same kits to minimize inter-assay variation. All thyroid analyses were performed at the Maxima Medical Centre in Eindhoven/Veldhoven, The Netherlands. TSH concentrations were measured using a solid-phase, two site chemiluminescent enzyme immunometric assay (IMMULITE Third generation TSH, Diagnostic Products Corporation, Los Angeles, USA). The intra-assay coefficients of variation were 5.0 and 4.4% at concentration of 0.22 and 2.9 mIU/l, respectively. The FT₄ concentrations were measured using a solid-phase immunometric assay.
(IMMULITE Free T4). The intra-assay coefficients of variation for this technique were 6.7 and 4.4% at concentration of 11.6 and 31.5 pmol/l, respectively. For both assays, the above-mentioned non-pregnancy reference ranges were used: 0.4–4 mIU/l and 10.3–25.7 pmol/l, respectively. TSH <0.4 mIU/l with FT4 within reference range was defined as subclinical hyperthyroidism.

The IMMULITE Anti-TPO Ab kit was used to assay the concentration of TPO antibodies. The intra-assay coefficients of variation for this analysis were 9.0 and 9.5% for concentrations of 40 and 526 IU/ml, respectively. TPO antibodies concentrations >35 IU/ml were considered to be elevated.

Statistical analysis

Comparisons of the prevalence of depressive disorder and thyroid dysfunction at the three assessment periods were made using 2×3 cross-table χ²-test. Comparisons of the TSH and FT4 concentrations between women with and without depressive disorder were made using paired t-tests. Comparisons of the prevalences of thyroid dysfunction and increased TPO antibody concentrations in women with and without depressive disorder were evaluated using 2×2 cross-table χ²-tests. All hypothesis testing was performed using a 5% significance level. Statistical analysis was performed using SPSS 13.

Results

The prevalence rate of a depressive disorder was 6.5% (n=13), 3.0% (n=6) and 3.5% (n=7) in early, mid and late pregnancy, respectively. Eleven women met criteria for major depression during early pregnancy, four during mid pregnancy and five during late pregnancy. Two women consistently met criteria for dysthymia during each assessment period. Differences in the prevalence of depressive disorder in the three phases of pregnancy were not statistically significant (Table II).

According to reference ranges for non-pregnant women, none of the subjects had overt thyroid dysfunction at any assessment time point during pregnancy. A substantial proportion of women had below normal range concentrations of TSH (<0.4 mIU/l) with normal concentrations of FT4 indicating subclinical hyperthyroidism; 23% (n=46) in early, 5% (n=10) in mid and 6% (n=12) in late gestation. We found significant differences in thyroid measures among assessment time periods with the lowest TSH concentrations, highest FT4 concentrations and highest prevalence of subclinical hyperthyroidism early in pregnancy (Table II).

Elevated concentrations of TPO antibodies were found in 11.6% of the women.

Comparisons of TSH and FT4 concentrations between subjects with and without current depressive disorders were significantly different only in late pregnancy (Table III). Depressed women had significantly higher FT4 concentrations (P=0.04), a strong trend towards lower TSH concentrations (P=0.062) and a strong trend towards higher prevalence of subclinical hyperthyroidism (P=0.059). The prevalence of depressive disorders as well as TSH and FT4 concentrations did not differ during any assessment period between women with elevated TPO antibody concentrations and women with normal antibody concentrations.

Discussion

Our study has demonstrated relatively low prevalence of depressive disorders during pregnancy with highest prevalence at the beginning of pregnancy, the lowest in mid-pregnancy. Prevalence rate of depressive disorders in our study ranges from 3.5 to 6.1% and correspond to data from other studies that reported prevalence rate from 3.1 to 4.9% at different times during pregnancy (Gaynes et al. 2005).

In this study we found a significant association between thyroid axis function and presence of depressive disorders during late pregnancy; women with depressive disorder in comparison to women without depressive disorder had higher FT4 concentrations and strong trends towards lower TSH concentrations as well as a higher prevalence of subclinical hyperthyroidism. We found no significant relationships between the prevalence of depressive disorder and elevated concentrations of TPO antibodies during pregnancy.

Our findings of lower concentrations of TSH and higher concentrations of FT4 during early pregnancy are consistent with previous reports (Burrow et al. 1994; Glinoer 1997; Kurioka et al. 2005). Lower TSH during early pregnancy is related to the elevated chorionic gonadotropin concentrations which exert a significant thyroid gland-stimulating effect (Burrow et al. 1994; Glinoer 1997). Therefore, it can be argued that the greater prevalence of TSH concentrations below the normal range during early pregnancy does not reflect a truly higher prevalence of subclinical hyperthyroidism. Increases in thyroid binding protein concentrations during mid and later pregnancy contribute to a decline in FT4 concentrations (Roti et al. 1991; Glinoer 1997). Considering these normal changes in thyroid measurements as pregnancy progresses, it is all the more remarkable that FT4 concentrations are significantly
higher, TSH concentrations trend toward being lower and the prevalence of subclinical hyperthyroidism trends toward being greater during late pregnancy in women with depressive disorders. These findings during late pregnancy may equally reflect a presence of transient hyperthyroxinemia, a phenomenon that has been widely reported in depression unassociated with pregnancy (Prange 1998).

Our findings on relationships between hyperactivity of thyroid gland and depression during pregnancy are consistent with findings from other studies. An association between subclinical hyperthyroidism and mood disorders has been demonstrated in non-pregnant women with Graves’ disease (Bunevicius et al. 2005). However, experimentally induced subclinical thyrotoxicosis in patients treated for hypothyroidism was found to improve mental status and mood (Samuels et al. 2008). It has been suggested that in the initial phase of hyperthyroidism stimulation of noradrenergic system by thyroid hormones may elevate mood; however, long lasting hyperthyroidism may cause exhaustion of the noradrenergic transmission and contribute to depression (Bunevicius and Prange 2006). We found most significant associations between presence of depressive disorder and increased thyroid axis functioning in late pregnancy, despite highest thyroid axis activity in early pregnancy, suggesting that duration of increased thyroid functioning rather than subclinical hyperthyroidism by itself is associated with depression. Not all reports are consistent with our findings. Pop et al. (2006) showed that women with subclinical hyperthyroidism in the first trimester of pregnancy had 2.8-fold greater risk for major depression in the same trimester of pregnancy. The much larger number of women studied by Pop et al. (n=1017) may have revealed a relationship between thyroid function and depression during early pregnancy that was not apparent in the current study.

A relationship between depression and thyroid immunity independent of thyroid dysfunction has been reported in the general population (Carta et al. 2004), including women during the postpartum period (Kuipjens et al. 2001), in primary care patients (Bunevicius et al. 2007) as well as in psychiatric population (Laske et al. 2008). However, there are conflicting reports regarding the relationship between depression and thyroid immunity during pregnancy. In the Netherlands (Kuipjens et al. 2001; Pop et al. 2006) it was found that elevated concentrations of TPO antibodies are

### Table II. Depression and thyroid axis function at three occasions during pregnancy.

<table>
<thead>
<tr>
<th>Assessment times during pregnancy</th>
<th>Early (12-16 weeks)</th>
<th>Middle (22-26 weeks)</th>
<th>Late (32-36 weeks)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive disorder, n (%)</td>
<td>13 (6.5)</td>
<td>6 (3.0)</td>
<td>7 (3.5)</td>
<td>0.177</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (TSH), mIU/l (mean ± SD)</td>
<td>0.88 ± 0.69</td>
<td>1.11 ± 0.64</td>
<td>1.02 ± 0.55</td>
<td>0.001</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism, n (%)</td>
<td>46 (23.1)</td>
<td>10 (5.0)</td>
<td>12 (6.0)</td>
<td>0.000</td>
</tr>
<tr>
<td>Subclinical hypothyroidism, n (%)</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Free thyroxine (FT4), pmol/l (mean ± SD)</td>
<td>17.1 ± 2.26</td>
<td>14.60 ± 1.92</td>
<td>13.99 ± 1.82</td>
<td>0.000</td>
</tr>
<tr>
<td>Thyroid peroxidase antibodies &gt;35 IU/ml, n (%)</td>
<td>23 (11.6)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Subclinical hyperthyroidism, TSH < 0.4 mIU/l; FT4, 10.3–25.7 pmol/l.
Subclinical hypothyroidism, TSH > 4.0; mIU/l, FT4, 10.3–25.7 pmol/l.

### Table III. Thyroid axis function in pregnant women with and without depressive disorder.

<table>
<thead>
<tr>
<th></th>
<th>No depressive disorder</th>
<th>Depressive disorder</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early gestation (12-16 weeks)</strong></td>
<td>n=186</td>
<td>n=13</td>
<td></td>
</tr>
<tr>
<td>Thyroid stimulating hormone (mIU/l)</td>
<td>0.9 ± 0.7</td>
<td>0.8 ± 0.7</td>
<td>0.732</td>
</tr>
<tr>
<td>Free thyroxine (pmol/l)</td>
<td>17.1 ± 2.3</td>
<td>17.8 ± 2.3</td>
<td>0.271</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism n (%)</td>
<td>43 (23.1)</td>
<td>3 (23.1)</td>
<td>0.649</td>
</tr>
<tr>
<td>Thyroid peroxidase antibodies &gt;35 IU/ml n (%)</td>
<td>22 (11.8)</td>
<td>1 (7.7)</td>
<td>0.542</td>
</tr>
<tr>
<td><strong>Middle gestations (22-26 weeks)</strong></td>
<td>n=193</td>
<td>n=6</td>
<td></td>
</tr>
<tr>
<td>Thyroid stimulating hormone (mIU/l)</td>
<td>1.1 ± 0.6</td>
<td>0.8 ± 0.5</td>
<td>0.282</td>
</tr>
<tr>
<td>Free thyroxine (pmol/l)</td>
<td>14.6 ± 1.9</td>
<td>14.2 ± 1.0</td>
<td>0.565</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism n (%)</td>
<td>9 (4.8)</td>
<td>1 (7.7)</td>
<td>0.269</td>
</tr>
<tr>
<td><strong>Late gestation (32-36 weeks)</strong></td>
<td>n=192</td>
<td>n=7</td>
<td></td>
</tr>
<tr>
<td>Thyroid stimulating hormone (mIU/l)</td>
<td>1.0 ± 0.6</td>
<td>0.6 ± 0.3</td>
<td>0.062</td>
</tr>
<tr>
<td>Free thyroxine (pmol/l)</td>
<td>13.9 ± 1.8</td>
<td>15.4 ± 2.5</td>
<td>0.040</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism n (%)</td>
<td>10 (5.2)</td>
<td>2 (15.4)</td>
<td>0.059</td>
</tr>
</tbody>
</table>

Subclinical hyperthyroidism, TSH < 0.4 mIU/l; FT4, 10.3–25.7 pmol/l.
associated with the presence of major depression, especially in early pregnancy. This association was independent from thyroid dysfunction. In the UK, Oretti et al. (1997) did not find any relationship between the scores on the standard self-rating scales for depression and increased TPO antibodies concentrations in serum. In the current study, we also found no relationship between thyroid autoimmunity and depressive disorder. Our negative results may be the consequence of the weaker statistical power of our study compared to the Dutch studies. In the latter studies, however, the significant association between depression and thyroid autoimmunity found during early pregnancy did not persist into later gestation, suggesting that other factors may alter that association as pregnancy progresses. Cortisol concentrations, for example, increase dramatically during pregnancy (Carr et al. 1981) and may affect thyroid autoimmunity as well as depression (Field et al. 2008).

Given strong evidence that depression during gestation is related to impaired postnatal infant development (Deave et al. 2008) it is important better understand biological risk factors for depression during pregnancy. To that end, future studies should include a broader range of biological measurements, such as cortisol and chorionic gonadotropin, in addition to thyroid functioning and thyroid autoimmunity. Polymorphisms in several genes affecting thyroid axis functioning (Dayan and Panicker 2009) should also be taken into consideration. Results of this relatively small study should be considered as preliminary and further studies with larger sample size are needed.

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Statement of Interest
None

References


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