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Late pregnancy thyroid-binding globulin predicts perinatal depression

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ABSTRACT

Previously we found that late pregnancy total and free thyroxine (TT4, FT4) concentrations were negatively related to greater pre and/or postpartum depressive symptoms. In a much larger cohort, the current study examined whether these thyroid indices measured earlier in the third trimester (31–33 weeks) predict subsequent perinatal depression and anxiety ratings as well as syndromal depression. Thyroid-binding globulin (TBG) concentrations increase markedly during pregnancy and may be an index of sensitivity to elevated estrogen levels. TBG was examined in this study because prior findings suggest that postpartum depression is related to sensitivity to mood destabilization by elevated sex hormone concentrations during pregnancy. Our cohort was 199 euthyroid women recruited from a public health obstetrics clinic (63.8% Hispanic, 21.6% Black). After screening and blood draws for hormone measures at pregnancy weeks 31–33, subjects were evaluated during home visits at pregnancy weeks 35–36 as well as postpartum weeks 6 and 12. Evaluations included psychiatric interviews for current and life-time DSM-IV psychiatric history (M.I.N.I.-Plus), subject self-ratings and interviewer ratings for depression and anxiety (Edinburgh Postnatal Depression Scale, Montgomery-Åsberg Depression Rating Scale; Spielberger State-Trait Anxiety Inventory, Hamilton Anxiety Inventory), as well as a standardized interview to obtain life-time trauma history. Numerous covariates were included in all regression analyses. Trauma and major depression history were robustly significant predictors of depression and anxiety ratings over the study period when these variables were analyzed individually or in a combined model including FT4 or TBG ($p < .001$). When analyzed alone, FT4 levels were a less strong but still significant predictor of all depression and anxiety ratings ($p < .05$) while TBG levels was a significant or nearly significant predictor of most ratings. FT4, TBG and trauma history, but not major depression history, were significant individual predictors of syndromal depression during the study period ($p < .05$) in single predictor models. In models combining each with trauma and major depression history, FT4 and TBG generally were not significantly predictive of depression or anxiety ratings, and FT4 was also not a significant predictor of syndromal depression: however, in the combined model TBG was a particularly strong predictor of perinatal syndromal depression ($p = .005$) and trauma history was also significant ($p = .016$). Further study of the interactions among TBG, FT4, sex hormones, trauma history and perinatal depression may provide insights into the pathophysiological basis of individual variance in vulnerability to mood destabilization by the hormone conditions of pregnancy.

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1. Introduction

The combined prevalence of DSM-IV major or minor depression is approximately 10–15% during pregnancy and the postpartum period (Gavin et al., 2005; Banti et al., 2011; Le Strat et al., 2011). Antenatal and postpartum anxiety disorders may be as or more common (Wenzel et al., 2003, 2005; Sutter-Dallay et al., 2004; O'Hara and Wisner, 2014). Numerous large shifts in hormone levels occur during pregnancy and postpartum. Many have been examined as correlates of depression in mothers, primarily during the postpartum period but also during pregnancy (Bloch et al., 2003; Zonana and Gorman, 2005; Skalkidou et al., 2012; Schiller et al., 2015).

Hypothalamic-pituitary-thyroid (HPT) axis regulation undergoes profound changes during pregnancy. An approximately 150%

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increase in thyroid-binding globulin (TBG) concentrations is caused by marked elevations in estrogen concentrations (Glinoer, 1997; Gaberscek and Zaletel, 2011). Thyroid hormone secretion increases considerably to fill the expanded binding space and maintain adequate free thyroid hormone concentrations. Recent studies have established that the ranges of thyroid stimulating hormone (TSH) and free thyroxine (FT4) concentrations during pregnancy are lower than in non-pregnant women. FT4 levels are below the non-pregnant reference range in a substantial minority of pregnant women (Kurioka et al., 2005; Cotzias et al., 2008; Wang et al., 2011; Yan et al., 2011). The usual negative correlation between TSH and FT4 in non-pregnant women is lost during later pregnancy (Kurioka et al., 2005; Jonklaas et al., 2009).

Overt and subtle abnormalities of the HPT axis have been linked to major depression and anxiety disorders by many studies, but not all (Roy et al., 1994; Hoffman et al., 2001; Sait Gönen et al., 2004; Olff et al., 2006; Bauer et al., 2008; Hage and Azar, 2012; Giynas Ayhan et al., 2014). Some abnormalities, such as blunted TSH response to TRH, are only found in a minority of major depressed patients (Hage and Azar, 2012). Thyroid hormone levels have been reported to correlate with symptoms in syndromal depression (Williams et al., 2009). Significant associations between a number of thyroid indices and either pregnancy or postpartum depression have been published (Stewart et al., 1988; Harris et al., 1992; Pop et al., 1993; Abou-Saleh et al., 1998; Ijuin et al., 1998; Kuijpens et al., 2001; McCoy et al., 2008; Lambrinoudaki et al., 2010; Keshavarzi et al., 2011; Sylvén et al., 2013; Saleh et al., 2013). In the only studies to examine antenatal thyroid correlates of pre and postpartum mood, we found that late pregnancy FT4 and total thyroxine (TT4) concentrations were negatively related with late pregnancy and/or postpartum depression scores (Pedersen et al., 1993, 2007).

The rapid postpartum declines in estrogen and progesterone from very high concentrations during pregnancy have long been hypothesized to play a role in the postpartum onset of depression. Although differences in postpartum levels of these hormones have occasionally been reported in depressed mothers, no consistent relationships between sex hormone levels and postpartum depression have been confirmed (Bloch et al., 2003; Zonana and Gorman, 2005; Schiller et al., 2015; Skalkidou et al., 2012). Evidence published by Bloch et al. (2000) suggested for the first time that vulnerability to postpartum depression may be related to variance in sensitivity to rather than differences in concentrations of sex hormone during pregnancy. Specifically, 8 weeks of high dose estrogen and progesterone treatment followed by abrupt cessation of treatment significantly increased depressive symptoms in women who had prior episodes of postpartum major depression from which they fully recovered (most of the rise in symptoms occurred late during high dose hormone treatment) but had no effect on mood in women who had born children but had negative depression history.

In a substantially larger sample, the current study further tested the validity of our earlier finding that lower late pregnancy TT4 and FT4 concentrations are related to perinatal depression (Pedersen et al., 1993, 2007). Because TBG concentrations during pregnancy may be an index of sensitivity to elevated estrogen levels, and postpartum depression has been linked to greater sensitivity to mood destabilization by high sex steroid concentrations similar to pregnancy Bloch et al. (2000), we examined whether late pregnancy TBG may be associated with perinatal depression. This is the first study to examine TBG relationships with perinatal depression and anxiety.

Associations between late pregnancy thyroid indices and perinatal anxiety were also studied. Because major depression history and trauma history have been established as risk factors for perinatal depression (Rich-Edwards et al., 2011; Howard et al., 2013; Robertson-Blackmore et al., 2013; Alvarez-Segura et al., 2014; O'Hara and Wisner, 2014; Norhayati et al., 2015), we measured these variables and included them as covariates in analyses testing our hypotheses.

2. Materials and methods

The study was approved by the University of North Carolina Biomedical Institutional Review Board as well as the Wake County Human Services Board and conducted in accordance with The Code of Ethics of the World Medical Association. The study included 4 visits, two during pregnancy and two postpartum.

2.1. Participants

Patients from a public health prenatal clinic located at Wake County Human Services in Raleigh, NC were screened at 31–33 weeks of pregnancy and during home visits at 35–36 weeks of pregnancy. Patients had to be 18–45 years of age without the following exclusion criteria: (1) TSH concentration outside the non-pregnant reference range for our assay (0.3–6.5 μIU/ml); (2) lifetime history of DSM-IV psychotic, bipolar, cyclothymic, somatoform or dissociative disorder; substance dependence or eating disorder in the last two years; use of street drugs or consumption of alcoholic beverages more than 3 days per week or more than 2 drinks/day during the current pregnancy; (3) body mass index (BMI) >35 or <18 upon obstetric clinic intake; (4) chronic or acute serious medical illness or pregnancy complications (e.g., heart disease, cancer, diabetes, recent surgery); (5) use of psychotropic medications in the preceding 2 months or other medications during the 2 weeks prior to screening or during the protocol except vitamins, iron, acetaminophen, or diphenhydramine, or for pain control during labor and delivery, or for short duration treatment of brief, mild illnesses (e.g., antibiotics, decongestants, acetaminophen or NSAIDs for flu, upper respiratory or urinary tract infections); (6) smoking >10 cigarettes/day; and (7) not fluent in spoken and written English or Spanish. To assure that a high percentage of our sample had syndromal depression history, approximately half of the mothers were selected if they screened positive for previous persistent depressed mood and/or loss of interest or enjoyment for 2 weeks or more. Subjects were not excluded if they delivered by cesarean section (C-section); however, cesarean delivery was included as a control variable in postpartum analyses.

We approached 325 pregnant women whose medical records and screening indicated that they met study inclusion/exclusion criteria. Of those, 278 (85.5%) initially agreed to be in the study and gave informed consent. A total of 216 women completed all home visits and 222 (68.3% of those qualified; 79.9% of those initially agreeing to be in the study) completed all but the last postpartum visit. Eight subjects were omitted because thyroid assays were not available; 4 were omitted due to TSH levels outside the non-pregnant reference range at screening or other time points during the study; and 11 with serum thyroid peroxidase titers ≥110 U/ml at weeks 35–36 of pregnancy or 12 weeks postpartum were omitted because thyroid autoimmunity may affect thyroid hormone levels (Harris et al., 1992; Pop et al., 1993). No subjects had elevated thyroglobulin antibody titers. Thus, our final sample size was 199.

2.2. Design and measures

After reviewing medical records to identify potential subjects, clinic nurses described the study to patients during clinic visits at 31–33 weeks of pregnancy, obtained written informed consent and screened subjects for participation. Subjects were assessed during home visits at three time points: 35–36 weeks of pregnancy (late pregnancy), and 6 and 12 weeks postpartum. Study staff conducting visits were fluently bilingual and conducted interviews and administered questionnaires in English or Spanish depending on