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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-Ásberg 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

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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.

Keywords

thyroid; trauma; pregnancy; postpartum; anxiety; major depression history

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; LeStrat 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% 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; Yu et al., 2010; 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; Jonklass 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; Hofmann 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., 2012; 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 four 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 caesarean section (C-section); however, caesarean 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 the primary language of the participant. During each home visit, subjects rated themselves on the “gold standard” Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987) and the state portion of the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983) with instructions reading, “Indicate how you have felt in the past week.” Study staff rated subjects using the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) and the Hamilton Anxiety Ratings Scale (HAMA; Hamilton, 1959).

Acceptable inter-rater reliability was established during training by having study staff and a Board-certified psychiatrist (SMB) independently rate patients on both instruments (weighted kappa =.79 on MADRS and .82 on HAMA). A modified MINI Plus 5.0.0 International Neuropsychiatric Interview (Sheehan et al., 1998) which included both lifetime and current diagnoses of major and minor depression was administered during the late pregnancy and postpartum week-12 visits. DSM-IV-R major depression and Research Diagnostic Criteria (RDC, Spitzer et al., 1978) minor depression diagnoses were determined by consensus during weekly meetings. A Structured Trauma Interview (e.g., sexual and physical abuse, childhood neglect, and other DSM-IV-R type traumas often associated with PTSD; Leserman et al., 2007) was administered at the postpartum week-12 visit. One investigator (JL) trained study staff to administer the trauma interview and reviewed all interviews. The sum of all categories of lifetime trauma was used as a predictor variable in analyses.

Blood was drawn immediately after screening for study eligibility at 31-33 weeks of pregnancy to obtain serum for thyroid assays as well as assay of 17β-estradiol and progesterone concentrations. Primary thyroid variables, total thyroxine (TT4), free thyroxine (FT4), and thyroid binding globulin (TBG), were assayed along with thyroid variables of secondary interest; thyroid stimulating hormone (TSH), total triiodothyronine (T3), free triiodothyronine (FT3), and T3 resin uptake (T3U). Blood was also collected at all home visits for TSH assay; at pregnancy weeks 35-36 and postpartum week 12 for assay of thyroid peroxidase and thyroglobulin antibody titers; and at postpartum week 12 for FT4 assay. Serum concentrations of thyroid hormones, 17β-estradiol, and progesterone were assayed using coated tube radioimmunoassay kits (MP Biomedicals, Costa Mesa, CA). Serum thyroid antibody and TBG concentrations were also measured using coated tube radioimmunoassays (Alpco Diagnostics, Salem, NH). The estradiol and progesterone sensitivities were 4.5 pg/ml and 0.06 ng/ml., respectively. All inter- and intra-assay coefficients of variation were less than 10%.

2.3. Statistical Analyses

Descriptive statistics were run on all variables, including percentages for categorical variables and means and standard deviations for continuous variables. All variables were checked for approximate normality, skewness and outliers.

Our primary analysis fit repeated measures models with each thyroid variable (TT4, FT4, TBG) measure at 31-33 weeks of pregnancy (baseline) predicting each mood (depression or anxiety) measure (EPDS, MADRS, STAI, HAMA) at three subsequent time points: 35-36 weeks of pregnancy as well as 6 and 12 weeks postpartum. An unstructured covariance was used to model the covariance between measures at the three home-visit time points. Each model included fixed effects predictors for a categorical time variable, the thyroid predictor, and the interaction of the thyroid variable and time. When the hypothesis test for the interaction term was non-significant, the interaction term was removed. The following control variables were also included as potential predictors in all models: age, education, race, BMI, number of previous pregnancies, delivery by cesarean-section, breastfeeding, and screening values for progesterone and estradiol. Control variables for each model were

assessed via a backwards elimination procedure; only those variables that remained significant in the final model obtained from the backwards elimination procedure were included.

These same models predicting mood outcomes were also fit including thyroid predictors of secondary interest (TSH, FT3, TT3, and T3U). Models assessing mood outcome measures were repeated substituting number of lifetime traumas or lifetime major depression in place of the thyroid variable predictor. Additional models were run including each thyroid variable, the total trauma variable, and lifetime depression together as predictors in the same model.

All models including thyroid predictors, the lifetime trauma predictor, lifetime major depression history, or their combination were also repeated as logistic regression models with a categorical outcome for syndromal depression (major or minor) diagnosis during the study period. Since the MINI was administered at pregnancy weeks 35-36 and 12 weeks postpartum, we created an outcome measure indicating current major or minor depression at any time during the study. Logistic regression models were fit as univariate models and not repeated measures models.

All analyses were conducted with SAS version 9.3. Repeated measures models were fit with PROC GLIMMIX. Logistic regression models were fit with PROC LOGISTIC.

3. Results

Table 1 shows data on the whole sample for demographic, pregnancy, breastfeeding, lifetime major depression history, syndromal depression during the study period, lifetime anxiety disorder history, anxiety disorders during the study period, trauma history, and screening thyroid and endocrine variables. The majority of our sample was Hispanic (63.8%), 21.6% were Black, and almost half (50.3%) had not completed high school. Roughly half of the sample (52.8%) had experienced major depression during their lifetime. Women had experienced on average 4.5 categories of traumatic events (e.g., sexual and physical abuse, childhood neglect and violence) in their lifetime. Serum FT4 concentrations at screening were below the non-pregnant reference range (0.7-1.7 ng/dL) in 20 subjects. FT4 concentrations for all subjects were within the non-pregnant reference range at 12 weeks postpartum. TBG concentrations at screening were above the pregnant reference range (16.4-64.4 mg/L) in 9 subjects. TT4 concentrations at screening ranged from 6.07 to 22.48 μg/dL with 50 subjects having concentrations above the non-pregnant reference range (5-13 μg/dL). TSH concentrations were within the non-pregnant reference range for our assay (0.3-6.5 μIU/ml) at all time-points for all subjects due to study inclusion/exclusion criteria. FT4, TBG, and TT4 were highly correlated ($r=0.27$, FT4/TBG; $r=0.39$ FT4/TT4; $r=0.35$ TBG/TT4; all $p<0.0001$), but were not significantly correlated with TSH ($r=-0.003$ - 0.06; all $p>0.45$).

3.1. Depression and Anxiety

Table 2 shows all the depression and anxiety measures over time from pregnancy weeks 35-36 to postpartum weeks 6 and 12. Although some women had moderate to high levels of

depression and anxiety during pregnancy, most scored below accepted cut-offs for clinically significant levels of symptoms on EPDS (N=148, 74.3% below 10) and HAMA (N=155, 77.9% below 15). The mood measures were moderately correlated with each other during late pregnancy ranging from 0.60 to 0.84 (all $p<0.0001$). Of note, women as a group tended to become significantly less depressed and anxious over time. The repeated measures time variable was significant for all mood measures ($p<.001$).

Based on MINI-Plus interviews, 22 (11.1%) of subjects met DSM-IV criteria for major depression or RDC minor depression during late pregnancy (35-36 weeks), and 24 (12.1%) met criteria postpartum (week 12). Nine met criteria during pregnancy and postpartum so the total number meeting criteria during the perinatal study period was 37 (18.6%). 45 subjects (22.6%) met criteria for a current DSM-IV anxiety disorder during the study period including: 14 (7.0%) with generalized anxiety disorder; 2 (1.0%) with posttraumatic stress disorder (PTSD); 4 (2.0%) with obsessive-compulsive disorder; 31 with specific phobias (15.6%); 4 with social phobia (2.0%); 6 with agoraphobia (3.0%); and 3 with panic disorder (1.5%). A far larger number had lifetime history of one or more anxiety disorders (98, 49.2%) including: 12 (6%) for generalized anxiety disorder; 54 (27.1%) for PTSD; 11 (5.5%) for obsessive-compulsive disorder; 33 (16.6%) for specific phobias; 9 (4.5%) for social phobia; 14 (7%) for agoraphobia; and 19 (9.6%) for panic disorder. This prevalence of anxiety disorders during the perinatal period is comparable to findings by others (Wenzel et al., 2003; 2005; Sutter-Dallay et al., 2004; O'Hara and Wisner, 2014). It is beyond the scope of this report to include relationships of perinatal anxiety disorders and biological and psychosocial variables, although we do so for anxiety ratings. 67 (33.7%) of participants met criteria for DSM-IV major depression or RDC minor depression and/or a DSM-IV anxiety disorder diagnosis during the study period while 15 (7.5%) met criteria for both a depression and an anxiety disorder during the study period often not concomitantly.

3.2. Relationships of Demographic and Pregnancy-Related Control Variables with Depression and Anxiety

All models included control variables as predictors. Covariates were chosen via a backwards elimination procedure separately for each model, so that individual models may retain different significant covariates. Space does not allow description of the specific control variables retained in every model fit for each combination of mood outcome and thyroid, trauma history, or lifetime major depression predictor variables. Control variables were similar for all models fit for each particular mood outcome (EPDS, MADRS, HAMA, STAI), therefore, for brevity, we describe the control variables retained in a backwards elimination from a model for each outcome that contains no thyroid, trauma, or lifetime major depression predictors. We comment when these relationships change when thyroid, trauma, and lifetime major depression predictors are added to the model. Regression coefficients are provided for models with all predictors on their original scale (labeled "B") as well as for models where continuous outcomes and predictors were scaled to have a mean of zero and standard deviation of one (labeled "StB"). Categorical outcomes and predictors were not scaled in either model. Odds ratios describing the odds of developing major or minor depression are described as the odds ratio for Afro-American race compared to Caucasian race and as a one standard deviation increase for progesterone.

Afro-Americans were significantly more likely to be depressed on the EPDS (p=.008, B=1.74, StB=0.38) and anxious on the STAI (p=.008, B=3.60, StB=0.39) over time compared to all other races; they were also at greater risk for major or minor depression (p=.019, B=0.96, StB=0.96, OR=2.61). Race remained a significant predictor of EPDS, STAI, and risk of perinatal major or minor depression (perinatal syndromal depression) when thyroid variables, trauma, and lifetime major depression were included together as predictors in the model.

Those with more previous pregnancies had significantly worse depression and anxiety on all continuous mood measures [ranging from STAI (p=.0006, B=1.51, StB=0.21) to MADRS (p=.027, B=0.71, StB=0.13)]. The gravidity effect remained only on STAI when trauma, lifetime depression, and thyroid variables were in the model together. Additionally, number of previous pregnancies became a significant predictor of risk of perinatal syndromal depression, when trauma, lifetime depression, and thyroid variables were included in the model together.

Higher pregnancy progesterone was associated with worse mood on the EPDS (p=.023, B=0.016, StB=0.13) and MADRS (p=.035, B=0.023, StB=0.12) over time, and greater risk of major or minor depression (p=.021, B=0.011, StB=0.40, OR=1.49). Progesterone was a significant predictor of perinatal syndromal depression when trauma, FT4, and lifetime major depression were included in the model.

Finally, having a C-section was only associated with higher scores on the MADRS (p=.023, B=2.47, StB=0.35), perhaps reflecting higher somatic symptoms included in this scale. C-section birth continued to predict MADRS whether trauma, thyroid, and/or lifetime major depression were included in the model. EPDS was significantly predicted by C-section birth when TBG, trauma, and lifetime major depression were included in the model.

3.3. Thyroid Hormone Measure Relationships with Depression and Anxiety

Table 3 describes the relationships between thyroid variables, trauma, and lifetime depression history and mood outcome measures in models that include one of baseline FT4, baseline TBG, lifetime trauma, or lifetime depression history as predictors. To facilitate comparison of outcomes and predictors with different scales, estimated regression coefficients for predictors in each model are displayed with their original scale (labeled “Non-standardized”) as well as from models fit where continuous outcomes, predictors, and covariates have been scaled to have mean of zero and standard deviation of one (labeled “Standardized”). Categorical outcomes, predictors, and covariates (e.g., syndromal depression outcome, lifetime major depression predictor) were not standardized in any model.

Adjusting for significant control variables, repeated measures models showed that baseline FT4 and TBG were consistently negatively associated with mood variables when number of lifetime traumas and major depression history were not included in analyses (Table 3; FT4 p=0.002-0.052; TBG p=0.023-0.155). Because the interactions of thyroid variables and measurement time were not significant, we focused on examining the effects of thyroid hormones on each mood measure averaging over all three time points. Table 3 shows that

for each one standard deviation decrease (=0.21, not show, calculated from data) in FT4 there was a 0.13 standard deviation increase (=0.59) on the EPDS. FT4 was similarly associated with the other mood measures. The odds of having clinical depression during the study period were 1.60 times higher for a one standard deviation decrease in FT4 (95% CI: 1.04 - 2.46).

For every one standard deviation (=8.1) decrease in TBG, there was a 0.13 standard deviation (=0.91) increase on the MADRS. Similar negative effects were found with increases in STAI and, at marginal significance, HAMA, but not with EPDS. The odds of becoming clinically depressed are 1.54 times higher for a one standard deviation decrease in TBG (95% CI: 1.06 - 2.24).

TT4, TSH and other secondary thyroid variables were not associated with any of the depression and anxiety measures over time ($p>0.10$; results not shown).

3.4. Number of Categories of Lifetime Trauma or Lifetime Major Depression History with Depression and Anxiety

Table 3 also shows the consistent effects of lifetime trauma and lifetime major depression history on mood. For every one standard deviation increase (=2.85) in number of trauma categories, there was a 0.22 – 0.34 standard deviation (=1.23 for EPDS; =2.02 for STAI; =2.24 for MADRS; =1.85 for HAMA) increase in depressed and anxious mood (all $p<0.001$). The odds of becoming clinically depressed are 1.53 times higher for a one standard deviation increase in number of trauma categories (95% CI: 1.06 – 2.23; $p=0.024$).

Similar significant relationships are seen between mood outcomes and lifetime major depression history. Participants with a lifetime history of major depression show 0.40 – 0.69 standard deviation (=2.38 for EPDS; =3.68 for STAI; =3.92 for MADRS; =3.75 for HAMA) increases in depressed and anxious mood (all $p<0.001$). The odds of becoming clinically depressed are 2.02 times higher for participants with a lifetime history of major depression (95% CI: 0.93 – 4.37); however this relationship is only marginally significant ($p=0.075$).

3.5. Thyroid Hormone Measures, Lifetime Trauma, and Lifetime Major Depression History Together Predicting Depression and Anxiety

Table 4 shows the effects of FT4 or TBG, number of trauma categories, and lifetime history of major depression when these predictors are included together in the same model. While the effects of FT4 become less significant with the inclusion of trauma and lifetime major depression history, the negative associations between FT4 and mood variables remain significant or at trend level ($p=0.020$-0.081), except for STAI ($p=0.202$). Relationships between TBG and mood outcomes remain largely at a trend level ($p=0.043$-0.061), with the EPDS relationship notably improving in significance. Number of categories of trauma and lifetime history of major depression both remain significant in models with each thyroid variable included, and continue to be the strongest predictors of all depression and anxiety mood measures (all $p<0.016$).

Notably, the relationship between TBG and clinical depression diagnosis becomes considerably more significant when trauma and lifetime depression history are included

(p=0.005); however, the relationship between FT4 and clinical depression diagnosis become less significant (p=0.067). Neither number of traumas or lifetime history of depression is a significant predictor of clinical depression when they are included together in a model with FT4 (Trauma p=0.101, Lifetime depression p=0.228). When TBG is included instead, trauma becomes a significant predictor of clinical depression (p=0.016), while lifetime major depression history continues to show a non-significant relationship (p=0.122).

The odds of becoming clinically depressed are similar (1.39 – 1.91) for a one standard deviation decrease in thyroid variables, a one standard deviation increase in trauma, or for having a lifetime history of major depression (FT4: OR=1.52, 95% CI=0.97-2.38; Trauma in FT4 model: OR=1.39, 95% CI=0.94-2.05; Lifetime major depression in FT4 model: OR=1.64, 95% CI=0.73-3.68; TBG: OR=1.75, 95% CI= 1.18-2.58; Trauma in TBG model: OR=1.67, 95%CI=1.10-2.53; Lifetime major depression in TBG model: OR=1.91, 95% CI: 0.84-4.35).

Number of trauma categories and lifetime major depression history are themselves significantly related. The mean (SD) number of trauma categories for participants with and without lifetime major depression history are, respectively, 5.3 (2.7) and 3.6 (2.8) ($p<0.0001$ for test of difference in these means).

4. Discussion

In an earlier study (Pedersen et al., 2007, N = 31), we found that TT4 and FT4 near the end of pregnancy (38 weeks) correlated negatively with late pregnancy and postpartum depression ratings. In the much larger current study (N=199), we hypothesized that we would find the same relationships between these thyroid variables measured earlier in the third trimester (31-33 weeks) and perinatal depression and anxiety scores as well as perinatal syndromal (major and minor) depression. In the current study, we also tested a new hypothesis about early third trimester TBG. During pregnancy, marked increases in estrogen levels stimulate an approximately 150% increase in TBG concentrations (Glinoer, 1997). Therefore, TBG concentrations during pregnancy may be an index of estrogen sensitivity. Bloch et al. (2000) found that women differ considerably in their vulnerability to mood disturbance during treatments simulating the sex hormone conditions of pregnancy. Specifically, 8 weeks of high dose estrogen and progesterone significantly increased depression symptoms in women with postpartum major depression history (who subsequently had full remission) but had no mood effects in women with negative depression history. Therefore, we hypothesized that TBG concentrations at 31-33 weeks of pregnancy would differ in women who developed greater perinatal depression. Our results support the FT4 and the TBG hypotheses but not the TT4 hypothesis. Furthermore, our findings indicate that lower pregnancy week 31-33 TBG concentrations robustly predict subsequent perinatal syndromal depression.

In addition to its relatively large cohort and focus on perinatal anxiety as well as depression, the current study has numerous strengths. These include comprehensive psychiatric evaluation of subjects including a MINI-Plus interview at pregnancy weeks 35-36 to determine subjects' lifetime as well as current history of DSM-IV disorders and repeat of the

interview at postpartum week 12 to identify disorders with onset since study entry; obtaining both self- and interviewer-ratings for depression and anxiety during each home visit; and conducting a structured interview at 12 weeks postpartum to quantify life-time history of 13 categories of trauma. In addition to a complete battery of thyroid indices, estradiol and progesterone were assayed in serum collected at pregnancy weeks 31-33. To ensure that subjects included in analyses were truly euthyroid, several thyroid measures were also conducted at time points other than pregnancy weeks 31-33 including: TSH assay at all time points (pregnancy weeks 31-33, each home visit), measurement of thyroid antibody titers at pregnancy weeks 35-36 and at 12 weeks postpartum; and FT4 assays at 12 weeks postpartum. Evaluation of subjects during home visits certainly contributed to a very high rate of retention and completion of the entire protocol. Our cohort, composed almost exclusively of low SES women consisting of a majority of largely Spanish-speaking, Hispanic mothers and a sizable minority of Black mothers, is unique for a study of biological, psychiatric history and other psychosocial correlates of perinatal depression and anxiety.

In this study, lifetime major depression history and trauma history were highly significant predictors of greater depression and anxiety scores when evaluated as individual predictors or when included in a combined model with early third trimester FT4 or TBG (Tables 3 and 4). Trauma history was a weaker, albeit still significant, predictor of perinatal syndromal depression. However, major depression history did not significantly predict perinatal syndromal depression. Our trauma history findings are consistent with the results of a few recent studies of the relationship between abuse history and perinatal depression (Rich-Edwards et al., 2011; Robertson-Blackmore et al., 2013; Howard et al., 2013; Alvarez-Segura et al., 2014). However, our major depression history findings contrast with the conclusions of most other studies that major depression history is a strong predictor of syndromal depression during pregnancy and postpartum (O'Hara and Wisner, 2014; Norhayati et al., 2015). We found that lifetime major depression history strongly correlated with lifetime trauma history. The latter was highly prevalent and often severe in our low SES cohort composed primarily of a majority of Hispanics and a sizable minority of Blacks. The strong relationship between lifetime trauma and major depression history and the high rates of trauma in our sample may have diminished the predictive power of major depression history.

In contrast to trauma and major depression history, FT4 and TBG at 31-33 weeks of pregnancy were, overall, less significant individual predictors of perinatal depression and anxiety scores. (Table 3) The exception was FT4 being highly significantly predictive of interviewer-ratings of depression and anxiety (MADRS, HAMA scores). TBG was only marginally significant as an individual predictor of depression and anxiety ratings. FT4 and TBG were both significant individual predictors of perinatal syndromal depression (Table 3). In a combined model with trauma and major depression history (Table 4), FT4 was no longer significantly predictive of depression and anxiety ratings and TBG remained a marginally significant predictor. In the combined model, FT4 only trended toward being a significant predictor of perinatal syndromal depression (Table 4). In stark contrast, TBG was a highly significant predictor. Remarkably, in the combined model, TBG was a stronger

predictor of perinatal syndromal depression than trauma history (and major depression history that was not a significant predictor in this study).

Our TBG finding is unique and has potentially significant implications. This is the first study of the relationship of thyroid indices and perinatal depression to include TBG. While the size of our cohort provides some confidence that this finding is valid, it clearly requires confirmation and extension in future studies. It is unclear if TBG concentrations during pregnancy may be clinically useful in identifying mothers who are at risk of developing syndromal depression. In the data from this study, there is considerable overlap in the distribution of pregnancy week 31-33 TBG levels among subgroups of subjects who did and did not develop perinatal syndromal depression with or without the risk factors of trauma and/or major depression history. So there is no distinctly lower range of early third trimester TBG concentrations at 31-33 weeks of pregnancy that clearly identifies which mothers are at higher risk. Future studies should examine how early in pregnancy TBG concentrations predict subsequent syndromal depression. Perhaps a lower range of TBG concentrations (and possibly FT4) will be found earlier in gestation that is more definitely predictive. Diagnostic interviews should be conducted in future studies at the times serum samples are collected for measurement of thyroid indices to determine if lower TBG concentrations are coincident with as well as predictive of syndromal depression. This was not done in the current study and is a weakness. Some women with major or minor depression at 35-36 weeks in our cohort may have been in a syndromal depression episode at 31-33 weeks when serum samples for TBG were collected.

FT4 was a very significant individual predictor of objective depression and anxiety symptom ratings (MADRS, HAMA; Table 3) and a somewhat weaker, but still significant, sole predictor of subjective depression and anxiety symptom ratings (EPDS, STAI) as well as perinatal syndromal depression. However, when included in a model with trauma and lifetime major depression history (Table 4), FT4 became a weaker predictor; remaining significant only for HAMA scores, but still trending toward significance for EPDS and MADRS scores. Prediction of perinatal syndromal depression also became weaker for FT4 in the combined model, in stark contrast to the greater predictive strength of TBG in the combined model. FT4 and TBG concentrations correlated positively and very significantly ($r=0.27$, $p<.0001$). In a model in which trauma and major depression history strengthened TBG prediction of perinatal syndromal depression, the high correlation between FT4 and TBG may have weakened FT4 as a predictor. Nonetheless, future studies should examine how early during pregnancy FT4 becomes a predictor of syndromal depression and FT4 interactions with trauma and major depression history.

Our results suggest that mothers who are more likely to develop perinatal syndromal depression are less sensitive to estrogen elevations during pregnancy increasing TBG concentrations. Future studies should more directly test this hypothesis. TBG is a glycoprotein. Synthesis in the liver involves incorporation of sialic acid molecules (sialylation) as branching chains of varying lengths within the TBG protein structure. A mechanism contributing to the rise of TBG concentrations during pregnancy is that elevated estrogen causes higher sialylation of a larger percentage of TBG molecules (Gärtner et al., 1981). Greater sialic acid content decreases the rate of TBG enzymatic degradation, slows

clearance, and, therefore, causes a rise in concentrations (Ain et al., 1987). If future studies find less sialylation of TBG molecules from pregnant mothers who develop perinatal syndromal depression, it would support our hypothesis that they are less sensitive to elevated estrogen.

TBG concentrations increase during the first half of pregnancy, reach their peak at approximately 20 weeks of pregnancy, and then remain at those levels until parturition (Glinoer, 1997). There is considerable individual variation in TBG changes during early pregnancy. Plateauing of TBG levels during late pregnancy may partly explain the lack of significant correlation between TBG and estradiol concentrations at 31-33 weeks in this study ($r = -0.102$, $p = 0.154$). If in future studies the correlation between TBG and estrogen concentrations is lower during the first half of pregnancy in mothers who develop perinatal syndromal depression, it would suggest they are less sensitive to rising estrogen levels.

We found that higher progesterone concentrations at 31-33 weeks of pregnancy were associated with greater risk of developing perinatal syndromal depression. This result and our TBG-based evidence that perinatal syndromal depression may be related to lower sensitivity to elevated estrogen raise additional important questions that require future investigation. Might high progesterone concentrations during pregnancy potentially increase depression in vulnerable mothers? This hypothesis is supported by the only randomized clinical trial of postpartum progestin treatment in which norethisterone enanthate administration within 48 hours after parturition significantly increased the risk of developing postpartum depression (Lawrie et al., 1998). Could elevated concentrations of estrogen during pregnancy counteract adverse mood effects of elevated progesterone? Might mothers who are less sensitive to estrogen be more vulnerable to elevated progesterone-induced depression?

Sialylation is an important mechanism regulating the activity of some brain areas. Of particular interest is that polysialylation of neural cell adhesion molecules (producing PSA-NCAMs) in regions such as the dorsolateral prefrontal cortex, hippocampus and amygdala affects plasticity and possibly connectivity of those areas (Gilabert-Juan et al., 2012; Schnaar et al., 2014). Reduced PSA-NCAM in specific brain areas has been linked to psychiatric disorders (Gilabert-Juan et al., 2012). Future brain imaging studies should examine whether lower TBG concentrations that predict perinatal syndromal depression are related to differences in regional brain activity, especially in brain areas where diminished PSA-NCAM content is associated with depression. Brain region PSA-NCAM content during pregnancy and the effects of sex hormone concentrations on PSA-NCAM content have not been examined except in the hypothalamus of rodents where rising estrogen up-regulation of PSA-NCAM content has been linked to GnRH release during the ovarian cycle (Naftolin et al., 2007).

We report the first evidence that lower late pregnancy concentrations of an estrogen sensitive endocrine variable, TBG, predict perinatal syndromal depression. This result is particularly strong when trauma and major depression history are included in the statistical model. Our TBG finding may permit extension of previous evidence that women differ in their vulnerability to depression during high dose sex hormone treatment simulating

pregnancy (Bloch et al., 2000) by identifying, for the first time, a physiological system in which perinatal depression-associated differences in hormone sensitivity can be examined. Our results suggest that further investigation of interactions among TBG regulation, sex hormones, risk factors and brain activity may provide new insights into the basis of variance among women in vulnerability to mood destabilization by the hormone conditions of pregnancy.

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Highlights

- Thyroid assays antenatal; psychiatric measures antenatal, postpartum weeks 6, 12.
- Trauma and major depression history strongly predict depression and anxiety ratings.
- Trauma history, but not major depression history predicts syndromal depression.
- Antenatal FT4 predicts perinatal mood; FT4 and TBG predict syndromal depression.
- In a mixed model, TBG is the strongest predictor of perinatal syndromal depression.

Table 1

Demographics

Outcome	Statistic/Category	Value
Age (years)	Mean (SD)	26.1 (5.8)
	Min - Max	18 - 44
Race (5 Categories)	Hispanic – n(%)	127 (63.8)
	Black – n(%)	43 (21.6)
	White Non-Hispanic – n(%)	24 (12.1)
	Asian – n(%)	3 (1.5)
	American Indian or Alaskan Native – n(%)	2 (1.0)
Education (years)	Mean (SD)	10.8 (3.1)
	Min - Max	2 - 18
Early Pregnancy BMI	Mean (SD)	26.0 (4.7)
	Min - Max	15.8 - 40.3
Previous Pregnancies (#)	Mean (SD)	1.7 (1.5)
	Min - Max	0 - 10
C-Section	Yes – n(%)	33 (16.6)
	No – n(%)	166 (83.4)
Breastfeeding	Yes – n(%)	133 (66.8)
	No – n(%)	66 (33.2)
Lifetime Major Depression	Yes – n (%)	105 (52.8)
	No – n (%)	94 (47.2)
Current Major or Minor Depression	Yes – n (%)	37 (19%)
	No – n (%)	162 (81%)
Lifetime Anxiety Disorder	Yes – n (%)	98 (49.2)
	No – n (%)	101 (50.8)
Current Anxiety Disorder	Yes – n (%)	45 (22.6)
	No – n (%)	154 (77.4)
Lifetime Trauma (Category #)	Mean (SD)	4.5 (2.9)
	Min - Max	0 - 13
Screening Progesterone (ng/ml)	Mean (SD)	141.4 (36.6)
	Min - Max	65.9 – 283.9
Screening Estradiol (ng/mL)	Mean (SD)	18.0 (5.1)
	Min - Max	6.2 – 40.5
Screening TT4 (μg/dL)	Mean (SD)	11.8 (2.6)
	Min - Max	6.1 – 22.5
Screening FT4 (ng/dL)	Mean (SD)	0.91 (0.21)
	Min - Max	0.49 - 1.65
Screening TBG (mg/L)	Mean (SD)	51.4 (8.1)
	Min - Max	25.9 - 76.5
Screening TSH (μIU/ml)	Mean (SD)	1.64 (0.73)
	Min - Max	0.41 - 4.94

Note: N=199 on all variables

Table 2

Mood Outcomes Over Time

Outcome	Pregnancy Weeks 35-35 Mean (SD) Min-Max	Postpartum Week 6 Mean (SD) Min-Max	Postpartum Week 12 Mean (SD) Min-Max
EPDS	6.7 (4.7) 0 - 23	5.6 (4.5) 0 - 22	4.7 (4.3) 0 - 20
STAI	35.9 (9.5) 20 - 70	32.8 (8.9) 20 - 65	31.9 (8.8) 20 - 62
MADRS	9.3 (7.2) 0 - 36	8.5 (6.7) 0 - 30	7.2 (7.0) 0 - 32
HAMA	9.8 (5.4) 0 - 25	8.3 (5.3) 0 - 23	7.6 (5.5) 0 - 25

EPDS: Edinburgh Postnatal Depression Scale

STAI: State portion of Speilberger State-Trait Anxiety Inventory

MADRS: Montgomery-Åsberg Depression Rating Scale

HAMA: Hamilton Anxiety Rating Scale

Table 3

Predicting Mood with Thyroid Measures, Trauma, or Lifetime Depression History Separately

Mood Outcome	Predictor	Standardized Beta (SE)**	Non-Standardized Beta (SE)	P-value
EPDS	FT4 (ng/L)	−0.13 (0.06)	−2.90 (1.23)	0.019
STAI		−0.11 (0.06)	−4.97 (2.55)	0.052
MADRS		−0.17 (0.06)	−5.71 (1.88)	0.003
HAMA		−0.19 (0.06)	−4.84 (1.51)	0.002
Depression Diagnosis		−0.47 (0.22)	−2.20 (1.04)	0.034
EPDS	TBG (mg/L)	−0.08 (0.06)	−0.047 (0.033)	0.155
STAI		−0.12 (0.06)	−0.132 (0.067)	0.051
MADRS		−0.13 (0.06)	−0.110 (0.049)	0.027
HAMA		−0.11 (0.06)	−0.072 (0.041)	0.077
Depression Diagnosis		−0.43 (0.19)	−0.053 (0.023)	0.023
EPDS	Lifetime Trauma	0.27 (0.05)	0.43 (0.09)	<.001
STAI		0.22 (0.06)	0.69 (0.19)	<.001
MADRS		0.32 (0.05)	0.78 (0.13)	<.001
HAMA		0.34 (0.06)	0.64 (0.11)	<.001
Depression Diagnosis		0.43 (0.19)	0.15 (0.07)	0.024
EPDS	Lifetime Major Depression	0.52 (0.11)	2.37 (0.51)	<.001
STAI		0.40 (0.12)	3.72 (1.08)	<.001
MADRS		0.56 (0.11)	3.94 (0.76)	<.001
HAMA		0.69 (0.11)	3.73 (0.60)	<.001
Depression Diagnosis		0.70 (0.39)	0.70 (0.39)	0.075

Regression coefficients and p-values for EPDS, STAI, MADRS, and HAMA outcomes were computed from a repeated measures model measuring the outcome at 3 time points (late pregnancy, 6 weeks, and 12 weeks postpartum). Coefficients and p-values for the depression diagnosis outcome were computed from a univariate logistic regression model for the outcome of major or minor depression during the study period (yes/no). All models include the following predictors: baseline (pregnancy weeks 31-33) thyroid values (either FT4 or TBG), lifetime trauma, or lifetime major depression history, as well as significant covariates (e.g., age, race, sex hormone concentrations, etc.). Estimated regression coefficients for predictors in each model are displayed with their original scale (labeled “Non-standardized”) as well as from models fit where continuous outcomes, predictors, and covariates have been scaled to have mean zero and standard deviation one (labeled “Standardized”). Categorical outcomes, predictors, and covariates (e.g., depression diagnosis, lifetime major depression, race, etc.) were not standardized in any model. The standard deviations used for the standardization are as follows: FT4: 0.21; TBG: 8.12; Lifetime trauma: 2.85; EPDS: 4.57; STAI: 9.20; MADRS: 7.00; HAMA: 5.44.

Table 4

Predicting Mood with Thyroid Measures, Trauma, and Lifetime Depression History Together

		----------Thyroid Predictor----------			----------Trauma Predictor----------			---Lifetime Major Depression Predictor---		
		Standardized	Non-Standardized		Standardized	Non-Standardized		Standardized	Non-Standardized	
Mood Outcome	**Thyroid Predictor**	**Beta (SE)**	**Beta (SE)**	**P-value**	**Beta (SE)**	**Beta (SE)**	**P-value**	**Beta (SE)**	**Beta (SE)**	**P-value**
EPDS	FTA (ng/L)	−0.10 (D.Q5)	−2.22 (1.17)	0.061	0.23 (0.06)	0.37 (0.09)	<.001	0.32 (0.11)	1.48 (0.51)	0.004
STAI		−0.07 (0.06)	−3,18 (2.49)	0.202	0.17(0.06)	0.54 (0.19)	0.005	0.30 (0.12)	2.72 (1.10)	0.014
MADRS		−0.09 (0.05)	−3,10 (1.77)	0.081	0.25 (0.05)	0.61 (0.13)	<.001	0.39 (0.11)	2.72(0.76)	<.001
HAMA		−0.12 (0.05)	−3.21 (1.37)	0.020	0.24 (0.06)	0.46 (0.11)	<.001	0.49 (0.11)	2.65 (0.60)	<.001
Depression Diagnosis		−0.42 (0.23)	−1,97 (1.08)	0.067	0.33(0.20)	0.11 (0.07)	0.101	0.50 (0.41)	0.50 (0.41)	0.228
EPDS	TDG (mg/L)	−0.10 (0.05)	−0.057 (0.030)	0.059	0.24 (0.06)	0.39 (0.09)	<.001	0.34 (0.11)	1.55 (0.51)	0.003
STAI		−0.11 (0.06)	−0.123 (0.064)	0.057	0.18 (0.06)	0.58 (0.19)	0.002	0.29 (0.12)	2.66 (1.10)	0.016
MADRS		−0.10 (0.05)	−0.090 (0.044)	0.043	0.26 (0.05)	0.64 (0.13)	<.001	0.39 (0.11)	2.72 (0.76)	<.001
HAMA		−0.10 (0.05)	−0.067 (0,035)	0.061	0.26 (0.06)	0.50 (0.10)	<.001	0.49 (0.11)	2.69 (0.60)	<.0O1
Depression Diagnosis		−0.56 (0.20)	−0.069 (0.024)	0.005	0.51 (0.21)	0.18(0.07)	0.016	0.65 (0.42)	0.65(0.42)	0.122

Regression coefficients and p-values for EPDS, STAI, MADRS, and HAMA outcomes were computed from a repeated measures model measuring the outcome at 3 time points (late pregnancy, 6 weeks, and 12 weeks postpartum). Coefficients and p-values for the depression diagnosis outcome were computed from a univariate logistic regression model for the outcome of major or minor depression during the study period (yes/no). All models include the following predictors: baseline (pregnancy weeks 31-33) thyroid values (either FT4 or TBG), lifetime trauma, or lifetime major depression history, as well as significant covariates (e.g., age, race, sex hormone concentrations, etc.). Estimated regression coefficients for predictors in each model are displayed with their original scale (labeled “Non-standardized”) as well as from models fit where continuous outcomes, predictors, and covariates have been scaled to have mean zero and standard deviation one (labeled “Standardized”). Categorical outcomes, predictors, and covariates (e.g., depression diagnosis, lifetime major depression, race, etc.) were not standardized in any model. The standard deviations used for the standardization are as follows: FT4: 0.21; TBG: 8.12; Lifetime trauma: 2.85; EPDS: 4.57; STAI: 9.20; MADRS: 7.00; HAMA: 5.44.