Context: While correlations have been demonstrated between postpartum depression and psychosocial and circumstantial risk factors, some evidence exists for a similar relationship between postpartum depression and thyroid measures.

Objective: To search at 4 weeks postpartum for correlations of numerical scores on a postnatal depression screening tool and thyroid measures.

Methods: Subjects took the Edinburgh Postnatal Depression Scale (EPDS) prenatally and at 4 weeks postpartum. Participants were also given blood tests for thyroid-stimulating hormone (TSH), free thyroxine (FT4), thyroid peroxidase, and thyroglobulin at the same testing intervals.

Results: Fifty-one subjects aged 18 years or older were recruited. Subjects with higher serum TSH at 4 weeks postpartum tended to have higher EPDS scores. Similarly, the 7 subjects (13.7%) with positive postnatal thyroid antibody tests were more likely than their counterparts to have higher EPDS scores.

Conclusions: Presence of thyroid autoantibodies or higher TSH levels during the postpartum period may be related to depressive symptoms or dysphoric mood, even when clinical depression is not present. Either or both of these associations may contribute, along with other physiologic and psychosocial risk factors, to postpartum depression. (ClinicalTrials.gov number NCT00565032)
Study protocols and informed consent agreements were reviewed and approved by the OSUCHS Institutional Review Board before study initiation. Patient confidentiality was closely guarded. Once recorded, data were reported in the completed study as mean scores of all participants. Volunteers were paid for their participation.

**Subject Testing**
At the prenatal and 4-week postpartum physician visits, subjects were asked to take the self-administered EPDS with pencil and paper before the blood draw. At both testing intervals, subjects’ blood was drawn, immediately separated in a centrifuge, and frozen until testing.

To enhance subject compliance with study protocols, postpartum data collection was scheduled for the standard 4-week postnatal visit, rather than a later date. This study design was necessary because subjects were OSUCHS patients, a moderately transient population.

Assays to determine plasma concentrations of the various substances were performed at Regional Medical Lab Inc, also in Tulsa. Levels of TSH, FT₄, and antibodies against thyroid peroxidase and thyroglobulin were all reported.

**Instruments**
The 10-item EPDS self-report scale was developed in Scotland in 1987 and is easy for researchers to score. A threshold score of 12 or 13 is used to screen for possible depression. Test sensitivity of the EPDS is reported as 86% with specificity reported at 78%.

The test for TSH is a two-site sandwich immunoassay that uses direct chemiluminescence. With this method, there is a direct relationship between the amount of prolactin in a sample tested and the amount of relative light units detected by the system (ACS:Centaur 10440; Chiron Diagnostics, East Walpole, Mass).

The FT₄ test used is a competitive immunoassay that uses direct chemiluminescence. The hormone to be tested competed with acridinium ester-labeled cortisol (ie, FT₄) for binding to polyclonal rabbit antibody against the hormone of choice. With this method, an inverse relationship exists between the amount of hormone in a sample tested and the amount of relative light units detected by the system (ACS:Centaur 10440; Chiron Diagnostics, East Walpole, Mass). According to manufacturer guidelines, the normal range for FT₄ is 0.65 ng/dL to 1.5 ng/dL. The instrument was carefully calibrated with control samples sent from the manufacturer before each batch of tests was run. According to the test’s manufacturer, the normal range for TSH levels is 0.47 mIU/mL to 6.8 mIU/mL.

All tests were performed in summer 2000 by Regional Medical Lab Inc at St John Medical Center (Tulsa, Okla). The reference ranges and values came on the advice of the manufacturers via their Web sites.

The tests for both thyroglobulin antibody and peroxidase antibody were performed using a Biochem Personal Lab machine (Wampole Laboratories, Princeton, NJ) with enzyme immunoassay kits and reagent. A thyroglobulin antibody result greater than 19 IU/mL serum was considered positive. A peroxidase antibody result greater than 21 IU/mL serum was considered positive.

**Statistical Analysis**
The results were analyzed by simple linear regression so that depression scores could be treated as a continuum rather than a dichotomy (ie, “depressed” vs “not depressed”). Regressions were performed separately for each of the independent variables to determine any individual effects that each might have on EPDS scores.

**Results**
During the study period, a total of 208 women were invited to participate in the study. Of that number, 133 either refused or were disqualified by exclusion criteria, resulting in a participation rate of 36%. Of the remaining 75 participants, only 51 subjects were in compliance with study protocols at their 4-week postpartum check-up—taking the EPDS and undergoing a blood test for TSH, FT₄, thyroid peroxidase, and thyroglobulin.

**Thyroid-Stimulating Hormone**
Only 7 of the 51 subjects had TSH values outside the normal range of 0.47 mIU/mL to 6.8 mIU/mL; 6 of these scores were low. The median TSH value was 1.251 mIU/mL, and the range was 0.11 mIU/mL to 10.12 mIU/mL. The standard deviation was 1.3.

Subjects with higher serum TSH levels at 4 weeks postpartum tended also to have higher EPDS scores (P = .0416) (Figure 1). The correlation coefficient (r) was 0.286. The coefficient of determination, r², was 0.082. In other words, about 8% of the variability of EPDS scores at 4 weeks postpartum is associated with the range of serum TSH values.

**Free Thyroxine₄**
There was no statistically significant correlation between FT₄ values and EPDS scores (P = .6671). The mean for FT₄ was 0.99 ng/dL. The range for FT₄ was 0.094 ng/dL to 1.36 ng/dL. The standard deviation was 0.18.

**Thyroid Antibodies**
Seven of the 51 subjects had positive thyroid antibody tests at 4 weeks postpartum, though these were not necessarily the same 7 participants who had abnormal TSH values. Three subjects had positive results for thyroid antibodies during prenatal screening. The 7 participants with positive antibody tests were more likely than their counterparts to have higher EPDS scores (P = .0428) (Figure 2). The correlation coefficient, r, was 0.285. The coefficient of determination, r², was 0.0811. In
other words, about 8% of the variability of EPDS scores taken at 4 weeks postpartum correlates with the variation in serum thyroid antibodies measured at that time. On average, patients with positive thyroid antibody tests had maximum EPDS scores that were almost 5 points higher than patients who did not have similar laboratory results. Although the mean EPDS score for both groups was still below 12, the thyroid antibody–positive group had greater depressive symptomology.

No statistically significant correlation was found between TSH values and thyroid antibodies, $r = 0.1725 \ (P = .18)$. A power analysis revealed that, with 51 subjects from a population with an $r^2$ of 0.10, a significant effect would be detected approximately 60% of the time. For an $r^2$ of 0.15, a significant effect would be detected more than 80% of the time.10

Comment

Previous studies have reported a relationship between PPD and TSH or FT$_4$ levels. For example, two reports11,12 published more than a decade ago noted that transient postpartum hypothyroidism, as evidenced by low FT$_4$, seemed to be linked to PPD. However, Lazarus13 reported that thyroid function did not relate to recurrence of PPD in a group of 54 women during 6 months of follow-up.

Regarding the present study, Figure 1 might suggest that, for subjects whose EPDS scores are in the normal range, mood correlates somewhat with plasma TSH concentrations. However, for those who scored in the “depressed” range, any correlation does not seem to hold. We believe that small sample size may be, at least in part, responsible for these results. The “non-depressed” group (n = 42) was more than four times as large as the “depressed” group (n = 9) and would have a statistically greater chance of reflecting the average of the general population than their counterparts.

The simple linear regression of Figure 1 revealed two noteworthy items. First, the relationship between EPDS results and TSH had a statistically significant $P$ value—such that these results could only occur by chance one in 20 times. Second, the graphed data do not appear to be linear, nor do they follow an easily identifiable pattern. It is obvious that lower EPDS scores and their corresponding lower TSH values are clustered. Perhaps a larger study would make it clear whether the relationship might actually be linear in nature.

Only 1 subject in this study group had a TSH value above the upper range of normal. However, a correlation between higher TSH levels at 4 weeks postpartum and higher EPDS scores is suggestive of a trend toward mood disruption and thyroid disturbance. Increasing EPDS scores reflect an increasing number of depressive symptoms even if the threshold for a positive depression screen is not reached. Further, depression is a known feature of subclinical hypothyroidism, occurring in perhaps 15% of cases.2 Although the etiology of thyroid disruption is unclear from the present data, association between mood state and thyroid hormone level is supported. However, our data show only associations and cannot support cause-and-effect relationships.

Elevated levels of antithyroid antibodies have been associated with higher TSH values at 4 weeks postpartum. However, the correlation between TSH levels and thyroid antibodies, $r = 0.1725 \ (P = .18)$, is not statistically significant. A power analysis revealed that, with 51 subjects from a population with an $r^2$ of 0.10, a significant effect would be detected approximately 60% of the time. For an $r^2$ of 0.15, a significant effect would be detected more than 80% of the time.10

Figure 1. Simple linear regression of serum thyroid-stimulating hormone (TSH) at 4 weeks postpartum vs concurrent Edinburgh Postnatal Depression Scale (EPDS) score. Thyroid-stimulating hormone is measured in mIU/mL ($N = 51; \ P = .0416; \ \text{slope} = 2.5; \ \text{correlation coefficient}, \ r = .286; \ \text{coefficient of determination}, \ r^2 = .082$).

Figure 2. Results of serum thyroid antibody status (positive or negative) at 4 weeks postpartum vs concurrent Edinburgh Postnatal Depression Scale (EPDS) score ($N = 51; \ n = 44$ in negative antibody group; $n = 7$ in positive antibody group; $P = .0428$). Boxes contain middle 50% of data. Line inside box denotes median; means indicated by (+) inside boxes; data range indicated by lines extending from the boxes.

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associated with PPD. Harris found an excess of depressive symptoms (though not major depression) in women who demonstrated thyroid antibodies in the first 8 months postpartum, even when conventional tests for thyroid dysfunction did not show abnormalities. Results also showed that women with thyroid antibody–positive results had higher mean scores for depression on several scales regardless of whether they became hypothyroid. Harris speculated that cytokines may be released as thyroid antibody concentrations increase after delivery and that these substances have an effect on the brain, causing many of the behaviors associated with PPD.

Our data may further support Harris’ conclusions. In our study, 4 of the 7 subjects with thyroid antibody–positive test results had negative results during prenatal screening. In women who have other physiologic or psychosocial risk factors for PPD, the addition of a thyroid antibody element postnaturally may become a clinically significant contributor to mood disorders.

Custro et al showed that, of 9 patients suffering from major depression, 5 individuals were subclinically hypothyroid. All 5 of these women tested positive for antibodies against thyroid peroxidase, thyroglobulin, or both, revealing a symptomless autoimmune thyroiditis. In contrast, none of the 70 subjects who were euthyroid and diagnosed as either severely depressed (n=4) or having minor depression (n=66) were seropositive for thyroid autoantibodies. These researchers suggested that major depression is accompanied by subclinical autoimmune thyroiditis in a significant proportion of women. Perhaps the possibility of autoimmune disease should be considered whenever women diagnosed with depression display biochemical thyroid dysfunction.

Researchers have found that about 3 in 100 women will have PPD that is related to positive thyroid antibody status and presence of normal blood levels of total and free triiodothyronine and FT4. Possible reasons for these findings include poor methodology and a general malaise due to the thyroiditis that is unrelated to actual thyroid hormone levels. A study by Harris may support the latter hypothesis. In that study, FT4 was administered prophylactically to women in the postpartum period with thyroid antibody–positive test results. These women were found to have depression just as often as their antibody–positive counterparts who did not receive FT4. Harris concluded that depression occurring in thyroid antibody–positive subjects was likely associated with malaise following the thyroid antibody–positive state rather than thyroid dysfunction. Another hypothesis for the etiology of depression mediated by thyroid antibodies maintains that activated leukocytes produce cytokines that cross the blood–brain barrier, attach to specific receptors, and mediate neurotransmission.

Limitations of the present study include the small sample size and limited data sampling—taking place prenatally and then at 4 weeks postpartum only, a relatively early point in the postpartum period. Further investigation with a larger study group and data collection at multiple postpartum intervals is warranted.

No data is available beyond the 4-week postpartum visit or regarding whether the volunteers who screened positive for PPD continued in that state, recovered, or had any other outcome. Out of ethical necessity, the women with positive EPDS results were immediately referred to a physician for counseling, antidepressants, or other treatment. Therefore, we could not determine whether their conditions changed as a result of some natural physiologic process or because of treatment. Later data would not have been comparable to early data, which reflected the natural coincidence of EPDS scores, TSH values, FT4 values, and thyroid antibody status.

Conclusions

Women with positive test results for serum thyroid antibodies tended to have higher scores on the EPDS at 4 weeks postpartum than their counterparts who were negative for serum thyroid antibodies, even when PPD was not present. In addition, women with higher, albeit still normal, TSH levels tended to have higher EPDS scores. Either or both of these associations may contribute, along with other physiologic and psychosocial risk factors, to PPD in some women. However, data are insufficient to conclude that overt PPD is associated with subclinical thyroid dysfunction. Because PPD can have consequences for neonates—such as alienation, indifference, detachment with lack of love, and resentment—awareness and treatment of its various etiologies, including thyroid dysfunction, are worthwhile endeavors for future research.

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References


5. Oretti RG, Harris B, Lazarus JH, Parkes AB, Crownshaw T. Is there an asso-


