ORIGINAL ARTICLE

Risk of Postpartum Depressive Symptoms With Elevated Corticotropin-Releasing Hormone in Human Pregnancy

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Context: Postpartum depression (PPD) is common and has serious implications for the mother and her newborn infant. A possible link between placental corticotropin-releasing hormone (pCRH) and PPD incidence has been hypothesized, but empirical evidence is lacking.

Objective: To determine whether accelerated increases in pCRH throughout pregnancy are associated with PPD symptoms.

Design: Pregnant women were recruited into this longitudinal cohort study. Blood samples were obtained at 15, 19, 25, 31, and 37 weeks' gestational age (GA) for assessment of pCRH, cortisol, and adrenocorticotropic hormone (ACTH). Depressive symptoms were assessed with a standardized questionnaire at the last 4 pregnancy visits and post partum.

Setting: Subjects were recruited from 2 southern California medical centers, and visits were conducted in research laboratories.

Participants: One hundred adult women with a singleton pregnancy.

Main Outcome Measure: Symptoms of PPD were assessed at a mean (SD) of 8.7 (2.94) weeks after delivery with the Edinburgh Postnatal Depression Scale.

Results: Sixteen women developed PPD symptoms. At 25 weeks' GA, pCRH was a strong predictor of PPD symptoms (R^2=0.21; β=0.46 [$P<.001$]), an effect that remained significant after controlling for prenatal depressive symptoms. No significant associations were found for cortisol and ACTH. Receiver operating characteristic curve analyses revealed that pCRH at 25 weeks' GA is a possible diagnostic tool (area under the curve, 0.78 [$P=.001$]). Sensitivity (0.75) and specificity (0.74) at the ideal cutoff point (pCRH, 56.86 pg/mL) were moderate. Growth curve analyses indicated that the trajectories of pCRH in women with PPD symptoms are significantly accelerated from 23 to 26 weeks' GA.

Conclusions: At a critical period in midpregnancy, pCRH is a sensitive and specific early diagnostic test for PPD symptoms. If replicated, these results have implications for the identification and treatment of pregnant women at risk for PPD.

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POSTPARTUM MOOD DISORders range from the mild and common postpartum "blues" to much rarer incidences of severe postpartum psychosis.[1] The most commonly studied postpartum mood disorder is postpartum depression (PPD), which is similar to major depressive disorder but has its onset within the first 4 weeks (*International Statistical Classification of Diseases, 10th Revision*)[2] to 6 weeks (*DSM-IV*)[3] after delivery. Postpartum depression not only influences the well-being of the new mother but also has adverse effects on the cognitive and behavioral development of her infant.[4] Reports of PPD prevalence vary widely; a recent meta-analysis estimates it at 19.2% (7.1% for major PPD alone) within the first 3 months post partum.[5]

The high incidence and severe consequences of PPD make the identification of women at risk an important research goal. The most consistently identified risk factors include previous PPD; a history of depression, anxiety, stress, and depression during pregnancy; stressful life events; lack of social support; and low self-esteem[6,7]; however, these risk factors explain only a portion of the variance in the incidence of PPD. Endocrine risk factors for PPD have been identified as well, including changes in reproductive hormones during pregnancy, a history of premenstrual syndrome, and a history of oral contraceptive–induced mood changes.[8-10]

Little research interest has been directed toward the role of corticotropin-releasing hormone (CRH), a 41–amino acid neuropeptide central in the regula-

tion of the hypothalamic-pituitary-adrenal (HPA) axis,[11] as a potential predictor of PPD.[12] This is surprising because several lines of evidence suggest the possibility that increased CRH may be a risk factor for PPD. First, CRH plays an important role in the etiology of depression in the nonpregnant state.[13] For example, depressed patients are more likely to have an increased number of hypothalamic CRH neurons, and these neurons tend to be hyperactive.[14,15] This evidence has led to the development of a CRH hypothesis of depression, suggesting that the hyperactivity of CRH neurons and the HPA axis may trigger depressive symptoms.[16]

Second, pregnancy is characterized by marked changes in maternal HPA axis regulation. In the central nervous system, CRH is produced in the paraventricular nucleus of the hypothalamus and released into the median eminence, a local portal system connecting the hypothalamus with the pituitary, where CRH stimulates the release of adrenocorticotropic hormone (ACTH). Binding by ACTH causes the adrenal cortex to release the glucocorticoid cortisol.[17] During pregnancy, CRH is also produced by the placenta and, unlike CRH of hypothalamic origin, is detectable in maternal peripheral blood.[18,19] Placental (pCRH) and hypothalamic CRH are similar with regard to their structure, immunoreactivity, and bioactivity.[20,21] However, in contrast to the role of cortisol in the negative feedback regulation of the HPA axis, cortisol stimulates CRH production in the placenta. As a result, levels of pCRH in maternal plasma increase exponentially throughout pregnancy[18,22] and reach levels similar to those of hypothalamic CRH in the median eminence under conditions of acute stress.[23] The sudden disappearance of the placenta after delivery results in a sharp drop of pCRH levels. The postpartum period is therefore characterized by pCRH withdrawal, resulting in transient suppression of hypothalamic CRH release and HPA axis dysregulation. It has been suggested that this may explain the occurrence of postpartum depressive disorders.[24-29]

Finally, there are marked interindividual differences in the trajectories of pCRH throughout pregnancy.[22] It has been demonstrated that accelerated trajectories of pCRH are associated with race/ethnicity[30] and preterm birth[22,31-34]; are implicated in pregnancy complications such as preeclampsia,[35-37] fetal growth retardation,[38] and diminished umbilical artery blood flow[39]; and have consequences for the developing infant, including lower newborn physical and neuromuscular maturity[40] and increased irritability.[41] Because of the established association between CRH and depression, accelerated increases in pCRH throughout pregnancy may also serve as a potential early marker to identify women at high risk for PPD. It is the goal of the present study to address this possibility.

METHODS

PARTICIPANTS

One hundred pregnant women with a singleton, intrauterine pregnancy were selected from a larger sample[30,40-42] that was recruited in a longitudinal study at Cedars-Sinai Medical Center and the University of California, Irvine, Medical Center. In this study, subjects with conditions known to affect HPA axis function, subjects with alcohol or other drug abuse within 6 months before the index pregnancy, and non–English-speaking subjects were excluded from participation.

The present sample consisted of the 100 women with complete data for pCRH and depressive symptoms. Mean (SD) age at delivery was 31.2 (5.3) years. The ethnic composition was 54% non-Hispanic white, 22% Hispanic white, 12% Asian, 7% African American, and 5% multiethnic or other. Most women were married (79%), had graduated from high school (97%), and were college graduates (52%). The annual household income varied from $5000 to more than $100 000, and median income was in the range of $80 000 to $90 000. All pregnancies resulted in live births, and 53 girls and 47 boys were delivered. Deliveries were 72% vaginal and 28% cesarean section. Mean (SD) infant birth weight was 3514 (469) g (range, 2340-4450 g), and gestational length at term was 39.4 (1.3) weeks (range, 36.57-42.0 weeks). Because completion of the full study was an inclusion criterion, and because the last study visit occurred around 37 weeks' gestational age (GA), most women had full-term infants (97% had a gestational length >37 weeks), and no woman delivered before 36.6 weeks' GA. Most women had no previous live-born children (61%).

OVERALL PROCEDURE

Blood samples were obtained at a mean (SD) of 15.3 (0.92), 19.2 (0.72), 25.0 (0.94), 31.0 (0.76), and 36.7 (0.70) weeks' GA for assessment of pCRH, cortisol, and ACTH. Depressive symptoms were assessed at the last 4 time points during pregnancy and again at the postpartum visit (mean [SD], 8.7 [2.9] weeks). Written informed consent was obtained from all women before participation. This protocol was approved by the institutional review boards of the participating institutions.

HORMONE MEASURES

A 25-mL blood sample was obtained by antecubital venipuncture. Samples were drawn into chilled EDTA-treated test tubes (Vacutainers; Becton Dickinson and Company, Sumter, South Carolina) and spun for 15 minutes at 2000*g*. The plasma was then decanted into polypropylene tubes containing 500-kallikrein inhibitor units/mL of aprotinin (Sigma-Aldrich Corp, St Louis, Missouri) and stored at −70°C until assayed.

The concentration of total CRH was determined by means of radioimmunoassay using antiserum directed at human CRH (Bachem Peninsula Laboratories, San Carlos, California). Plasma samples (1-2 mL) were extracted with 3 volumes of ice-cold methanol, mixed, allowed to stand for 10 minutes at 4°C, and then centrifuged (20 minutes, 1700*g*, 4°C).[43] The pellets were washed with 0.5 mL of methanol, and the combined supernatants dried in a concentrator (SpeedVac; Savant Instruments, Holbrook, New York). Reconstituted samples were incubated (100 µL/assay tube) with antiserum (100 µL/assay tube) for 48 hours at 4°C followed by an overnight incubation with iodine 125 –labeled CRH at 4°C. Labeled and unlabeled CRH samples were collected by means of immunoprecipitation, and the aspirated pellets were counted using a gamma counter (Isoflex; ICN Biomedical, Costa Mesa, California). Crossreactivity was less than 0.01 for ovine CRH, 36% for bovine CRH, and nondetectable for human ACTH. Intra-assay and interassay coefficients of variance were 5% and 15%, respectively. Using this technique, our laboratory has reliably detected pCRH at as early as 15 weeks' GA.[30,40-42]

Plasma levels of ACTH were measured by a solid-phase 2-site immunoradiometric assay using human ACTH antibodies with nonsignificant cross-reactivity with β-endorphin and ACTH fragments, and with reported detection limits of 1.0 pg/mL (Nichols Institute Diagnostics, San Juan Capistrano, Califor-

Table 1. Sample Characteristics for Women With and Without PPD Symptoms[a]

Characteristic	PPD (n=16)	No PPD (n=84)
Maternal age at delivery, mean (SD), y[b]	34.2 (4.2)	30.6 (5.3)
Race/ethnicity		
Non-Hispanic white	9 (56)	45 (54)
Hispanic white	3 (19)	19 (23)
Asian	4 (25)	8 (10)
African American	0	7 (8)
Multiethnic/other	0	5 (6)
Married	11 (69)	68 (81)
Education		
High school graduates	15 (94)	83 (99)
College graduates	10 (63)	42 (50)
Annual household income, $		
Range	5000 to >100 000	10 000 to >100 000
Median range	80 000-90 000	70 000-80 000
Female infant sex	8 (50)	45 (54)
Cesarean section	5 (31)	23 (27)
Birth weight, mean (SD), g	3532 (433)	3510 (478)
Gestational age, mean (SD), wk	39.7 (1.5)	39.4 (1.2)
Nulliparous	10 (63)	51 (61)

Abbreviation: PPD, postpartum depression.

[a] Unless otherwise indicated, data are expressed as the number (percentage) of women.

[b] Women with PPD symptoms were significantly older than women without PPD symptoms (t_{98}=2.58 [P=.01]). All other comparisons were nonsignificant.

nia) (to convert ACTH to picomoles per liter, multiply by 0.22). Briefly, 200-µL samples combined with 100 µL of ACTH-labeled antibody and a coated bead were incubated at room temperature for a mean (SD) of 20 (1) hours. The bound radiolabeled antibody complex was quantified using the gamma counter. Intra-assay and interassay coefficients of variation were 4.4% and 10.8%, respectively.

Plasma cortisol levels were determined using a competitive antibody-coated tube radioimmunoassay with reported sensitivity of 0.22 µg/dL (American Laboratory Products Company, Windham, New Hampshire) (to convert cortisol to nanomoles per liter, multiply by 27.588). Plasma samples (25 µL) were incubated with 500 µL of ^{125}I-labeled cortisol in antibody-coated tubes for 45 minutes in a 37°C water bath. The aspirated radiolabeled antibody-bound labeled tubes were counted on a gamma counter. Cross-reactivities of the cortisol assay were less than 5% with 11-deoxycortisol, cortisone, and prednisone, and less than 1% with other steroids. Intra-assay and interassay coefficients of variation were 7% and 11%, respectively.

Concentrations of CRH, ACTH, and cortisol were interpolated from standard curves computed by a 4-parameter logistics program.[44]

ASSESSMENT OF DEPRESSIVE SYMPTOMS

Depressive symptoms were assessed 4 times during pregnancy with a 9-item version of the Center for Epidemiological Studies–Depression Scale (CES-D).[45] On a 4-point scale, participants indicated how often they experienced a symptom during the past week. Because validation analyses show higher associations with the Structured Interview for *DSM-III-R* when items are rescored into a bivariate score,[45] each item was scored 0 if option 0 or 1 was endorsed, and was scored 1 if option 2 or 3 was endorsed. Bivariate scores ranged between 0 and 9, with a suggested cutoff score of 4 or more. This scale has good internal consistency (Kuder-Richardson formula 20, 0.87), and the scores correlate highly with the original scale (r=0.97).

At the postpartum visit, participants completed the 10-item Edinburgh Postnatal Depression Scale (EPDS),[46] a scale specifically developed to assess postpartum depressive symptoms. Participants indicated how often they experienced a symptom in the past week on a 4-point scale. Total scores ranged from 0 to 30. A cutoff score of 10 or more has been suggested by the authors of the EPDS for studies including minor depression[46] and has been confirmed in other studies.[47] The scale has good reliability (split-half, 0.88; standardized α=.87).[46]

STATISTICAL ANALYSIS

All pCRH, cortisol, and ACTH levels were log transformed to reduce skewness. Pearson product moment correlations were performed to test for associations between relevant variables. The time of day of the blood draw was covaried when appropriate and in no case changed the significance of the results.

Variables that were significantly correlated with PPD symptoms were included in a stepwise linear regression model, and the model fit (adjusted R^2), the change in R^2, and the regression coefficient β are reported. Emerging significant predictors were included in a hierarchical linear regression model to assess the unique and separate contributions of each variable. A series of ancillary analyses (2-tailed, independent samples t tests and χ^2 tests) revealed no evidence that sociodemographic (ethnicity, marital status, education, and household income) or pregnancy-related variables (birth weight, length of gestation, infant sex, mode of delivery, and parity) were significantly associated with PPD symptoms (for all associations, $\chi^2<9.33$ [$P>.38$] and $t<1.00$ [$P>.32$]), with the exception of maternal age (t_{98}=2.58 [P=.01]). Controlling for maternal age, however, did not change the significance of the results. At the postpartum visit, no association was found between the number of weeks since delivery and PPD symptoms (t=1.33 [P=.19]).

The sample was then divided into women with and without PPD symptoms (**Table 1** lists the sample characteristics). Receiver operating characteristic (ROC) curves were computed to assess sensitivity and specificity of relevant variables as potential diagnostic markers for PPD symptoms. For this analysis, non–log-transformed pCRH values were used to provide practical guidelines for actual pCRH cutoff scores. The areas under the ROC curve (AUCs) were computed to compare the usefulness of each diagnostic test. The AUC values can range from 0.5 to 1.0, with 1.0 indicating a perfect test. The Youden index (sensitivity + [specificity – 1]) was computed to obtain an optimal cutoff score. The Youden index can range from –1 to 1, with 1 indicating a perfect test.[48,49] Positive and negative predictive values (PPV and NPV, respectively) were computed to express the probability that PPD is present when the test is positive (PPV) and absent when the test is negative (NPV) at the optimal cutoff.

To estimate when differences in pCRH emerge as a predictor of PPD symptoms, multilevel modeling techniques (HLM 6)[50] were used. First, an unconditional means model was computed to assess how much variance in pCRH can be attributed to between-subject (99.6%) and within-subject (0.4%) variation. Two unconditional growth models were then computed to assess the linear (coefficient, 18.48; SE, 1.07 [$P<.001$]) and quadratic (0.85; 0.13 [$P<.001$]) effects of time (level 1 predictor) on pCRH, which explained 68.9% and 80.4% of the variance, respectively. A comparison of the deviance scores revealed that the quadratic model fit the data significantly better than the linear model (χ^2_3=137.04 [$P<.001$]). Postpartum depressive symptoms (coded 0 for no and 1 for yes) were then included as a level 2 predictor into a series

Table 2. Correlation Between pCRH, ACTH, and Cortisol Levels and CES-D Scores at Each GA With PPD Symptoms

	Correlation With PPD Symptoms by GA, wk				
	15	19	25	31	37
pCRH	0.08	0.14	0.46[a]	0.22[b]	–0.01
ACTH	0.06	0.11	0.21[b]	0.14	0.17
Cortisol	–0.13	0.02	0.03	–0.06	0.04
CES-D[c]		0.31[d]	0.33[d]	0.26[b]	0.25[b]

Abbreviations: ACTH, adrenocorticotropic hormone; CES-D, Center for Epidemiological Studies–Depression; GA, gestational age; pCRH, placental corticotropin-releasing hormone; PPD, postpartum depression.
[a] $P<.001$.
[b] $P<.05$.
[c] CES-D scores were not obtained at 15 weeks' GA.
[d] $P<.01$.

of quadratic models that tested differences in the intercept and the instantaneous rate of change at each GA within the range of actual pCRH assessments available (12-39 weeks' GA). The error term was allowed to vary randomly in each equation.

RESULTS

DESCRIPTIVES

Consistent with earlier reports, pCRH increased significantly throughout pregnancy ($F_{3.4,332.5}=586.83$ [$P<.001$]; $\eta^2=0.86$). Likewise, significant increases in cortisol ($F_{3.8,370.3}=160.92$ [$P<.001$]; $\eta^2=0.62$) and ACTH ($F_{3.5,351.4}=186.63$ [$P<.001$]; $\eta^2=0.65$) were observed. Depressive symptoms did not change throughout pregnancy ($F_{2.8,276.5}=1.30$ [$P=.28$]).

PREDICTORS OF PPD SYMPTOMS

At no time during pregnancy were any of the endocrine measures significantly associated with concurrent depressive symptoms (pCRH, $r=0.02$ to $r=0.15$ [$P>.14$ for all comparisons]; ACTH, $r=-0.01$ to $r=-0.16$ [$P>.12$ for all comparisons]; and cortisol, $r=-0.002$ to $r=-0.06$ [$P>.53$ for all comparisons]). However, when pCRH, ACTH, cortisol, and CES-D scores at each time point during pregnancy were correlated with PPD symptoms (**Table 2**), significant correlations emerged for pCRH at 25 and 31 weeks' GA, for ACTH at 25 weeks' GA, and for CES-D scores at 19, 25, 31, and 37 weeks' GA. The 2 strongest associations (pCRH and CES-D scores at 25 weeks' GA) are depicted in **Figure 1**. These correlational analyses suggest no significant association between HPA axis hormones and depressive symptoms when assessed concurrently and provide evidence that HPA axis hormones (in midpregnancy) and depressive symptoms (throughout pregnancy) are significant predictors of PPD symptoms.

To assess which variables are the strongest predictors of PPD symptoms, all variables that were significantly correlated with PPD symptoms (pCRH at 25 and 31 weeks' GA, ACTH at 25 weeks' GA, and CES-D scores at 19, 25, 31, and 37 weeks' GA) were included in a stepwise linear regression. Elevated pCRH at 25 weeks' GA

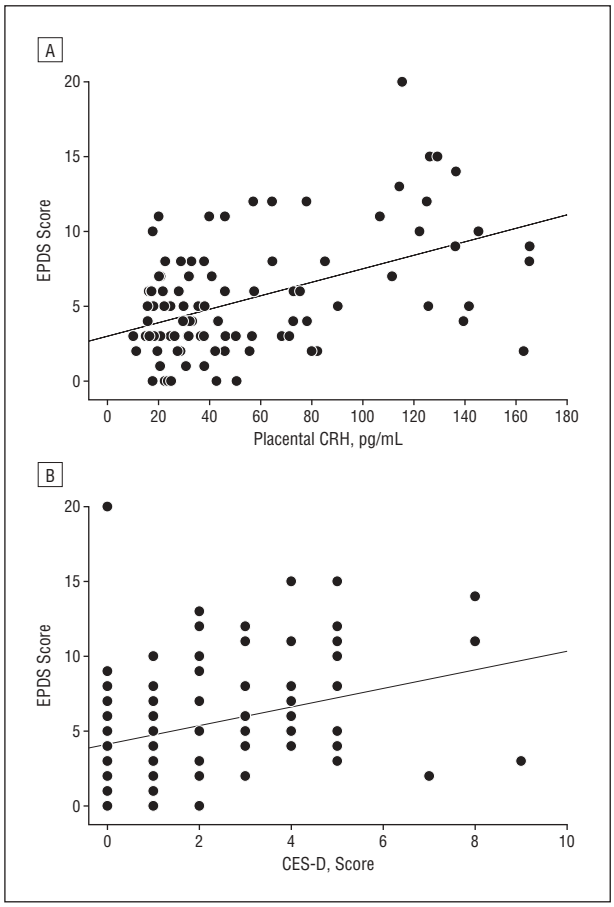

Figure 1. Relation of placental corticotropin-releasing hormone (CRH) (A) and Center for Epidemiological Studies–Depression (CES-D) scores (B) at 25 weeks' gestational age to scores on the Edinburgh Postnatal Depression Scale (EPDS).

emerged as the strongest predictor for PPD symptoms (step 1: $R^2=0.21$; $\beta=0.46$ [$P<.001$]). The prediction of PPD symptoms was improved by including CES-D scores at 25 weeks' GA into the model, accounting for 7% additional variance (step 2: $\beta_{CRH}=0.42$; $\beta_{CES\text{-}D}=0.26$ [$P<.001$]), whereas the influence of all other variables was not statistically significant. Because pCRH at 25 weeks' GA emerged as the best predictor, a hierarchical linear regression was performed to test the unique predictive value of pCRH on PPD symptoms after controlling for CES-D scores at this time point. After CES-D scores were entered into the model in step 1, pCRH was still a significant and independent predictor of PPD symptoms (step 2: R^2 change $=0.17$ [$P<.001$]). This further indicates that pCRH and CES-D scores explain different portions of the variance in the risk of developing PPD symptoms.

pCRH LEVELS AND CES-D SCORES AS DIAGNOSTIC TESTS FOR PPD SYMPTOMS

To test whether pCRH and CES-D scores at 25 weeks' GA may be useful diagnostic tests for PPD symptoms, the sample was divided into women with (n=16) and without (n=84) PPD symptoms. An ROC curve for pCRH was computed, and the AUC was 0.78 (95% confidence interval [CI], 0.65-0.91 [$P=.001$]), suggesting that at this

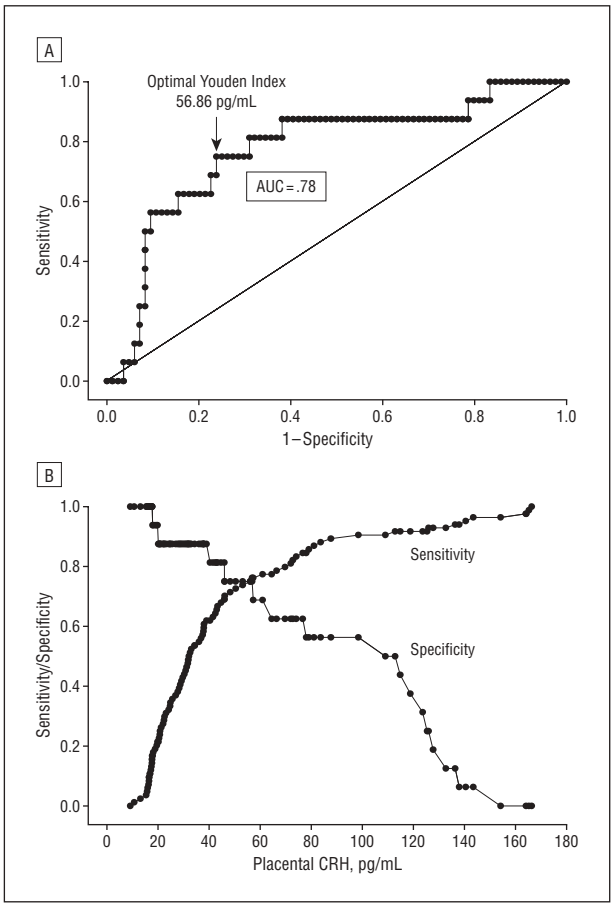

Figure 2. Receiver operating characteristic (ROC) curve (A) and sensitivity and specificity at each possible cutoff point (B) for placental corticotropin-releasing hormone (CRH) at 25 weeks' gestation. The Youden index is calculated as sensitivity + (specificity – 1). Sensitivity indicates the probability that a case is correctly identified (true positive), and 1 – specificity is the probability that a nonsymptomatic subject is falsely identified as a case (false positive). AUC indicates the area under the ROC curve.

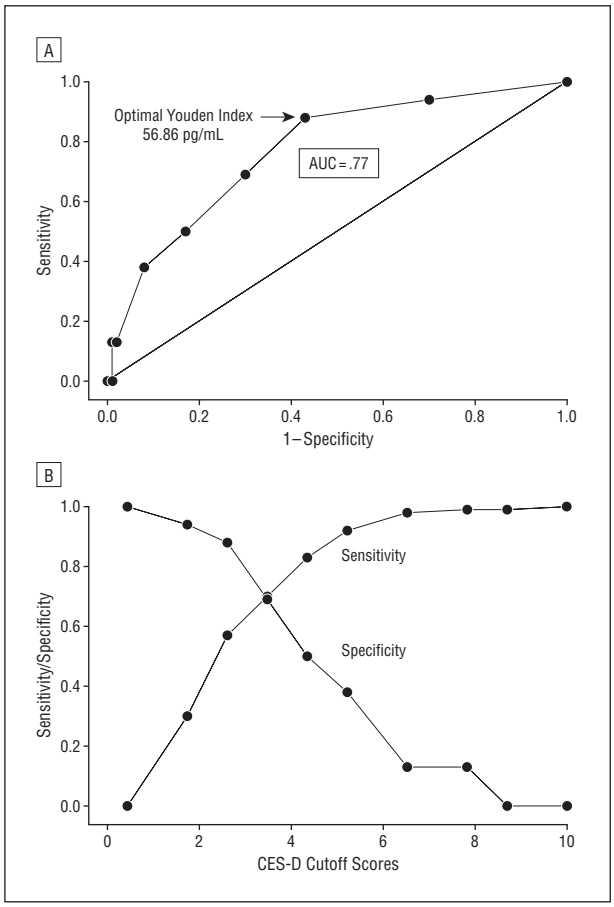

Figure 3. Receiver operating characteristic (ROC) curve (A) and sensitivity and specificity at each possible cutoff point (B) for Center for Epidemiological Studies–Depression (CES-D) scores at 25 weeks' gestation. The Youden index and sensitivity and specificity are defined in the legend to Figure 2. AUC indicates the area under the ROC curve.

time point pCRH is a moderate predictor of PPD (**Figure 2**A). The AUCs were lower at all other time points (15 weeks, 0.53 [$P = .74$]; 19 weeks, 0.62 [$P = .14$]; 31 weeks, 0.66 [$P = .04$]; 37 weeks, 0.61 [$P = .17$]). The optimal cutoff score for pCRH at 25 weeks' GA (Youden index, 0.51) was 56.86 pg/mL. At this cutoff, 75.0% of cases would have been correctly identified (sensitivity) (95% CI, 47.6%-92.6%), whereas in 23.8% of euthymic women PPD symptoms would have been falsely predicted (1 – specificity) (95% CI, 15.2%-34.4%). The PPV was 37.5% (95% CI, 21.1%-56.3%) and the NPV was 94.1% (85.6%-98.3%). Sensitivity and specificity for all possible cutoff scores are shown in Figure 2B.

The ROC analyses for CES-D scores at 25 weeks' GA showed that this measure was a similarly strong predictor of PPD symptoms (AUC = 0.77 [$P = .001$]; 95% CI, 0.65-0.89) (**Figure 3**A), confirming previous research that identified depression during pregnancy as an important predictor. In contrast to the ROC analyses for pCRH levels, the AUCs for depressive symptoms were significant for all other time points (19 weeks, 0.80 [$P < .001$]; 31 weeks, 0.71 [$P = .009$]; 37 weeks, 0.69 [$P = .02$]), suggesting that the predictive value of depressive symptoms is not specific to midpregnancy. At 25 weeks' GA, the optimal CES-D cutoff score (Youden index, 0.45) was 1.5. With this cutoff (ie, an actual score of ≥2 because CES-D scores have no decimals), 87.5% (95% CI, 61.6%-98.1%) of women with PPD symptoms would have been correctly identified; however, 42.9% (95% CI, 32.1%-54.1%) of women without future PPD symptoms would have been misclassified. The PPV was 28.0% (95% CI, 16.2%-42.5%) and the NPV was 96.0% (95% CI, 86.3%-99.4%). Sensitivity and specificity for all possible cutoff scores are shown in Figure 3B. At the ideal cutoff points, the CES-D is the more sensitive diagnostic test (CES-D score vs pCRH, 88% vs 75%), whereas pCRH is more specific (pCRH vs CES-D score, 76% vs 57%) for the detection of PPD symptoms.

TIME-SENSITIVE PERIODS FOR THE PREDICTION OF PPD SYMPTOMS

The analyses in the previous section suggest that the predictive value of pCRH for PPD symptoms may be limited to midpregnancy. With hierarchical linear modeling analyses, it is possible to model increases in pCRH throughout pregnancy and to estimate (1) the time range during which the instantaneous rate of change in pCRH predicts PPD symptoms and (2) the earliest time during

gestation that differences in pCRH predict PPD symptoms. The growth curve analysis suggests that the *instantaneous rate of change in pCRH* in women with PPD symptoms is significantly accelerated from 23 to 26 weeks' GA (coefficients, 4.62-5.86; SE, 2.31-2.86 [$P < .05$ for all comparisons]), with a nonsignificant trend for weeks 22, 27, and 28 ($P < .10$ for all comparisons), compared with women without PPD symptoms (**Figure 4**). No differences in the instantaneous rate of change could be detected before 22 or after 28 weeks' GA. Significant differences in the *levels of pCRH* emerge at 18 weeks' GA (coefficient, 4.67; SE, 1.84 [$P = .01$]) and increase throughout pregnancy, with the greatest differences at 39 weeks' GA (coefficient, 38.79; SE, 4.43 [$P < .001$]). These data suggest that it is the rate of change in pCRH at about 25 weeks' GA, the time when differences in pCRH start to emerge, that makes some women more vulnerable to the development of PPD symptoms, and that pCRH in these women then remains at an accelerated trajectory until delivery.

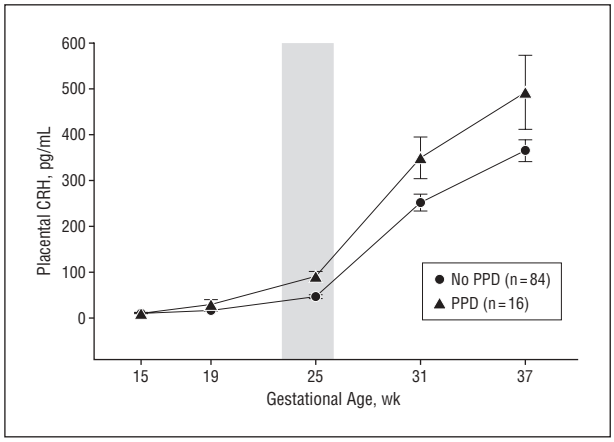

Figure 4. Placental corticotropin-releasing hormone (CRH) across gestational ages in women with and without later postpartum depressive (PPD) symptoms. The gray shaded area indicates the gestational ages during which the instantaneous rate of change in placental CRH significantly predicts PPD symptoms (23-26 weeks' gestational age).

COMMENT

These data are, to our knowledge, the first to suggest a sensitive period in midpregnancy during which pCRH, as measured in maternal plasma, is a moderate and independent predictor of PPD symptoms. We propose that pCRH during this period may serve as a sensitive and specific early diagnostic test to identify women at high risk for developing PPD symptoms. Our data also suggest that the predictive power of pCRH during this period can be further increased by assessing midpregnancy depressive symptoms.

Our data indicate that pCRH is a possible diagnostic tool to identify women at risk for the development of PPD symptoms. This is plausible from a neuroendocrine point of view. The postpartum period is characterized by a transient blunting of hypothalamic CRH secretion, which has been implicated in the pathophysiologic mechanisms of PPD.[25,28] Consistent with this view, it has been shown that women who develop PPD show a more pronounced and longer-lasting suppression of ACTH responses to stimulation with exogenous (ovine) CRH within the first 12 weeks post partum, compared with women who remain euthymic.[26] Our data now provide evidence that the HPA-placental system is already dysregulated during pregnancy among women at risk for PPD symptoms, such that they show accelerated pCRH increases. This is clinically relevant because the assessment of pCRH in maternal blood may provide a method to identify women at risk for PPD symptoms, months before symptoms occur.

Placental CRH in this study was a moderately sensitive and specific marker for PPD symptoms that allows for the correct identification of 75% of women with future PPD symptoms, and at the same time was characterized by a low misclassification rate (24%). The strength of pCRH as a diagnostic test for an early detection of PPD symptoms is indicated by an AUC of 0.78 at 25 weeks' GA. This association is high given that (1) a single endocrine marker was used to predict PPD symptoms and (2) the AUC for depressive symptoms, which are among the strongest and most consistently identified predictors of PPD in the previous literature,[6,7] is almost identical (0.77).

Our data also show that elevated pCRH but not cortisol or ACTH is a significant predictor of PPD symptoms (except for a correlation between ACTH at 25 weeks' GA and PPD symptoms that did not remain significant in the regression analyses). Few studies have investigated the link between cortisol or ACTH during pregnancy and PPD symptoms. Results are mixed, but the clearest evidence for an existing association comes from studies that have assessed the stimulated activity of these hormones.[26,51-53] In our study, however, baseline measures of cortisol and ACTH were used, which may explain the lack of association we found.

Remarkably, pCRH is an independent predictor of PPD symptoms. Placental CRH at 25 weeks' GA has unique and significant predictive value for PPD symptoms, even after controlling for concurrent depressive symptoms. It indicates that assessing pCRH allows the identification of women at risk for developing PPD symptoms who would not be identified on the basis of self-reports of depressive symptoms during pregnancy. This is plausible because hormone measures are independent of a woman's willingness to disclose feelings of depression. Thus, the combined assessment of both markers may be an ideal strategy for identifying women at risk for the development of PPD symptoms.

Depressive symptoms at each time point during gestation are associated with PPD symptoms; however, the predictive value of pCRH for PPD symptoms is time sensitive and is maximized during midpregnancy (23-26 weeks' GA). The emergence of pCRH as a predictor of PPD symptoms around this time roughly coincides with a marked surge in pCRH.[22,42] Detrimental influences at the time of this initial surge may slightly accelerate the exponential trajectory of pCRH, resulting in marked differences in pCRH toward the end of gestation. We do not know which factors may precipitate the surge in pCRH, but some evidence suggests an association between elevated cortisol early in pregnancy and increased pCRH late in pregnancy.[42]

To our knowledge, only one other study has addressed the link between pCRH and PPD symptoms, and that study suggests a lack of association.[12] In that study, pCRH was assessed once within a wide range of GAs (24.6-37.4 weeks). Major changes occur in pCRH levels across pregnancy, and pCRH is characterized by significant individual differences.[22] It is possible that we found an effect because we were able to take advantage of a longitudinal study design. In addition, PPD symptoms in our study were assessed nearer to parturition, at about 9 weeks after delivery, compared with 6 months post partum. These differences in timing may also explain, at least in part, our different results.

Although pCRH in our sample emerged as a strong predictor of PPD symptoms, at no time point was it associated with concurrent depressive symptoms. Two other studies have investigated this association: one suggested a positive correlation[12] and the other suggested a negative correlation[54] between pCRH and concurrent depressive symptoms. These conflicting results could be explained by differences in maternal age (in one of the studies, teenage pregnancies were studied[54]), GA at assessment, GA at delivery, and measures of depressive symptoms across studies.

There is clear evidence that pCRH predicts the length of gestation.[22,31-34] It is a strength of this study that our sample consists of women with full-term deliveries (except for 3 women who delivered between 36.5 and 37.0 weeks' GA), and that GAs at delivery were almost identical in women with and without PPD symptoms. Because pCRH predicts the length of gestation, and because we herein show that pCRH predicts PPD symptoms in a sample of women who delivered at full term, future research should investigate the link between pCRH and PPD symptoms in a sample including preterm deliveries.

There are 2 notable limitations to this study. First, our assessment of PPD symptoms relies on a self-report questionnaire and not on a clinical diagnosis. However, validation studies of the EPDS with the same cutoff score used in our report document a high sensitivity (*DSM-III* criteria, 100%[55] and Research Diagnostic Criteria, 89%[56]) and specificity (*DSM-III* and Research Diagnostic Criteria, 82%[55,56]) of this measure. Because of the quality of this measure, we are fairly confident that our results reflect clinically significant symptoms of depression. We acknowledge, however, the importance of replicating our findings using further diagnostic instruments. Second, although we controlled for depressive symptoms in the index pregnancy, we did not have information about a lifetime history of depression. Although it is reasonable to assume that the effects of current depressive symptoms would be much stronger than any additional variance explained by a history of depression, the general importance of this variable as a predictor of PPD is evident.[6,7] Future research, ideally prospective in nature, is needed to explain the importance of this variable.

Our study has important clinical and theoretical implications. If our results are replicable, it may be considered useful to implement a pCRH PPD screen into standard prenatal care. Because blood draws to screen for gestational diabetes are typically performed at 24 to 28 weeks' GA,[57] a potential PPD screen could be completed at the same time. In addition, a better understanding of the role of pCRH in the pathophysiologic mechanism leading to PPD may contribute to the development of preventions targeted at this rather common disorder.

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