Evaluation of the Association Between Placental Corticotrophin-Releasing Hormone and Postpartum Depressive Symptoms

Laura M. Glynn, PhD, and Curt A. Sandman, PhD

Objective: Postpartum depression (PPD) represents a significant threat to maternal-child health. Although PPD is common, with an estimated prevalence of 10% to 15%, critical questions concerning its etiology remain unanswered. Existing studies seem to provide conflicting evidence regarding the relation between placental corticotrophin-releasing hormone (pCRH) and the development of PPD. The purpose of the present investigation was to determine whether maternal prepartum hypothalamic-pituitary-adrenal and placental dysregulation, in particular elevated midgestational pCRH, represent markers of risk for the development of PPD symptoms. **Methods:** One hundred seventy adult women with singleton, term pregnancies were recruited during the first trimester and participated in study visits at 15, 19, 25, 31, and 36+ weeks' gestation and at 3 and 6 months postpartum. At each prenatal visit, blood samples were obtained and assayed to determine maternal cortisol, adrenocorticotropic hormone, and pCRH concentrations. Depressive symptoms were assessed at all visits. **Results:** Depressive symptoms at 3 months postpartum were associated with elevated midgestational pCRH (partial $r = 0.26$; $p < .01$) and also accelerated trajectories of pCRH (B values ranged from 6.9 to 8.3, $p < .05$). Placental CRH was not predictive of PPD symptoms at 6 months postpartum. Furthermore, prepartum cortisol and corticotrophin profiles were not associated with PPD symptoms. **Conclusions:** The current prospective study provides results that reconcile both the positive and negative findings in the existing literature and identifies elevated pCRH as a marker of risk for the development of PPD symptoms. **Key words:** postpartum depression, pregnancy, prenatal, cortisol, corticotrophin-releasing hormone, adrenocorticotropic hormone.

ACTH = adrenocorticotropic hormone; **EPDS** = Edinburgh Postnatal Depression Scale; **HPA** = hypothalamic-pituitary-adrenal; **pCRH** = placental corticotrophin-releasing hormone; **PPD** = postpartum depression.

INTRODUCTION

Among the women who give birth each year, between 10% and 15% will experience postpartum depression (PPD), and less than half will be identified and treated (1). Successful and cost-effective therapies exist (2,3); however, the limited ability to detect those women at risk for PPD constitutes a significant impediment to provision of care. Untreated PPD poses a serious threat to the emotional well-being of the mother and is associated with substance abuse, loss of employment, divorce, risk for later development of bipolar disorder, and, at its most extreme, suicide and infanticide (4–6). In addition to the severe psychological distress experienced by the mother, PPD persistently undermines the mother's confidence and her capacity to care for her infant (7). Infants of mothers experiencing PPD are at risk for exhibiting less than optimal cognitive development, decreased social engagement, psychopathology, and disrupted behavioral and stress regulation (8–11). These adverse consequences persist at least into adolescence and may confer life-long impairments (12–15). Given the profound disruptive influences of PPD, the detection of vulnerable women at risk for PPD is essential. Early recognition and treatment of PPD has the potential to decrease maternal distress, enhance family functioning, optimize infant development, and reduce suicides and infanticides.

During human pregnancy, the endocrine stress system is profoundly altered. The pituitary gland doubles in size, and the synthesis and release of peptides and hormones from the hypothalamic-pituitary-adrenal (HPA) axis and placenta increase several fold as gestation progresses (16). By the seventh week of gestation, the human placenta and amniotic membrane express the genes for corticotrophin-releasing hormone (CRH), which is synthesized by syncytial cells in the human placenta and released into the maternal and fetal compartments (17,18). Maternal circulating levels of CRH increase dramatically over gestation, reaching levels only observed within the hypothalamic-pituitary portal system during stress (19). Placental CRH (pCRH) production is stimulated by adrenal cortisol (20), in stark contrast to the well-characterized inhibitory influence of cortisol on expression of the *CRH* gene in the hypothalamus. In vivo and in vitro studies have documented that cortisol stimulates the production of *CRH* messenger RNA and protein from placental cells in a dose-response manner (20–24). This positive feedback loop results in increasing elevations of maternal cortisol and pCRH as gestation progresses (16).

Although a debate exists concerning whether major depressive disorder and PPD represent distinct syndromes, there is evidence that PPD is a significant risk factor for the later development of nonpuerperal depression and vice versa (25,26), suggesting that they may share common etiological roots. Consistent with this view, accumulating evidence implicates dysregulated HPA-axis function in both puerperal and nonpuerperal affective disorders (27–29). Refinements of models linking HPA regulation to major depressive disorder suggest that different clinical subtypes may be characterized by unique HPA profiles (30–32). The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) identifies two distinct clinical depressive syndromes—melancholic and atypical depression. These are based on patterns of psychological and neurovegetative symptoms and are independent of the unipolar/bipolar distinction. Melancholic depression, with symptoms including loss of

From the Crean College of Health and Behavioral Sciences (L.M.G.), Chapman University, Orange, California; and Department of Psychiatry and Human Behavior (L.M.G., C.A.S.), University of California, Irvine, Orange, California.

Address correspondence and reprint requests to Laura Glynn, PhD, Early Human and Lifespan Development Program, Chapman University, One University Drive, Orange, CA 92866. E-mail: lglynn@chapman.edu

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.psychosomaticmedicine.org).

Received for publication May 21, 2013; revision received March 13, 2014.
DOI: 10.1097/PSY.0000000000000066

0033-3174/14/7605–0355

pleasure, depressed mood at its worst in the morning, insomnia, reduced appetite and/or substantial weight loss, and psychomotor alterations, is consistently associated with the HPA hyperactivation (33–36). In contrast, atypical depression, which is characterized by retention of mood reactivity, weight gain, hypersomnia, interpersonal rejection sensitivity, and depressive symptoms that worsen as the day progresses, is associated with hyporesponsiveness in the system. Atypical patients exhibit enhanced glucocorticoid suppression (37), lower cortisol levels at awakening, and also flattened diurnal cortisol patterns (38). Because the postpartum period is one of mild adrenal suppression, it has been proposed that PPD is more closely aligned with the hyporesponsive atypical subtype (39,40).

Previously, four studies in adult women, each with different study designs, examined the relation between pCRH and PPD and arrived at different conclusions. Yim et al. (41) assessed pCRH five times during pregnancy and reported a positive association between pCRH and PPD symptoms at 8 weeks postpartum. Hahn-Holbrook et al. (42), with three measures of pCRH, also documented a positive association with PPD symptoms at 8 weeks postpartum. In contrast, two other studies failed to detect an association between pCRH and PPD symptoms. In one case, depressive symptoms were measured at 6 months postpartum, and no relation was found (43). In the second study (44), pCRH was assessed at less than 20 weeks (range not given) and between 24 and 29 weeks' gestation and PPD symptoms at 3 months postpartum, a competitive enzyme immunoassay was used, and no association was detected. The current study, which is conducted in a fifth independent cohort, with repeated assessments of pCRH using the gold-standard assay technique for the determination of pCRH and measures of PPD at both 3 and 6 months postpartum, provides results that reconcile both the positive and negative findings in the existing literature and examines whether pCRH is associated with an increased risk of developing PPD symptoms.

METHODS

Design Overview

Pregnant participants were recruited by a research nurse during the first-trimester of pregnancy. Participants attended study visits at 14 to 16 (mean [standard deviation; M {SD}] = 15.5 [0.90]), 18–20 (M [SD] = 19.9 [1.0]), 24 to 26 (M [SD] = 25.8 [0.93]), 30 to 32 (M [SD] = 31.1 [0.82]), 36+ weeks' gestation (M [SD] = 36.8 [0.82]). The postpartum visits took place at 3 (M [SD] = 12.3 [1.6] weeks) and 6 (M [SD] = 26.3 [1.2] weeks) months postpartum. At each visit, depressive symptoms were assessed. Blood samples obtained at the prepartum visits were assayed to determine levels of pCRH, ACTH, and cortisol. The study protocol was approved by the institutional review board of the University of California, Irvine.

Participants

The 170 women who comprised the study cohort were recruited from prenatal clinics associated with a large university medical center from October of 2002 to June of 2007 based on the following criteria: a) singleton pregnancy, b) less than 16 weeks' gestation, c) older than 18 years, d) English speaking, e) nonsmoking, and f) absence of any condition that could dysregulate neuroendocrine function (such as endocrine, hepatic, or renal disorders or use of corticosteroid medications). Potential participants were serially screened from the clinics for inclusion and of those screened over the study period, 43% were initially eligible to participate. The most common reasons for ineligibility were as follows: advanced gestational week (53%), non–English speaking (19%), and multiple gestation (10%). Of those who were eligible, 46% were consented. The most common reasons for declining participation included work or school conflicts (70%) and child care issues (17%). Criteria for inclusion in these analyses further included the following: a) term delivery (≥37 weeks), b) data for at least three of the five prepartum study visits, and c) a 3-month postpartum study visit (see Figure S1, Supplemental Digital Content 1, for a STROBE flowchart describing study inclusion, http://links.lww.com/PSYMED/A126.) Table 1 describes the demographic and medical characteristics of these women. Race/Ethnicity was self-identified.

Assessment of Depression

Prepartum depressive symptoms were evaluated using the short form of the Center for Epidemiologic Studies Depression Inventory (45). Responses to each of the nine items in this measure were recorded on a 4-point Likert scale, with a range of 0 to 3. Anchor points, in days per week, were "rarely or none of the time (less than 1 day)" to "most or all of the time (5–7 days)." The final score could span from 0 to 27, with a higher score indicating greater impairment. This measure has been extensively used, and published studies demonstrate good internal consistency ($\alpha = .84$) and validity of this measure (45). The Center for Epidemiological Studies Depression Scale is a commonly used instrument for the study of depression in the general population and has been validated in samples of pregnant women (46).

At the postpartum visits, participants completed the 10-item Edinburgh Postnatal Depression Scale (EPDS (47)), an instrument 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 and has been validated in other studies (47). Scores above a cutoff of 13 are representative of probable major depression (48). The scale has good reliability (split-half = 0.88, standardized = 0.87) and validity (49,50).

Endocrine Measures

In the afternoon, blood samples (20 ml/draw) were withdrawn by antecubital venipuncture into EDTA (purple top) vacutainers. EDTA vacutainers were chilled on ice immediately, and Aprotinin (Sigma Chemical Co, St Louis, MO) was added at 500 KIU/ml blood. Samples were then centrifuged at 2000*g* (15 minutes) and decanted into polypropylene tubes and stored at –70°C until assayed.

Plasma cortisol levels were determined by a competitive binding solid-phase enzyme-linked immunosorbent assay. Plasma samples (20 μl) and enzyme conjugate (200 μl) were added to the antibody-coated microtiter wells, thoroughly mixed, and incubated for 60 minutes at room temperature. Prior to a 15-minute incubation at room temperature with substrate solution (100 μl), each well was washed three times with wash solution (400 μl per well). The absorbance units were measured at 450 nm within 10 minutes after adding the stop solution. The assay has less than 9% cross-reactivity with progesterone and less than 2% cross-reactivity with five other naturally occurring steroids (testosterone, estradiol, estrone, estriol, and aldosterone). The interassay and intra-assay coefficients of variance are reported as less than 8% with a minimum detectable level of 0.25 μg/dl.

Plasma levels of ACTH were measured by a solid-phase two-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, CA). 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.

The concentration of total CRH was determined by radioimmunoassay (RIA; Bachem Peninsula Laboratories, San Carlos, CA). Plasma samples (1–2 ml) were extracted with three volumes of ice-cold methanol, mixed, allowed to stand for 10 minutes at 4°C, and then centrifuged for 20 minutes at 1700*g* and 4°C by the modified method of Linton and colleagues (51). The pellets were washed with 0.5 ml methanol, and the combined supernatants dried down (Savant SpeedVac concentrator). Reconstituted samples in assay buffer were

TABLE 1. Participant Characteristics

	Complete Sample (*n* = 170)	Euthymic (*n* = 136)	Depressed (*n* = 34)
Race/Ethnicity, *n* (%)			
Latina	35 (21)	30 (22)	5 (15)
Non-Hispanic white	89 (52)	72 (53)	17 (50)
Asian	19 (11)	15 (11)	4 (12)
Other	27 (16)	19 (14)	8 (23)
Maternal age, M (SD), y	29.5 (5.2)	29.9 (5.0)	27.9 (5.9)
Education, *n* (%)			
High school or less	20 (12)	14 (10)	6 (18)
Associates or vocational degree	69 (41)	55 (40)	14 (41)
4-y college degree	48 (28)	38 (28)	10 (29)
Graduate degree	33 (19)	29 (21)	4 (12)
Annual household income, M (SD), US$	65,676 (32,923)	69,577 (31,807)	50,073 (33,146)
Body mass index, M (SD), kg/m^2	24.8 (6.4)	24.9 (6.2)	25.0 (7.0)
Parity, % primiparous	68 (40)	(39)	(44)
Length of gestation, M (SD), wk	39.5 (1.1)	39.5 (1.1)	39.4 (1.0)
Prepartum depression, M (SD), CES-D score			
15-wk gestation	5.3 (4.0)	4.6 (3.5)	8.3 (4.5)
19-wk gestation	4.8 (4.6)	4.1 (3.7)	8.5 (6.6)
25-wk gestation	5.2 (4.4)	4.6 (4.2)	7.4 (4.6)
31-wk gestation	5.8 (4.7)	5.0 (4.2)	9.1 (5.0)
36+-wk gestation	6.6 (4.9)	5.3 (4.0)	11.3 (5.2)
Postpartum depression, mean EPDS score			
3 mo postpartum	5.1 (4.3)	3.3 (2.6)	12.1 (1.8)
6 mo postpartum	4.5 (4.6)	3.4 (3.7)	8.9 (5.2)

M = mean; SD = standard deviation; CES-D = Center for Epidemiologic Studies Depression Scale; EPDS = Edinburgh Postnatal Depression Scale. Depressed participants include those who are above the cutoff of 10 on the EPDS at 3 months postpartum.

incubated with anti-CRH serum (human) for 48 hours at 4°C, followed by a 24-hour incubation with ^{125}I-CRH. Both labeled and unlabeled CRH were collected by immunoprecipitation with goat antirabbit IgG serum and normal rabbit serum after 90 minutes of incubation at room temperature. Samples were centrifuged for 20 minutes at 1700*g* and 4°C, and the aspirated pellets were quantified with a gamma scintillation counter. The CRH assay had less than 0.01% cross-reactivity with ovine CRH, 36% cross-reactivity with bovine CRH, and nondetectable reactivity with human ACTH. The intra- and interassay coefficient of variance ranged from 5% to 15%, respectively. The minimum detectable dose of the assay is 2.04 pg/ml (95% confidence interval; see Supplemental Digital Content 2 for additional assay details, http://links.lww.com/PSYMED/A127).

Data Analytic Techniques

Partial correlations were conducted to examine the association between prepartum hormones and depressive symptoms during pregnancy and postpartum. Unadjusted Pearson correlations also were conducted and are reported in Table S1 (Supplemental Digital Content 3, http://links.lww.com/PSYMED/A128) and Table S2 (Supplemental Digital Content 4, http://links.lww.com/PSYMED/A129). To assess the association between PPD status and prepartum hormone trajectories, multilevel modeling using hierarchical linear modeling growth curve analysis (52) was conducted. Initial testing indicated that a cubic model provided the best fit for the prepartum CRH trajectories. In each full two-level model, the effects of PPD status on hormone levels at the initial assessment (14 weeks) and change across time were evaluated. Specifically, the Level 1 variables (or the time-variant variables) included hormone levels at each study visit and timing of these study visits in weeks. The Level 2 variables (or time-invariant variables) included PPD status (depressive symptoms versus euthymic) and relevant covariates (see below). The full models were then repeated at 1-week intervals for each week until the week at which the last study visit occurred (36 weeks' gestation). Covariates in all analyses included maternal age, body mass index, education, income, parity, and gestational week at blood draw. Each of these variables exhibited a statistically significant relation ($p < .05$) between prepartum hormone trajectories, PPD, or both. For all analyses involving cortisol, time of sample collection also was included as a covariate (neither pCRH nor ACTH was related to time of sample collection). In addition, in all analyses with PPD symptoms, prepartum depression level (averaged across the study visits) also was included.

RESULTS

Prediction of Prepartum Depressive Symptoms

There were no significant associations between concurrent measures of prepartum depressive symptoms and maternal concentrations of pCRH, ACTH, or cortisol (Table 2). Moreover, analyses of all possible lagged relations (e.g., CRH at 19 weeks predicting depressive symptoms at 25 weeks) did not reveal any significant associations. Unadjusted correlations can be found in Table S1 and did not differ substantively from those taking covariates into account.

Prediction of Postpartum Depressive Symptoms

Table 3 displays the associations between prepartum hormone levels and PPD symptoms at 3 and 6 months postpartum. Women who exhibited higher levels of pCRH at midgestation were at increased risk for exhibiting symptoms of depression at 3 months postpartum. Specifically, pCRH at 25, 31, and 36+ weeks'

TABLE 2. Partial Correlations Between Prepartum Hormones (pCRH, ACTH, and Cortisol) and Prenatal Depressive Symptoms (CES-D)

Prepartum Hormones, Week of Gestation	CES-D, Week of Gestation				
	15	19	25	31	36+
15					
pCRH	−0.01 (129)	0.01 (128)	0.15 (133)	0.15 (132)	0−0.01 (104)
ACTH	0.08 (159)	0.11 (155)	−0.02 (163)	0.02 (163)	0.03 (126)
Cortisol	0.09 (159)	0.09 (155)	0.00 (163)	0.03 (163)	0.10 (126)
19					
pCRH		−0.11 (140)	−0.06 (141)	0.01 (141)	−0.12 (113)
ACTH		−0.05 (158)	−0.11 (159)	−0.12 (159)	−0.10 (124)
Cortisol		−0.11 (158)	−0.12 (159)	0.01 (159)	−0.02 (124)
25					
pCRH			−0.16 (162)	−0.10 (162)	−0.04 (122)
ACTH			0.01 (167)	0.03 (167)	0.00 (127)
Cortisol			−0.13 (167)	−0.03 (167)	−0.07 (127)
31					
pCRH				0.00 (159)	0.01 (126)
ACTH				0.02 (167)	0.06 (127)
Cortisol				0.14 (167)	0.06 (127)
36+					
pCRH					−0.10 (118)
ACTH					.00 (129)
Cortisol					−0.02 (129)

pCRH = placental corticotrophin-releasing hormone; ACTH = adrenocorticotropic hormone; CES-D = Center for Epidemiologic Studies Depression Scale.
Partial correlations adjust for the following: maternal age, race/ethnicity, parity, income, and week of gestation at blood draw. Cortisol analyses also adjust for time of day of sample collection. *N* Values are given in parentheses.
* $p < .05$, ** $p < .01$,

gestation predicted PPD symptoms at 3 months postpartum, but not at 6 months. Notably, restricting the analyses to the 145 women with EPDS data at both the 3- and 6-month visits revealed the same positive associations between midgestation CRH and PPD symptoms at 3 months postpartum (see Table 4). Neither prepartum cortisol nor ACTH was associated with depressive symptoms at 3 or 6 months (Table 3). Table S2 contains the unadjusted correlations for the relations between prepartum hormones and postpartum EPDS. Again only pCRH emerged as a potential predictor of PPD symptoms at 3 months postpartum, although the strength of the relations was diminished compared with those analyses that took into account important covariates.

TABLE 3. Partial Correlations Between Prepartum Hormones (pCRH, ACTH, and Cortisol) and PPD Symptoms (EPDS)

	Week of Gestation				
	15	19	25	31	36+
EPDS at 3 mo postpartum					
pCRH	0.02 (133)	0.15 (124)	0.24** (163)	0.21** (167)	0.16*** (158)
ACTH	−0.13 (164)	−0.02 (160)	−0.06 (168)	0.03 (167)	−0.06 (164)
Cortisol	0.02 (164)	.005 (160)	0.08 (168)	−0.01 (167)	−0.13 (164)
EPDS at 6 mo postpartum					
pCRH	0.02 (118)	−0.11 (124)	0.01 (138)	0.01 (143)	0.00 (130)
ACTH	−0.12 (141)	0.11 (142)	0.05 (143)	0.11 (143)	0.02 (140)
Cortisol	−0.10 (141)	0.03 (142)	−0.03 (143)	−0.10 (143)	−0.15 (140)

pCRH = placental corticotrophin-releasing hormone; ACTH = adrenocorticotropic hormone; PPD = postpartum depression; EPDS = Edinburgh Postnatal Depression Scale.
Partial correlations adjust for the following: maternal age, race/ethnicity, parity, income, education, prenatal depression, and gestational week at blood draw. Cortisol analyses also adjust for time of blood draw. *N* Values are given in parentheses.
* $p < .05$, ** $p < .01$, *** $p = .05$.

TABLE 4. Partial Correlations Between pCRH and PPD Symptoms Among Women With PPD Data at Both 3 and 6 Months

	Week of Gestation				
	15	19	25	31	36+
EPDS at 3 mo	−0.02 (118)	0.17 (124)	0.277** (138)	0.21* (143)	0.17 (135)
EPDS at 6 mo	−0.04 (118)	−0.12 (124)	0.03 (138)	0.01 (143)	0.01 (135)

pCRH = placental corticotrophin-releasing hormone; PPD = postpartum depression; EPDS = Edinburgh Postnatal Depression Scale.
Partial correlations adjust for the following: maternal age, race/ethnicity, parity, income, education, prenatal depression, and week of gestation at blood draw. Cortisol analyses adjust for time of blood draw. *n* Values are given in parentheses.
* $p < .05$, ** $p < .01$.

Analysis of pCRH Trajectories and PPD Symptoms

Figure 1 shows pCRH trajectories for those women above ($n = 34$) and below ($n = 136$) the EPDS cutoff (EPDS score ≥ 10). Multilevel mixed modeling revealed that from 25 to 31 weeks' gestation, women who exhibited PPD symptoms at 3 months postpartum also exhibited significant elevations in CRH levels (*B* values ranged from 44.2 to 66.3; *p* values < .05; all *B* values and relevant statistics can be found in Table S3, Supplemental Digital Content 5, http://links.lww.com/PSYMED/A130). In addition, those women who went on to express PPD symptoms also exhibited accelerated rates of increase in pCRH from 21 to 25 weeks (*B* values ranged from 6.9 to 8.3; *p* values < .05). Similar results were achieved when using the more stringent EPDS cutoff of 13 ($n = 12$), indicative of probable major depression. In this second set of analyses, women above the cutoff exhibited elevated levels of CRH from 25 to 32 weeks (*B* values ranged from 58.1 to 100.7; *p* values < .05; see Table S4, Supplemental Digital Content 6, http://links.lww.com/PSYMED/A131) and also accelerated pCRH trajectories from 19 to 26 weeks' gestation (*B* values ranged from 6.7 to 12.6; *p* values < .05).

DISCUSSION

In the current study, elevated levels of pCRH beginning at midgestation and also accelerated trajectories of pCRH were associated with risk for depressive symptoms at 3 months postpartum. Importantly, the association between pCRH and PPD symptoms was observed among women who delivered at term and was independent from prepartum depressive symptoms. The precise reason that mid, as opposed to early, pCRH levels are predictive of PPD is currently not known. However, individual differences in pCRH are not as pronounced before 25 weeks (in fact, it also is not until midgestation that pCRH is predictive of length of gestation either (53–55)). It also is possible that the rate of increase in pCRH (which accelerates dramatically after 20 weeks' gestation), in addition to absolute levels, may be critical (55) in determining the extent of HPA-axis dysregulation in the postpartum period.

These results are consistent with those from three other independent cohorts, including the positive findings of Yim et al. (41) and Hahn-Holbrook et al. (42) and also with the negative findings of Rich-Edwards et al. (43), specifically showing that for depressive symptoms assessed at 2 to 3 months, an association with pCRH is observed, but that when examining depressive symptoms at 6 months, no association is detected. In the fourth study (44), in which pCRH was not associated with depressive symptoms despite the fact that PPD was assessed at 2 months postpartum, a less well-validated CRH assay was applied. The most widely used and recommended assay technique for determination of pCRH is RIA (56). This is preferred to the competitive enzyme immunoassay, used in the study by Meltzer-Brody et al. (44), because both published reports and commercial laboratories document greater sensitivity with the RIA assay for CRH (56). Consistent with the possibility that the assay approach may have limited the ability to detect an association between pCRH and PPD in the study by Meltzer-Brody et al. is the fact that the widely replicated association between pCRH and length of gestation (53–55,57,58) also did not reach statistical significance in their investigation despite a very large sample size ($n = 1230$). In the current study, the expected negative association between pCRH and length of gestation was statistically significant ($\beta = -0.21$; $p < .01$), although the variability and power to detect an effect were diminished because the study cohort was restricted to women who delivered at term. In summary, there are plausible and also likely explanations for differences among the existing study findings that support the argument that prepartum pCRH is a marker of risk for postpartum mood disturbance.

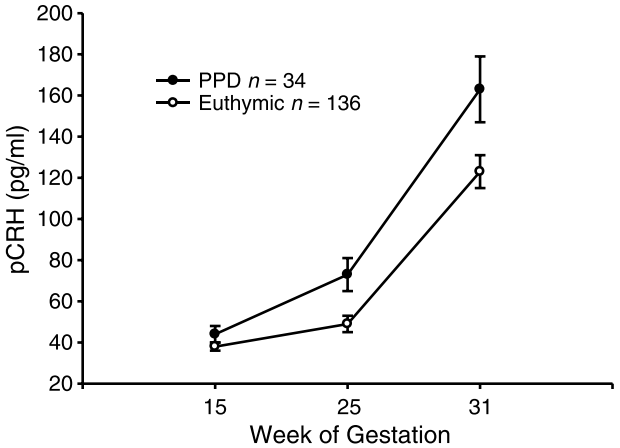

Figure 1. Comparison of pCRH trajectories across gestations among women exhibiting depressive symptoms at 3 months postpartum compared with those who are euthymic (values represent observed means with standard error). pCRH = placental corticotrophin-releasing hormone; PPD = postpartum depression.

Currently, the DSM-IV applies the "postpartum onset" specifier when an episode begins within the first 4 weeks after delivery, and the ICD-10 criteria extend this window to 6 weeks postpartum. Furthermore, among women who meet the DSM-IV criteria for major depression during the first postpartum year, 78% report onset before 6 weeks postpartum (25). The finding that pCRH is predictive of PPD symptoms at 2 to 3 months, but not 6 months, is consistent with the possibility that depression that arises earlier in the postpartum period may represent a distinct syndrome from that which presents later postpartum or outside the perinatal period. At the very least, it underscores the necessity of considering different risk factors and mechanisms that are dependent on the timing of presentation of depression among women, even during the first postpartum year.

Although it was not the main focus of this study, this investigation did examine relations between pCRH and prepartum depressive symptoms. Given the current state of the existing literature examining this relation among adult women, it was not possible to formulate a clear a priori hypothesis about direction or timing of effects for the following reasons: two studies have documented a positive association (43,59), one has documented a negative association (44), and three have not detected an association (41,42,60). The current study revealed neither concurrent nor lagged associations between pCRH and prepartum symptoms.

In contrast to the negative feedback regulation of hypothalamic CRH, cortisol stimulates the expression of pCRH, establishing a positive feedback loop that allows for the simultaneous increase in pCRH, ACTH, β-endorphin, and cortisol over the course of gestation. The hypercortisolism present during the latter half of gestation is associated with suppressed hypothalamic CRH secretion during pregnancy and the immediate postpartum (40). It has been proposed that an extended HPA-axis refractory period may contribute to the development of depressive symptoms because it is associated with a central CRH deficiency (40). Consistent with this hypothesis, women who experience postpartum "blues" or PPD show more blunted ACTH responses to ovine CRH stimulation (61) and also are characterized by a flattened cortisol awakening response (62) when compared with euthymic women during the first postpartum months. To date, it is not known whether pCRH trajectories are predictive of postpartum HPA-axis dysregulation, but clearly, this is an important direction for future research.

The findings are consistent with the view that the precipitous drop in pCRH at delivery may play a role in depressive episodes during the postpartum period. This view shares conceptual overlap with other endocrine models that similarly focus on extreme fluctuations in hormones during the perinatal period, such as those implicating estrogens and progesterone (63–65). It also is possible, given the interactive relations between pCRH and gonadal steroids, that these interrelations may be involved in the etiology of PPD. For example, pCRH stimulates the production of estradiol from the placenta (66), and elevations in estradiol at the end of gestation and the subsequent drop have been hypothesized to contribute to PPD (67).

The strengths of this study include the prospective design in which women were examined repeatedly during pregnancy with precise windows of assessment, the carefully characterized study cohort of women who delivered at term, assessment of depressive symptoms at both 3 and 6 months postpartum, and the use of the gold standard for the determination of pCRH (RIA (56)). There was also one principal limitation, which was the reliance on self-reports of depression 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% (50), and Research Diagnostic Criteria, 89% (49)) and specificity (DSM-III and Research Diagnostic Criteria, 82% (49,50)) of this measure. Another more minor concern relates to the potential for Type 1 error given the number of hormones assessed as well as the number of gestational time points. However, some confidence can be derived from the fact that although a specific timing effect for one hormone was detected, pCRH, this was consistent with our hypothesis based on previous findings from other large independent cohorts.

Increasing evidence indicates that the compromised maternal care associated with PPD is a singular and potent environmental influence conferring risk for adverse consequences for the child that can persist throughout a lifetime (14,68–72). Recent studies in humans demonstrate that these negative effects cannot be explained solely by genetic vulnerabilities (73), and work with animal models document plausible epigenetic pathways affecting brain and behavior (74–76), rendering it extremely likely that maternal PPD is one mechanism through which affective disorders and compromised maternal care are transmitted across generations. Fortunately, effective interventions exist (2,3), and therefore, early identification of at-risk mothers and infants is central to advancing maternal and child health.

Conflicts of Interest and Source of Funding: The authors have no financial interests or potential conflicts of interest to disclose. This research was supported by grants from the National Institutes of Health (HD-40967 to L.M.G. and NS-41298 to C.A.S.).

REFERENCES

1. di Scalea TL, Wisner KL. Pharmacotherapy of postpartum depression. Expert Opin Pharmacother 2009;10:2593–607.
2. Ickovics JR, Reed E, Magriples U, Westdahl C, Schindler Rising S, Kershaw TS. Effects of group prenatal care on psychosocial risk in pregnancy: results from a randomised controlled trial. Psychol Health 2011;26:235–50.
3. Phipps MG, Raker CA, Ware CF, Zlotnick C. Randomized controlled trial to prevent postpartum depression in adolescent mothers. Am J Obstet Gynecol 2013;208:192.e1–6.
4. Goodman SH. Depression in mothers. Annu Rev Clin Psychol 2007;3:107–35.
5. O'Hara MW. Postpartum depression: what we know. J Clin Psychol 2009;65:1258–69.
6. Di Florio A, Forty L, Gordon-Smith K, Heron J, Jones L, Craddock N, Jones I. Perinatal episodes across the mood disorder spectrum. Arch Gen Psychiatry 2012;70:1–8.
7. Lovejoy MC, Graczyk PA, O'Hare E, Neuman G. Maternal depression and parenting behavior: a meta-analytic review. Clin Psychol Rev 2000;20:561–92.
8. Dawson G, Ashman SB, Panagiotides H, Hessl D, Self J, Yamada E, Embry L. Preschool outcomes of children of depressed mothers: role of maternal

behavior, contextual risk, and children's brain activity. Child Dev 2003;74:1158–75.
9. Halligan SL, Herbert J, Goodyer IM, Murray L. Exposure to postnatal depression predicts elevated cortisol in adolescent offspring. Biol Psychiatry 2004;55:376–81.
10. Feldman R, Granat A, Pariente C, Kanety H, Kuint J, Gilboa-Schechtman E. Maternal depression and anxiety across the postpartum year and infant social engagement, fear regulation, and stress reactivity. J Am Acad Child Adolesc Psychiatry 2009;48:919–27.
11. Goodman SH, Rouse MH, Connell AM, Broth MR, Hall CM, Heyward D. Maternal depression and child psychopathology: a meta-analytic review. Clin Child Fam Psychol Rev 2011;14:1–27.
12. Douglas JL, Harmer CJ. Early morning cortisol response and emotional processing in adults exposed to postnatal depression in infancy. Eur Psychiatry 2011;26:479–81.
13. Verbeek T, Bockting CL, van Pampus MG, Ormel J, Meijer JL, Hartman CA, Burger H. Postpartum depression predicts offspring mental health problems in adolescence independently of parental lifetime psychopathology. J Affect Disord 2012;136:948–54.
14. Murray L, Arteche A, Fearon P, Halligan S, Goodyer I, Cooper P. Maternal postnatal depression and the development of depression in offspring up to 16 years of age. J Am Acad Child Adolesc Psychiatry 2011;50:460–70.
15. Hay DF, Pawlby S, Waters CS, Sharp D. Antepartum and postpartum exposure to maternal depression: different effects on different adolescent outcomes. J Child Psychol Psychiatry 2008;49:1079–88.
16. Glynn LM, Sandman CA. Prenatal origins of neurological development: a critical period for fetus and mother. Curr Dir Psychol Sci 2011;20:384–9.
17. Economides D, Linton E, Nicolaides K, Rodeck CH, Lowry PJ, Chard T. Relationship between maternal and fetal corticotropin-releasing hormone-41 and ACTH levels in human mid-trimester pregnancy. J Endocrinol 1987;114:497–201.
18. Goland RS, Wardlaw SL, Blum M, Tropper PJ, Stark RI. Biologically active corticotropin-releasing hormone in maternal and fetal plasma during pregnancy. Am J Obstet Gynecol 1988;159:884–90.
19. Lowry PJ. Corticotropin-releasing factor and its binding protein in human plasma. Ciba Found Symp 1993;172:108–15.
20. Cheng YH, Nicholson RC, King B, Chan EC, Fitter JT, Smith R. Glucocorticoid stimulation of corticotropin-releasing hormone gene expression requires a cyclic adenosine 3′,5′-monophosphate regulatory element in human primary placental cytotrophoblast cells. J Clin Endocrinol Metab 2000;85:1937–45.
21. Robinson BG, Emanuel RL, Frim DM, Majzoub JA. Glucocorticoid stimulates expression of corticotropin-releasing hormone gene in human placenta. Proc Natl Acad Sci U S A 1988;85:5244–8.
22. King BR, Smith R, Nicholson RC. The regulation of human corticotrophin-releasing hormone gene expression in the placenta. Peptides 2001;22:1941–7.
23. Scatena CD, Adler S. Characterization of a human-specific regulator of placental corticotropin-releasing hormone. Mol Endocrinol 1998;12:1228–40.
24. Sandman CA, Glynn LM, Dunkel Schetter C, Wadwha PD, Garite T, Hobel C. Elevated maternal cortisol early in pregnancy predicts third trimester levels of placental corticotropin releasing hormone (CRH): priming the placental clock. Peptides 2006;27:1457–63.
25. Stowe ZN, Hostetter AL, Newport DJ. The onset of postpartum depression: implications for clinical screening in obstetrical and primary care. Am J Obstet Gynecol 2005;192:522–6.
26. Robertson E, Grace S, Wallington T, Stewart DE. Antenatal risk factors for postpartum depression: a synthesis of recent literature. Gen Hosp Psychiatry 2004;26:289–95.
27. Lloyd RB, Nemeroff CB. The role of corticotropin-releasing hormone in the pathophysiology of depression: therapeutic implications. Curr Top Med Chem 2011;11:609–17.
28. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. JAMA 1992;267:1244–52.
29. Brummelte S, Galea LA. Depression during pregnancy and postpartum: contribution of stress and ovarian hormones. Biol Psychiatry 2010;34:766–76.
30. Gold P, Chrousos G. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. Mol Psychiatry 2002;7:254–75.
31. O'Keane V, Frodl T, Dinan TG. A review of atypical depression in relation to the course of depression and changes in HPA axis organization. Psychoneuroendocrinology 2012;37:1589–99.
32. Antonijevic IA. Depressive disorders—is it time to endorse different pathophysiologies? Psychoneuroendocrinology 2006;31:1–15.
33. Nemeroff CB, Owens MJ, Bissette G, Andorn AC, Stanley M. Reduced corticotropin releasing factor binding sites in the frontal cortex of suicide victims. Arch Gen Psychiatry 1988;45:577–9.
34. Raadsheer FC, van Heerikhuize JJ, Lucassen PJ, Hoogendijk WJ, Tilders FJ, Swaab DF. Corticotropin-releasing hormone mRNA levels in the paraventricular nucleus of patients with Alzheimer's disease and depression. Am J Psychiatry 1995;152:1372–6.
35. Jarcho MR, Slavich GM, Tylova-Stein H, Wolkowitz OM, Burke HM. Dysregulated diurnal cortisol pattern is associated with glucocorticoid resistance in women with major depressive disorder. Biol Psychol 2013;93:150–8.
36. Vrshek-Schallhorn S, Doane LD, Mineka S, Zinbarg RE, Craske MG, Adam EK. The cortisol awakening response predicts major depression: predictive stability over a 4-year follow-up and effect of depression history. Psychol Med 2013;43:483–93.
37. Levitan RD, Vaccarino FJ, Brown GM, Kennedy SH. Low-dose dexamethasone challenge in women with atypical major depression: pilot study. Psychiatry Neurosci 2002;27:47–51.
38. Lamers F, Vogelzangs N, Merikangas K, de Jonge P, Beekman A, Penninx B. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. Mol Psychiatry 2012;18:692–9.
39. Kammerer M, Taylor A, Glover V. The HPA axis and perinatal depression: a hypothesis. Arch Womens Ment Health 2006;9:187–96.
40. Mastorakos G, Ilias I. Maternal hypothalamic-pituitary-adrenal axis in pregnancy and the postpartum period: postpartum-related disorders. Ann N Y Acad Sci 2000;900:95–106.
41. Yim IS, Glynn LM, Dunkel-Schetter C, Hobel CJ, Chicz-DeMet A, Sandman CA. Risk of postpartum depressive symptoms with elevated corticotropin-releasing hormone in human pregnancy. Arch Gen Psychiatry 2009;66:162–9.
42. Hahn-Holbrook J, Dunkel Schetter C, Chander A, Hobel CJ. Placental corticotropin-releasing hormone mediates the association between prenatal social support and postpartum depression. Clin Psychol Sci 2013;1:253–65.
43. Rich-Edwards JW, Mohllajee AP, Kleinman K, Hacker MR, Majzoub J, Wright RJ, Gillman MW. Elevated midpregnancy corticotropin-releasing hormone is associated with prenatal, but not postpartum, maternal depression. J Clin Endocrinol Metab 2008;93:1946–51.
44. Meltzer-Brody S, Stuebe A, Dole N, Savitz D, Rubinow D, Thorp J. Elevated corticotropin releasing hormone (CRH) during pregnancy and risk of postpartum depression (PPD). J Clin Endocrinol Metab 2011;96:E40–7.
45. Santor DA, Coyne JC. Shortening the CES-D to improve its ability to detect cases of depression. Psychol Assess 1997;9:233–43.
46. Marcus SM, Flynn HA, Blow FC, Barry KL. Depressive symptoms among pregnant women screened in obstetrics settings. J Womens Health 2003;12:373–80.
47. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 1987;150:782–6.
48. Matthey S, Henshaw C, Elliott S, Barnett B. Variability in use of cut-off scores and formats on the Edinburgh Postnatal Depression Scale: implications for clinical and research practice. Arch Womens Ment Health 2006;9:309–15.
49. Murray L, Carothers AD. The validation of the Edinburgh Post-natal Depression Scale on a community sample. Br J Psychiatry 1990;157:288–90.
50. Harris B, Huckle P, Thomas R, Johns S, Fung H. The use of rating scales to identify post-natal depression. Br J Psychiatry 1989;154:813–7.
51. Linton EA, Perkins AV, Hagan P, Poole S, Bristow AF, Tilders F, Corder R, Wolfe CD. Corticotrophin-releasing hormone (CRH)–binding protein interference with CRH antibody binding: implications for direct CRH immunoassay. J Endocrinol 1995;146:45–53.
52. Raudenbush SW, Bryk AS. Hierarchical Linear Models: Application and Data Analysis Methods. Thousand Oaks: Sage Publications; 2002.
53. Wadhwa PD, Garite TJ, Porto M, Glynn L, Chicz-DeMet A, Dunkel-Schetter C, Sandman CA. Placental corticotropin-releasing hormone (CRH), spontaneous preterm birth, and fetal growth restriction: a prospective investigation. Am J Obstet Gynecol 2004;191:1063–9.
54. McLean M, Bisits A, Davies J, Woods R, Lowry P, Smith R. A placental clock controlling the length of human pregnancy. Nat Med 1995;1:460–3.
55. Smith R, Smith JI, Shen X, Engel PJ, Bowman ME, McGrath SA, Bisits AM, McElduff P, Giles WB, Smith DW. Patterns of plasma corticotropin-releasing

hormone, progesterone, estradiol, and estriol change and the onset of human labor. J Clin Endocrinol Metab 2009;94:2066–74.
56. Latendresse G, Ruiz RJ. Bioassay research methodology: measuring CRH in pregnancy. Biol Res Nurs 2008;10:54–62.
57. Erickson K, Thorsen P, Chrousos G, Grigoriadis DE, Khongsaly O, McGregor J, Schulkin J. Preterm birth: associated neuroendocrine, medical, and behavioral risk factors. J Clin Endocrinol Metab 2001;86: 2544–52.
58. Holzman C, Jetton J, Siler-Khodr T, Fisher R, Rip T. Second trimester corticotropin-releasing hormone levels in relation to preterm delivery and ethnicity. Obstet Gynecol 2001;97:657–63.
59. O'Keane V, Lightman S, Marsh M, Pawlby S, Papadopoulos AS, Taylor A, Moore R, Patrick K. Increased pituitary-adrenal activation and shortened gestation in a sample of depressed pregnant women: a pilot study. J Affect Disord 2011;130:300–5.
60. Latendresse G, Ruiz RJ. Maternal coping style and perceived adequacy of income predict CRH levels at 14–20 weeks of gestation. Biol Res Nurs 2010;12:125–36.
61. Magiakou MA, Mastorakos G, Rabin D, Dubbert B, Gold PW, Chrousos GP. Hypothalamic corticotropin-releasing hormone suppression during the postpartum period: implications for the increase in psychiatric manifestations at this time. J Clin Endocrinol Metab 1996;81:1912–7.
62. Taylor A, Glover V, Marks M, Kammerer M. Diurnal pattern of cortisol output in postnatal depression. Psychoneuroendocrinology 2009;34: 1184–8.
63. Bloch M, Daly RC, Rubinow DR. Endocrine factors in the etiology of postpartum depression. Compr Psychiatry 2003;44:234–46.
64. Green AD, Barr AM, Galea LA. Role of estradiol withdrawal in 'anhedonic' sucrose consumption: a model of postpartum depression. Physiol Behav 2009;97:259–65.
65. Moses-Kolko EL, Berga SL, Kalro B, Sit DK, Wisner KL. Transdermal estradiol for postpartum depression: a promising treatment option. Clin Obstet Gynecol 2009;52:51629.
66. You X, Yang R, Tang X, Gao L, Ni X. Corticotropin-releasing hormone stimulates estrogen biosynthesis in cultured human placental trophoblasts. Biol Reprod 2006;74:1067–72.
67. Bloch M, Aharonov I, Ben Avi I, Schreiber S, Amit A, Weizman A, Azem F. Gonadal steroids and affective symptoms during in vitro fertilization: implication for reproductive mood disorders. Psychoneuroendocrinology 2010;36:790–6.
68. Anderson SE, Gooze RA, Lemeshow S, Whitaker RC. Quality of early maternal-child relationship and risk of adolescent obesity. Pediatrics 2012;129:132–40.
69. Nachmias M, Gunnar M, Mangelsdorf S, Parritz RH, Buss K. Behavioral inhibition and stress reactivity: the moderating role of attachment security. Child Dev 1996;67:191–204.
70. Stams GJM, Juffer F, Van IJzendoorn MH. Maternal sensitivity, infant attachment, and temperament in early childhood predict adjustment in middle childhood: the case of adopted children and their biologically unrelated parents. Dev Psychol 2002;38:806–21.
71. Lupien SJ, Parent S, Evans AC, Tremblay RE, Zelazo PD, Corbo V, Pruessner JC, Seguin JR. Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. Proc Natl Acad Sci U S A 2011;108:14324–9.
72. Luby JL, Barch DM, Belden A, Gaffrey MS, Tillman R, Babb C, Nishino T, Suzuki H, Botteron KN. Maternal support in early childhood predicts larger hippocampal volumes at school age. Proc Natl Acad Sci U S A 2012;109:2854–9.
73. Laurent HM, Leve LD, Neiderhiser JM, Natsuaki MN, Shaw DS, Harold GT, Reiss D. Effects of prenatal and postnatal parent depressive symptoms on adopted child HPA regulation: independent and moderated influences. Dev Psychol 2013;84:528–42.
74. Francis D, Diorio J, Liu D, Meaney MJ. Nongenomic transmission across generations of maternal behavior and stress responses in the rat. Science 1999;286:1155–8.
75. Champagne F, Meaney MJ. Like mother, like daughter: evidence for nongenomic transmission of parental behavior and stress responsitivity. Prog Brain Res 2001;133:287–302.
76. Champagne FA, Weaver IC, Diorio J, Dymov S, Syzf M, Meaney MJ. Maternal care associated with methylation of the estrogen receptor-alpha1b promoter and estrogen receptor-alpha expression in the medial preoptic area of female offspring. Endocrinology 2006;147:2909–15.