Research Article

MID-PREGNANCY CORTICOTROPIN-RELEASING HORMONE LEVELS IN ASSOCIATION WITH POSTPARTUM DEPRESSIVE SYMPTOMS

Stavros I. Iliadis, PhD,[1]* Sara Sylvén, PhD,[1] Charlotte Hellgren, PhD,[1] Jocelien D. Olivier, PhD,[1,2] Dick Schijven,[1] Erika Comasco, PhD,[1,3] George P. Chrousos, PhD,[4] Inger Sundström Poromaa, PhD,[1] and Alkistis Skalkidou, PhD[1]

Background: *Peripartum depression is a common cause of pregnancy- and postpartum-related morbidity. The production of corticotropin-releasing hormone (CRH) from the placenta alters the profile of hypothalamus–pituitary–adrenal axis hormones and may be associated with postpartum depression. The purpose of this study was to assess, in nondepressed pregnant women, the possible association between CRH levels in pregnancy and depressive symptoms postpartum.* **Methods:** *A questionnaire containing demographic data and the Edinburgh Postnatal Depression Scale (EPDS) was filled in gestational weeks 17 and 32, and 6 week postpartum. Blood samples were collected in week 17 for assessment of CRH. A logistic regression model was constructed, using postpartum EPDS score as the dependent variable and log-transformed CRH levels as the independent variable. Confounding factors were included in the model. Subanalyses after exclusion of study subjects with preterm birth, newborns small for gestational age (SGA), and women on corticosteroids were performed.* **Results:** *Five hundred thirty-five women without depressive symptoms during pregnancy were included. Logistic regression showed an association between high CRH levels in gestational week 17 and postpartum depressive symptoms, before and after controlling for several confounders (unadjusted OR = 1.11, 95% CI 1.01–1.22; adjusted OR = 1.13, 95% CI 1.02–1.26; per 0.1 unit increase in log CRH). Exclusion of women with preterm birth and newborns SGA as well as women who used inhalation corticosteroids during pregnancy did not alter the results.* **Conclusions:** *This study suggests an association between high CRH levels in gestational week 17 and the development of postpartum depressive symptoms, among women without depressive symptoms during pregnancy. Depression and Anxiety 33:1023–1030, 2016.*

Key words: *corticotropin-releasing hormone; EPDS; HPA axis; peripartum depression; postpartum depression; pregnancy*

[1]**Department of Women's and Children's Health, Uppsala University Hospital, Uppsala, Sweden**
[2]**Department of Behavioural Neuroscience, Groningen Institute for Evolutionary Life Sciences, University of Groningen, Groningen, the Netherlands**
[3]**Department of Neuroscience, Uppsala University, Uppsala, Sweden**
[4]**Department of Pediatrics, Athens University Medical School, Athens, Greece**

*Correspondence to: Stavros Iliadis, Department of Women's and Children's Health, Uppsala University Hospital, 75185 Uppsala, Sweden
E-mail: stavros.iliadis@kbh.uu.se
Received for publication 27 October 2015; Revised 21 February 2016; Accepted 23 April 2016

DOI 10.1002/da.22529
Published online 27 May 2016 in Wiley Online Library (wileyonlinelibrary.com).

INTRODUCTION

Peripartum depression, defined as depressive episodes initiating during pregnancy or the first 4 weeks postpartum,[1] is a common cause of pregnancy- and postpartum-related morbidity and may have severe consequences for mothers and newborns. Depressive symptoms may have their onset in pregnancy or appear only postpartum. In fact, up to 50% of depressive episodes detected postpartum have their onset before partus.[1]

Physiological endocrine changes occurring during the course of pregnancy alter the profile of several hormones including those related to the hypothalamic–pituitary–adrenal (HPA) axis, where a transient, yet physiologic, state of hypercortisolism is noted.[2] In fact, cortisol levels in saliva, plasma, and urine reach their peak shortly before partus and decline through the postpartum period.[3]

The alteration of the HPA axis during pregnancy is mainly attributed to the production of corticotropin-releasing hormone (CRH) from the placenta (pCRH).[4] In contrast to the nonpregnant state, where CRH in plasma is very low or undetectable, during pregnancy, pCRH contributes to an increase in the circulating levels of HPA axis–related hormones.[4] Although the CRH-binding protein (CRHBP) may affect the concentration of free plasma CRH, during the first, second, and early third trimesters of pregnancy, it is interesting to note that the CRHBP concentrations are similar to those in nonpregnant individuals. This implies that CRHBP is not influenced by the increasing estrogen levels that physiologically occur in pregnancy.[5] In late pregnancy though, CRHBP levels decrease by two thirds, whereas total CRH levels rapidly increase.[6] This results in an increase in the availability of free and potentially bioactive CRH, which stimulates the release of ACTH from the maternal pituitary.[5] Moreover, in nonpregnant and pregnant individuals, glucocorticoids exert an inhibitory effect on hypothalamic CRH synthesis. However, during pregnancy, maternal cortisol enhances, within the placenta, a positive feed-forward loop including glucocorticoids, adrenocorticotropic hormone (ACTH), and placental CRH, which further stimulates placental CRH gene expression.[7–9] This in turn leads to placental CRH production and release in maternal circulation, making pCRH detectable in maternal blood at 16–20 gestational weeks.[10] Thereafter, circulating pCRH increases exponentially during pregnancy, peaks during labor, and becomes gradually undetectable after parturition.[4]

It has been hypothesized that the abrupt decline that occurs postpartum, in the considerably elevated CRH pregnancy levels, may be a vulnerability factor contributing to the occurrence of postpartum depression.[6] Moreover, the postpartum is a refractory period associated with central suppression of hypothalamic CRH secretion as a result of the prolonged hypercortisolism of pregnancy.[6,11] Additionally, women experiencing postpartum depression show more blunted ACTH responses to ovine CRH stimulation testing than euthymic women in postpartum.[11] These data point to the fact that differential gradual recuperation of the HPA axis in the postpartum may be implicated in the development of mood disorders during that period.[11] In a recent study from our group, focusing on prenatal depressive symptoms and CRH levels, it was shown that women on selective serotonin reuptake inhibitor (SSRI) treatment had higher second trimester CRH levels than controls or untreated depressed women.[12] On the other hand, only a few studies have examined possible associations between CRH and the development of depressive symptoms with postpartum onset.

Glynn and Sandman found higher CRH levels in pregnancy (gestational week 25, 31, and ≥36) among women with depressive symptoms 3 months postpartum compared with healthy controls.[13] In another study with similar findings, authors reported greater increase in CRH from gestational week 29 to 37 and higher CRH in week 37 in women with depression 8 weeks postpartum.[14] Similarly, Yim et al. reported significantly higher CRH in gestational week 25 among women with high Edinburgh Postnatal Depression Scale (EPDS) scores 8–9 weeks postpartum (cutoff 10 points).[15] In these studies, the association between CRH levels in pregnancy and postpartum depressive symptoms remained significant even after adjustment for prenatal depressive symptoms. On the contrary, two other studies[16,17] found no association between CRH and postpartum depression. Discrepancies between results of these studies and our work may rely on different methodological approaches and study design. Specifically, the aforementioned studies examined peripartum depression on another basis, without focusing on de novo postpartum depressive symptoms. Rich-Edwards et al. found that CRH levels at gestational week 28 were positively associated with depressive symptoms in midgestation, but not postpartum. However, the presence of prenatal depressive symptoms was not taken into account when examining the association between prenatal CRH and postpartum depressive symptoms, since the authors did not adjust for or exclude women with high prenatal EPDS scores. Moreover, the postpartum assessment of depressive symptoms took place at a time point long after delivery, namely 6 months postpartum.[17] Similarly, prenatal depressive symptoms were not taken into consideration in the study of Meltzer-Brody et al.,[16] where CRH was measured before pregnancy week 20 and between weeks 24 and 29. The analyses yielded no association between maternal CRH and depressive symptoms at 12 weeks and 1 year postpartum. Regarding prenatal depression, studies have reported a positive association between CRH levels and depressive symptoms in pregnancy.[17,18]

Although the recently suggested term of peripartum depression by the Diagnostic and Statistical Manual of Mental Disorders (fifth edition) does not differentiate prenatal from postpartum depression, the relatively large present study focuses on exclusively postpartum depressive symptoms, since it has been suggested that prenatal

and postpartum depression may have different pathophysiological underpinnings regarding the function of the HPA axis.[19] This could also, at least partly, explain the inconsistent results presented in the literature so far. Two subtypes of major depression have been described, namely, melancholic and atypical depression. Melancholic depression is a state of pathological hyperarousal where patients experience intense anxiety, insomnia, and loss of appetite. On the other hand, atypical depression can be described as nearly the opposite of melancholia. Indeed, these individuals exhibit a reverse symptomatology where feelings of emptiness, fatigue, sleepiness, and increase in food intake dominate the clinical manifestations of the condition.[19,20] The same pattern has been demonstrated at the hormonal level, where melancholic depression has been associated with elevated CRH whereas atypical depression is characterized by decreased CRH production.[6,21] It has also been suggested that peripartum depression is a heterogeneous disorder with substantial differences in the pathophysiology and clinical expression of depressive symptoms occurring before and after delivery. The idea that depression with antenatal onset may resemble melancholic whereas depression with postpartum onset is more like atypical depression has been introduced by previous studies.[19] The aim of this study was to assess, in nondepressed pregnant women, the possible association between pCRH in midgestation and the development of depressive symptoms in the postpartum period, taking into account several possible confounders, which are often overlooked.

MATERIALS AND METHODS

STUDY POPULATION

The current study was undertaken as a part of two population-based projects conducted at the Department of Obstetrics and Gynecology at Uppsala University Hospital in Sweden; the BASIC project (Biology, Affect, Stress, Imaging, Cognition), a longitudinal study on psychological well-being during pregnancy and postpartum, and the Uppsala Biobank of Pregnant Women, where blood samples are collected in conjunction with the routine ultrasound screening (gestational week 17). These projects are described in detail elsewhere.[12,22] Briefly, a self-administered structured questionnaire containing questions on sociodemographic and personal history and pregnancy-related variables, and a Swedish validated version of the EPDS[23] were filled in gestational weeks 17 and 32, as well as at 6 weeks postpartum. Moreover, data were retrieved from medical records. CRH levels were analyzed in maternal blood samples.

To account for the increased placental mass in multiple pregnancies,[24] the 21 twin pregnancies in the study sample were excluded. Data on EPDS scores in pregnancy weeks 17 and 32 and 6 weeks postpartum, as well as a valid CRH measurement were available for 536 women scoring lower than 12 in the EPDS in pregnancy week 17 and/or 32. One woman with an abnormally high level of CRH = 226.8 pg/ml, scoring 27 at the EPDS at 6 weeks postpartum, was considered as outlier (after calculation of standardized *z*-scores, cutoff $\geq \pm 3$) and was therefore also excluded. Women with significant depressive symptoms (EPDS $\geq$ 12) in pregnancy weeks 17 and/or 32 were excluded from the study sample (n = 98, 15.4%). Of those, 25 women had EPDS $\geq$12 only in pregnancy week 17, 41 women only in pregnancy week 32, and 32 women had EPDS $\geq$12 in pregnancy weeks 17 and 32. Finally, 535 women were included in the analyses.

HORMONAL ASSAY

Total CRH levels were estimated with radioimmunoassay (RIA). Details on the method are described elsewhere.[12]

PSYCHOMETRIC MEASURES

The Swedish version of the EPDS, a validated and internationally used 10-item self-reported questionnaire, designed as a screening tool to identify depressive symptoms in the peripartum period,[23] was used to assess depressive symptoms during pregnancy and postpartum. Different cut-off values have been suggested for perinatal depression screening. According to the latest NICE guidelines (National Institute for Health and Care Excellence, antenatal and postnatal mental health: clinical management and service guidance), the EPDS had good pooled sensitivity (Se = 0.68, 95% *CI* 0.66–0.71) and excellent pooled specificity (Sp = 0.92, 95% *CI* 0.92–0.93) for a cutoff of 13 points postpartum.[25] A cutoff of 12 points is often used to screen for postpartum depression in clinical settings in Sweden.[26] The 12-point cutoff provides sensitivity between 72%[27] and 77%[28] and specificity between 88%[27] and 92.5%.[28] In the present study, EPDS $\geq$12 was used as cutoff for defining significant depressive symptoms during pregnancy and postpartum.

To assess the number of stressful life events (SLE) that occurred up to 1 year prior to the postpartum evaluation, a 10-item scale developed by Rosengren et al.[29] was administered to study participants via a web-based questionnaire 6 weeks after the delivery. An index was created; range 0–10 and the cutoff was set at three or more SLE. The following were considered as significant SLE: serious illness in family member, serious concern about family member, death of family member, divorce or separation, involuntary change of residence, involuntary change of work, feelings of redundancy, feelings of insecurity at work, serious financial trouble, and legal prosecution.

STATISTICAL ANALYSES

The assumption of normality of the CRH levels was examined via P–P plots, which yielded a nonnormal distribution. To account for nonnormality, nonparametric univariate analyses were performed to compare CRH levels in relation to various psychiatric, lifestyle, obstetric, and anthropometric characteristics (Mann–Whitney *U* test). Dichotomized EPDS scores were compared to population characteristics by use of Pearson's chi-square test or Fisher's exact test. The independent samples *t*-test was performed to assess log-transformed CRH levels in association with dichotomized EPDS scores.

A logistic regression model was constructed, using the dichotomized postpartum EPDS score as the dependent variable and log-transformed CRH levels as the independent variable. In a further step, possible confounding factors were identified as those being associated with CRH levels and postpartum depressive symptoms at a significance level of P–value <.25[30] and were included in the logistic regression models. These factors included age, self-reported history of depression (no vs. yes), coexisting medical conditions (migraine, hypertension, diabetes, thyroid dysfunction, allergy, irritable bowel syndrome, significant alcohol consumption or chronic pain, present during pregnancy), and pregnancy day of CRH sampling (dichotomized at the median value). SSRI use was also introduced in the models[12] and women treated with SSRI, being in remission at the time of the study, were not excluded from the study sample. In a later step, other factors known to be associated with postpartum depression such as SLE (0–2 vs. $\geq$3 events out of the Rosengren scale[29]), poor sleep (difficulties in falling back to sleep after waking up in the night, no vs. yes), breastfeeding (exclusive and nonexclusive vs. none), and body mass index

(BMI; ≤24.9 vs. ≥25 kg/m^2, measured in early pregnancy)[31] were also introduced in the regression models.

Subanalyses. In further subanalyses, study subjects with preterm birth (<37 gestational weeks, $n = 15$) and with newborns characterized as small for gestational age (SGA; >2 standard deviations under the mean birth weight for newborns of same sex, born during the same gestational week, according to the national birth weight curves used in clinical practice in Sweden[32]; $n = 4$) were excluded from the study population, due to the possible correlation between CRH levels and gestational length as well as suboptimal fetal growth.[33,34] Moreover, women on corticosteroids ($n = 12$) were also excluded to account for a potential medication effect on the HPA axis.

The IBM SPSS version 20 (SPSS, Chicago, IL) was used for data analysis. Statistical significance was set at a *P*–value of <.05.

The Regional Ethical Review Board in Uppsala approved the study protocol. Written informed consent was obtained from all women participating in the study, after being informed about the course and aim of the study. The study was performed in accordance with the latest version of the Declaration of Helsinki.

RESULTS

The CRH median value was 60 pg/ml (sample minimum 24.4 pg/ml, maximum 139 pg/ml). The proportion of women scoring 12 or more points on the EPDS at 6 weeks postpartum was 44/535 (8.2%).

Table 1 presents various study population characteristics in relation to plasma CRH levels and postpartum EPDS scores. Log-transformed CRH levels were significantly higher among women with 12 or more points on postpartum EPDS, compared with those with nonsignificant depressive symptoms (mean log CRH 4.19 vs. 4.08, respectively). Moreover, an association was observed between CRH levels and employment status as well as gestational day of CRH sampling (median CRH 59.2 vs. 76.3 pg/ml, employed vs. unemployed [$P = .007$] and median CRH 57.7 vs. 61.6 pg/ml, gestational day ≤127 vs. >127 [$P = .05$], respectively). Additionally, women older than 34 years and those with coexisting medical conditions during pregnancy (as defined in the Methods section), hypertension and poor sleep, were more likely to experience depressive symptoms postpartum.

A binary logistic regression model with dichotomized postpartum EPDS score as the dependent variable and log-transformed CRH concentration as the independent variable showed a positive association between CRH levels in gestational week 17 and self-reported postpartum depressive symptoms (*OR* = 1.11, 95% *CI* 1.01–1.22, per 0.1 unit increase in log CRH). This association remained significant even after adjusting for age, history of depression, coexisting medical conditions, CRH sampling day, and use of SSRI (adjusted *OR* = 1.12, 95% *CI* 1.01–1.25). Additionally, these findings persisted when sleep problems, SLE, and breastfeeding at 6 weeks postpartum were introduced in the model (adjusted *OR* = 1.13, 95% *CI* 1.02–1.26; Table 2). In further subanalyses, the exclusion of women with preterm birth and newborns SGA as well as study subjects who used inhalation corticosteroids during pregnancy did not change the significant association between CRH levels and postpartum depressive symptoms. The insertion of BMI in the models did not change the results but was not included in the final models as it caused the estimation of unrobust coefficients. Finally, adjusting for nicotine use during pregnancy ($n = 13$) did not alter the results.

DISCUSSION

The main finding of the present study demonstrates an association between high levels of pCRH among nondepressed women in gestational week 17 and postpartum depressive symptoms. In line with previous findings that have suggested an alteration of the HPA axis prior to development of postpartum depressive symptoms,[13–15] our results, from the largest to date sample of nondepressed pregnant women, point to an even earlier dysregulation of the HPA axis, already in pregnancy week 17. These results are consistent with the hypothesis that, after delivery, the HPA axis may be differentially temporarily suppressed due to an effect of high circulating levels of CRH during late pregnancy on adrenal function.[6,11]

The present study results indicate an association between high pCRH levels in pregnancy and the development of depressive symptoms first in the postpartum period, after the exclusion of women with depressive symptoms in pregnancy. As suggested by Chrousos and Gold in earlier studies,[20,21] atypical depression is characterized by centrally mediated hypoactivity of the HPA axis with reduced secretion of CRH that may lead to pathological hypoarousal. Moreover, more recent studies have introduced the hypothesis of a pathophysiological resemblance between atypical and postpartum depression.[19] It seems plausible that an abnormal and prolonged elevation of CRH during pregnancy may result in greater residual hypothalamic suppression and HPA axis hypoactivity in the postpartum period, which can predispose vulnerable individuals for depression with postpartum onset. This hypothesis is supported by Magiakou et al.,[11] who showed that women with depressive symptoms postpartum exhibited a more severe suppression of hypothalamic CRH secretion that lasted longer. In fact, even though depressive episodes before and after childbirth may have a number of common psychosocial, biological, and possibly genetic factors in common, they may also present with some distinctive features, such as changes in the HPA axis, that might be specific for depression with postpartum onset. It should also be taken into account that other circumstances, that is, breastfeeding, changes in sleep patterns, and genetic factors are more specific to the postpartum period.[35]

Two previous studies were not able to demonstrate a clear association between CRH in pregnancy and postpartum depressive symptoms.[16,17] This could be at least partly explained by the fact that these studies did not take into consideration prenatal depressive symptoms in their analyses. This is an interesting aspect, since depression during pregnancy and postpartum might have different

TABLE 1. Demographic data of the study population in association with CRH in gestational week 17 and depressive symptoms 6 weeks postpartum

		CRH (pg/ml)				EPDS 6 weeks postpartum		
			($N = 535$)			Controls (<12 points) ($n = 491$)	Cases (≥12 points) ($n = 44$)	
		N	Median	Min–Max	*P**	*n* (%)	*n* (%)	*P***
Age (years)	≤34	417	59.0	(24.4-139)	.26	390 (80)	27 (61)	.005
	≥35	117	62.8	(25.5–135.7)		100 (20)	17 (39)	
BMI (kg/m^2)	≤24.9	166	63.4	(24.7–135.7)	.242	155 (58)	11 (58)	.996
	≥25	121	59.2	(30.5–139)		113 (42)	8 (42)	
Parity	Primipara	277	59.2	(24.7–139)	.787	254 (57)	23 (56)	.903
	Multipara	209	57.9	(24.4–131)		191 (43)	18 (44)	
SSRI	No	521	60.0	(24.4–139)	.54	479 (98)	42 (95)	.322
	Yes	14	60.2	(24.7–94.9)		12 (2)	2 (5)	
Education	Higher	425	59.8	(24.4–139)	.452	389 (80)	36 (82)	.720
	Lower	108	60.2	(31.6–131)		100 (20)	8 (18)	
Employment	Employed	491	59.2	(24.4–139)	.007	450 (95)	41 (98)	.999
	Unemployed	23	76.3	(42.6–115.6)		22 (5)	1(2)	
Depression history	No	417	57.1	(24.4–139)	.118	384 (87)	33 (79)	.115
	Yes	65	63.1	(24.7–131)		56 (13)	9 (21)	
Nicotine use before pregnancy	No	477	60.3	(24.4–139)	.534	434 (89)	43 (98)	.071
	Yes	56	57.7	(26.3–114.1)		55 (11)	1 (2)	
Nicotine use in Pregnancy	No	461	57.3	(24.4–131)	.997	423 (97)	38 (95)	.301
	Yes	13	59.2	(42.1–78.7)		11 (3)	2 (5)	
Alcohol use before pregnancy	No	311	59.8	(24.4–139)	.495	286 (59)	25 (58)	.903
	Yes	216	60.5	(26.8–127.3)		198 (41)	18 (42)	
Alcohol use in early pregnancy	No	528	60.0	(24.4–139)	.107	484 (99)	44 (100)	.999
	Yes	2	41.8	(34.8–48.8)		2 (1)	0 (0)	
CRH sampling (gestational day)	≤127	290	57.7	(24.4–127.3)	.055	271 (55)	19 (43)	.126
	>127	245	61.6	(25.5–139.0)		220 (45)	25 (57)	
Coexisting medical conditions[a]	No	267	61.9	(25.5–127.3)	.095	252 (52)	15 (34)	.023
	Yes	262	58.7	(24.4–139)		233 (48)	29 (66)	
Pregnancy length (days)	≥259	519	60.0	(24.4–139)	.978	477 (97)	42 (96)	.355
	<259	15	54.5	(37.4–127.3)		13 (3)	2 (4)	
Ethnicity	Caucasian	514	60.0	(24.4–139)	.323	472 (98)	42 (98)	.999
	Other	13	57.8	(35.2–104.1)		12 (2)	1 (2)	
Corticosteroids during pregnancy	No	523	59.9	(24.4–139)	.742	480 (98)	43 (98)	.999
	Yes	12	64.3	(37.4–88.1)		11 (2)	1 (2)	
IVF	No	495	60.0	(24.4–139)	.753	457 (93)	38 (86)	.121
	Yes	39	58.7	(28–131)		33 (7)	6 (14)	
Pregnancy week w32								
Diabetes	No	489	60.5	(24.4–139)	.148	448 (99)	41 (98)	.235
	Yes	3	77.4	(61.3–100.9)		2 (1)	1 (2)	
Hypothyroidism	No	480	60.4	(24.4–139)	.774	439 (98)	41 (98)	.999
	Yes	12	63.2	(32.1–86)		11 (2)	1 (2)	
Hypertension	No	478	60.7	(24.4–139)	.454	440 (98)	38 (91)	.025
	Yes	14	63.1	(40–127.3)		10 (2)	4 (9)	
Preeclampsia	No	492	60.7	(24.4–139)	–	450 (100)	42 (100)	–
	Yes	0	–	–		0 (0)	0 (0)	
6 weeks postpartum								
Stressful life events[b]	0 – 2	485	60.0	(24.7–139)	.291	449 (91)	36 (82)	.053
	≥3	50	58.6	(24.4–115.3)		42 (9)	8 (18)	

(*Continued*)

TABLE 1. Continued

		CRH (pg/ml) ($N = 535$)				EPDS 6 weeks postpartum		
						Controls (<12 points) ($n = 491$)	Cases (≥12 points) ($n = 44$)	
		N	Median	Min–Max	*P**	*n* (%)	*n* (%)	*P***
Breastfeeding	Yes	500	60.6	(24.4–139)	.962	461 (94)	39 (91)	.315
	No	32	58.3	(33.7–100)		28 (6)	4 (9)	
Partner support	Yes	525	60.0	(24.4–139)	.577	482 (99)	43 (100)	.999
	No	3	70.8	(53.3–72.6)		3 (1)	0 (0)	
Nicotine use	No	520	59.8	(24.4–139)	.479	478 (98)	42 (96)	.292
	Yes	13	63.1	(42.1–105.8)		11 (2)	2 (4)	
Poor sleep[c]	No	515	60.0	(24.4–139)	.28	475 (98)	40 (91)	.036
	Yes	16	72.4	(26.3–127.3)		12 (2)	4 (9)	
CRH vs. EPDS						Controls (<12 points)	Cases (≥12 points)	*P*^
Log-transformed CRH (mean)		–	–	–	–	4.08	4.19	.033

*Mann–Whitney *U* test derived *P*–value; significance level <.05.
**Pearson χ^2 test or Fisher's exact test (in cases that >20% cells have expected count less than 5) derived *P*–value.
^Independent samples *t*–test derived *P*–value.
[a]Migraine, hypertension, diabetes, thyroid dysfunction, allergy, irritable bowel syndrome, significant alcohol consumption, or chronic pain (during pregnancy).
[b]Refer to past 12 months.
[c]Difficulties in falling back to sleep after waking up in the night.
BMI, body mass index; CRH, corticotropin-releasing hormone; SSRI, selective serotonin reuptake inhibitor (during pregbrnancy); IVF, in vitro fertilization; EPDS, Edinburgh Postnatal Depression Scale.

pathophysiologic mechanisms involving dissimilar levels of hypothalamic CRH, cortisol, and estrogen. Including women with depressive symptoms in pregnancy could neutralize the association between high CRH levels in pregnancy and postpartum depression, a CRH, estrogen and, possibly, cortisol deficiency state,[6] as was seen even in our material.

One might also consider the possibility that women who were in remission during pregnancy, due to SSRI treatment, could have suffered from a relapse postpartum and thus could also have driven the observed association between CRH levels and postpartum depressive symptoms, due to the higher levels of CRH in women with SSRI treatment that have been recently demonstrated in another study.[12] However, no direct comparison to

TABLE 2. Logistic regression derived *OR* and 95% *CI* for self-reported exclusively postpartum depressive symptoms in relation to log-transformedCRH levels

	Model 1 (unadjusted)		Model 2		Model 3	
	OR	95% *CI*	*OR*	95% *CI*	*OR*	95% *CI*
CRH (log)[a]	1.11	1.01–1.22	1.12	1.01–1.25	1.13	1.02–1.26
Age			1.07	0.99–1.14	1.07	0.99–1.15
History of depression			1.39	0.56–3.45	1.27	0.50–3.25
Coexisting medical conditions[b]			2.29	1.15–4.56	2.10	1.03–4.28
CRH sampling day			1.54	0.80–2.96	1.73	0.87–3.43
SSRI			1.26	0.22–7.18	1.64	0.28–9.57
Sleep problems[c]					5.18	1.35–19.95
Stressful life events[d]					2.39	0.93–6.14
Breastfeeding[e]					1.70	0.52–5.52
	$n = 535$		$n = 475$		$n = 468$	

[a]*OR* per 0.1 unit increase in log CRH.
[b]Migraine, hypertension, diabetes, thyroid dysfunction, allergy, irritable bowel syndrome, significant alcohol consumption, or chronic pain (during pregnancy).
[c]Difficulties in falling back to sleep after waking up in the night.
[d]Refer to past 12 months.
[e]Exclusive and nonexclusive vs. none.
CRH, corticotropin-releasing hormone; SSRI, selective serotonin reuptake inhibitors.

that study's results is feasible, as the SSRI-treated group in the earlier study included women with and without depression symptoms, as well as women receiving SSRI for conditions other than depression. Nevertheless, the observed association between CRH levels and depressive symptoms in the present study was not altered after adjusting for SSRI treatment.

Inconsistencies between the present results and nonsignificant findings of other studies may also depend on methodological issues, concerning the psychometric and hormonal assessment tools. Specifically, Meltzer-Brody et al.[16] assessed CRH by using competitive enzyme immunoassay, while radioimmunoassay is the most common technique used for CRH measurement, among studies focusing on CRH during pregnancy[13,14,17,36] and in general.[37] Contributing factors for the selection of RIA by the majority of relevant studies are the use of RIA in the initial studies measuring CRH and the greater sensitivity characterizing this method.[37] Regarding the time of mood assessment in the postpartum period, Rich-Edwards et al.[17] assessed maternal mood at 6 months postpartum, when the effect of HPA dysregulation may already have declined, which may also account for this study's nonsignificant results regarding the postpartum period.

More of this study's results are also in line with the literature. The expected progressive rise in CRH levels during the course of pregnancy was confirmed by the present results that showed a positive association between CRH and gestational day of blood sampling. Moreover, unemployed study subjects had higher CRH levels in gestational week 17. In a similar study that explored associations between CRH and prenatal depressive symptoms, women with lower perceived adequacy of income exhibited higher CRH levels in pregnancy.[36] A link may exist between HPA axis dysregulation and employment that could be further explained by the association between CRH and stress-related conditions, which may be related to poor socioeconomic status and unemployment.[38] The rather low proportion of postpartum depressed women, at 8.2%, is most probably due to the design-indicated absence of depressed pregnant women in this sample. The CRH levels observed in the present study are in line with findings from previous studies, taking into account the pregnancy week of the CRH measurement.

The relatively large number of study participants; the longitudinal, population–based design of the present study; and the availability of information on several population characteristics should be accounted as strengths of this study. On the contrary, a study limitation is the use of a self-reporting psychometric measure instead of a psychiatric interview that may have been more accurate but also more difficult to conduct in a research setting. Since the EPDS is a self-reporting instrument, misclassification of study subjects may occur. However, this scale is validated and widely used and has a quite high sensitivity and specificity.[26–28] Moreover, one should be cautious in the generalizability of the study findings and should bear in mind the participation rate in the BASIC study (22%), where healthier, highly educated mothers are overrepresented. The measurement of free, rather than total, plasma CRH can be regarded as a study limitation. However, previous studies attempting to evaluate CRH levels measure total CRH, since reports on the measurement of free CRH are lacking. Finally, the present results should be interpreted with caution, since pCRH levels were operationalized as a continuous variable, without a further distinction between high and low pCRH levels. This strategy was adopted since the primary purpose of this study, similar to previous studies in this research field, was to elucidate certain pathophysiological aspects of postpartum depression, and not draw any direct clinical conclusions.

CONCLUSIONS

The findings of this study suggest an association between high CRH levels in nondepressed women in gestational week 17 and the development of postpartum depressive symptoms, taking into account several possible confounding factors.

Acknowledgments. We thank all the women participating in the BASIC study and the Uppsala Biobank for Pregnant Women; Pepita Knuutila for valuable help with medical record data; and Marianne Kördel and Lena Moby for their creative thinking, hard work, and dedication in the organization and management of this project.

Conflict of interest. None.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
2. Allolio B, Hoffmann J, Linton EA, Winkelmann W, Kusche M, Schulte HM. Diurnal salivary cortisol patterns during pregnancy and after delivery: relationship to plasma corticotrophin-releasing-hormone. Clin Endocrinol (Oxf) 1990;33:279–289.
3. Jung C, Ho JT, Torpy DJ, et al. A longitudinal study of plasma and urinary cortisol in pregnancy and postpartum. J Clin Endocrinol Metab 2011;96:1533–1540.
4. Glynn LM, Davis EP, Sandman CA. New insights into the role of perinatal hpa-axis dysregulation in postpartum depression. Neuropeptides 2013;47:363–370.
5. Linton EA, Perkins AV, Woods RJ, et al. Corticotropin releasing hormone-binding protein (crh-bp): plasma levels decrease during the third trimester of normal human pregnancy. J Clin Endocrinol Metab 1993;76:260–262.
6. Chrousos GP, Torpy DJ, Gold PW. Interactions between the hypothalamic-pituitary-adrenal axis and the female reproductive system: clinical implications. Ann Intern Med 1998;129:229–240.
7. Robinson BG, Emanuel RL, Frim DM, Majzoub JA. Glucocorticoid stimulates expression of corticotropin-releasing hormone gene in human placenta. Proc Natl Acad Sci USA 1988;85:5244–5248.
8. Jones SA, Brooks AN, Challis JR. Steroids modulate corticotropin-releasing hormone production in human fetal

membranes and placenta. J Clin Endocrinol Metab 1989;68:825–830.
9. Cheng YH, Nicholson RC, King B, et al. 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;85:1937–1945.
10. McLean M, Bisits A, Davies J, et al. A placental clock controlling the length of human pregnancy. Nat Med 1995;1:460–463.
11. Magiakou MA, Mastorakos G, Rabin D, et al. Hypothalamic corticotropin-releasing hormone suppression during the postpartum period: implications for the increase in psychiatric manifestations at this time. J Clin Endocrinol Metab 1996;81:1912–1917.
12. Hannerfors AK, Hellgren C, Schijven D, et al. Treatment with serotonin reuptake inhibitors during pregnancy is associated with elevated corticotropin-releasing hormone levels. Psychoneuroendocrinology 2015;58:104–113.
13. Glynn LM, Sandman CA. Evaluation of the association between placental corticotrophin-releasing hormone and postpartum depressive symptoms. Psychosom Med 2014;76:355–362.
14. Hahn-Holbrook J, Schetter CD, Arora C, Hobel CJ. Placental corticotropin-releasing hormone mediates the association between prenatal social support and postpartum depression. Clin Psychol Sci 2013;1:253–264.
15. Yim IS, Glynn LM, Dunkel-Schetter C, et al. Risk of postpartum depressive symptoms with elevated corticotropin-releasing hormone in human pregnancy. Arch Gen Psychiatry 2009;66:162–169.
16. Meltzer-Brody S, Stuebe A, Dole N, et al. Elevated corticotropin releasing hormone (crh) during pregnancy and risk of postpartum depression (ppd). J Clin Endocrinol Metab 2011;96:E40–E47.
17. Rich-Edwards JW, Mohllajee AP, Kleinman K, et al. Elevated midpregnancy corticotropin-releasing hormone is associated with prenatal, but not postpartum, maternal depression. J Clin Endocrinol Metab 2008;93:1946–1951.
18. O'Keane V, Lightman S, Marsh M, et al. Increased pituitary-adrenal activation and shortened gestation in a sample of depressed pregnant women: a pilot study. J Affect Disord 2011;130:300–305.
19. Kammerer M, Taylor A, Glover V. The HPA axis and perinatal depression: a hypothesis. Arch Womens Ment Health 2006;9:187–196.
20. Gold PW, Chrousos GP. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. Mol Psychiatry 2002;7:254–275.
21. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. JAMA 1992;267:1244–1252.
22. Iliadis SI, Comasco E, Sylven S, et al. Prenatal and postpartum evening salivary cortisol levels in association with peripartum depressive symptoms. PLoS One 2015;10:e0135471.
23. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10–item Edinburgh Postnatal Depression Scale. Br J Psychiatry 1987;150:782–786.
24. Warren WB, Goland RS, Wardlaw SL, et al. Elevated maternal plasma corticotropin releasing hormone levels in twin gestation. J Perinat Med 1990;18:39–44.
25. NICE Guidelines (CG 192). Antenatal and postnatal mental health: clinical management and service guidance. 2014. Available at: https://www.nice.org.uk/guidance/cg192.
26. Wickberg B, Hwang CP. The Edinburgh Postnatal Depression Scale: validation on a Swedish community sample. Acta Psychiatr Scand 1996;94:181–184.
27. Statens Beredning för Medicinsk Utvärdering (SBU). Diagnostik och uppföljning av förstämningssyndrom. En systematisk litteraturöversikt. 2012. Available at: http://www.sbu.se/forstamningssyndrom.
28. Murray L, Carothers AD. The validation of the edinburgh postnatal depression scale on a community sample. Br J Psychiatry 1990;157:288–290.
29. Rosengren A, Orth-Gomer K, Wedel H, Wilhelmsen L. Stressful life events, social support, and mortality in men born in 1933. BMJ 1993;307:1102–1105.
30. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. Am J Epidemiol 1989;129:125–137.
31. Stirrat LI, O'Reilly JR, Riley SC, et al. Altered maternal hypothalamic-pituitary-adrenal axis activity in obese pregnancy is associated with macrosomia and prolonged pregnancy. Pregnancy Hypertens 2014;4:238.
32. Marsal K, Persson PH, Larsen T, et al. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatr 1996;85:843–848.
33. Petraglia F, Imperatore A, Challis JR. Neuroendocrine mechanisms in pregnancy and parturition. Endocr Rev 2010;31:783–816.
34. Wadhwa PD, Garite TJ, Porto M, et al. Placental corticotropin-releasing hormone (crh), spontaneous preterm birth, and fetal growth restriction: a prospective investigation. Am J Obstet Gynecol 2004;191:1063–1069.
35. Murphy-Eberenz K, Zandi PP, March D, et al. Is perinatal depression familial? J Affect Disord 2006;90:49–55.
36. 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;12:125–136.
37. Latendresse G, Ruiz RJ. Bioassay research methodology: measuring CRH in pregnancy. Biol Res Nurs 2008;10:54–62.
38. Stratakis CA, Chrousos GP. Neuroendocrinology and pathophysiology of the stress system. Ann N Y Acad Sci 1995;771:1–18.