Prolonged periods without food intake during pregnancy increase risk for elevated maternal corticotropin-releasing hormone concentrations

Tracy S. Herrmann, PhD,[a] Anna Maria Siega-Riz, PhD,[a, b] Calvin J. Hobel, MD,[c] Chandra Aurora, PhD,[c] and Christine Dunkel-Schetter, PhD[d]

Chapel Hill, NC, and Los Angeles, Calif

OBJECTIVE: Fasting during pregnancy stimulates preterm delivery in animals and increases women's risk for preterm delivery. Fasting stimulates hypothalamic corticotropin-releasing hormone production in animals. Elevated maternal corticotropin-releasing hormone concentrations are associated with preterm birth. We hypothesized that prolonged periods without food during pregnancy increase maternal corticotropin-releasing hormone concentrations, which lead to preterm delivery.

STUDY DESIGN: In the Behavior in Pregnancy Study, we examined prolonged periods without eating during pregnancy and corticotropin-releasing hormone concentrations and gestational age at delivery with multivariate logistic regression analysis (n = 237).

RESULTS: Prolonged periods without food lasting 13 hours or longer were associated with elevated maternal corticotropin-releasing hormone concentrations compared with prolonged periods without food lasting less than 13 hours at two time points during pregnancy, controlling for pregravid body mass index, energy intake, income, race, smoking, and maternal age (18-20 weeks: adjusted odds ratio, 2.5; 95% CI, 0.9-7.1; 28-30 weeks: adjusted odds ratio, 1.7; 95% CI, 0.7-4.2). There was an inverse, linear relationship between maternal corticotropin-releasing hormone concentrations and gestational age at delivery.

CONCLUSIONS: Prolonged periods without food intake during pregnancy are associated with elevated maternal corticotropin-releasing hormone concentrations and with preterm delivery. (Am J Obstet Gynecol 2001;185:403-12.)

Key words: Pregnancy, food intake, corticotropin-releasing hormone

Animal experiments indicate that a 12- to 48-hour fast during late gestation stimulates early and preterm delivery.[1, 2] Short-term food deprivation also upregulates hypothalamic corticotropin-releasing hormone (CRH) messenger RNA (mRNA) in various regions of the brain in rats.[3, 4] These data suggest that the production of CRH is partly controlled by the availability of nutrients, and thus low blood glucose or hypoglycemia during pregnancy may induce preterm delivery through the stimulation of these neuroendocrine events. This cascade of neuroendocrine events may stimulate placental-fetal signaling during late gestation to hasten delivery of the infant from an adverse environment.

In two separate analyses, we have reported that meal patterns of pregnant women and the frequency of food intake during pregnancy are relevant to the relationship between maternal nutrition status and preterm birth.[5] Women who ate fewer than 3 meals and 2 snacks per day had a 30% higher risk for delivering preterm when compared with pregnant women who met this level.[5] There was no difference in risk by gestational age, but women delivering after premature rupture of the membranes had a higher risk than women who delivered after preterm labor (adjusted odds ratio [AOR], 1.87; 95% CI, 1.02-3.43; and AOR, 1.11; 95% CI, 0.65-1.89; respectively). In the same cohort, pregnant women who reported not eating for ≥13

From the Departments of Nutrition[a] and Maternal and Child Health,[b] School of Public Health, University of North Carolina at Chapel Hill, the Department of Obstetrics and Gynecology, the Burns and Allen Research Institute, Cedars-Sinai Medical Center,[c] and the Department of Psychology, University of California at Los Angeles.[d]

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Reprint requests: Tracy S. Herrmann, PhD, RD, University of Utah, Department of Perinatal Genetics, 729 Arapeen Dr, #136, Salt Lake City, UT 84108. E-mail: tracy.herrmann@hsc.utah.edu.

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hours per day had a 3-fold greater risk of delivering preterm at ≤34 weeks' gestation when compared with women who reported <13 hours without food per day (T. S. Herrmann, unpublished data, 1999).

CRH was first identified in the hypothalamus[6] and has now been characterized in a variety of other sites, including the placenta and plasma of pregnant women.[7, 8] CRH is the primary modulator of hypothalamic-pituitary-adrenal axis activation in response to stress by stimulating the secretion of corticotropin from the pituitary, followed by cortisol release from the adrenal glands. Scientists postulate that cortisol stimulates placental CRH gene expression, which causes the increase in circulating concentrations of plasma CRH. Two studies have shown that women who deliver preterm have significantly elevated concentrations of plasma CRH compared with gestational age-matched controls.[9, 10] Thus we hypothesized that fasting during pregnancy stimulates cortisol secretion from the adrenal, which stimulates placental CRH gene expression, thereby increasing maternal CRH concentrations and leading to preterm delivery. This neuroendocrine pathway is similar to the pathway proposed for the relationship between psychosocial stress and preterm birth.[10, 11]

The aim of this study was to examine the longest period without food, including an overnight fast, that women reported during pregnancy and its association with maternal plasma CRH concentrations. We used data from a longitudinal, prospective, cohort study of pregnant women in which dietary information and plasma CRH concentrations reflected the same 24-hour period. This enabled us to look at the short-term effects of fasting or prolonged periods without food on plasma CRH concentrations at two time points during pregnancy, one during the middle of the second trimester and one during the early third trimester.

Material and methods

Study design and sample. The Behavior in Pregnancy Study (BIPS) was a National Institutes of Health–funded project at the Department of Obstetrics and Gynecology of Cedars-Sinai Medical Center in Los Angeles, California. This study was a prospective study of pregnant women assessed from 18 to 20 weeks' (time 1), 28 to 30 weeks' (time 2), and 35 to 36 weeks' (time 3) gestation, as well as from 4 to 6 weeks post partum.[10] The objective of BIPS was to determine the relationship of chronic stress and physical strain to preterm birth and low birth weight. Women were recruited and enrolled from 1993 to 1996. At each assessment, self-reported psychosocial and behavioral measurements were collected by interview. Specific biochemical and biophysical measures were also obtained by assay of urine and venous blood samples and by obtaining fetal and maternal parameters. The same procedures for data collection were used during each assessment.

Women were recruited from 3 sources of patients who deliver at Cedars-Sinai Medical Center. These sources included the Cedars Public Clinic, Cigna Health Care Plan, and private patients. Approximately one third of the sample came from each of the 3 sites (clinic, health maintenance organization, and private practice), which represent a variety of women with different social, demographic, and economic characteristics. Recruitment of patients was conducted similarly at all 3 sites. Medical complications and outcome data were obtained from prenatal labor, delivery, postpartum, and newborn records. All pregnant women who were 18 years of age or older, English- or Spanish-speaking, and less than 20 weeks pregnant with a single gestation were eligible for participation in the study. The study population of 688 was composed of 32% Hispanic, 20% white, and 43% black pregnant women. Women in the cohort were in their primary childbearing age (20-33 years old), with a mean age of 27.7 years. The mean education level was 12 years, with 51% having a high school education or less.

Ascertainment of main outcome

CRH. Biologic samples from BIPS were collected and stored at the Cedars-Sinai Perinatal Research Laboratory for the CRH assays. Plasma CRH concentrations were determined at all 3 time points during the study. Blood was collected and chilled in glass tubes containing ethylenediaminetetraacetic acid (1 mg/mL blood) and aprotinin (500 kIU/mL blood) and was centrifuged at 4°C. Plasma was stored at –70°C. Plasma was extracted with Sep-Pak (Waters Associates, Milford, Mass) C-18 cartridges for measurement of immunoreactive CRH levels. Acidified plasma was loaded onto columns previously activated with 60% acetonitrile in 1% trifluoroacetic acid. The columns were washed twice with 3 mL of 1% trifluoroacetic acid. The absorbed peptide was eluted with 3 mL of acetonitrile, trifluoroacetic acid buffer, and eluant dried in a speed-vacuum concentrator (Savant Instruments, Micksville, NY). The dried extracts were stored at –80°C and resuspended in radioimmunoassay buffer at the time of assay. Plasma CRH concentrations were measured by specific double-antibody radioimmunoassay. Specific polyclonal rabbit antisera and the iodinated peptides were obtained from Peninsula Laboratories in Belmont, California. Cross-reactivities of CRH antiserum were 100% for human and rat CRH and 0% for the precursor of CRH for human CRH. The detailed radioimmunoassay procedure has been previously described.[12]

There were 237 women with CRH values at time 1 and 236 women with CRH values at time 2 who also reported their dietary intake and thus were used in these data analyses. Plasma CRH concentrations were examined in continuous and categoric form at 18 to 20 weeks' and 28 to 30 weeks' gestation (times 1 and 2). To examine the risk of having high plasma CRH concentrations at times 1 and 2, CRH values were divided into categories repre-

Table I. Mean plasma CRH concentrations among women who fasted for different time periods

	Fasting duration		
Time of gestation (wk)	*≤9 h*	*10-12 h*	*≥13 h*
18-20	8.2 ± 0.4 (n = 25)	7.9 ± 0.1 (n = 99)	8.5 ± 0.4 (n = 113)
28-30	245.2 ± 4.9 (n = 25)	245.7 ± 2.7 (n = 113)	243.9 ± 3.1 (n = 98)

senting <75th percentile, the 75th to 90th percentile, and >90th percentile of the sample distribution and were examined in relation to various categories of time without food.

Ascertainment of primary exposure

Fasting. Because the dietary assessment component of BIPS began in 1994, not all of the women in the study completed this component. Three hundred forty women completed one 24-hour dietary recall at 18 to 20 weeks' and 28 to 30 weeks' gestation. A self-reported, 24-hour recall questionnaire was designed to follow the Nutrition Data System format for data collection (Nutrition Data System, version 2.91, Minneapolis, Minn). These 24-hour recalls captured the time of day at which meals and snacks were eaten, the amount of food and beverages consumed, the brand name of the food or beverage, and the method of food preparation. The questionnaires were filled out by the study participants during a clinic visit and reviewed by the study nurse for completion during each visit. The dietary data were entered into the data system for analysis. Mealtime data from the assessments at 18 to 20 weeks' and 28 to 30 weeks' gestation were used to determine the longest period without food that women reported. The risk of having high plasma CRH concentrations was explored with multiple categories of time without food in the data analysis. However, the risk for high CRH concentrations increased significantly among those women who fasted for ≥13 hours at times 1 and 2 (Table I). Previously, we reported that women who fasted ≥13 hours in the Pregnancy, Infection, and Nutrition study had a significantly higher risk for preterm birth (AOR, 3.2; 95% CI, 1.1-9.7). Therefore in this study we examined the same exposure of fasting ≥13 hours during pregnancy on the outcome of interest.

Measurement of selected covariates. Potential confounders of the relationship between prolonged time without food and elevated CRH values as noted in previous published studies included the following: age, psychosocial stress, energy intake, pregravid body mass index (BMI), illicit drug or alcohol use, physical activity, socioeconomic status, education, income, and race.[10, 11] Information on confounders was obtained from clinic visits, study questionnaires, and medical records. Women provided the following background information: date of birth, race, marital status, number of years of school, prepregnancy weight, height, pregnancy history, and previous medical history. Current pregnancy information such as use of medications, drugs, alcohol, or cigarettes, as well as information on infection, fever, hospitalization, obstetric complications, and laboratory tests, was collected at each study visit. Women were also asked to state whether they had actively exercised, had been bothered by events or people, or had eaten on the day of the study visits for time 1 and time 2. Gestational age was assessed on the basis of a reliable estimate of the woman's last menstrual period, when available, or by ultrasonography if the last menstrual period was unknown. When both were available and the two estimates were within 10 days of each other, the last menstrual period was used. When the two estimates were not within 10 days of each other, the ultrasonographic estimate was used.

Energy intake may be a primary determinant of plasma CRH concentration. Furthermore, the effects of prolonged periods without food on plasma CRH concentrations may be confounded by total energy intake. Dietary data from the 24-hour recalls collected at both 18 to 20 and 28 to 30 weeks' gestation allowed for the examination of energy intake as a potential confounder, an effect modifier, or both during the first two trimesters of pregnancy. Thus we evaluated the effects of total energy intake as a continuous variable and categorically (quartiles). An additional dietary factor taken into consideration was caffeine intake. The stimulatory effect of high caffeine intake on the central nervous system may be a primary determinant of plasma CRH concentrations. Thus we examined the effects of total caffeine intake on a continuous scale, in addition to examining the percentage of women who consumed more than 200 mg/d. This cutoff point was chosen to represent the effects of more than 2 cups of brewed coffee per day.

Exposure to psychosocial stress during pregnancy predicts significant changes in CRH from 18 to 20 weeks' gestation to 28 to 30 weeks' gestation.[10] Psychosocial stress may also exacerbate or initiate negative eating behaviors during pregnancy such as skipping meals, thus sustaining prolonged periods without food. Certain psychosocial domains, such as perceived stress, perceived control over one's life, and feelings of anxiety or worry, may significantly affect eating behavior. The psychosocial data obtained in BIPS were measured in behavioral interviews with various instruments including the Perceived Stress Scale, Spielberger's State Inventory Scale, and a Life Events Questionnaire. The Perceived Stress Scale and Spielberger's State Inventory Scale were previously used

to predict high plasma CRH values in a separate sample of BIPS.[10] The Life Events Questionnaire has been previously used to ascertain the relationship between high stress and fasting during pregnancy. However, there was no association between negative life events and prolonged periods without food. Thus only the Perceived Stress Scale and Spielberger's State Inventory Scale were used to examine the psychosocial characteristics of women who have prolonged periods without food during pregnancy. These two instruments, which have been used previously to measure chronic stress and feelings of anxiety in several studies examining pregnant women, are described below in more detail.

An 8-item abbreviated version of the Perceived Stress Scale was used to ascertain general feelings of stress during pregnancy.[13] This scale measures the woman's perception of situations in her life as unpredictable, uncontrollable, and taxing. It has been previously used as a measure of chronic stress levels in studies with pregnant women.[14, 15] The questions ask the women how often in the last month they felt unable to control important things in their lives, deal with daily stressors, cope with life changes, handle personal problems, control irritations, or overcome difficulties, and how often they felt that things were going well. Responses were rated on a 5-point scale anchored by 1 (never) and 5 (almost always).

A shortened 10-item version of Spielberger's State Inventory was used to measure subjective feelings of anxiety during pregnancy.[16] This scale has also been used in studies of pregnant women.[17] Women are presented with a list of adjectives including calm, tense, at ease, nervous, jittery, relaxed, worried, steady, and frightened and asked to describe their feelings during the last few days. Responses are rated on 4-point scale anchored by 1 (not at all) and 4 (very much). The scores from the Perceived Stress Scale and State Anxiety Inventory were highly correlated, and thus the standardized scores for each scale are combined to create a composite score of stress levels at time 1 and time 2.[10]

Statistical analysis. Descriptive statistics were generated to describe the distributions of the exposure, outcome, and covariates. A Student *t* test and χ^2 test were used to evaluate statistical significance of differences between groups for various demographic and dietary characteristics. A *P* value of .05 was used to determine significant differences. The following crude bivariate relationships were examined: (1) exposure and outcome variables, (2) exposure and covariates, and (3) covariates and outcome. Stratified analyses were conducted to identify potential confounders and to examine potential effect modification.

Multivariate logistic regression was used to control for multiple covariates in the analysis. Potential confounders were entered into the model according to stepwise logistic regression and only those covariates that changed the β coefficient of the crude relationship between the exposure and outcome variables by more than 10% were retained. The AOR and 95% CI were then calculated. Maternal plasma CRH concentrations at 18 to 20 weeks' gestation have been found to predict maternal CRH concentrations at 28 to 30 weeks' gestation.[10] Thus structural equation models with latent variables were developed to adjust for the longitudinal effect of CRH at 18 to 20 weeks' gestation on CRH at 28 to 30 weeks' gestation. This technique is similar to a combination of factor analysis and path analysis performed simultaneously. Factor analysis assumes that a reduced set of underlying factors (latent variables) are responsible for the correlations among the variables actually observed (observed variables). Latent variables are produced, which represent the variance shared by the observed variables. Structural equation modeling assumes that the latent constructs (CRH at 18-20 weeks' gestation) caused the observed responses (CRH at 28-30 weeks' gestation). In path analysis, a causal model is hypothesized, and path coefficients between latent variables are estimated from a sample's covariance matrix. The path coefficients reflect the extent to which the criterion variable (CRH at 28-30 weeks' gestation) increases or decreases with an increase of 1 SD in the predictor variable. Finally, ordinary least regression was used to assess the relationship between CRH at each time period and gestational age at delivery. SAS software (version 6.12; SAS, Cary, NC) was used for data management and STATA (version 6.0; Stata Corporation, College Station, Tex) and SAS software were used for statistical calculations.

Results

The age distribution of these women was 15 to 17 years (3%), 18 to 24 years (30%), 25 to 34 years (58%), and 35 years and older (9%). The ethnic distribution was 24% white, 33% Hispanic, 39% black, and 5% Asian and Native American. Forty-five percent of the women had not completed a high school degree, and 54% of the women were currently married. In the current study, we had access to plasma CRH values for 237 pregnant women from BIPS at time 1 and CRH values on 236 pregnant women at time 2 who also had dietary information. The longest time periods without food in this sample of BIPS ranged from 6.0 to 21.75 hours. Multiple categories of time without food were examined. Ten percent of the women reported ≤9 hours without food, 42% of the women reported 10 to 12 hours without food, and 48% of the women reported ≥13 hours without food at 18 to 20 weeks' gestation. Ten percent of the women reported ≤9 hours without food, 48% of the women reported 10 to 12 hours without food, and 42% of the women reported ≥13 hours without food at 28 to 30 weeks' gestation. The mean CRH values were not significantly different between women in the groups representing multiple fasting periods at times 1 and 2 (Table I).

Table II. Relative risk of fasting ≥13 hours and having high plasma CRH values*

		Plasma CRH concentrations		
Time of gestation (wk)	*Exposure (h)*	*<75th percentile*	*75-90th percentile*	*>90th percentile*
18-20	≥13	1.0 (n = 177)	0.7 (0.4-1.3)† (n = 35)	1.9 (0.9-4.0)† (n = 25)
28-30	≥13	1.0 (n = 175)	1.2 (0.6-2.1)† (n = 37)	2.0 (0.9-4.2)† (n = 24)

*Cutoff points of plasma CRH concentrations used for the sample distribution.
†Compared with referent group of <75th percentile.

Table III. Relative risks for high plasma CRH concentrations among women who fasted for different time periods

		Fasting period		
Time of gestation (wk)	*Outcome*	*≤9 h*	*10-12 h*	*≥13 h*
18-20	CRH ≥90th percentile	1.0	1.2 (0.6-2.5)*	1.3 (0.7-2.4)*
28-30	CRH ≥90th percentile	1.0	1.2 (0.7-2.3)*	1.3 (0.6-2.8)*

*Compared with referent group of ≤9 h fasting.

There was not a linear relationship between prolonged periods without food and plasma CRH concentrations. Therefore the relationship between prolonged periods without food and CRH was examined in two additional ways. The first evaluation was for the risk of having prolonged periods without food intake ≥13 hours and having high plasma CRH; this was determined with cutoff points for increasing concentrations of plasma CRH at times 1 and 2 (Table II). The risk for having CRH values in the 90th percentile or higher of the sample distribution among women who had prolonged periods without food intake ≥13 hours was highest at 18 to 20 weeks' and at 28 to 30 weeks' gestation. The second evaluation examined the risk for having CRH values in the 90th percentile or higher among women with different time periods without food (Table III). The risk for having CRH values in the 90th percentile or higher of the sample distribution was highest among women who had prolonged periods without food intake ≥13 hours when compared with women who had prolonged periods without food intake for ≤9 hours at 18 to 20 weeks' and 28 to 30 weeks' gestation.

Baseline information obtained from the women included sociodemographic, anthropometric, and health behavior characteristics. There were additional characteristics collected during time 1, such as number of hours spent at work or caring for children. We compared the differences in characteristics between women who had prolonged periods without food intake for ≥13 hours with women who sustained ≤13 hours without food at time 1 and time 2. We also compared the differences in characteristics between women with plasma CRH values in the 90th percentile or higher with women who had plasma CRH values in the less than the 90th percentile at time 1 and time 2. There were strong similarities between the baseline characteristics of these groups at times 1 and 2.

Table IV represents the differences in characteristics between these groups at time 1. Women who had prolonged periods without food intake for ≥13 hours were more likely to be black, married, have >3 children, and have a family income of $20,000 or less per year than the women who sustained <13 hours without food (Table IV). Women in the exposed group were less likely to be working yet reported working a second job. They were more likely to be working a lower number of hours per week at their jobs while performing a higher number of hours per week at household duties than the women who sustained <13 hours without food at time 1. These women were also more likely to smoke during their pregnancy and to be obese before pregnancy (BMI, >29) (Table IV). Women with CRH values in the 90th percentile or higher were more likely to be black, have one child, have a family income less than $20,000 per year, have a normal body weight (BMI, 19.8-26), smoke during pregnancy, and were less likely to be working when compared with women who had CRH values less than the 90th percentile (Table IV).

Table V represents the differences in dietary and additional health behavior characteristics that were collected at both time 1 and time 2 between the exposed versus the unexposed women. The women who had prolonged periods without food intake ≥13 hours consumed less energy and were more likely to be in the lowest quartile of energy intake than the unexposed group at times 1 and 2. These women were also less likely to have high caffeine intake at times 1 and 2 than the women who had prolonged periods without food intake <13 hours (Table V). Furthermore, the women who had prolonged periods without food intake ≥13 hours consumed significantly less carbohydrates and more protein than the comparison group at time 1 and significantly less calcium at time 2.

Table VI represents the same information in relation to levels of high or low CRH. The women with high CRH

Table IV. Baseline information on women from BIPS who fasted for ≥13 hours and had high plasma CRH concentrations at 18 to 20 weeks' gestation*

Trait	*Fasted ≥13 h (n = 112)*	*Fasted <13 h (n = 125)*	*High CRH (n = 25)*	*Low CRH (n = 212)*
Married (%)	53†	38	48	56
Single (%)	47	62	52	44
No. of Children (%)				
1	51	59	67‡	55
2	34	29	27	32
3	6	8	6	7
>3	9†	4	0	6
<High school education (%)	21	18	20	19
Working (%)§	45†	62	48‡	55
Have second job (%)§	22†	10	16	15
No. of h/wk working a job§¶	33.0 ± 1.7‖	38.3 ± 0.9	31.6 ± 4.0	36.4 ± 0.9
No. of h/wk performing household duties§¶	3.1 ± 0.2‖	2.6 ± 0.1	2.8 ± 0.3	2.9 ± 0.1
No. of h/wk performing child care duties§¶	8.3 ± 0.5	7.1 ± 0.5	7.5 ± 1.1	7.7 ± 0.4
Income (%)				
<$20,000	45†	34	45‡	38
$20,000-$40,000	26	26	25	26
>$40,000-$70,000	17	18	10‡	19
>$70,000	12†	22	20	17
Age (y)¶	27.7 ± 0.5	27.9 ± 0.5	29.9 ± 1.4	27.6 ± 0.4
Race (%)				
Black	42†	27	48‡	33
White	18	32	24	25
Hispanic	37	37	28	38
Asian	3	4	0	4
Pregravid BMI (kg/m^2) (%)				
Low (<19.8)	8†	14	4‡	12
Normal (19.8-26)	55	57	68‡	55
High (>26-29)	10	12	4	12
Obese (>29)	27†	17	24	21
Smoking during pregnancy (%)	19†	10	24‡	13

*n = 237.
†Relative risk changes by ≥30% when compared with women who have prolonged periods without food for <13 hours.
‡Relative risk changes by ≥30% when compared with women who have low CRH concentrations.
§Information was collected only during study interview at 18 to 20 weeks' gestation.
‖$P < .05$ when compared with women who have prolonged periods without food for <13 hours.
¶Mean ± SEM.

Table V. Differences between women in BIPS who fasted for ≥13 hours versus <13 hours during two different trimesters of pregnancy

	Time 1 (18-20 wk) (n = 237)		*Time 2 (28-30 wk) (n =236)*	
	≥13 h (n = 112)	*<13 h (n = 125)*	*≥13 h (n = 98)*	*<13 h (n = 138)*
Trait				
High stress level	27	23	31	25
Actively exercised on day of study (%)	7	5	4	9
Experienced hassles on day of study (%)	34	33	16	23
Ate on day of study (%)	81	85	88	79
Dietary intake				
Energy (kcal)*	1625 ± 48.7†	1829 ± 52.5	1619 ± 50.7†	1831 ± 55.1
Lowest quartile of energy (%)	30‡	21	36‡	25
Caffeine intake (mg)§	13.3 ± 3.0†	24.3 ± 5.1	13.7 ± 3.1	17.5 ± 4.1
High caffeine intake (>200 mg/d) (%)	2‡	3	1‡	3
Carbohydrate (g)§	123.2 ± 2.0†	129.3 ± 2.2	124.2 ± 2.7	128.9 ± 2.0
Protein (g)§	44.3 ± 1.0†	41.5 ± 0.9	43.0 ± 1.2	42.5 ± 0.8
Fat (g)§	37.6 ± 0.7	36.8 ± 0.8	37.9 ± 0.9	36.4 ± 0.8
Folate (μg)§	154.1 ± 7.6	168.5 ± 8.7	158.9 ± 9.3	164.0 ± 7.2
Vitamin C (mg)§	61.4 ± 5.5	71.8 ± 5.2	66.9 ± 4.8	68.7 ± 4.3
Iron (mg)§	8.6 ± 0.4	8.3 ± 0.3	8.1 ± 0.4	8.2 ± 0.3
Calcium (mg)§	447.7 ± 18	478.1 ± 17	435.1 ± 21†	526.9 ± 18
Zinc (mg)§	6.0 ± 0.2	6.0 ± 0.2	5.7 ± 0.2	5.8 ± 0.2

*Mean ± SEM.
†$P < .05$ when compared with women who have prolonged periods without food <13 hours.
‡Relative risk changes by ≥30% compared with women who have prolonged periods without food <13 hours.
§Adjusted for energy intake (nutrient/1000 kcal).

Table VI. Differences in women from BIPS with high or low plasma concentrations of CRH in the first two trimesters of pregnancy

	Time 1 (18-20 wk) (n = 237)		*Time 2 (28-30 wk) (n =236)*	
	High CRH (n = 25)	*Low CRH (n = 212)*	*High CRH (n = 24)*	*Low CRH (n = 212)*
Trait				
High stress level	32†	24	29	27
Actively exercised on day of study (%)	4	6	4†	9
Experienced hassles on day of study (%)	24	34†	16†	23
Ate on day of study (%)	84	83	88†	79
Dietary intake				
Energy (kcals)*	1512 ± 134.0	1751 ± 37.7	1664 ± 96.3	1753 ± 42.1
Lowest quartile of energy (%)	40†	23	33†	25
Caffeine (mg)§	20.6 ± 10.8	18.8 ± 3.2	25.4 ± 15.4	14.8 ± 2.4
High caffeine intake (>200 mg/d) (%)	4†	2	4†	2
Carbohydrate (g)§	129.0 ± 7.5	126.1 ± 1.5	129.0 ± 6.4	126.7 ± 1.7
Protein (g)§	43.1 ± 2.2	42.8 ± 0.7	43.4 ± 2.4	42.6 ± 0.7
Fat (g)§	35.6 ± 2.4	37.3 ± 0.6	36.3 ± 2.4	37.1 ± 0.6
Folate (μg)§	170.9 ± 22.9	160.7 ± 6.0	190.4 ± 19.7‡	158.5 ± 5.9
Vitamin C (mg)§	81.3 ± 18.0	65.5 ± 3.8	77.7 ± 11.0	66.8 ± 3.3
Iron (mg)§	7.6 ± 0.6	8.5 ± 0.3	9.6 ± 1.0‡	8.0 ± 0.3
Calcium (mg)§	472.2 ± 45.3	462.7 ± 13.2	480.2 ± 41.6	489.8 ± 15.0
Zinc (mg)§	5.5 ± 0.3	6.0 ± 0.2	5.7 ± 0.3	5.8 ± 0.2

*Mean ± SEM.
†Relative risk changes by ≥30% when compared with women who have low CRH concentrations.
‡$P < .05$ when compared with women who have low CRH concentrations.
§Adjusted for energy intake (nutrient/1000 kcal).

Table VII. Prevalence of high plasma CRH concentrations among women in BIPS who fasted ≥13 hours during the first two trimesters of pregnancy

	18-20 wk gestation (n = 237)		*28-30 wk gestation (n = 236)*	
Fasting (h)	*No. of women with CRH ≥90th percentile (%) (≥9.9 pg/mL)*	*No. of women with CRH <90th percentile (%) (<9.9 pg/mL)*	*No. of women with CRH ≥90th percentile (%) (≥290 pg/mL)*	*No. of women with CRH <90th percentile (%) (<290 pg/mL)*
≥13	16 (7)	96 (41)	14 (6)	84 (36)
<13	9 (4)	116 (49)	10 (4)	128 (54)

concentrations were less likely to have exercised and were more likely to have eaten a meal on the day of blood sampling and questionnaire administration at 28 to 30 weeks' gestation. They were more likely to be highly stressed at 18 to 20 weeks' gestation and to have experienced hassles with people or events at 18 to 20 and 28 to 30 weeks' gestation. They were also more likely to be in the lowest quartile of energy intake and to have high caffeine intake at 18 to 20 and 28 to 30 weeks' gestation (Table VI). However, these women consumed more folate and iron at 28 to 30 weeks' gestation than the women with low CRH levels.

The prevalence of high CRH was highest among women who had prolonged periods without food intake ≥13 hours at times 1 and 2 (Table VII). The crude relative risk (RR) for high plasma CRH concentrations was 2.6 (95% CI, 1.0-6.4) at time 1 and 1.8 (95% CI, 0.9-3.8) at time 2 among women who had prolonged periods without food intake ≥13 hours when compared with women who had prolonged periods without food intake <13 hours. Multivariate logistic regression was used to evaluate the effects of confounding on the exposure outcome relationship. At time 1, a simple logistic regression model was used. The following covariates were added to the model using stepwise logistic regression: maternal age, race, income, work status, education, smoking, lowest quartile of energy intake, pregravid BMI ≤26, high caffeine intake (>200 mg/d), >2 children, high psychosocial stress level (>75th percentile of composite stress score), and marital status. The following 5 covariates remained in the final model: lowest quartile of energy intake, pregravid BMI ≤26, maternal age, black race, and smoking during pregnancy. Results suggested that the women who had prolonged periods without food intake ≥13 hours had a higher risk for high CRH concentrations (AOR, 2.5; 95% CI, 0.9-7.1). There was little attenuation of the risk estimate after controlling for confounders. Effect modification of pregravid BMI ≤26, lowest quartile of energy intake, and black race on the exposure outcome relationship was also explored. There was no effect modification of these variables on the risk for high CRH among

the women who had prolonged periods without food intake ≥13 hours in this BIPS cohort. However, the numbers were very small, and thus the results from the stratified analysis were imprecise.

At time 2, structural equation modeling was used to examine the effect of a predicted exogenous CRH value at time 1 on the risk of having a high CRH value at time 2. In a previous report, CRH at time 2 was highly correlated with CRH at time 1 ($r = 0.78$; $P < .01$), and CRH values at time 1 predicted CRH values at time 2.[10] In our subsample of women who participated in BIPS, the correlation between plasma CRH at time 1 and 2 was moderate ($r = 0.38$; $P < .05$). The predicted CRH value from the multivariate logistic model at time 1 was added to the crude model of fasting ≥13 hours and high CRH at time 2. The following covariates were added to the model at time 2 to evaluate their effect of confounding: composite score of psychosocial stress at time 2, lowest quartile of energy intake at time 2, and high caffeine intake at time 2. Only the predicted CRH value at time 1 remained in the final model for time 2. The structural equation results from time 2 indicate that prolonged periods without food ≥13 hours at 28 to 30 weeks' gestation increase a woman's risk for having high plasma CRH concentrations at 28 to 30 weeks' gestation (AOR, 1.7; 95% CI, 0.7-4.2).

Ordinary least-square regression was used to examine the linear relationship between plasma CRH concentrations at time 1 and 2 and gestational age at delivery. There was a significant linear relationship between CRH in the continuous form at time 1 (β level, –0.74; $P < .0001$) and time 2 (β level, –3.86; $P < .019$) with gestational age at delivery. However, this sample of women from the BIPS cohort contained only 8 women who delivered preterm.

Comment

This study shows that women who had prolonged periods without food intake ≥13 hours had a higher risk for elevated plasma CRH concentrations at 18 to 20 weeks' and 28 to 30 weeks' gestation, although the results were imprecise. Furthermore, plasma CRH concentrations at 18 to 20 weeks' and 28 to 30 weeks' gestation were linearly associated with gestational age at delivery. A previous investigation using BIPS data reported an association between high CRH and preterm birth.[10] In this previous report, psychosocial stress at 18 to 20 weeks' gestation predicted high plasma CRH values at 28 to 30 weeks' gestation and preterm birth. Psychosocial stress was also found to increase the risk for preterm birth in a sample of women from the Pregnancy, Infection, and Nutrition study. We hypothesized that psychosocial stress may confound the relationship between prolonged periods without food intake and preterm birth because of its potential to exacerbate or trigger poor eating habits. We found that high levels of psychosocial stress were not associated with prolonged periods without food intake ≥13 hours during pregnancy in the Pregnancy, Infection, and Nutrition study (T. S. Herrmann, unpublished data 1999) or in BIPS. However, psychosocial stress may have an effect on other nutritional status exposures.

We hypothesized that prolonged intervals without eating during pregnancy stimulate the neuroendocrine pathway controlled by CRH, which triggers events leading to preterm delivery. This hypothesis is based on experimental data that demonstrate that fasting during late pregnancy exaggerates the normal metabolic response to an extended overnight fast observed in nonpregnant women.[18] Extending an overnight fast by delaying the first meal of the day is associated with the development of hypoglycemia, increased urinary nitrogen excretion, raised plasma concentrations of free fatty acids, and increased plasma and urinary ketones in pregnant women compared with a normal response in nonpregnant women.[18] Furthermore, animal experiments have shown that fasting 12 to 48 hours during late gestation results in preterm delivery for mares and ewes.[1] The most effective way for the body to protect the maternal nutrient reserves is to reduce the rate of nutrient transfer to the fetus. However, the manner in which this occurs is not well elucidated. Food restriction in pregnant rats results in a reduction in the expansion of intravascular blood volume and cardiac output that normally occurs during pregnancy.[19] This decreased expansion of blood volume and cardiac output was directly correlated with decreases in placental and uterine blood flow. These effects of food restriction on reduced blood volume expansion during pregnancy may contribute to physiologic stress that initiates the cascade of neuroendocrine events leading to preterm delivery.

Experiments in rats indicate that short-term food deprivation induces rapid expression of CRH mRNA in several brain regions.[3-4] Twelve hours of fasting induced a rapid expression of CRH mRNA and in mRNAs encoding the CRH receptors of type 1 and type 2 in several regions of the brain of obese Zucker rats.[3] CRH concentrations were also significantly increased in the hypothalamus, midbrain, and neurointermediate lobe in male Wistar rats after 7 days of food restriction.[4] These studies demonstrate a direct action of CRH on CRH receptors in the brain. Identification of another neuropeptide in the CRH family, urocortin, demonstrates that other endogenous neuropeptides activate central CRH receptors and modify behavior related to food intake.[20] A recent study reported that central infusion of urocortin into the rat brain suppressed food intake in a dose-dependent manner that was similar to the effects of urotensin, an antiappetite agent.[20] CRH also activates physiologic mechanisms in other mammalian tissues important in the regulation of labor and delivery.[21-23] CRH has been

demonstrated to increase the release of prostaglandins (PGE_2, PGFM, and $PGF_{2\alpha}$) in primary cultures of human fetal membranes, decidua, and placenta in vitro.[21] CRH increases the myometrial response to increased production of $PGF_{2\alpha}$[22] and potentiates the exogenous effect of oxytocin in isolated gestational myometrium.[23]

A major strength of this study was the simultaneous collection of dietary and CRH data during a study visit that allowed for the evaluation of the association between prolonged periods without eating and high plasma CRH concentrations within a similar 24-hour period. These data and other descriptive information used in the analyses were all collected prospectively, which minimized the potential reporting bias that could have resulted from the occurrence of an adverse pregnancy outcome. Furthermore, there were extensive psychosocial and demographic data available on these women to make a detailed assessment of the effects of confounding. However, our cutoff points for high CRH values were data driven; more studies need to be conducted on maternal plasma CRH concentrations to determine a biologically meaningful cutoff point. Stratification of the exposure reduced the sample size and thus limited our power to find a true effect. There were also limitations in our ability to obtain a true representation of the prevalence of prolonged periods without food intake ≥13 hours throughout pregnancy as a chronic stressor. The dietary data were collected via one self-reported 24-hour dietary recall per trimester. Multiple recalls during the 18 to 20 weeks' and 28 to 30 weeks' gestation periods would have yielded a more representative estimate of the true dietary intake of the population. This population reported energy intakes of 1743 ± 599 kcal/d (mean ± SD) at 18 to 20 weeks' gestation and 1731 ± 599 kcal/d at 28 to 30 weeks' gestation, which is lower than what has been found in other studies and lower than what was found in the Pregnancy, Infection, and Nutrition study (T. S. Herrmann, unpublished 1999). Thus dietary intake in the current study may have been underestimated; this may have occurred in two ways. Women may not have reported all of the food items eaten during their meals or they may not have reported all of their eating occasions. Only the latter would affect our results; however, we have no way of examining which bias occurred more frequently. Women who had prolonged periods without food intake ≥13 hours were more likely to be obese and thus may have been more likely to underreport their dietary intake as has been shown in other studies.[24] Furthermore, underestimation of the frequency of eating may have caused an overestimation of the prevalence of prolonged periods without food intake ≥13 hours in this cohort of women. There are additional data that would have been useful for a thorough examination of the effects of prolonged periods without food on high CRH levels during pregnancy. Urinary ketone concentrations and blood glucose concentrations corresponding with reported food intake would enhance the accuracy of assessing our exposure frequency. This would allow us to evaluate whether the women who reported prolonged periods without food intake ≥13 hours also experienced hypoglycemia, ketosis, or both.

This study has contributed to our understanding of one of many potential physiologic links between maternal nutrition, pregnancy outcome, and the future health of the offspring. These findings corroborate the results of other studies with both pregnant women and animals that suggest that skipping meals and sustaining prolonged periods without food may stimulate neuroendocrine events that lead to preterm delivery. Nutrition education during pregnancy without supplementation has been previously shown to improve dietary intake during pregnancy and is positively associated with a reduction in the rate of preterm birth.[25] Nutrition education that focuses on increasing the frequency of food intake in addition to adequate nutritional intake during pregnancy may also positively affect the health of pregnant women and their offspring.

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