Maternal Prenatal Anxiety and Corticotropin-Releasing Hormone Associated With Timing of Delivery

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Objective: The high rate of preterm births is an imposing public health issue in the United States. Past research has suggested that prenatal stress, anxiety, and elevated levels of maternal plasma corticotropin-releasing hormone (CRH) are associated with preterm delivery in humans and animals. Studies to date have not examined all three variables together; that is the objective of this paper. **Methods:** Data from 282 pregnant women were analyzed to investigate the effect of maternal prenatal anxiety and CRH on the length of gestation. It was hypothesized that at both 18 to 20 weeks (Time 1) and 28 to 30 weeks gestation (Time 2), CRH and maternal prenatal anxiety would be negatively associated with gestational age at delivery. CRH was also expected to mediate the relationship between maternal prenatal anxiety and gestational age at delivery. **Results:** Findings supported the mediation hypothesis at Time 2, indicating that women with high CRH levels and high maternal prenatal anxiety at 28 to 30 weeks gestation delivered earlier than women with lower CRH levels and maternal prenatal anxiety. Women who delivered preterm had significantly higher rates of CRH at both 18 to 20 weeks gestation and 28 to 30 weeks gestation ($p < .001$) compared with women who delivered term. **Conclusions:** These findings are the first to link both psychosocial and neuroendocrine factors to birth outcomes in a prospective design. **Key words:** corticotropin-releasing hormone, maternal prenatal anxiety, preterm delivery.

ANOVA = analysis of variance; **BIPS** = Behavior in Pregnancy Study; **CRH** = corticotropin-releasing hormone; **HPA** = hypothalamic-pituitary-adrenal axis; **SNS** = sympathetic nervous system.

INTRODUCTION

Although there have been significant advances in medicine and technology, the rate of preterm deliveries and low birthweight infants in the United States averages 11% of all births, which is conspicuously high compared with other developed nations. In fact, preterm birth and low birthweight are among the leading causes of perinatal mortality and have been associated with a wide range of negative outcomes in the physical and cognitive development of children (1–3). For example, premature infants who survive the perinatal period are more likely to suffer from cerebral palsy, respiratory illness, learning disabilities, and other handicaps than infants born at term (4,5). A prospective cohort study conducted by Strauss (6) recently reported that individuals who had been low birthweight infants had significant deficits in academic achievement as children and deficits in professional achievement as adults compared with individuals who were a normal weight at birth. In recent years, researchers have focused on gaining a better understanding of the interplay between psychosocial and neuroendocrine processes and their relation to birth outcomes in order to reduce costs and improve maternal and infant health.

Psychosocial Factors and Birth Outcomes

Several studies published within the last decade suggest that psychosocial variables, including prenatal stress and anxiety, are related to adverse birth outcomes (7,8). A prospective study conducted by Lobel et al. (9) showed that higher scores on a stress index (comprised of life events, state anxiety, and perceived stress) predicted significantly shorter gestational age at delivery in an ethnically diverse sample. A similar investigation of the influence of maternal psychosocial stress on birth outcomes (10) showed that life event stress during pregnancy was associated with lower birthweight, and a single unit increase in prenatal pregnancy-related anxiety was associated with a 3-day decrease in gestational age. Recent results from another study (11) confirmed that women with higher prenatal anxiety delivered earlier than women with lower anxiety, controlling for income, education, marital status, ethnicity, age, and parity. In the same study, women with greater mastery, self-esteem, and optimism reported lower stress and had higher birthweight babies.

Physiology of Stress and Anxiety

The prototypical stress response engages both the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), resulting in neuroendocrine alterations. Specifically, the HPA axis involves the release of corticotropin-releasing hormone (CRH) and adrenocorticotropin hormone (ACTH), which stimulates the adrenal cortex to release cortisol. When the SNS is activated, it causes the release of norepinephrine from SNS nerve terminals and epinephrine from the adrenal medulla.

Within the past 15 years, it has been theorized that interactions between the maternal HPA axis and the fetal placental unit may explain the apparent effects of maternal stress on birth outcomes. During pregnancy, there is a progressive increase in maternal ACTH, cortisol, and CRH (12,13). Although some have advocated that placental CRH is not directly related to the maternal endocrine system, we believe that the increase in maternal hormones is partly due to the effect of the placenta, a "transient" endocrine unit, on the maternal HPA axis (14). However, the relationship between the placenta and HPA axis is bidirectional. Maternal stress results in an influx of adrenal cortisol, epinephrine, and norepinephrine that stimulates placental CRH production. The

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Received for publication March 31, 2003; revision received April 12, 2004.

This research was supported by the National Institute for Child Health and Development, Grant RO1-HD29553 and National Institute of Mental Health Training Grant 15750.

DOI: 10.1097/01.psy.0000138284.70670.d5

0033-3174/04/6605-0762

placenta secretes CRH, which may affect or even amplify both fetal and maternal HPA responsiveness to stress (13–17).

There is also evidence that anxiety in particular, compared with depression and other negative psychological states, leads to increases in both HPA activation and SNS arousal, resulting in greater levels of CRH, cortisol, and catecholamines (18,19). Studies of physiological responses to anxiety indicate that anxious individuals have a significantly higher baseline of SNS arousal than nonanxious individuals (20). Thus, anxious individuals are believed to be in a perpetually anticipatory state, potentially resulting in greater wear and tear on the body. Although many questions regarding the link between CRH and preterm labor remain unanswered, we postulate that within the context of pregnancy, heightened anxiety could lead to a pronounced influx of maternal and placental CRH and cortisol, which could further intensify feelings of anxiety and potentially result in adverse birth outcomes.

CRH, Stress, and Preterm Delivery

Recent evidence suggests that maternal plasma CRH is associated with stress and the timing of delivery in animal and human models (13). Our understanding of the processes for both term and preterm parturition are still rudimentary; however, several possible mechanisms involve CRH in the physiology of parturition. CRH is known to interact with prostaglandins and oxytocin, which are both mediators of uterine contractility during parturition. CRH stimulates the release of prostaglandins from the placenta and fetal membranes, and treatment of human placental cells with prostaglandins stimulates CRH release (15,21). Thus, there is a bi-directional effect resulting in a cascade of events initiating uterine contractility.

In addition, the myometrium expresses CRH receptors whose affinity states increase as term approaches, resulting in increased receptor binding (22). It is currently thought that CRH exerts both a priming and a potentiating effect for the action of oxytocin on uterine contractility (23). Thus, the increase in CRH in patients who deliver preterm and those at term may have both a priming effect on the myometrium before the onset of labor and a potentiating effect by maintaining myometrial contractility during labor.

Although the source of CRH affecting both stress and the timing of delivery (whether from the placenta or the maternal HPA axis) is still under investigation, elevated levels of CRH as early as 18 to 20 weeks gestation have been associated with a greater risk for preterm delivery (24). In one study comparing preliminary data from 18 women who had a spontaneous preterm delivery with 18 full-term matched controls, women who delivered preterm had significantly higher elevations of CRH. The same study also showed that perceived stress and state anxiety at 18 to 20 weeks gestation were significant predictors of CRH at 28 to 30 weeks (14), but there was not evidence for CRH as the intermediary neuroendocrine mechanism between stress and preterm birth.

Measures of Stress

A number of the studies on psychosocial factors and birth outcomes have focused on general measures of stress and emotion, such as the Perceived Stress Scale (25) and the Spielberger State Anxiety Scale (26), as predictor variables. This provides for a powerful test of the hypothesis, but a weakness of this strategy is that such general measures can reflect very diverse components such as the quantity of stressful life events, emotional states such as anxiety and depression, and even individual differences in coping. Although the findings of these studies are important, the conclusions that can be drawn are somewhat limited in their implications for theory building because it is difficult to determine which psychological component is the most critical mechanism linking psychosocial factors with physiological outcomes. Also, these measures do not focus on the specific context within which stress occurs (such as a pregnancy, marriage, or other life event), hence yielding too little insight into stress-reducing interventions. We chose to extend the literature by focusing on a model with greater emotion and context specificity, using the Pregnancy-Specific Anxiety Scale (27) as a measure of maternal prenatal anxiety.

Hypotheses

The current study sought to extend the research on stress, CRH, and preterm delivery by testing precisely how specific psychosocial and neuroendocrine mechanisms are related to the length of gestation. It was hypothesized that women with higher CRH levels at 18 to 20 weeks (Time 1) and at 28 to 30 weeks gestation (Time 2) would deliver significantly earlier than women with lower levels of CRH at both time points. It was also hypothesized that there would be a positive association between CRH and pregnancy-specific anxiety at both time points, and a negative association between pregnancy-specific anxiety at both time points and length of gestation. Finally, we hypothesized that CRH would mediate the relationship between pregnancy-specific anxiety and gestational age at delivery, such that for each time point, women with high pregnancy-specific anxiety scores and greater CRH levels would have significantly shorter gestations than women who were less anxious and had lower levels of CRH. Through our emphasis on pregnancy-specific anxiety rather than a general measure of stress, we hope to gain insight about the combined effect of maternal prenatal anxiety and neuroendocrine processes on birth outcomes.

METHOD

Subjects

Participants were a subsample of 282 women from the Behavior in Pregnancy Study (BIPS). The BIPS study included 688 women with a singleton intrauterine pregnancy who gave birth to liveborn infants and were receiving prenatal care in prenatal clinics and private practices in Los Angeles, California. They were recruited into the study from the aforementioned clinics and private practices before their 20th week of gestation. The study involved three prepartum psychosocial assessments, and a collection of medical records for birth outcomes, health history, and physiological measures. Participants were excluded from the larger study due to maternal age of less

than 18 years ($n = 17$), stillborn births ($n = 6$), multiple gestation births ($n = 3$), lack of birth outcome data ($n = 53$), and incomplete psychosocial data ($n = 165$). Individuals who were excluded from analyses were significantly older ($M = 28.81$ vs. $M = 27.73$; $p = .02$), had significantly shorter gestational ages ($M = 38.02$ vs. $M = 39.56$), and experienced greater state anxiety at Time 1, perceived stress at Time 2, and pregnancy-specific anxiety at Time 2 than those who remained in the analysis sample ($p < .05$).

Our sample of 282 women was also based on the availability of completed CRH assays in the larger BIPS dataset, and was ethnically and socioeconomically diverse, consisting of 43% African-Americans, 32% Latinas, 24% European-Americans, and 2 women of unspecified ethnicity. We chose to limit our analyses to data collected at Time 1 and Time 2 since the focus of our research questions was preterm delivery and many preterm births occur before 35 weeks gestation. The mean age of women in this sample was 27.58 ($SD = 5.10$). Of the 282 women in our sample, 99 had spontaneous labors, 91 were augmented, 62 were induced, and 23 women had caesarian sections without labor. Labor data for the remaining seven women were unavailable.

Measures

Pregnancy-Specific Anxiety

The Pregnancy-Specific Anxiety Scale, developed by our team of investigators, is an exploratory measure designed to assess women's level of anxiety about their pregnancy (27). Participants completed the scale by responding to the question "How have you felt about being pregnant in the past week, including today?" They were asked to rate, on a 5-point scale (where 1 was "never" and 5 was "always"), how anxious, concerned, afraid, and panicky they felt about their pregnancy. These four items were chosen from a larger set of items created to assess pregnancy-specific affective states. A factor analysis led to the inclusion of the four items, and they were summed to create a pregnancy-specific anxiety score. Internal reliability analyses of the Pregnancy-Specific Anxiety Scale resulted in a Cronbach's alpha of 0.72 at Time 1. At Time 2, the reliability coefficient was 0.65. This suggests adequate but not extremely high internal reliability, and is indicative of the exploratory nature of the measure.

Hormonal Assays

At each time point, blood was collected in chilled glass tubes containing ethylenediaminetetraacetic acid (1 mg/ml blood) and aprotinin (500 kIU/ml blood), and centrifuged at 4°C. Plasma was stored at −70°C until extraction. Plasma was extracted with Sep-Pak C-18 cartridges (Waters Associates, Milford, Mass) 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 1% trifluoroacetic acid. The absorbed 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 levels were measured by specific double-antibody radioimmunoassays. Specific polyclonal rabbit antisera and the iodinated peptides were obtained from Peninsula Laboratories (Belmont, CA). Cross-reactivities of CRH antiserum were 100% for human and rat CRH and none for the precursor of CRH (0%). Additional details of the radioimmunoassay procedure have been described in an article by Castro et al. (28).

Birth Outcomes

Birth outcome data were obtained from medical charts after delivery. Gestational age at delivery was the outcome of interest in this study. It was estimated using participant reports of their last menstrual period and was then verified or adjusted by pelvic ultrasound, which was performed at each time point. Gestational age at delivery for this sample ranged from 29.0 to 42.3 weeks, with a mean of 39.26 ($SD = 1.82$).

Socioeconomic Variables

Maternal level of education and annual household income were assessed by interviews. Level of education was measured in years completed, with 12 years equivalent to completion of high school. The mean level of education was 13.22 years ($SD = 2.32$). Annual household income was measured using an ordinal scale ranging from 1 (under $2,500) to 13 (over $100,000), with categories designed to clearly differentiate lower income groups. The mean for this sample was approximately $30,000 (see Table 1).

Parity

Parity was included as a dichotomous variable, with a score of 0 assigned to each woman who was pregnant with her first baby (primiparous) and a score of 1 assigned to women who had previously given birth (multiparous). Approximately 40% of the participants were giving birth for the first time while 60% had previously given birth.

Medical Risk

Medical risk was calculated as the total number of medical risk factors present during each woman's pregnancy. The list of possible risk factors, developed in previous research, included 37 medical conditions (9). Items in this list included factors such as a past history of infertility, urinary tract infections, anemia, vaginal infections, fever during pregnancy, and lifestyle factors such as smoking. As shown in Table 1, for this sample, the highest number of medical risk factors tallied for a given pregnancy was 5.00, with of mean of 1.85 ($SD = 1.25$).

Procedure

Eligible participants were approached by the research staff and asked to participate in the study. Informed consent was obtained and the rights of participants were protected in accordance with Human Subjects Research guidelines. Participants were recruited no later than the early second trimester of pregnancy, and were interviewed and evaluated at three time points: 18 to 20 weeks, 28 to 30 weeks, and 35 to 36 weeks gestation. Psychosocial data were collected during the interviews, which were conducted by trained bilingual interviewers. Maternal blood samples were collected at each time point so that neuroendocrine data could be obtained using plasma bioassays.

TABLE 1. Descriptive Statistics for Key Variables (N = 282)

Variable	M	SD	Range	Skewness
Medical Risk[a]	1.85	1.25	5.0	0.53
Annual Household Income[b]	5.84	3.07	12.0	0.86
Level of Education	13.22	2.32	14.0	–0.27
Parity	0.60	0.49	1.0	–0.42
Pregnancy Specific Anxiety, Time 2	10.80	3.48	15.0	0.17
CRH, Time 2	248.66	35.36	170.40	0.67
Gestational Age	39.26	1.82	13.3	–1.9

Note. [a] Additional details regarding the medical risk variable can be obtained by contacting the first author of this manuscript.
[b] A score of 5.84 represents a mean annual household income of between $20,000 and $40,000.

RESULTS

Descriptive Statistics

Mean scores on the Pregnancy-Specific Anxiety Scale were 11.25 ($SD = 3.51$) at Time 1, and 10.80 ($SD = 3.48$) at Time 2. CRH levels at Time 1 averaged 9.00 pg/ml ($SD = 7.47$), and at Time 2, 248.66 pg/ml ($SD = 35.36$). These levels were normative compared with other samples of pregnant women studied by our research team.

Using univariate analysis of variance (ANOVA) models, we determined whether the type of labor (spontaneous, augmented, induced, or caesarian section) predicted differences in pregnant-specific anxiety, CRH, and gestational age at delivery. There were no significant differences in pregnant-specific anxiety or CRH levels by type of labor. However, type of labor did predict differences in gestational age at delivery. Women who had caesarian sections had significantly shorter gestational ages at delivery ($M = 38.03$, $SD = 2.29$; $F(3,4) = 5.69$, $p < .01$) than women who had spontaneous, augmented, or induced labor ($M = 39.13$, $SD = 1.74$; $M = 39.63$, $SD = 1.34$; $M = 39.48$, $SD = 2.04$, respectively).

We also tested for ethnic differences in pregnancy-specific anxiety, CRH, and gestational age at delivery using univariate ANOVA models. No ethnic differences were found for CRH or gestational age at delivery. However, there were ethnic differences in pregnancy-specific anxiety at both time points. At Time 1, African-American women ($M = 12.02$, $SD = 3.40$) reported significantly greater anxiety about pregnancy than European-American women ($M = 10.26$, $SD = 3.41$; $F(3,280) = 4.36$, $p < .01$). At Time 2, the same pattern emerged; African-American women ($M = 11.75$, $SD = 3.60$) again reported significantly greater anxiety about pregnancy than European-American women ($M = 9.24$, $SD = 2.81$; $F(3,281) = 10.09$, $p < .01$). Although data on ethnic differences in CRH have previously been presented by our colleagues, the analyses in this manuscript include appropriate control variables, thus providing a more reliable pattern of findings.

Correlational Analyses

Pearson product-moment correlations were calculated to test the hypotheses that pregnancy-specific anxiety and CRH would be negatively associated with gestational age at delivery and that pregnancy-specific anxiety and CRH would be positively correlated. As shown in Table 2, there was a significant negative correlation between CRH at Time 1 and gestational age at delivery ($r = -0.37$, $p < .01$), but we did not find support for the remaining two hypotheses at Time 1. For Time 2, however, all three of our hypotheses were supported. Analyses of pregnancy-specific anxiety and CRH at Time 2 yielded significant negative correlations with gestational age at delivery ($r = -0.19$, $r = -0.41$, respectively, $p < .01$). Moreover, pregnancy-specific anxiety and CRH at Time 2 were positively correlated ($r = 0.15$, $p < .05$). Thus, four out of six tests were significant in the direction predicted.

To compare pregnancy-specific anxiety with general measures of stress, we calculated the same series of correlations using the Perceived Stress Scale and the Spielberger Anxiety Scale in place of the Pregnancy-Specific Anxiety Scale. As shown in Table 2, at Time 1 and Time 2, these measures were significantly correlated with pregnancy-specific anxiety ($r = 0.15$ to 0.45, $p < .05$), but there were no significant correlations with CRH and gestational age at delivery for either of the measures at either time point.

Mediation

Hierarchical regression analyses were then used to test for the presence of a mediating relationship between CRH at Time 2, pregnancy-specific anxiety at Time 2, and gestational age at delivery. The results of this procedure are reported in Table 3. As described by Baron and Kenny (29), a mediating variable changes the relationship between the antecedent and the outcome variable. In order for mediation to occur, the mediating variable must be significantly correlated with both the antecedent and the outcome; the antecedent and outcome variables must also be correlated with one another. The pres-

TABLE 2. Correlation Matrix of Perceived Stress, Spielberger State Anxiety, Pregnancy-Specific Anxiety, CRH, and Gestational Age

Variable	1	2	3	4	5	6	7	8
1. PSS1								
2. PSS2	0.58**							
3. SSA1	0.37**	0.37**						
4. SSA2	0.40*	0.54**	0.61**					
5. PSA1	0.15*	0.16*	0.43**	0.35**				
6. PSA2	0.17**	0.20**	0.32**	0.45**	0.56**			
7. CRH1	0.02	–0.03	0.11	0.07	0.02	0.02		
8. CRH2	–0.02	0.03	0.10	0.12	0.01	0.15*	0.44**	
9. Gestational Age	0.04	0.03	–0.06	–0.00	–0.07	–0.19**	–0.37**	

Note. PSS1 = Perceived Stress Scale, 18–20 weeks; PSS2 = Perceived Stress Scale, 28–30 weeks; SSA1 = Spielberger State Anxiety, 18–20 weeks; SSA2 = Spielberger State Anxiety, 28–30 weeks; PSA1 = Pregnancy-Specific Anxiety, 18–20 weeks; PSA2 = Pregnancy-Specific Anxiety, 28–30 weeks; CRH1 = Maternal Plasma Corticotropin-Releasing Hormone, 18–20 weeks; CRH2 = Maternal Plasma Corticotropin-Releasing Hormone, 28–30 weeks.
* $p < .05$; ** $p < .01$.

TABLE 3. Regression Analysis: CRH as Mediator of Pregnancy-Specific Anxiety and Gestational Age

Variable	R^2	Adjusted R^2	B	SE B	β^a
Model 1					
Gestational Age					
Medical Risk			–0.13	0.09	–0.09
Income			–0.01	0.04	–0.02
Education			–0.01	0.06	–0.01
Parity			–0.47	0.24	–0.13*
	0.03	0.01			
Model 2					
Gestational Age					
Medical Risk			–0.12	0.09	–0.08
Income			–0.02	0.04	–0.03
Education			–0.03	0.06	–0.04
Parity			–0.55	0.24	–0.15*
PSA2			–0.07	0.03	–0.14*
	0.04	0.03*			
Full Model					
Gestational Age					
Medical Risk			–0.09	0.08	–0.06
Income			0.01	0.04	0.01
Education			–0.06	0.06	–0.08
Parity			–0.60	0.22	–0.16*
PSA2			–0.05	0.03	–0.10
CRH2			–0.02	0.00	–0.35*
	0.16	0.14**			

Note. PSA2 = Pregnancy-Specific Anxiety, 28–30 weeks; CRH2 = Maternal Plasma Corticotropin-Releasing Hormone, 28–30 weeks. The identical model was run after calculating a data transformation to correct for the negatively skewed distribution of gestational age; no differences between the models emerged.

[a] Standardized beta coefficient.

* $p < .05$; ** $p < .01$.

ence of mediation is confirmed when, after controlling for the effects of the mediating variable, the correlation between the antecedent and outcome variables becomes nonsignificant.

In the first step of the mediational analyses, Model 1, we controlled for possible confounding factors including medical risk, income, education, and parity. These factors were included as control variables because previous studies conducted by our research team have illustrated that they are associated with birth outcomes (30). As shown in Table 3, however, only parity explained a significant amount of variance in gestational age for this sample. Descriptive statistics for all variables included in the mediational analyses are reported in Table 1.

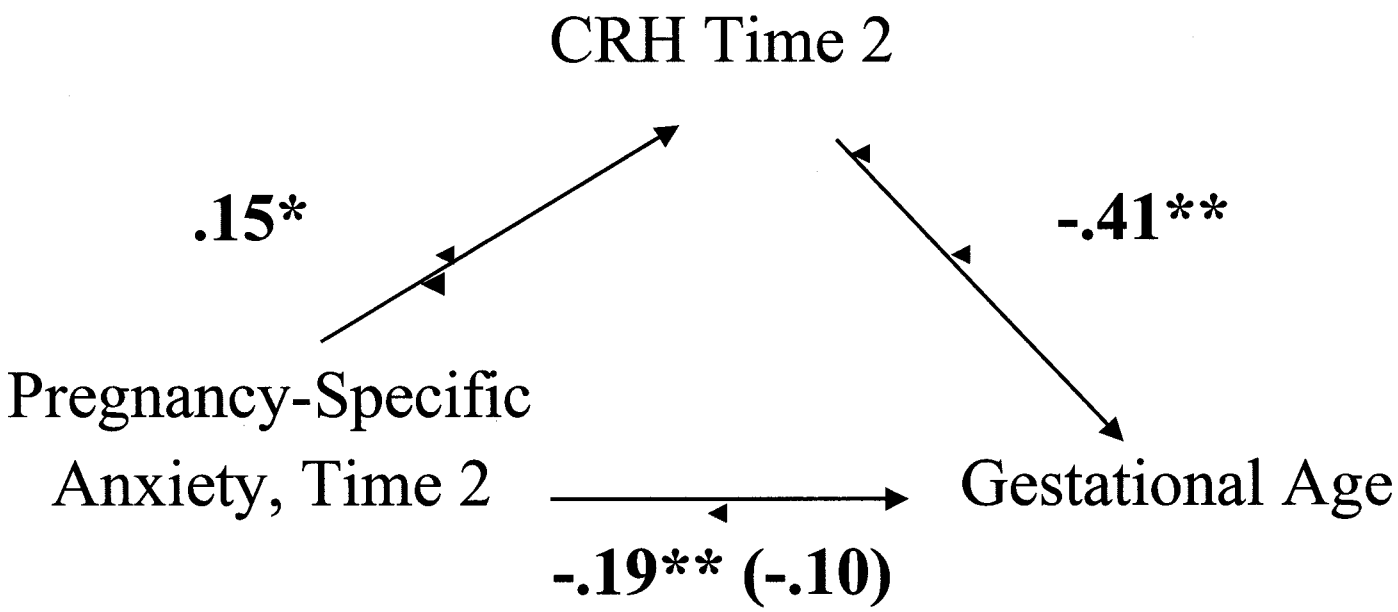
For Model 2, we added pregnancy-specific anxiety at Time 2, and found that it was a significant predictor of gestational age at delivery, over and above the control variables ($\beta = -0.14$, $p < .05$). For the Full Model, CRH at Time 2 was entered into the regression equation ($\beta = -0.35$, $p < .05$). In this model, shown in Figure 1, pregnancy-specific anxiety at Time 2 was no longer a significant predictor ($\beta = -0.10$, ns), indicating that CRH at Time 2 mediated the relationship between pregnancy-specific anxiety at Time 2 and gestational age at delivery, controlling for confounding factors. These results remained significant when women whose pregnancies ended in caesarian section were omitted from our analyses.

Finally, gestational age was divided into two groups of less than 37 weeks for preterm delivery and 37 weeks or more for term delivery per medical definition. Using this dichotomous variable in a one-way ANOVA, women who delivered preterm had significantly higher levels of CRH than those with term deliveries at both Time 1 (*Preterm*: $M = 25.6$, $SD = 22.22$; *Term*: $M = 7.74$, $SD = 1.51$; $F(1,241) = 143.96$, $p < .001$) and Time 2 (*Preterm*: $M = 316.74$, $SD = 36.70$; *Term*: $M = 244.01$, $SD = 30.16$; $F(1,281) = 95.2$, $p < .001$). Women who delivered preterm also reported marginally greater pregnancy-specific anxiety at Time 2 compared with women who delivered at term. (*Preterm*: $M = 12.17$, $SD = 3.45$; *Term*: $M = 10.71$, $SD = 3.47$; $F(1,281) = 2.98$, $p = .09$).

DISCUSSION

As hypothesized, there was a positive association between maternal prenatal anxiety and CRH at Time 2, suggesting that higher levels of maternal prenatal anxiety were related to elevations in CRH. We also found support for the hypotheses that both maternal prenatal anxiety and CRH in mid-pregnancy are negatively associated with gestational age at delivery. Moreover, the pattern of results reported here supports our theorized mediational model. Controlling for medical risk, income, education, and parity, women who reported greater maternal prenatal anxiety delivered their babies significantly earlier than women with lower maternal prenatal anxiety, and CRH appears to account for this relationship, at least in part.

With regard to our tests of mediation, we note that the



- **p < .05. ** p < .01.**
- **Note. Please see Table 2 for bivariate correlations.**

Figure 1. Mediation model predicting gestational age.

analyses that assess mediation are currently the topic of critical evaluation by statisticians and researchers in the field. Some experts believe that the aforementioned Baron and Kenny (29) technique is adequate, while others prefer using methods such as those recently developed within structural equation software. All of these techniques have their limitations as well as advantages. We present our findings with the caveat that we have used mediation analysis as a preliminary test of causal pathways between variables for which we have developed a solid theoretical rationale. Our results justify and, indeed, necessitate future experimental studies, using these variables in predicting birth outcomes, where causal relationships can be thoroughly tested.

These results support previous research showing that the neuroendocrine system is a key component in the timing of delivery. In view of the fact that our hypotheses were supported mainly at 28 to 30 weeks rather than 18 to 20 weeks, our findings also suggest that this mid-pregnancy time may be a critical period in which specific psychosocial and biological variables are especially detrimental to birth outcomes. This result requires replication in larger studies, especially given other findings (including some of our own) suggesting that psychophysiological responses to stress may be more potent during the first trimester and become less reactive over the course of pregnancy (13,31).

We believe that the use of specific (rather than general) measures of stress in our study better elucidates the pathways between psychosocial and physiological factors affecting birth outcomes (32). Our evidence supports the relationships among maternal prenatal anxiety, CRH, and gestational age at delivery, but these associations did not hold for general measures of perceived stress and state anxiety. Likewise, previous studies on the effects of stressful life events on birth outcomes have led to somewhat inconsistent results, perhaps due to wide variability in the type and severity of stressful life events experienced by women during pregnancy.

Future research should attend to variations in causes of the onset of labor and delivery. For instance, in our sample, two thirds of the pregnancies had spontaneous or augmented labor (vs. induced). Although there were no significant differences in levels of CRH corresponding to these differences, future samples should include spontaneous onset only, if possible. In addition, gestational age at delivery was approximately 1.5 weeks shorter for women who had caesarian sections, but the mediation model remained significant when these cases were omitted.

The strength of the relationship between CRH and gestational age found in our study is noteworthy for several reasons. Our relatively small sample, heterogeneous with respect to causes of the onset of labor, would tend to reduce the effect size, suggesting that more homogeneous and larger samples could yield stronger effects. Likewise, drawing from our own previous research and that of our colleagues, we postulate that if a sample with more preterm births (less than 37 weeks) was obtained, a stronger effect may emerge. In addition, the study of both the continuous variable of gestational age and the categorical variable of preterm delivery suggests that the processes at work are affecting timing of delivery *both* within term deliveries and in more extreme cases of preterm delivery as well. This is indicative of the types of models and interventions that must be considered. These points underline the importance of our results and of developing a further under-

standing of the role of the neuroendocrine system in birth outcomes.

Secondly, it is notable that a measure of maternal prenatal anxiety that was brief and exploratory was significant in the model. Again, it suggests that the effects may be underestimated in these analyses. We acknowledge that the amount of variance it explains is modest, but this does not lessen its presence as a significant psychosocial predictor. Arguably, a more developed measure designed specifically for assessing maternal prenatal anxiety, and consequently, one that is higher in internal reliability, should show even stronger effects (11). In addition, the inclusion of a measure of anxiety that focuses on narrower concepts such as worry (a cognitive aspect of anxiety) or other specific dispositional factors (such as the predisposition to develop an anxiety disorder) might be valuable for addressing comorbidity issues with generalized negative affect and depression (33).

Preliminary evidence of CRH mediating the relationship between maternal prenatal anxiety and gestational age at delivery in humans is a particularly important contribution because maternal prenatal anxiety may be modifiable, making it an ideal candidate for interventions aimed at decreasing the rate of preterm birth. Moreover, the presence of ethnic differences in maternal prenatal anxiety at both time points in this study warrants further attention. In our lab, we examine the differential impact of various psychosocial variables on women of diverse ethnic origins. For example, stress is hypothesized to account, in part, for the persistent ethnic differences in the rate of preterm births in the United States (34–36). Finally, other mechanisms besides the HPA axis may be involved in mediating stress and preterm associations, including health behaviors and infections such as bacterial vaginosis (37). Further investigations in all of these directions are worthwhile in light of these findings.

The results described in this study contribute to our increasing knowledge of the role of psychosocial and neuroendocrine factors in the timing of labor and delivery. It is hoped that this line of research can lead to a better understanding of the complex etiology of preterm labor and delivery, and will provide insights into more effective multidisciplinary prevention efforts.

We would like to acknowledge Drs. Grace Woo, Lony C. Castro, and Chander Arora, who were integral members of the research team. We would also like to thank Drs. Pathik Wadhwa and Curt Sandman for feedback on an earlier version of this work.

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