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Maternal corticotropin-releasing hormone levels in the early third trimester predict length of gestation in human pregnancy

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OBJECTIVE: Corticotropin releasing hormone, a hypothalamic neuropeptide, plays a major role in regulating pituitary-adrenal function and the physiologic response to stress. During pregnancy corticotropin-releasing hormone is synthesized in large amounts by the placenta and released into the maternal and fetal circulations. Various endocrine, autocrine, and paracrine roles have been suggested for placental corticotropin-releasing hormone. The aim of this study was to prospectively assess the relationship between maternal plasma concentrations of corticotropin-releasing hormone in the early third trimester of pregnancy and the length of gestation in two groups of deliveries, with and without spontaneous labor.

STUDY DESIGN: In a sample of 63 women with singleton intrauterine pregnancies, maternal plasma samples were collected between 28 and 30 weeks' gestation and corticotropin-releasing hormone concentrations were determined by radioimmunoassay. Each pregnancy was dated on the basis of last menstrual period and early ultrasonography. Parity, antepartum risk conditions, presence or absence of spontaneous labor, and birth outcomes were abstracted from the medical record.

RESULTS: Maternal corticotropin-releasing hormone levels between 28 and 30 weeks' gestation significantly and negatively predicted gestational length ($P < .01$) after adjustment for antepartum risk. Moreover, subjects who were delivered preterm had significantly higher corticotropin-releasing hormone levels in the early third trimester ($P < .01$) than did those who were delivered at term. In deliveries preceded by spontaneous onset of labor, maternal third-trimester corticotropin-releasing hormone levels significantly and independently predicted earlier onset of labor ($P < .01$) and preterm labor ($P < .05$), whereas in deliveries effected by induction of labor or cesarean delivery, maternal corticotropin-releasing hormone levels were a marker of antepartum risk but not a statistically independent predictor of gestational length.

CONCLUSION: These findings support the premise that placental corticotropin-releasing hormone is potentially implicated in the timing of human delivery in at least two ways. First, placental corticotropin-releasing hormone may play a role in the physiology of parturition. Premature or accelerated activation of the placental corticotropin-releasing hormone system, as reflected by precocious elevation of maternal corticotropin-releasing hormone levels, may therefore be associated with earlier onset of spontaneous labor and resultant delivery. Second, placental corticotropin-releasing hormone may be a marker of antepartum risk for preterm delivery and therefore an indirect predictor of earlier delivery. The implications of these findings are discussed in the context of the neuroendocrinology of placental corticotropin-releasing hormone and human parturition. Furthermore, the role of corticotropin-releasing hormone as a possible effector of prenatal stress in producing alterations in the timing of normal delivery is detailed. (*Am J Obstet Gynecol* 1998;179:1079-85.)

Key words: Corticotropin-releasing hormone (CRH), gestational length, parturition, prenatal stress, preterm birth, spontaneous labor

Corticotropin-releasing hormone (CRH), a 41-amino acid neuropeptide synthesized primarily in the paraventricular nucleus of the hypothalamus, plays a major role

in regulating pituitary-adrenal function and the physiologic response to stress.¹ During pregnancy the CRH gene is also expressed in the human placenta and membranes, with levels of human corticotropin-releasing hormone messenger ribonucleic acid increasing more than 20 times in the weeks leading up to delivery and resulting in significant and exponentially rising elevations in maternal plasma concentrations of CRH through the course of the second half of pregnancy (see Challis et al² and Petraglia et al³ for recent reviews).

Placental CRH is identical to hypothalamic CRH in structure, immunoreactivity, and bioactivity.³ There is, however, one crucial difference in regulation between

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hypothalamic and placental CRH. In contrast to the negative control on hypothalamic CRH, glucocorticoids stimulate the expression of human CRH messenger ribonucleic acid in the placenta, establishing a positive feedback loop that results in elevated levels of CRH, adrenocorticotrophic hormone, and cortisol during the course of gestation.⁴

A corticotropin-releasing hormone binding protein, produced in the liver, trophoblast, and intrauterine tissues during pregnancy, binds to circulating CRH, reducing its biologic action.⁵ CRH binding protein levels, which are constant in the first, second, and early third trimesters, fall by approximately 60% at 36 to 38 weeks gestation,⁶ resulting in a dramatic increase in the availability of free and bioactive CRH in the peripheral circulation during the last 2 to 4 weeks of gestation.

Endocrine, autocrine, and paracrine roles have been suggested for placental CRH, including its involvement in the physiology of parturition.^{2,3} In clinical studies CRH levels during gestation or at delivery have been found to be significantly increased in maternal and cord plasma and in the placenta in pregnancies complicated by preterm labor, pregnancy-induced hypertension, preeclampsia, fetal asphyxia, fetal growth restriction, umbilical-placental vascular insufficiency, and multiple gestation.^{2,3} Moreover, CRH binding protein levels have been found to be significantly decreased in maternal plasma in pregnancies complicated by preeclampsia and preterm labor.⁶ To date 7 published studies have examined the association between maternal plasma concentrations of CRH and preterm labor or preterm rupture of membranes.⁷⁻¹³ Of these 7 studies, 5 were prospective, and concentrations of maternal CRH were measured from plasma collected ≥ 1 time before the initiation of preterm labor or preterm rupture of membranes in at least a subgroup of subjects in each study.⁹⁻¹³ Both cross-sectional studies found that women in preterm labor had significantly higher levels of CRH than did gestational age-matched control subjects^{7,8}; additionally, 4 of the 5 prospective studies found that elevated levels of CRH preceded the onset of preterm labor, in some instances by several weeks.¹⁰⁻¹³ Moreover, one study conducted serial assessments of CRH during the course of gestation and found that women with preterm delivery not only had significantly higher CRH levels than those with preterm delivery but also had a significantly accelerated rate of CRH increase during the course of gestation.¹¹

These reports suggest that maternal CRH levels may relate to the length of gestation in two ways. First, placental CRH may participate directly in processes involved in parturition and timing of onset of spontaneous labor. The second possibility is that placental CRH may be a marker of antepartum risk (maternal or fetal compromise) in such conditions as preeclampsia or pregnancy-induced hypertension. In such cases antepartum risk

would be expected to mediate the association of maternal CRH with the length of gestation. The aim of this study was to examine these possibilities to clarify the role of CRH in outcomes related to the length of human gestation. A prospective, longitudinal investigation was conducted in a sample of women with a singleton intrauterine pregnancy. The study sample included pregnancies with both low and high risk, and deliveries were differentiated on the basis of presence or absence of spontaneous labor.

Methods

Subjects. The study sample comprised 63 pregnant women attending prenatal care at a metropolitan teaching hospital. All subjects were private patients at the faculty practice in the Department of Obstetrics and Gynecology at the University of California, Irvine. Eligibility criteria for inclusion were as follows: (1) age >18 years, (2) singleton, intrauterine pregnancy, (3) gestational age at entry <28 weeks, and (4) English speaking. Subjects were recruited during an approximately 9-month period. All subjects had enrolled for prenatal care by the first or early second trimester of pregnancy, and all subjects received comparable prenatal care. The mean age at entry into the study was 30.4 ± 5.5 years; subjects were primarily multiparous (71.4%), Anglo (70%), married (82.5%), well educated ($>50\%$ had a college degree), employed (78.4%), of middle to high income ($>63\%$ had an annual family income $>\$40,000$).

Procedures. Eligible subjects were approached consecutively for participation during the second trimester of gestation. The consent rate was 78%. A 20-mL blood sample was withdrawn from each subject for hormone assays between 28 and 30 weeks' gestation (mean gestational age at assessment 28.8 ± 0.7 weeks). The time of day of blood drawing was noted. Parity, antepartum risk conditions, and outcomes of labor, delivery, and birth were abstracted from the medical record. Chart review was performed blinded to the results of the hormone assays. The study had been approved by the institutional review board, and signed, informed written consent was obtained from all subjects.

Measures

Corticotropin-releasing hormone assay. Blood samples were withdrawn into silicone-covered, ethylenediamine-tetraacetic acid-treated Vacutainer (Becton Dickinson, Franklin Lakes, NJ) blood-collecting tubes, placed on ice, and immediately centrifuged (within 5 minutes of the blood drawing) at 2000g for 10 minutes. The plasma was decanted into polypropylene tubes containing a protease inhibitor (500 KIU/mL aprotinin; Sigma Chemical Co, St Louis). The samples were then transported on dry ice and stored at -70°C until assay. Plasma CRH was determined by radioimmunoassay with a commercially prepared kit (Peninsula Laboratories, Belmont, Calif). The plasma

sample (2–4 mL) was acidified with an equal amount of 1% trifluoroacetic acid and centrifuged at 17,000g for 20 minutes at 4°C. CRH was extracted with C18 Spice-Pak (Analtech, Newark, Del) columns activated in advance with 60% acetonitrile in 1% trifluoroacetic acid (4 mL) and washed twice with 1% trifluoroacetic acid (4 mL each time). The plasma-loaded columns were eluted slowly with 60% acetonitrile in 1% trifluoroacetic acid (4 mL) and lyophilized. The radioimmunoassay is a 3-day procedure that is based on competition between added CRH tagged with iodine 125–labeled tyrosine and sample CRH for binding sites on a primary antibody (rabbit anti-CRH). Samples were incubated overnight with rabbit anti-CRH serum (16–24 hours) at 4°C before the addition of the labeled tracer, followed by a second overnight incubation. Labeled and unlabeled CRH was collected by immunoprecipitation with a second antibody (goat anti-rabbit immunoglobulin G) and normal rabbit serum after a 90-minute incubation at room temperature. The samples were then centrifuged at 1700g for 20 minutes at 4°C and the pellets were quantified with a gamma scintillation counter (Isoflex Gamma Counter; ICN Biomedical, Costa Mesa, Calif). The CRH assay has <0.01% cross-reactivity with ovine CRH, 2% cross-reactivity with sauvagine CRH, 36% cross-reactivity with bovine CRH, and undetectable reactivity with human adrenocorticotrophic hormone. The coefficient of variation at normal physiologic levels is 5% with 4 mL plasma or 8% with 2 mL, with a minimum detectable dose (95% confidence level) of 2.04 pg/sample. Tissue linearity has been evaluated in as much as 4.0 mL plasma with quantitative recovery.

Antepartum risk. Antepartum risk was determined by the presence of antepartum complications. Risk conditions in this sample included diabetes, intrauterine growth retardation, nonimmune hydrops, placenta previa, pregnancy-induced hypertension, preterm labor, and premature rupture of membranes. Because there are currently no standard criteria for the computation of degree or weight of specific antepartum risk conditions, a conservative strategy was adopted and a dichotomous risk variable (high or low) was created.¹⁴ A subject was categorized as at low risk for an adverse outcome if she did not have any of the listed conditions during pregnancy and as being at high risk if she had ≥ 1 of the listed conditions during pregnancy.

Birth outcomes. Birth outcomes included mode of delivery (vaginal or cesarean), presence and type of labor (spontaneous or induced), gestational age at delivery, and infant birth weight. Gestational age was determined by best obstetric estimate with a combination of last menstrual period and early uterine size and was confirmed by obstetric ultrasonographic biometry. In cases in which there was a discrepancy between last menstrual period, clinical examination, and ultrasonographic biometry by more than the margin of error of ultrasonography for

gestational age, the estimate of gestational age was revised according to the results of ultrasonographic biometry. Two gestational length–related variables were computed: the first was a continuous variable measured in completed weeks of gestation at delivery and the second was a dichotomous variable for preterm birth with the <37 completed weeks' gestation clinical criterion.

Results

The mean plasma concentration of CRH was 73.3 pg/mL, the SEM was 6.9 pg/mL, and values ranged between 8.5 and 240 pg/mL. CRH levels were approximately normally distributed (skewness <2) after one outlier was coded in.

On the basis of the presence of ≥ 1 of the antepartum risk conditions, a quarter of the sample ($n = 16$, 25.4%) were categorized as at high risk. The other three quarters ($n = 47$, 74.6%) were categorized as at low risk.

Delivery was preceded by spontaneous labor in 51 cases (81%). Labor was induced or delivery was effected by cesarean delivery in the other 12 cases. In the spontaneous labor group 9 subjects (17.6%) had ≥ 1 of the antepartum risk conditions and were classified in the high-risk group; the other 42 subjects were classified in the low-risk group. Antepartum risk was more evenly divided among subjects in the non-spontaneous labor group, with 7 subjects in the high-risk group and 5 subjects in the low-risk group. Forty-six subjects (72%) in the study sample were delivered vaginally, whereas the remaining 17 were delivered by cesarean delivery.

The mean length of gestation for the entire study sample was 38.8 weeks (SD 2.1 weeks); gestational length ranged between 32 and 42 weeks. Twelve of these deliveries (19.0%) were preterm (before 37 completed weeks' gestation). Eight of the 12 preterm deliveries occurred in the spontaneous labor group. The mean infant birth weight was 3326.6 g (SD 567.6 g); birth weight ranged between 2110 and 4955 g. Four infants (6.3%) were classified as low birth weight (<2500 g).

Bivariate analyses were performed to examine the associations between maternal CRH levels, parity, antepartum risk, presence or absence of spontaneous labor, and the major outcomes of interest, gestational length and infant birth weight. Pearson product-moment correlation coefficients were computed for continuous variables, and Student *t* tests (for independent samples with unequal sample sizes) and χ^2 tests were used to compare categorical variables. Multivariate analyses with linear and logistic regression techniques were performed to examine the joint contributions of ≥ 2 predictors on outcomes, whereas an analysis of covariance approach was used to control for the effects of a single factor. All tests of statistical significance were 2-tailed.

In the complete sample CRH levels at between 28 and 30 weeks' gestation significantly and negatively predicted

Fig 1. Maternal levels of CRH during the early third trimester predict gestational length. A linear regression curve significantly predicted gestational length from maternal CRH between 28 and 30 weeks' gestation ($r = -0.43$, $P < .001$). However, a non-linear (cubic) regression curve accounted for a greater proportion of the variance in gestational length ($F[3,59] = 6.64$; $P < .001$; $R^2 = 25.2\%$), as shown. Subjects who were delivered before 36 to 37 weeks' gestation had higher third-trimester CRH levels, subjects who were delivered after 40 weeks showed a trend toward lower third-trimester CRH levels, and subjects who were delivered between 36 and 40 weeks exhibited a relatively wide scattering of third-trimester levels of CRH.

gestational length at delivery ($r = -0.43$, $P < .001$; Fig 1). Subjects who were delivered preterm had significantly higher CRH levels between 28 and 30 weeks' gestation than did subjects who were delivered at term (120.5 ± 23.0 vs 62.1 ± 5.7 pg/mL [$\pm$ SEM], respectively; $t = -3.6$, $P < .001$; Fig 2). The association between maternal CRH levels and infant birth weight was not statistically significant ($P = .16$); however, subjects who were delivered of a low birth weight infant (<2500 g) had higher third-trimester CRH levels than did those who were delivered of an infant with normal birth weight (158.2 ± 32.9 vs 67.5 ± 6.4 pg/mL [$\pm$ SEM], respectively; $t = -3.48$, $P < .001$).

Parity was not associated with CRH levels, antepartum risk, or gestational length and was therefore not included in subsequent analyses. Presence or absence of spontaneous onset of labor was not significantly related to either gestational length ($P = .12$) or preterm delivery ($P = .16$). Subjects who were delivered after spontaneous labor had higher third-trimester CRH levels than did subjects in the nonspontaneous labor group (94.3 ± 19.8 vs 68.3 ± 7.0 pg/mL [$\pm$ SEM], respectively); however, this difference was not statistically significant ($P = .23$). As expected, antepartum risk was associated with gestational age at delivery and with preterm delivery. Subjects in the high-risk group were delivered significantly earlier than were those in the low-risk group (37.0 ± 0.5 vs 39.6 ± 0.2 weeks [$\pm$ SEM], respectively; $t = 4.55$, $P < .001$) and were significantly more likely to have preterm delivery than

Fig 2. Maternal levels of CRH during the early third trimester predict preterm delivery. Subjects who were delivered preterm had significantly higher CRH levels between 28 and 30 weeks' gestation than did subjects who were delivered at term (120.5 ± 23.0 vs 62.1 ± 5.7 pg/mL [$\pm$ SEM], respectively; $t = -3.6$, $P < .001$).

were subjects in the low-risk group ($\chi^2 = 19.25$, $P < .001$). Subjects in the high-risk group had significantly higher third-trimester CRH levels than did those in the low-risk group (98.2 ± 17.0 vs 64.8 ± 6.9 pg/mL [$\pm$ SEM], respectively; $t = -2.17$, $P < .05$).

Because both maternal CRH levels and antepartum risk were associated with gestational age at delivery and because CRH levels were correlated with antepartum risk, multivariate models were constructed to examine their independent effects on the length of gestation (Tables IA and IB). Results from the linear regression analysis demonstrated that the overall model was significant ($F[2,60] = 15.9$, $P < .001$) and accounted for 35% of the variance of gestational duration at delivery. After we controlled for the effects of antepartum risk, the association between CRH levels and gestational length was significant ($t = -2.9$, $P < .01$). Similarly, after controlling for the effects of CRH, the association between antepartum risk and gestational length was significant ($t = -3.8$, $P < .001$). These findings indicate that CRH levels and antepartum risk exerted independent effects on gestational age at delivery. Next, with preterm birth treated as the outcome variable, results from the logistic regression analysis indicated that the overall model was significant ($\chi^2[2,60] = 22.9$, $P < .001$) and that the effects of CRH and antepartum risk on preterm birth were both significant and independent of each other. When we controlled for the effects of antepartum risk, CRH levels

were significantly associated with preterm birth (Wald = 5.10, $\exp[B] = 1.016$, $P < .05$); when we controlled for the effects of CRH levels, antepartum risk was significantly associated with preterm birth (Wald = 10.9, $\exp[B] = 16.5$, $P < .01$).

Next the role of maternal CRH in the timing of onset of spontaneous labor was examined. Among the subgroup in whom delivery was preceded by spontaneous onset of labor ($n = 51$), higher CRH levels between 28 and 30 weeks' gestation significantly predicted earlier onset of spontaneous labor ($r = -0.37$, $P < .01$). Moreover, subjects in this group who were delivered preterm ($n = 8$) had significantly higher third-trimester CRH levels than did subjects who were delivered at term ($n = 43$; 103.8 ± 29.5 vs 61.7 ± 6.5 pg/mL [$\pm$ SEM], respectively; $t = -2.2$, $P < .05$). After antepartum risk was covaried, maternal third-trimester CRH levels continued to significantly predict the timing of onset of spontaneous labor (partial $r = -0.36$, $P < .01$) and preterm delivery (partial $r = 0.29$, $P < .05$), indicating that the influence of maternal third-trimester CRH levels on the timing of onset of spontaneous labor was independent of the effects of antepartum risk.

In the nonspontaneous labor group ($n = 12$), maternal third-trimester CRH levels were also significantly correlated with gestational age at delivery ($r = -0.52$, $P < .05$), and subjects who were delivered preterm ($n = 4$) had significantly higher third-trimester CRH levels than did those who were delivered at term ($n = 8$; 153.9 ± 45.9 vs 64.4 ± 9.7 pg/mL [$\pm$ SEM], respectively; $t = -2.6$, $P < .05$). However, after antepartum risk was covaried, maternal third-trimester CRH levels did not significantly predict either gestational age at delivery ($P = .29$) or preterm delivery ($P = .11$). These findings in this small subgroup suggest that among subjects in whom spontaneous labor did not develop CRH levels were a marker of antepartum risk but not an independent predictor of the timing of delivery.

Comment

Results from this study extend the findings of earlier studies that demonstrated a prospective association between elevated CRH levels and preterm labor and delivery¹⁰⁻¹³ and may be the first to suggest that the effects of maternal CRH on the length of gestation are independent of the effects of antepartum risk. Moreover, our findings support the premise that placental CRH may be implicated in the timing of delivery in at least two ways. First, placental CRH may play a direct role in the physiologic characteristics of human parturition. Second, placental CRH may be a marker of antepartum risk conditions for preterm delivery and an indirect predictor of earlier delivery, even among women who do not have spontaneous labor.

These findings are consistent with those from 4 of the 5 prospective studies of CRH and preterm delivery¹⁰⁻¹³

Table IA. Multivariate analyses: Linear regression

Variable	B	SE B	β	t	P
CRH	-0.0125	0.004	-.318	-2.940	.004
Antepartum risk	-2.068	0.535	-.418	-3.865	.000

Outcome variable: Gestational length. Predictor variables: CRH, antepartum risk. Model $F(2,60) = 15.98$; $P = .0000$. $R^2 = 35.75\%$.

Table IB. Multivariate analyses: Logistic regression

Variable	B	SE	Wald	P	r	Exp(B)
CRH	0.016	0.007	5.103	.023	0.224	1.016
Antepartum risk	2.805	0.849	10.91	.001	0.381	16.52

Outcome variable: Preterm delivery. Predictor variables: CRH, antepartum risk. Model $\chi^2(2,60) = 22.96$; $P = .000$.

but are at variance with the results from the fifth study.⁹ Note, however, that data from even that study, which used a prospective, cross-sectional design to assess differences between term and preterm deliveries in CRH levels from maternal serum samples collected during 4 gestational intervals (20 to 24 weeks, 24 to 29 weeks, 29 to 33 weeks, and 33 to 37 weeks), reveal a trend that partially supports previous findings and our own present findings. Women whose serum was collected during the first 3 of the 4 previously mentioned intervals and who subsequently were delivered preterm had higher CRH levels than did those who were delivered at term, although these differences were not statistically significant. Moreover, the serum values of CRH reported in that study at each gestational period are substantially lower than those reported in other studies, including this study. For example, we report a mean CRH level of 72.3 ± 6.9 pg/mL ($\pm$ SEM) and a median value of 57.8 pg/mL at 28.8 ± 0.7 weeks' gestation, whereas in the Berkowitz et al⁹ study more than half of the CRH values measured before 29 weeks' gestation were <3 pg/mL (the assay's minimum detection limit). Thus one reason for these discrepant findings, as acknowledged by the authors of that study, may relate to the initial processing, age, or degradation of serum samples.

Independent of antepartum risk, subjects with higher CRH levels between 28 and 30 weeks' gestation were delivered significantly earlier and were significantly more likely to be delivered preterm. This finding supports a role for placental CRH in processes related to parturition and timing of onset of labor. The precise biomolecular mechanisms through which human parturition is initiated spontaneously, either at term or preterm, are not well understood; however, several possible mechanisms involve CRH in the physiology of parturition. CRH inter-

acts with both prostaglandins and oxytocin, the two major uterotonins implicated as mediators of the stimulation and maintenance of myometrial contractility at term and during labor. First, CRH stimulates the release of prostaglandins from the placenta and fetal membranes in a dose-dependent manner,² and treatment of human placental cells with prostaglandins stimulates CRH release.³ This bidirectional effect is believed to result in a series of positive feedforward cascades that drive myometrial contractility. Once initiated, there is no negative feedback control, and the only outcome is birth.² Second, the human myometrium expresses a specific receptor for CRH, which changes to a high-affinity state as term approaches and allows the myometrium to preferentially bind circulating, placentally derived CRH.¹⁵ Although CRH has no direct inotropic action on the human myometrium, it exerts both priming and potentiating effects for the actions of oxytocin on the myometrium *in vitro*¹⁶ and *in vivo*.¹⁷ The increase in maternal plasma CRH concentrations thus may have both a priming effect on the myometrium before the onset of labor and a potentiating effect to maintain myometrial contractility during labor.² It is also probable that the mature fetus plays a role in the retreat of paracrine support to initiate parturition. A recent study suggested a functional link between placental CRH and the fetal adrenal zone, wherein placental CRH stimulated the production of dehydroepiandrosterone, the precursor of estriol synthesis, in the placenta.¹⁸

Our results also supported an indirect role for placental CRH in delivery. Maternal CRH levels were positively correlated with antepartum risk, which in turn predicted the length of gestation. Various forms of prenatal stress have been associated with earlier delivery, and placental CRH may play a central role in modulating the effects of hypoxia, infections, decidual hemorrhage, and psychosocial stress on preterm labor, premature rupture of membranes, and delivery.¹⁹ A series of *in vitro* studies by Petraglia et al³ have demonstrated that placental CRH output is modulated in a positive, dose-response manner by all the major biologic effectors of stress, including catecholamines (norepinephrine), cortisol, oxytocin, angiotensin II, and both forms of interleukin 1; furthermore, acute fetal hypoxia has been shown to increase both maternal and fetal levels of CRH in sheep.²⁰ Thus, depending on the chronicity of the stressor, the resultant increase in CRH production may be a critical factor in the early initiation of labor.² The maternal environment may also modulate placental CRH through its influence on maternal pituitary-adrenal function. In two recent studies we found significant associations between maternal psychosocial factors and two effectors of placental CRH—maternal adrenocorticotrophic hormone and cortisol—in the early third trimester of gestation²¹ and between maternal adrenocorticotrophic hormone and CRH

levels.²² Last, a major role has been proposed for cytokines in mechanisms that may be associated with premature rupture of membranes and the initiation of infection-induced preterm labor.²³ Cytokines released in response to infections are known to stimulate the hypothalamic-pituitary-adrenal axis,²⁴ and both forms of interleukin 1 have been shown to stimulate CRH release in human cultured placental cells in a dose-dependent manner,³ suggesting a role for CRH in moderating the effects of infection and cytokines on the timing of delivery. Although one study reported no association between CRH levels and preterm labor in a small subgroup of subjects with clinical evidence of infection,¹² another recent study supported the possibility with its finding that subjects in preterm labor with evidence of microbial invasion of the amniotic cavity (measured by cultures for aerobic and anaerobic bacteria) had significantly higher plasma CRH levels than did subjects in preterm labor without evidence of infection.⁸

The precise quantification of the effect size of CRH on the length of gestation and risk for preterm delivery requires larger samples, stratified by risk and etiology of preterm delivery. Estimation of placental neuroendocrine function in this study was limited by the single assessment of CRH. Studies incorporating serial plasma sampling during the course of gestation will assist efforts to examine the effects of elevated CRH levels and differentiate them from those of accelerated rate of change.

Preterm birth is the leading cause of perinatal mortality and morbidity among nonanomalous neonates and is recognized as among the most significant problems in maternal and infant health in the United States today. A major limitation in current efforts to reduce the incidence of preterm birth is that the etiology is unknown in most cases.²⁵ The findings from this study add to the literature that supports a major role for placental CRH in processes related to the length of gestation, provide preliminary evidence for an independent effect of CRH, and have implications for examining the role of CRH as a possible effector of prenatal stress in producing alterations in the timing of normal delivery.

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A complete list of references is available from the authors on request.