

## Maternal Stress, HPA Activity, and Fetal/Infant Outcome<sup>a</sup>

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The consequences of perinatal stress and/or exposure to neuropeptides on the developing organism can include permanent influences on the brain and behavior. In human subjects, infant and early childhood separation stress is associated with a significant increase in adult psychopathology and permanent elevation in plasma  $\beta$ -endorphin ( $\beta$ E) and cortisol.<sup>1</sup> A study of over 3,000 patients<sup>2</sup> reported that the type of ante- or intrapartum stress significantly predicted the category of self-destructive behavior exhibited among adults. For instance, perinatal hypoxia was associated with significant tendencies to attempt suicide by asphyxial means such as suffocation. Intrapartum "mechanical" trauma (e.g., use of forceps) was associated with significant tendencies to self-destruct with instruments such as guns. Some less severe forms of self-injurious behavior related to developmental compromise observed among mentally retarded and autistic individuals can be attenuated by centrally acting drugs.<sup>3-6</sup> In these individuals the best predictor of a positive response to drugs is a history of perinatal stress.<sup>7,8</sup> These studies in clinical populations suggest that perinatal stress is strongly associated with developmental patterns and with influences on the central nervous system.

Controlled observations in animals provide evidence that early exposure to stressful events known to release peptides from the hypothalamic-pituitary-adrenal (HPA) axis have persisting influences on the brain and behavior. Restraint stress in pregnant rats results in decreased binding of  $\mu$ -opiate receptors in the striatum of the offspring at 42 days of age.<sup>9</sup> Hypothalamic levels of  $\beta$ E are elevated in 10-day-old rats prenatally stressed during the first or second trimester.<sup>10</sup> The finding that maternal pretreatment with opiate blockers protects rabbit fetuses from the damaging influence of stress and trauma<sup>11</sup> supports the pivotal role of the HPA in mediating the influence of stress on development.

Administration of peptides from the HPA axis also produces long-term influences on the nervous system and behavior. Rats exposed as fetuses directly to  $\beta$ E during the first and second trimester had "permanent" decreases (subsensitivity) in

the density of striatal, dopamine (D2) receptors,<sup>12</sup> and "permanent" alterations in behavior.<sup>13</sup> Perinatal exposure to MSH/ACTH and its analogues permanently altered learning, memory, and growth,<sup>14,15</sup> decreased central monoaminergic neurons, and disrupted the HPA axis during stress.<sup>16</sup> Offspring of rats administered corticotrophin-releasing hormone (CRH) during the third trimester weighed less at birth than controls and emitted more stress-related vocalizations.<sup>17</sup> Male offspring from the CRH-treated group had shorter anogenital distances at birth. These findings in the CRH-treated group are identical to findings observed in offspring of stressed mothers.

The primary objective of our research is to characterize the influence of stress during human pregnancy on the HPA axis, birth outcome, and fetal behavior. Understanding the effects of stress during human pregnancy is complicated by the development of the placenta as a significant endocrine, perhaps "stress-sensitive," organ.<sup>18,19</sup> All HPA-axis peptides increase during human gestation, but the dramatic elevations of placental CRH in maternal plasma during the course of pregnancy reach levels observed only in the hypothalamic portal system during physiological stress.<sup>20</sup> In addition to the increase in levels of CRH as pregnancy advances, a sharp increase is found in the availability of bioactive CRH in the peripheral circulation because of the reduction of CRH-binding protein during the last two to four weeks of gestation.<sup>21,22</sup> For these reasons, the role of CRH among the HPA products is of special interest.

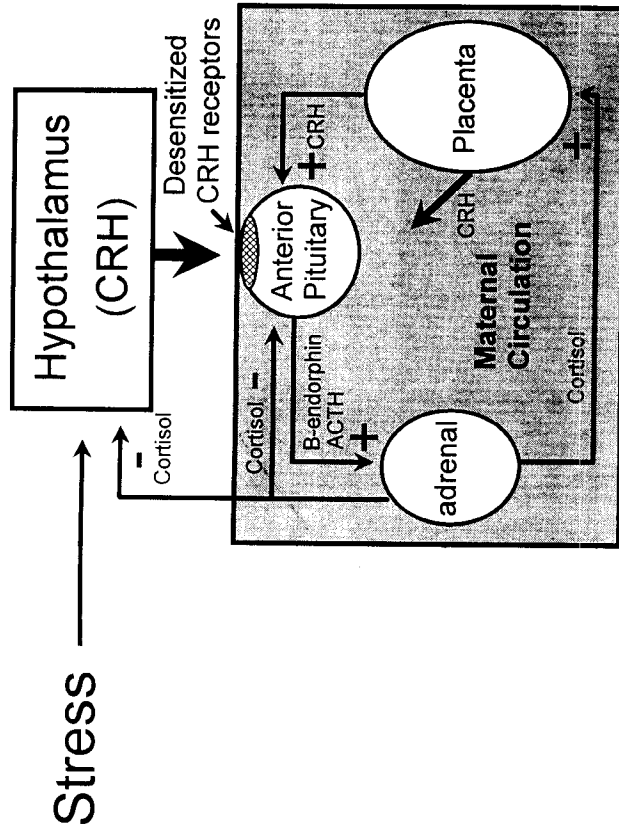
Placental CRH is identical to hypothalamic CRH in structure, immunoreactivity, and bioactivity,<sup>23,24</sup> however, in contrast to the negative control on hypothalamic CRH, glucocorticoids stimulate the expression of hCRH mRNA in the placenta. This establishes a positive feedback loop resulting in parallel increases of CRH, ACTH, and cortisol over the course of gestation.<sup>25</sup> Thus, during the course of pregnancy, the CRH system becomes increasingly activated and reaches the peak of bioactivity just before term. The consequences of increased CRH for maternal stress are not known, but several possibilities are suggested by the model in FIGURE 1. One possibility is that hypophysal corticotrophs may become desensitized as pregnancy develops. If this is true, the threshold is increased for stress-induced, pituitary release of ACTH and  $\beta$ E by hypothalamic CRH. The normal function of this feature of the model may effectively immunize pregnant women approaching term from the effects of CRH-modulated environmental stress. As the concentration of placental CRH rises in maternal circulation, the ability decreases for hypothalamic CRH to stimulate pituitary  $\beta$ E and ACTH and, in turn, for ACTH to stimulate adrenal cortisol. The classical HPA response to environmental stress may be greatly lessened as pregnancy proceeds.

A second possibility illustrated in FIGURE 1 is that the placenta may amplify the stress signal that does get transmitted. This possibility exists because placental CRH production is stimulated by adrenal cortisol. Thus, in this down-regulated system, the stress-induced release of ACTH from the pituitary eventually stimulates the release of adrenal cortisol, which in turn evokes the synthesis and release of placental CRH. In this model, even though the system is dampened, stress will ultimately result in an increase in CRH. The increase in CRH after stress in pregnant women may trigger a cascade of other events that contribute to specific birth outcomes. For instance, a precocious rise in CRH is associated with greater risk of preterm delivery.<sup>21</sup>

The purpose of our studies is to determine the relationship between psychosocial stress and the HPA axis and to characterize their joint and independent contribution to fetal behavior and birth outcome. Results are reported that (1) quantify the relationship between psychosocial stress and birth outcome, (2) illus-

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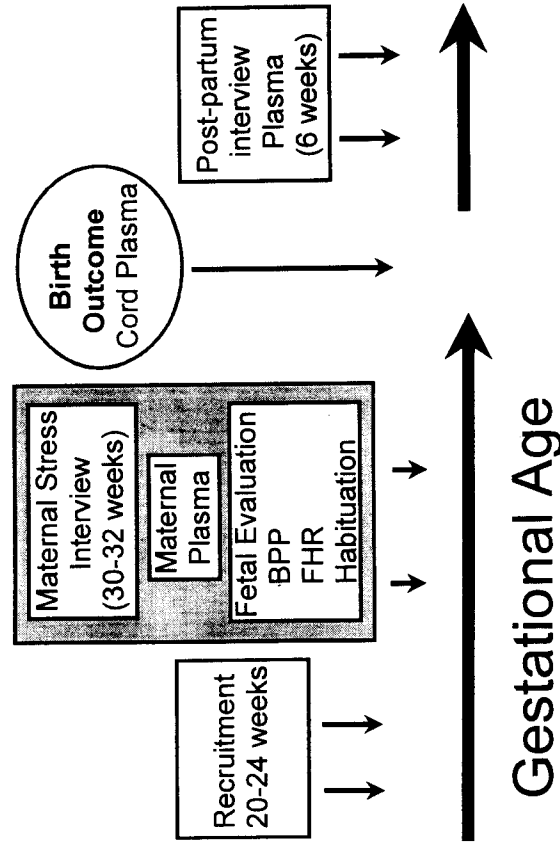
**FIGURE 1.** Model illustrating relationships among HPA-placental axis. Placental CRH is stimulated by adrenal cortisol resulting in (1) possible amplification of stress response in the placenta and (2) decreased sensitivity of anterior pituitary to effects of hypothalamic CRH.

trate the association between psychosocial stress and the HPA axis during pregnancy, (3) demonstrate the consequences of elevated maternal CRH on birth outcome, and (4) evaluate the effects of maternal HPA activity on fetal behavior.

### RESEARCH PROTOCOL

As illustrated in FIGURE 2, women are recruited during weeks 20–24 of pregnancy, and demographic information, obstetric history, and antepartum risk are obtained for each subject. During weeks 30–32, measures of prenatal psychosocial stress, sociodemographic factors, and health practices are collected by interview and questionnaire, 20 mL of plasma are drawn and assayed for CRH, ACTH,  $\beta$ E, and cortisol, and a comprehensive fetal evaluation is performed including an experimental fetal heart rate (FHR) habituation procedure to measure learning.

Transabdominal transducers for measuring FHR and uterine contractions were attached in 33 women during weeks 31–32 to test fetal habituation and dishabituation patterns to a vibroacoustic stimulus. As reported elsewhere,<sup>5</sup> a series of 15 vibroacoustic stimuli (S1) were presented on the mother's abdomen, over the fetal head, for two seconds with pseudorandom intervals between stimuli of 20 and 45 s. On the sixteenth stimulus, a novel (dishabituating) stimulus (change in db) was presented. Trials 17–31 repeated the S1 series. The difference between prestimulus HR during each trial was subtracted from each respective average FHR value.



**FIGURE 2.** Protocol for procedures followed in the study of the effects of stress on the fetus and birth outcome.

The influence of the novel stimulus was tested by computing the slope of the dFHR index for the last four trials of the first series of S1 (immediately before the novel S2) and the slope of the first four trials of the second series of S1 (immediately after the novel S2). The results in a larger sample ( $n = 93$ ) indicated that FHR followed a classical habituation and dishabituation pattern and that uterine contractions did not contribute to the patterns.<sup>26</sup>

Blood was collected at the time of the FHR assessment, at birth and at six weeks postpartum. At birth, intrapartum complications and indices of birth outcome were recorded. The 6-week sample provides a baseline of nonpregnancy so that peptide change during pregnancy can be estimated. At six weeks postpartum, maternal plasma was drawn and assayed from peptide concentration, and an abbreviated stress interview was conducted.

### RESULTS AND DISCUSSION

#### *Stress and Birth Outcomes*

In a subsample of 90 women, life event stress and pregnancy anxiety significantly predicted infant birth weight and gestational age at birth independent of obstetric risk.<sup>27</sup> Each unit increase of maternal life event stress during the third trimester was associated with a 55.03 g decrease in infant birth weight. Each unit increase of maternal pregnancy anxiety during the third trimester was associated with a 3-day decrease in gestational age at birth.

Previous research by members of our group<sup>28</sup> supports the role of stress in

preterm labor and delivery. Prenatal stress scores (a combination of the undesirability of life events, perceived chronic stress, and state anxiety aggregated over the course of pregnancy) predicted gestational age at delivery controlling for infant birth weight, parity, and medical risk (including substance use) in 130 low-income women of diverse ethnicity, who were interviewed on multiple occasions during the second trimester. These findings are consistent with studies from other groups. A study of 5,459 women in Denmark<sup>29</sup> concluded that generalized distress (anxiety and depression) in the 30th week of pregnancy was associated with risk of preterm delivery, controlling for smoking, education, parity, previous preterm delivery, maternal height, and prepregnancy weight. A study of 1,545 women<sup>30</sup> in Alabama indicated that the risk of having a fetal growth-retarded infant was significantly higher if an elevated psychosocial risk profile was present (stress, depression, and anxiety measured at 24 to 26 weeks or at 30 to 32 weeks). An interesting and rigorous study<sup>31</sup> concluded that change (increase) in life event scores from the second to the third trimester (but not high scores per se) was significantly associated with low birth weight. These selected studies reflect the general consensus that stress influences birth outcome. A number of unresolved issues include the effects of the timing and intensity of stress on outcome. Findings that change in stress levels during the course of pregnancy is more predictive than absolute levels of stress are consistent with HPA results from our research program as discussed below.

#### Stress and the Maternal HPA Axis

The relationship between psychosocial stress and HPA peptides was examined to a subsample of 54 women.<sup>32</sup> Plasma levels of ACTH,  $\beta$ E, and cortisol measured in maternal blood drawn at 28 weeks gestation were compared with measures of prenatal stress and social support administered at 28 and 30 weeks gestation. Elevated psychosocial stress was associated with higher plasma levels of ACTH and cortisol. A combination of the maternal psychosocial and sociodemographic factors during pregnancy accounted for 36% of the variance in ACTH, 13% of the variance in cortisol, and 3% of the variance in  $\beta$ E.

Physiological processes including neuroendocrine function are known to mediate the relationship between psychological stress and behavior;<sup>33-35</sup> however, virtually no human studies have systematically assessed this relationship during human pregnancy. Pregnancy is a unique condition for this relationship because, as reviewed above, neuroendocrine processes are altered significantly during pregnancy by the evolution of the placenta. Not only does the placenta contribute significant concentrations of endocrine products to the maternal and fetal circulation, it also changes the feedback and control mechanisms of the HPA. One possible consequence of these alterations, depicted in Figure 1, is the change in the stress-response threshold during pregnancy. Our results indicate for the first time that, despite the apparent "immunization" against the effects of stress during pregnancy, stress was associated with elevated plasma ACTH and cortisol between 28 and 32 weeks.

#### Maternal CRH Levels in the Early Third Trimester Predict the Timing of Human Delivery

In a sample of 63 women, early third trimester levels of maternal CRH were inversely and significantly correlated with gestational age at delivery ( $p < 0.001$ )

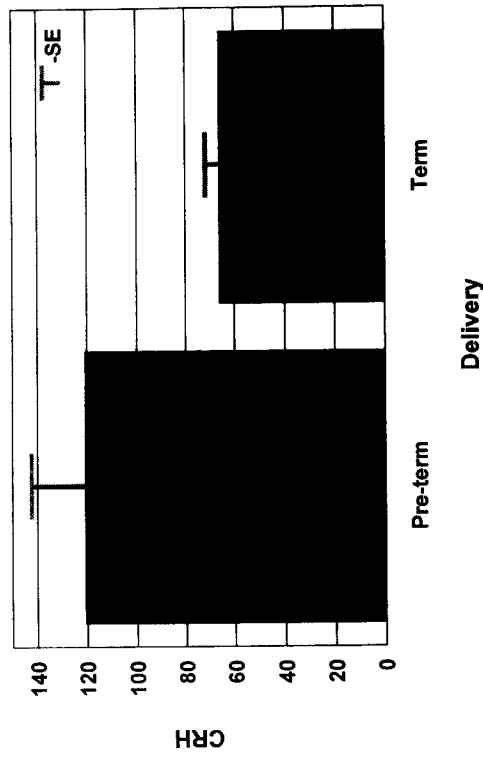
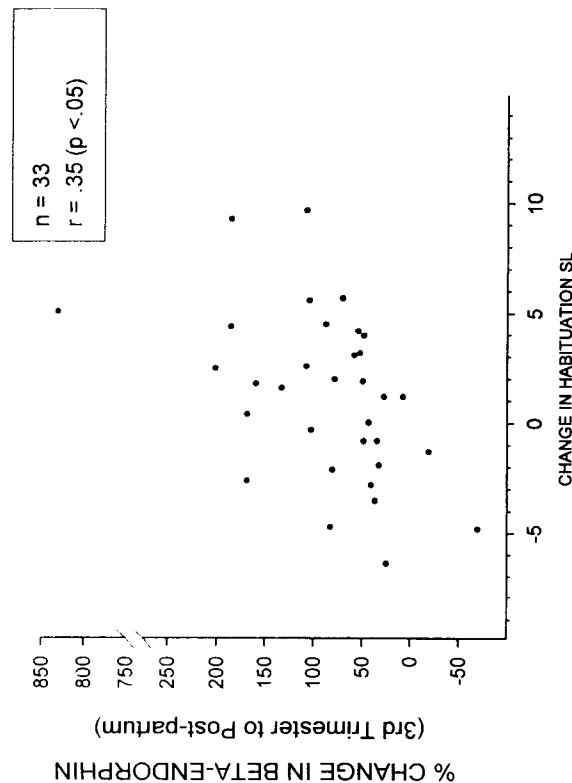


FIGURE 3. Third trimester levels of maternal CRH predict preterm birth.

after adjusting for biomedical correlates of outcome, including parity and antepartum risk. Gestational age at delivery was further dichotomized to differentiate term (after 37 weeks) and preterm (before 37 weeks) deliveries. Subjects who delivered preterm had significantly higher levels of CRH in the early third trimester of gestation ( $p < 0.01$ ) than those who delivered at term (Fig. 3).

These results are consistent with several reports from different laboratories.<sup>19,21,36-38</sup> In each of these studies, plasma CRH concentrations of women in preterm labor were significantly higher than those of gestational age-matched controls. Four of these studies included additional assessments of CRH levels at least one time during gestation *before* the initiation of preterm labor.<sup>21,36,38,39</sup> Each study found that compared to gestational age-matched controls, CRH levels were significantly elevated in women who developed preterm labor before the clinical signs of preterm labor were detected, and that in some instances, elevated CRH preceded the signs of preterm labor by several weeks. Two of these studies<sup>21,37</sup> included delivery as an end point. In the Kurki *et al.* study,<sup>37</sup> CRH levels were measured in 23 women admitted for treatment of preterm labor and followed until delivery. Among these women in preterm labor, the 12 subjects who subsequently delivered preterm had even higher CRH levels than the other 11 who went on to deliver at term.

The most convincing evidence of the role of CRH in the timing of human delivery was the prospective, longitudinal study of 485 women.<sup>21</sup> In this study, CRH levels were assessed up to four times during gestation, beginning between 16 and 20 weeks. Plasma CRH levels at 18-20 weeks gestation were significantly higher in women delivering preterm ( $n = 24$ ) than at term ( $n = 308$ ), and were significantly lower in women delivering post-term ( $n = 29$ ). Regression curves representing serial assessments of CRH over the course of gestation indicated that subjects delivering preterm had a precocious elevation of CRH and a steeper slope of increase as pregnancy continued. Together with results from our program these studies strongly argue that CRH plays a pivotal role in the timing of delivery and may be responsible for mediating the effects of stress on birth outcome.



**FIGURE 4.** Scatter plot of the relationship between change in maternal  $\beta E$  during the third trimester and fetal responsiveness to a novel stimulus.

#### Fetal Heart Rate Habituation

Previous research indicated that the procedures used in this study elicited reliable patterns of habituation in the fetus.<sup>5</sup> As presented in FIGURE 4, increased maternal  $\beta E$  during the third trimester was significantly associated with change in the fetal habituation slope (index of dishabituation) after a novel stimulus in a subsample of 33 women. Dishabituation is the *reemergence* of a previously habituated response.<sup>40,41</sup> The reemergence of an habituated response is typically elicited by the sensitizing or arousing effects of a novel stimulus or an altered context. Novelty is presumed to increase the level of arousal and potentiate the weak, habituated response.<sup>41</sup> Because dishabituation is evaluated by assessment of the reemergence of a response after a novel event, it eliminates the contribution of receptor fatigue or sensory adaptation to the response decrement.

No relationship existed between absolute concentrations of third trimester  $\beta E$  (or any other peptide) and FHR during challenge. The results suggest that fetal responses to the novel stimulus were attenuated in women exhibiting minimal changes (below the mean) in  $\beta E$  during the third trimester. In contrast, fetuses of women with very large changes of  $\beta E$  during the third trimester were most aroused by external novel stimuli. This is new evidence that changes in the level of maternal plasma  $\beta E$  during the third trimester (probably of pituitary origin) exert a significant influence on human fetal learning and, by inference, on the fetal nervous system. As reviewed above, these findings are consistent with animal studies indicating that early exposure either to stress that stimulates  $\beta E$  or to  $\beta E$  directly influences the central nervous system.<sup>9,10,12,13</sup> Because evidence from animal studies suggests that early exposure to endogenous opiates may have

enduring effects, long-term consequences of elevated maternal  $\beta E$  in human infants should be evaluated.

#### CONCLUSIONS

Preterm birth is a major cause of infant mortality and morbidity. Despite the significance of preterm birth as a health problem in the United States, the causes remain unknown. Findings from our project indicate that stress and the HPA axis account for a significant fraction of risk for preterm birth. Our findings and those of others<sup>21</sup> indicate that CRH may be critically linked to the timing of birth. Psychosocial stress is associated with adverse birth outcomes, including preterm birth and elevated ACTH and cortisol levels during the third trimester. This linkage early in gestation is important because it provides a credible mechanism for the effects of prenatal stress on pregnancy outcome. The effects of  $\beta E$ , although closely associated with CRH and ACTH, were primarily observed on fetal behavior and not birth outcome. Because the HPA axis and stress are associated, it is a reasonable conjecture that they exert both unique and common influences on the fetus and on birth outcome.

#### SUMMARY

Preliminary conclusions from our research include the possibility that each of the HPA products evaluated, even though correlated (e.g., ACTH and  $\beta E$ ), may be linked to unique and specific outcomes.

- Maternal stress during the 28–30 weeks of gestation is associated with birth outcome. Increased levels of psychosocial stress were significantly related to gestational age at birth and infant birth weight.
- Maternal stress during the third trimester was associated with increased maternal plasma levels of ACTH and cortisol. This finding is consistent with possible mechanisms whereby psychosocial stress influences birth outcome.
- CRH controls the timing of labor and delivery. Precocious elevation of CRH is related to the risk of preterm delivery. This system may be "stress-sensitive." Even though pregnant women may be immunized from stress, the stress signal that is transmitted (release of ACTH and cortisol) is amplified by the placental release of CRH. This possibility has at least two consequences: (1) influencing the timing of delivery and (2) desensitization of hypophyseal corticotrophs and further "protection" of the pregnant women from the results of stress (i.e., release of ACTH and  $\beta E$ ).
- $\beta E$  appears to influence fetal learning and perhaps the developing nervous system.

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