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EDITORS' CHOICE

# Placental corticotropin-releasing hormone (CRH), spontaneous preterm birth, and fetal growth restriction: A prospective investigation

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Obstetric risk
Prenatal stress

**Objectives:** Recent advances in the physiology of human pregnancy have implicated placental corticotropin-releasing hormone (CRH) as one of the primary endocrine mediators of parturition and possibly also of fetal development. The aim of this study was (1) to *prospectively* assess the relationship of maternal plasma concentrations of CRH in the early third trimester of gestation with two prematurity-related outcomes-spontaneous preterm birth (PTB), and small-for-gestational age birth (SGA), and (2) to determine whether the effects of CRH on each of these outcomes are independent from those of other established obstetric risk factors.

**Study design:** In a sample of 232 women with a singleton, intrauterine pregnancy, maternal plasma was collected at 33 weeks' gestation and CRH concentrations were determined by radioimmunoassay. Each pregnancy was dated on the basis of last menstrual period and early ultrasonography. Parity, obstetric risk conditions for prematurity, mode of delivery, and birth outcomes were abstracted from the medical record.

**Results:** After adjusting for the effects of established obstetric risk factors, elevated CRH levels at 33 weeks' gestation were significantly associated with a 3.3-fold increase in the adjusted relative risk (RR) for spontaneous preterm birth and with a 3.6-fold increase in the adjusted relative risk for fetal growth restriction. Women who delivered postterm had significantly lower CRH levels in the early third trimester than those who delivered at term. When outcomes were stratified by gestational length and birth weight, the lowest CRH levels at 33 weeks' gestation were associated with the term non-SGA births, intermediate and approximately equal CRH levels were associated with the preterm non-SGA and term SGA births, and the highest CRH levels were associated with the preterm SGA births.

**Conclusion:** For deliveries occurring after 33 weeks' gestation (the time of CRH sampling in this study), our findings support the notion that in humans placental CRH may play an impending,

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direct role in not only the physiology of parturition but also in processes related to fetal growth and maturation. Our results also support the notion that the timing of onset of parturition may be determined or influenced by events occurring earlier in gestation rather than those close to the time of actual onset of labor (ie, the notion of a "placental clock").


Prematurity (ie, preterm birth, fetal growth restriction) is presently the most significant problem in maternal-child health in the United State because it results in severe adverse health consequences, it has a relatively high prevalence rate that has remained essentially unchanged over the past four decades, and its causes are poorly understood.[1] There is, consequently, a compelling need to elucidate underlying etiologic mechanisms involved in prematurity and develop new markers to identify at-risk pregnancies.

Parturition and fetal growth involve a complex interplay of factors and signaling molecules within the maternal, placental, and fetal tissues. Recent advances have implicated placental corticotropin-releasing hormone (CRH) as one of the primary endocrine mediators of spontaneous labor and possibly fetal development.[2-4] CRH is a hypothalamic neuropeptide that plays a central role in regulating the activity of the hypothalamic-pituitary-adrenal (HPA) axis and physiologic response to stress.[5] During human pregnancy, the CRH gene also is expressed in the placenta and membranes, and results over the course of gestation in exponentially increased production and release of placental CRH into both maternal and fetal compartments.[2-4]

Several clinical studies have reported that CRH levels during gestation or at delivery are increased in maternal and cord plasma and in the placenta in pregnancies characterized by preterm labor and/or fetal growth restriction.[6-15] Other studies have found that CRH levels also are elevated in pregnancies complicated by high-risk conditions for preterm birth and/or fetal growth restriction.[16-18] These findings suggest that CRH levels may relate to the length of gestation and fetal growth either directly by participating in physiologic processes involved in parturition and fetal maturation, or indirectly as a surrogate marker of antepartum conditions that reflect maternal or fetal risk for prematurity. However, with one exception,[15] none of the current studies have systematically examined these two possibilities. Moreover, no study has examined the prospective relationship between maternal CRH and fetal growth restriction. The aim of this study was to examine these possibilities to clarify the role(s) of CRH in these outcomes.

## Material and methods

We conducted a prospective, longitudinal investigation in a sample of women recruited during pregnancy and monitored through delivery. Our sample included low-risk as well as high-risk pregnancies, and deliveries were differentiated on the basis of presence/absence of labor preceding delivery.

### Subjects

Two hundred forty-five pregnant women attending prenatal care at a university-based teaching hospital in Southern California were recruited during the second trimester of gestation. Inclusion criteria were: age older than 18 years; singleton, intrauterine pregnancy; English/Spanish speaking; less than 28 weeks' gestation. Women who delivered by elective cesarean section (n = 13) were excluded from the final sample (n = 232) because their delivery was not preceded by labor. The sociodemographic characteristics of the sample are depicted in Table I.

### Procedures

Eligible subjects were approached consecutively for participation. A 20-mL blood sample was withdrawn from each subject for hormone assays at 32.7 $\pm$ 0.07 (SEM) weeks' gestation. Parity, obstetric risk conditions and labor, delivery, and birth outcomes were abstracted from the medical record. Chart review was performed blind to the results of the hormone assays. The study had been approved by the Institutional Review Board and signed informed consent was obtained from all subjects.

### Measures

#### CRH Assay

Blood samples were collected from all subjects at the same time of day (between 2 and 4 PM), withdrawn into siliconized EDTA vacutainers, placed on ice, and immediately centrifuged (within 5 minutes of the blood draw) at $\times 2000g$ for 10 minutes. The plasma was decanted into polypropylene tubes containing a protease inhibitor (500 KIU/mL aprotinin; Sigma Chemical Company, St Louis, Mo). The samples were then transported on dry ice and stored at $-70°C$ until assayed. The free (unbound, bioactive) fraction of plasma CRH was determined by radioimmunoassay according to methods that have been described elsewhere.[15] Our CRH assay has less than 0.01 % cross reactivity with ovine CRH, 2% cross reactivity with sauvagine CRH, 36% cross reactivity with bovine CRH,

and nondetectable reactivity with human adrenocorticotropic hormone (ACTH). The coefficient of variation is 5% at normal physiologic levels with the use of 4 mL of plasma or 8% with the use of 2 mL, with a minimum detectable dose (95% CI) of 2.04 pg per sample.

### Obstetric risk

Obstetric risk for prematurity was determined by the presence of established historical (eg, history of prior preterm birth, >3 sponteneous abortions, >2 induced abortions) and antepartum risk conditions (eg, urinary tract infection, vaginal bleeding, placenta previa, hypertension, preeclampsia/eclampsia) during pregnancy.[15-19] Because there are no standard criteria for computing the weight of specific obstetric risk conditions, we adopted a conservative strategy and summed the number of risk conditions to compute separate risk scores for preterm birth and fetal growth restriction.[15] Because several of these risk factors may co-occur, the sum of the risk factors may inflate the magnitude of the obstetric risk indices. Thus, their use in our statistical models provides the most conservative effect of the *independent* effect of CRH on the outcomes of interest.

### Birth outcomes

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 by using standard clinical criteria.[20] Two gestational length-related variables were computed—a continuous variable indicating completed weeks' gestation at delivery and a categorical variable for preterm (<37 completed weeks), term (37-41 completed weeks), and postterm (>41 completed weeks) births. Two birth weight−related variables were created—a continuous variable indicating weight in grams at delivery and a categorical variable for low (<2500 g) and normal birth weight (>2500 g). Categorical measures of fetal growth (ie, small-for-gestational age [SGA], appropriate-for-gestational age [AGA], and large-for-gestational age [LGA]) were also computed by using the less than 10th percentile, 10th-90th percentile, and more than 90th percentile weight for gestational age criteria applied separately for male and female newborns (ie, sex-adjusted estimates) in the current sample.

## Statistical analysis

Associations among continuous variables were computed with Pearson product-moment correlation coefficients, whereas those involving categorical variables were computed with an exact test of significance (Student *t* tests for independent samples with unequal *N*s), $\chi^2$ or odds ratios. When necessary, the *t* test was modified to allow for unequal variances. The joint contributions of 2 or more predictors on categorical outcomes were computed by using multivariate logistic regression procedures to obtain estimates of adjusted relative risk. All tests of statistical significance were 2 tailed.

**Table I** Sociodemographic characteristics

| | | |
|---|---|---|
| N | 232 | |
| Age | 26.08 ± 5.6 y | Range: 18-40 y |
| Parity | Primiparous | 49.4% |
| | Multiparous | 50.6% |
| Ethnicity | Anglo | 48.1% |
| | Hispanic | 45.5% |
| | Asian | 2.6% |
| | African American | 1.3% |
| | Other | 2.5% |
| Marital status | Married | 62.6% |
| | Single/separated/divorced | 37.4% |

## Results

The mean plasma concentration of CRH (at 33 weeks' gestation) was 140.81 ± 10.35 pg/mL (±SEM). These values were approximately normally distributed (ie, skewness <2).

Delivery was preceded by labor in all subjects. The mean gestational age at birth was 39.3 ± 0.09 weeks (±SEM), and ranged between 34.5 and 43.1 weeks; 22 of these deliveries (9.5%) were preterm (<37 completed weeks' gestation) and 18 (7.8%) were postterm (>41 completed weeks' gestation). The mean infant birth weight was 3384 ± 34.9 g (±SEM) and ranged between 1840 and 4750 g; 13 infants (5.6%) were classified as low-birth weight (<2500 g), 20 (8.6%) and 23 infants (9.9%) were categorized as SGA and LGA births, respectively, and the remaining 189 infants (81.5%) were categorized as AGA births. (The unequal distribution of sex-adjusted estimates of SGA and LGA births reflects the unequal distribution of male [n = 109; 47%] and female [n = 123; 53%] newborn infants in the study sample.)

On the basis of the presence of 2 or more obstetric risk conditions for preterm birth, approximately a third of the sample (n = 68; 29.3%) was categorized as high-risk for preterm birth. (Cutoff values of 2 or more risk factors for categorization in the high-risk groups for preterm birth and fetal growth restriction were determined empirically, and were based on the results of logistic regressions predicting preterm birth and fetal growth restriction [SGA] by using the number of risk conditions for each outcome as a categorical variable and by determining the significance of the change in relative risk ratio for each category.) Similarly, on the basis of the presence of 2 or more obstetric risk conditions for low-birth weight, approximately a third

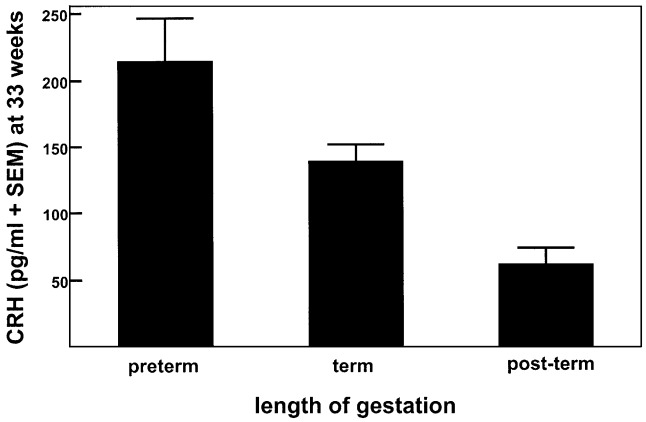


**Figure 1** Women who delivered preterm had significantly higher CRH levels at 33 weeks' gestation than those who delivered at term (215.0 ± 31.5 vs 139.6 ± 11.7 pg/mL (±SEM), respectively; $t = 2.24$, $P < .01$), and women who delivered postterm had significantly lower CRH levels at 33 weeks' gestation than those who delivered at term (62.0 ± 11.4 vs 139.6 ± 11.7 pg/ mL (±SEM), respectively; $t = 4.7$, $P < .001$.

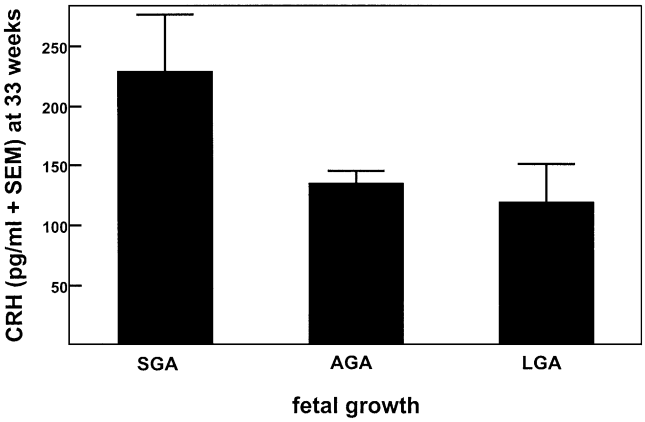


**Figure 2** Women who delivered SGA infants had significantly higher CRH levels at 33 weeks' gestation than those who delivered AGA infants (232.0 ± 43.5 vs 137.0 ± 11.3 pg/mL (±SEM), respectively; $t = 2.4$, $P < .01$). There were no significant differences in CRH levels between subjects who delivered LGA infants and those who delivered AGA infants (137.0 ± 11.3 vs 96.4 ± 24.1 pg/mL (±SEM), respectively.

of the sample (n = 65; 28%) was categorized as high-risk for fetal growth restriction.

Women who delivered preterm had significantly higher CRH levels at 33 weeks' gestation than those who delivered at term (215.0 ± 31.5 vs 139.6 ± 11.7 pg/mL (±SEM), respectively; $t = 2.24$, $P < .01$). Conversely, women who delivered postterm had significantly lower CRH levels at 33 weeks' gestation than those who delivered at term (62.0 ±11.4 vs 139.6 ± 11.7 pg/mL (±SEM), respectively; $t = 4.7$, $P < .001$; Figure 1).

Women who delivered SGA infants had significantly higher CRH levels at 33 weeks' gestation than those who delivered AGA infants (232.0 ± 43.5 vs 137.0 ± 11.3 pg/mL (±SEM), respectively; $t = 2.4$, $P < .01$). There were, however, no significant differences in CRH levels between subjects who delivered LGA infants and those who delivered AGA infants (137.0 ± 11.3 vs 96.4 ± 24.1 pg/mL (±SEM), respectively; Figure 2). Thus, all AGA and LGA infants were grouped together into a "nongrowth restricted" group in subsequent analyses.

Obstetric risk status was significantly correlated with CRH levels. Subjects in the high-risk for preterm birth group had significantly higher third trimester CRH levels than those in the low-risk group (193.7 ± 22.3 vs 118.9 ± 10.9 pg/mL (± SEM), respectively, $t = 3.4$, $P < .001$), and subjects in the high-risk for fetal growth restriction group had significantly higher third-trimester CRH levels than those in the low-risk group (190.6 ± 22.9 vs 121.4 ± 10.9 pg/mL (± SEM), respectively, $t = 3.0$, $P < .01$).

Because both CRH levels and obstetric risk were associated with preterm birth and because CRH levels also were associated with obstetric risk for preterm birth, a logistic multivariate model was constructed to examine the *independent* effects of CRH on preterm birth (Table II). CRH levels were categorized as either high or low on the basis of a median split (87.48 pg/mL). Results demonstrated that the overall model was significant ($\chi^2_{2,230} = 10.25$, $P < .01$), and that after adjusting for the effects of obstetric risk, women with high CRH levels were 3.3-times more likely to deliver preterm than subjects with low CRH levels.

Similarly, because both CRH levels and obstetric risk were associated with SGA birth and because CRH levels were also associated with obstetric risk for fetal growth restriction, a logistic multivariate model was constructed to examine the *independent* effects of CRH on SGA birth (Table III). Results demonstrated that the overall model was significant ($\chi^2_{2,230} = 9.36$, $P < .01$), and that after adjusting for the effects of obstetric risk, there was a 3.7-fold increase in the risk for fetal growth restriction in women with high CRH levels compared with those with low CRH levels.

Finally, because elevated levels of CRH were significantly and independently associated with both outcomes, and because there is considerable overlap between cases of preterm birth and fetal growth restriction, we assessed whether elevated placental CRH levels reflect underlying processes related to the timing of delivery or fetal growth or both. We stratified our outcomes into 4 groups: neither preterm nor SGA (n = 198), only preterm (n = 14), only SGA (n = 12), and both preterm and SGA (n = 8) births. Values of CRH were significantly different across these groups ($F_{3,228} = 3.04$, $P < .05$). The lowest CRH levels were associated with the term-normal growth group, intermediate and approximately equal CRH levels were associated with the only-preterm and the only-SGA

**Table II** Multivariate regression analyses predicting preterm birth

| Variable | Crude (univariate) RR (95% CI) | Adjusted (multivariate) RR (95%C1) |
|---|---|---|
| CRH | 3.8 (1.3-10.7) | 3.3 (1.2-9.4) |
| Antepartum risk | 2.7 (1.1-6.5) | 2.1 (0.9-5.4) |

Model $\chi^2 = 10.25$; $P = .006$.

**Table III** Multivariate regression analyses predicting fetal growth restriction (SGA)

| Variable | Crude (univariate) RR (95% CI) | Adjusted (multivariate) RR (95%CI) |
|---|---|---|
| CRH | 4.1 (1.3-12.9) | 3.7 (1.2-11.6) |
| Antepartum risk | 2.5 (1.0-6.5) | 2.0 (0.7-5.4) |

Model $\chi^2 = 9.36$; $P = .009$.

groups, and the highest CRH levels were associated with the preterm-SGA group (Figure 3). Post hoc tests show a significant difference only between the first and fourth groups, probably reflecting inadequate power to test for significant differences in all subgroups, but suggesting that elevated CRH may be a marker for processes related to both length of gestation and fetal growth.

## Comment

These results demonstrate that in humans, placental CRH plays an impending role in not only the physiology of parturition but also in processes related to fetal growth and maturation. Moreover, our findings are also among the first to suggest that placental CRH directly participates in these physiologic processes, as evidenced by the prospective relationship between elevated CRH levels and relative risk for preterm birth and fetal growth restriction after adjusting for the effects of other established risk obstetric factors. Finally, our results support the notion that the timing of onset of parturition may be influenced by events occurring earlier in gestation rather than those close to the time of actual onset of labor, as evidenced by the prospective association of elevated CRH levels with preterm birth and lower CRH levels with postterm birth.

Because the plasma samples for measurement of placental CRH were obtained in this study at 33 weeks' gestation, our results cannot be generalized to births occurring before this time point. However, for spontaneous deliveries after 33 weeks' gestation, women with elevated CRH were approximately 3 times more likely to deliver preterm than women with normal CRH levels,

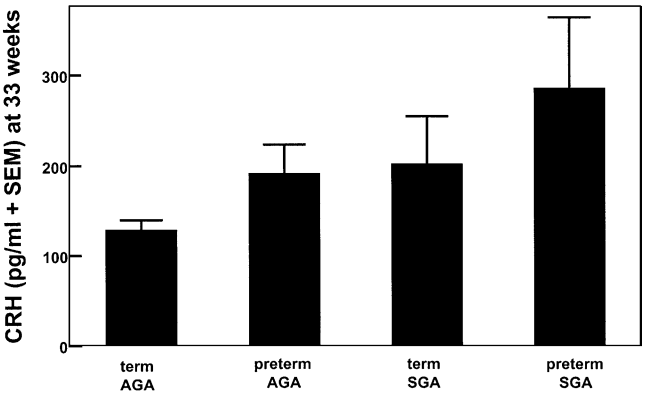


**Figure 3** Outcomes were classified into 4 groups: neither preterm nor SGA, only preterm, only SGA, and both preterm and SGA births. Values of CRH were significantly different across these groups ($F_{3,228} = 3.04$, $P < .05$).

even after adjusting for the effects of established risk factors. This finding supports a direct role for placental CRH in processes related to parturition and timing of onset of labor. It is well recognized that a shift in the balance from a progesterone-dominant to an estrogen-dominant milieu results in a sequence of events in the gestational tissues to promote labor, including gap junction formation, expression of oxytocin receptors, and synthesis of prostaglandins.[2-4] It is also known that unlike most other mammals, the primate placenta cannot convert progesterone to estrogen because it does not express the cortisol-responsive enzyme 17-hydroxylase required for this conversion. Instead, a precursor hormone produced in the fetal adrenal zone, dehydroepiandrosterone sulfate (DHEA-S), is used by the placenta to synthesize estrogens.[2-4] Placental CRH has recently been shown to directly and preferentially stimulate DHEA-S secretion by human fetal adrenal cortical cells[21] via a protein kinase C system.[22] Placental CRH is also known to exert direct actions on the uterus and cervix by upregulation of the nitric oxide pathway,[23] and also to augment changes produced by estrogens on these tissues. CRH interacts with both prostaglandins and oxytocin, the 2 major uterotonins implicated as mediators of the stimulation and maintenance of myometrial contractility at term and during labor, by stimulating the release of prostaglandins from the placenta and fetal membranes and exerting priming as well as potentiating effects for the actions of oxytocin on the myometrium.[2-4,24]

Our finding that low levels of placental CRH at 33 weeks' gestation were significantly associated with later onset of labor and delivery (>41 completed weeks' gestation) supports the notion of the existence of a "placental clock."[15] According to this notion, placental CRH may control the phase of the "placental clock." Thus, phase advancement of the clock, reflected by elevated placental CRH earlier in pregnancy, may accelerate the sequence of biomolecular events underlying

parturition and result in earlier delivery, whereas phase delay, reflected by lower CRH levels, may lengthen the time to initiate parturition.[13]

There was an approximately 3-fold increase in the relative risk for delivering a growth-restricted infant for women with elevated CRH at 33 weeks' gestation compared with those with normal CRH levels, after controlling for the effects of established obstetric risk factors for fetal growth restriction. This finding is consistent with earlier work that reported significant cross-sectional associations between elevated CRH levels in maternal or cord blood on delivery and fetal growth restriction[6] and is among the first to suggest that CRH levels are prospectively associated with SGA birth. Placental CRH may regulate fetal growth via its effects on placental perfusion and/or fetal cortisol production. Placental CRH elevations are associated with decreased uteroplacental flow and hypoxemia-known risk factors for fetal growth restriction.[16] Although CRH had powerful vasodilator properties in human fetal-placental circulation,[4] low oxygen perfusion has recently been shown to inhibit CRH-induced dilation of fetal-placental vascular responses.[25] Fetal cortisol plays a critical role in organ growth and maturation,[2] and placental CRH may also participate in this process by establishing a positive feedback loop with fetal cortisol production.[2,4,26]

Our data also suggest that placental CRH has separate and distinct roles in processes related to the timing of delivery and fetal growth. Levels of CRH at 33 weeks' gestation were elevated in 3 nonoverlapping groups of deliveries: women who delivered preterm but did not have a growth-restricted infant, women who gave birth to a growth-restricted infant but delivered at term, and women who delivered both preterm and had a growth-restricted infant. Moreover, these levels were the highest in the group with both adverse outcomes, suggesting that elevated placental CRH may result from the actions of multiple agonists and thereby place fetuses at double biologic jeopardy for developmental problems.[27]

Finally, our results supported an additional, indirect role for placental CRH in delivery and fetal growth. Maternal CRH levels were positively correlated with obstetric risk indices, which, in turn, predicted the length of gestation and fetal growth, respectively. Placental CRH trajectories over the course of gestation have been shown to vary depending on the cause of preterm birth.[28] Moreover, various forms of prenatal stress have been associated with earlier delivery and impaired fetal growth, and placental CRH may play a central role in modulating the effects of hypoxia, infections, decidual hemorrhage, and psychosocial stress on prematurity-related outcomes. A series of in vitro studies have shown that CRH is released from cultured human placental cells in a dose-response manner in response to *all* the major biologic effectors of stress, including cortisol, catecholamines oxytocin, angiotensin-II, and both forms of interleukin-1.[29] In vivo studies by our group[30] and others[31] have found significant correlations among maternal pituitary-adrenal stress hormones (ACTH, beta-endorphin, cortisol) and placental CRH levels. The maternal environment may also modulate placental CRH via its influence on maternal pituitary-adrenal function.[32,33] We have reported significant associations between maternal stress and 2 effectors of placental CRH-maternal ACTH and cortisol—in the early third trimester of gestation[34] and some other,[7,9,14] but not all,[35] studies have reported a direct positive association between indices of maternal social stress and elevated CRH levels. Thus, depending on the chronicity of the stressor, the resulting increase in CRH production may be a critical factor that contributes to the early initiation of parturition and/or growth restriction.

In summary, for spontaneous births occurring after 33 weeks' gestation, our findings support a major role for placental CRH in processes related to the timing of spontaneous delivery and fetal growth, and have implications for examining the role of CRH as a possible effector of prenatal stress in producing alterations in the length of gestation and fetal development.

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