Association of Lower Socioeconomic Position in Pregnancy with Lower Diurnal Cortisol Production and Lower Birthweight in Male Infants

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ABSTRACT

Purpose: Low maternal socioeconomic position (SEP) has been associated with adverse neonatal outcomes, including preterm birth, low birthweight, intrauterine growth restriction, and infant mortality. A key biological mechanism that has been proposed to explain this association is hypothalamic-pituitary-adrenal (HPA) activity, yet the association between SEP and HPA activity in pregnancy has received little attention. In this study we aimed to examine the associations between SEP and 2 forms of maternal cortisol regulation—diurnal slope and awakening response—across pregnancy. Furthermore, we aimed to assess whether these associations differed by the sex of the fetus.

Methods: A total of 217 pregnant women aged 18 to 40 years with singleton pregnancies participated. Women were excluded from participating if they were aged <18 or >40 years and if they were at risk for maternal or obstetric complications. Women provided information on socioeconomic characteristics of adults contributing to the participants’ household to compute a Hollingshead Four Factor Index of Social Status score of SEP. Women provided salivary cortisol samples on awakening, 30 minutes after wakeup, and at bedtime, at 3 times over pregnancy and once 30 days postpartum to calculate the diurnal slope and cortisol awakening response (CAR). Using linear regression analyses, we examined the relationships between maternal SEP and maternal diurnal slope and CAR. We explored the relationships between maternal SEP and cortisol by fetal sex using linear regression analyses. We also explored links between maternal SEP, maternal cortisol, and infant birth outcomes.

Findings: Women of lower SEP displayed smaller awakening responses and less change over the day compared with women of higher SEP. SEP was significantly associated with attenuated diurnal slope only among women carrying female fetuses, whereas for CAR, the association between SEP and attenuated CAR was significant only for women carrying male fetuses. Lower SEP was associated with decreased birthweight, and this association was partially explained by maternal HPA activity in pregnancy.

Implications: Women of low SEP displayed attenuated HPA activity across the perinatal period, and patterns varied by fetal sex and cortisol metric. Findings are in need of replication. More research is needed to understand the links between SEP, HPA activity, and neonatal health. (Clin Ther. 2016;38:265–274) © 2016 Elsevier HS Journals, Inc. All rights reserved.

Key words: cortisol, pregnancy, sex, socioeconomic position.
INTRODUCTION
Socioeconomic position (SEP) reflects the social standing of an individual or group, and is often measured as a combination of education, income, and occupation. Socioeconomic deprivation has been consistently associated with morbidity and mortality in nonpregnant adults. In pregnancy, low SEP is robustly associated with adverse pregnancy outcomes, including infant mortality, prematurity, low birthweight, and intrauterine growth restriction. Past studies have cited poor nutrition and access to health care as some factors explaining links between low SEP and adverse neonatal outcomes. A key physiologic process that has been proposed to explain the link between low SEP and poor health is the hypothalamic-pituitary-adrenal (HPA) axis. Low SEP may represent a chronic stressor that results in wear and tear on the HPA axis, resulting in HPA dysregulation and aberrant patterns of cortisol production. Low SEP has been associated with altered cortisol patterns in nonpregnant adults, with evidence for both elevated and attenuated concentrations among individuals of low SEP. In addition, some studies of nonpregnant adults suggest that the association between SEP and cortisol may differ by sex; Steptoe et al found that low SEP was associated with lower levels of cortisol among women carrying female fetuses before 30 weeks gestation, at which point there was a crossover, and women carrying female fetuses displayed elevated cortisol levels. The influence of SEP in the association between maternal cortisol and fetal sex was not examined in the DiPietro study. In addition, a recent study reported that associations among SEP and methylation of the gene encoding placental 11β-hydroxysteroid dehydrogenase (an enzyme involved in the inactivation of maternal cortisol, protecting the fetus from overexposure to maternal glucocorticoids) differed by fetal sex; Appleton et al found that women reporting the greatest economic adversity in pregnancy had the highest placental 11β methylation, particularly if they were carrying a male fetus. Given
evidence of differences in HPA activity over pregnancy by fetal sex, and evidence of sex differences in the SEP–cortisol association in nonpregnant adults, we also explored whether associations between SEP and maternal cortisol differed by fetal sex. Finally, given past evidence of links between maternal SEP and adverse neonatal outcomes,6,7 we explored associations between maternal SEP and birth outcomes, and whether associations were mediated by maternal cortisol levels.

**PATIENTS AND METHODS**

**Participants**

Participants were 217 pregnant women with singleton pregnancies who were part of a larger study of the effects of maternal mood on fetal and infant development (BAMBI [Behavior and Mood in Mothers, Behavior in Infants]). Maternal and infant characteristics, categorized according to low and high SEP and infant sex, are presented in Table I. Thirty-nine percent of the sample was considered “low” SEP (score of 4 or 5 on Hollingshead’s Four Factor Index of Social Status scale29). Approximately 12% of the sample had a score of 1 on the Hollingshead scale, indicating “high” SEP. Women in the current study were aged, on average, 27 years (SD, 6), were from racially and ethnically diverse backgrounds (45% non-Hispanic white, 17% non-Hispanic black, 26% Hispanic, 6% >1 race, 4% Asian, 1% Native American, and 1% “other”), 45% were married, 46% of pregnancies were planned, 35% had a high school education or less, and 17% of the sample reported an annual income of <$10,000. Approximately 25% of women in the study received public insurance.

Infants were born at 39 weeks’ gestation (SD, 2), mean (SD) weight was 3.36 (0.47) kg, and APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) score at 5 minutes after delivery was 9 (1), demonstrating good health among babies born in this sample. A total of 52% of babies were male. Women were at low risk for maternal or obstetric complications. This study was approved by the Women & Infants Hospital and Lifespan Hospital institutional review board.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low SEP/ Male</th>
<th>Low SEP/ Female</th>
<th>High SEP/ Male</th>
<th>High SEP/ Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age, y</td>
<td>23 (4)</td>
<td>25 (6)</td>
<td>28 (5)</td>
<td>28 (5)</td>
</tr>
<tr>
<td>Gravida</td>
<td>3 (1)</td>
<td>3 (2)</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Education &lt; high school, %</td>
<td>31</td>
<td>39</td>
<td>3</td>
<td>3</td>
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<td>White, %</td>
<td>8</td>
<td>42</td>
<td>52</td>
<td>57</td>
</tr>
<tr>
<td>Annual income &lt; $10K, %</td>
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<td>39</td>
<td>8</td>
<td>7</td>
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<tr>
<td>Married, %</td>
<td>6</td>
<td>6</td>
<td>61</td>
<td>62</td>
</tr>
<tr>
<td>Prepregnancy BMI</td>
<td>26 (7)</td>
<td>28 (8)</td>
<td>26 (7)</td>
<td>25 (6)</td>
</tr>
<tr>
<td>Cigarettes in pregnancy</td>
<td>113 (348)</td>
<td>41 (166)</td>
<td>23 (111)</td>
<td>11 (49)</td>
</tr>
<tr>
<td>Units of alcohol in pregnancy</td>
<td>6 (13)</td>
<td>5 (9)</td>
<td>7 (10)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>3</td>
<td>3</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Gestational diabetes, %</td>
<td>11</td>
<td>0</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Infant Gestational duration, wk</td>
<td>39 (4)</td>
<td>39 (1)</td>
<td>39 (1)</td>
<td>40 (1)</td>
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<tr>
<td>Birthweight, kg</td>
<td>2.14 (0.76)</td>
<td>3.24 (0.47)</td>
<td>3.45 (0.49)</td>
<td>3.38 (0.45)</td>
</tr>
<tr>
<td>APGAR score at 5 min</td>
<td>9 (1)</td>
<td>9 (0.3)</td>
<td>9 (0.5)</td>
<td>9 (1)</td>
</tr>
</tbody>
</table>

APGAR = Appearance, Pulse, Grimace, Activity, and Respiration scale; BMI = body mass index; SEP = socioeconomic position.
boards (Providence, Rhode Island). All women provided written informed consent before their participation.

**Procedure**

Pregnant women completed 1 to 3 study sessions during pregnancy (session 1, 24 [SD, 3] weeks; session 2, 30 [1] weeks; session 3, 36 [1] weeks) and 1 session in the postpartum period (~30 days after delivery). All participants completed at least 1 study session, 81% completed at least 2 study sessions, 72% completed all 3 pregnancy sessions, and ~85% completed the postpartum session. At baseline, participants provided information on socioeconomic characteristics of adults contributing to the participants’ household, maternal characteristics, and pregnancy health information. For 3 days after each session, participants provided saliva samples (passive drool) on awakening, 30 minutes after wakeup, and at bedtime. After participants completed the 3 days of saliva collection, study staff retrieved samples from participants’ homes and provided payment.

Maternal medical history was assessed via chart review at enrollment and after delivery. Neonatal outcomes, including fetal sex, gestational age at birth, birthweight, and APGAR scores, were collected from medical chart review after delivery.

**Measures**

**Socioeconomic Position**

Participants were asked to self-report the current occupation and highest level of education for themselves and another contributing adult at their first study session. To measure SEP we utilized the Hollingshead Four Factor Index of Social Status scale. This measure is an index of SEP based on weighted scores of education and occupation of contributing adults. Occupations were coded according to the Hollingshead Four Factor occupational codes. Occupation scores ranged from 1 to 9, with a score of 1 indicating a menial laborer and 9 indicating a higher executive and major professional. Educational attainment was scored on a scale of 1 to 7, with 1 indicating completion of less than 7th grade, and 7 indicating graduate training. Hollingshead scores ranged from 1 to 5, with scores of 4 and 5 indicating low SEP. The Hollingshead measure is a frequently used measure of SEP and has demonstrated good inter-rater reliability in past research.

**Maternal Cortisol**

Up to 36 total saliva samples were collected from each participant throughout the study and returned to the laboratory by study staff, aliquoted, and stored at −80°C until analysis. Samples were then shipped to the laboratory of Clemens Kirschbaum, PhD (Dresden University). Cortisol concentrations were analyzed with an immunoassay with time-resolved fluorescence detection. The intra- and interassay %CVs were <8%. A subset of the sample (17%) was given Medication Event Monitoring System caps (Aardex, Zurich, Switzerland) that time-stamp on every opening of bottles containing tubes used for collecting maternal saliva. For participants with both self-reported and Medication Event Monitoring System–recorded saliva sampling times, there was a mean (SD) time discrepancy of 8 (5) minutes, suggesting that a subset of participants was adherent to the sampling protocol.

**Statistical Analysis**

**Cortisol Data Reduction**

We calculated the CAR on each day of saliva collection by taking the difference between cortisol values on awakening and 30 minutes after wakeup and then averaging CAR across the 3 days of collection. The 3 CARs over pregnancy were also averaged to calculate a mean CAR in pregnancy. Morning saliva samples that were collected <20 or >40 minutes apart were omitted from analyses in order to accurately capture the morning awakening response. We calculated a measure of diurnal cortisol slope by taking the difference between samples collected on awakening and at bedtime on each day of collection. Slopes across the 3 days of collection were then averaged. The 3 slopes over pregnancy were also averaged to calculate a mean pregnancy diurnal slope measure. CAR and diurnal cortisol slope are regulated by different biological processes and thus were analyzed separately. CAR and diurnal slope values were logarithm-transformed due to skewed distributions.

**Hypothesis Testing**

To assess the influence of potential covariates, we performed Pearson correlation analyses (for continuous variables) and 1-way ANOVA (for categorical variables) to examine associations among maternal and infant characteristics and maternal cortisol
concentrations. Characteristics that were significantly associated with maternal cortisol were included as covariates in subsequent analyses. We performed linear regression analyses to examine the association between maternal SEP and: (1) mean maternal CAR and diurnal slope in pregnancy and (2) mean maternal CAR and diurnal slope by all study sessions (3 times in pregnancy and 1 time postpartum). Gestational age at sample collection was included as a covariate in regression analyses examining SEP and cortisol at separate gestational windows in pregnancy. To explore whether associations between SEP and maternal cortisol differed by fetal sex, we performed linear regression analyses examining the association between SEP and cortisol separately for women carrying male and female fetuses. Finally, we performed linear regression analyses to examine associations between maternal SEP, cortisol, and infant outcomes (gestational age at birth, birthweight, and APGAR score at 5 minutes after delivery).

RESULTS

Assessment of Potential Covariates

We first examined associations between maternal cortisol and maternal characteristics of age, gravida, parity, race/ethnicity, prepregnancy body mass index, number of cigarettes smoked, number of alcoholic drinks consumed in pregnancy, gestational diabetes, hypertension, hyper/hypothyroidism, maternal infection in pregnancy, and maternal corticosteroid use in pregnancy. Only maternal hypertension was significantly associated with maternal CAR ($F = 18.08; P < 0.001$) and was included as a covariate in subsequent analyses. Maternal age ($r = 0.21; P = 0.004$), the number of alcoholic drinks consumed in pregnancy ($r = 0.13; P = 0.05$), and race/ethnicity ($F = 5.63; P < 0.001$) were significantly associated with diurnal cortisol slope and were included as covariates in subsequent analyses.

Socioeconomic Position and Cortisol

Maternal SEP was significantly associated with mean diurnal slope ($\beta = -0.26; P = 0.002$), and mean CAR ($\beta = -0.18; P = 0.02$) in pregnancy, such that women of lower SEP displayed smaller awakening responses and smaller slopes in pregnancy compared with women of higher SEP. When we examined the association within each study session separately, we found that for slope, the association between SEP was significant at 24 weeks’ gestational age (GA) ($\beta = -0.21; P = 0.02$), 30 weeks’ GA ($\beta = -0.23; P = 0.01$), and 36 weeks’ GA ($\beta = -0.23; P = 0.01$), such that lower SEP was associated with smaller slopes at each time point. SEP was associated with CAR at 36 weeks’ gestation ($\beta = -0.20; P = 0.02$), but not at 24 ($\beta = -0.11; P = 0.28$) or 30 ($\beta = -0.05; P = 0.53$) weeks’ gestation; lower SEP was associated with smaller CAR only at 36 weeks’ gestation. The association between postpartum CAR and SEP was not significant ($\beta = 0.09; P = 0.42$). Postpartum slope was significantly associated with SEP ($\beta = -0.32; P = 0.001$); women who reported lower SEP had greater cortisol slopes in the postpartum period (Table II).

Socioeconomic Position and Cortisol by Fetal Sex

To explore whether the association between maternal SEP and cortisol differed by fetal sex, we ran regression analyses stratified by sex of the fetus. Results of these analyses revealed that SEP was significantly associated with mean maternal slope in pregnancy only among women carrying female fetuses ($\beta = -0.36; P = 0.002$) but was not significant for women carrying male fetuses ($\beta = -0.07; P = 0.58$). This pattern reversed in the postpartum period; SEP was associated with cortisol slope among women who delivered male babies ($\beta = -0.36; P = 0.004$) but was not significantly associated among women who delivered female babies ($\beta = -0.29; P = 0.06$). Women of lower SEP in pregnancy and who had male babies displayed attenuated cortisol slope in the postpartum period.

For CAR, the opposite pattern was observed; the association between SEP and mean CAR in pregnancy was significant for women carrying male fetuses ($\beta = -0.24; P = 0.03$) but not among women carrying female fetuses ($\beta = -0.12; P = 0.30$). A consistent pattern was observed in the postpartum period; SEP was associated with CAR among women who had male infants ($\beta = 0.33; P = 0.02$) but not female infants ($\beta = -0.12; P = 0.45$). Women of lower SEP in pregnancy and who had male babies displayed attenuated CAR in pregnancy and the postpartum period (Table II).

Examination of associations between SEP and maternal cortisol within each gestational window stratified by fetal sex revealed that, for women carrying female fetuses, SEP was significantly associated with maternal diurnal slope at 30 weeks’ GA ($\beta = -0.33;
P = 0.01) and 36 weeks’ GA (β = –0.28; P = 0.02) but was not statistically significant at 24 weeks’ GA (β = –0.19; P = 0.18). Among women carrying male fetuses, the association between SEP and maternal diurnal slope was not significant (all, β > –0.10; P > 0.09). For CAR, results revealed that associations among SEP and CAR were significant for women carrying male fetuses at 36 weeks’ gestation (β = –0.26; P = 0.02) but not at 24 (β = –0.12; P = 0.39) or 30 (β = 0.01; P = 0.87) weeks’ gestation. There were no significant associations between maternal SEP and CAR at any gestational time point among women carrying female fetuses (all, β > –0.13; P > 0.27) (Table II and Figure). In the Figure we present maternal cortisol patterns stratified by SEP category for ease of interpretation; however, SEP was examined as a continuous variable in analyses.

**Socioeconomic Position and Neonatal Outcomes**

Associations among SEP and neonatal outcomes revealed a significant association between infant birthweight and SEP (β = –0.19; P = 0.007); women with lower SEP in pregnancy had babies that weighed less at birth than did women of higher SEP in pregnancy. This association was significant for male (β = –0.21; P = 0.03) but not female (β = –0.16; P = 0.12) infants. The association between SEP and infant birthweight remained significant when average maternal cortisol slope over pregnancy was added to the model (β = –0.20; P = 0.01) but became nonsignificant when adjusting for average maternal CAR in pregnancy (β = –0.12; P = 0.16). These results suggest that the association between lower SEP and reduced birthweight is partially explained by maternal HPA functioning in pregnancy. There were no significant associations between SEP and gestational duration or APGAR score at 5 minutes after delivery (all, P > 0.35).

**Maternal Cortisol and Neonatal Outcomes**

Associations among maternal cortisol and neonatal outcomes were not statistically significant (all, P > 0.06).

**DISCUSSION**

Findings from this study reveal an association between maternal SEP and diurnal cortisol over pregnancy and in the postpartum period, such that women of lower
SEP displayed smaller diurnal cortisol slope and CAR. Attenuated cortisol production may be indicative of dysregulation of the HPA axis and have been associated with poor health in past research. Low SEP may represent a chronic stressor that results in wear and tear on the HPA axis, resulting in HPA attenuation and reductions in cortisol production over pregnancy. Decreases in cortisol production toward the end of gestation may impair production of fetal lung surfactant (a lipoprotein that increases the ability of the lungs and thorax to expand) and slow maturation of fetal lung.

The association between SEP and cortisol diurnal slope was significant across pregnancy and postpartum time points, whereas the association between SEP and CAR was significant only in the late third trimester. Over typically developing pregnancies, CAR and cortisol reactivity to stress becomes blunted as pregnancy progresses and circadian rhythms are maintained. In light of the typical changes in HPA activity over pregnancy, these results suggest that CAR attenuation and disruption in circadian patterns may be particularly pronounced among women of lower SEP. Findings are consistent with the small number of previous studies showing that socioeconomic deprivation is associated with altered diurnal cortisol patterns in late pregnancy. However, future studies are needed to further understand the SEP–cortisol association in the perinatal period.

We also examined whether the association between SEP and cortisol differed by the sex of the fetus. Results from this study revealed that women of low SEP who were carrying female fetuses displayed smaller diurnal cortisol slopes at 30 and 36 weeks’ gestation, whereas we observed no significant associations between SEP and diurnal cortisol slope in pregnancy among women carrying male fetuses. The pattern changed in the postpartum period; women of lower SEP who delivered male infants displayed attenuated diurnal slope. In contrast, lower-SEP women carrying male fetuses displayed smaller CAR, but only at 36 weeks’ gestation and postpartum. These results complement, in part, the findings reported by DiPietro et al., who found differences in maternal cortisol regulation according to the sex of the fetus and the gestational window of cortisol sampling. Results also support the hypothesis that fetal sex hormones may interact with environmental cues to dictate maternal HPA activity and cortisol production in pregnancy.

The diurnal cortisol slope represents the mean rate of decline in cortisol from wakeup to bedtime, whereas the CAR represents the increase in cortisol from wakeup time to 30 to 45 minutes after wakeup. Diurnal slope and CAR are under different regulatory control and may respond differently to environmental stress. Although in the present study the associations among SEP and these indices of diurnal cortisol rhythm varied by fetal sex, findings suggest that, among women of lower SEP, there is an overall reduction in cortisol production in pregnancy. Cortisol production modulates the inflammatory response. Chronic stress, such as experiencing low SEP, may alter the effectiveness of cortisol in regulating the inflammatory response, resulting in increased inflammation. Diminished cortisol production among low-SEP women, particularly at the end of gestation and if they are carrying a male fetus, may in turn increase the risk for inflammation. Elevated inflammation is a risk factor for adverse neonatal outcomes including preterm birth, and male fetuses are more likely to be born preterm. Taken together, results from the present study suggest that male fetuses of lower-SEP women may be particularly vulnerable to preterm birth, and 1 mechanism explaining this vulnerability may be diminished maternal cortisol production (and concurrent risk for inflammation/infection) in late pregnancy.
pregnancy. However, women in this study were selected to be at low risk for obstetric and neonatal complications, and we did not observe an association between SEP and gestational duration, so our data do not support the previously observed link between SEP and preterm birth.

We explored associations between maternal SEP and infant birth outcomes. Results reveal an inverse association between maternal SEP and infant birthweight, particularly among male infants, such that women of lower SEP delivered infants that weighed less, reflecting perhaps a suboptimal intrauterine environment. These results suggest that, even in this sample of predominantly healthy pregnancies, low SEP may have had a significant effect on fetal growth. This association became nonsignificant after adjustment for maternal CAR, suggesting that maternal HPA activity explained some of the variance in the relationship between SEP and infant birthweight.

Results from this study are the first, to our knowledge, to examine the association between SEP and cortisol by fetal sex, and findings extend the current literature by demonstrating an association between SEP and maternal cortisol at multiple gestational time periods. Results from this study, however, should be interpreted in light of several limitations. The aim of this study was to examine associations between maternal SEP and a biological system that may serve as a pathway to adverse neonatal outcomes. Other important behavioral factors that have been linked to birth outcomes, including health care utilization and nutrition, were not examined. These factors are important to consider in future studies. The Hollingshead measure of SEP incorporates data on the education and occupation of adults contributing to the household. This may not be an accurate representation of social status because it does not take into account other indices of social status, including income, neighborhood factors, and perceived social status. We also did not ask participants to report on socioeconomic characteristics of their childhood, despite research suggesting that childhood socioeconomic characteristics may be more predictive of adult stress physiology than adult SEP. In addition, we collected only 2 cortisol samples each morning over 3 days to capture the CAR. Ideally, we would have collected 3 or more samples per day for up to 6 days to accurately capture the CAR.

Another limitation of this study was our lack of assessment of the sexes of previous pregnancies. Some literature suggests that having a male fetus in a prior pregnancy increases preterm birth risk in subsequent pregnancies, leading to the speculation that the sex of a prior pregnancy may prime maternal hormonal profiles in subsequent pregnancies. This is an important consideration for future research.

Despite several limitations, we believe that results from this study make significant contributions to the extant literature. A consistent association between SEP and cortisol has been observed in nonpregnant samples, but this association has not been adequately examined in pregnancy or the early postpartum period. Results from this study add to our understanding of the relationships between SEP and cortisol during the perinatal period. This study is also the first, to our knowledge, to suggest that the relationships between SEP and maternal cortisol may differ by fetal sex. This difference is particularly important to consider in light of robust evidence indicating that male fetuses are at greater risk for preterm delivery and suggest that sex hormones may interact with environmental inputs (ie, SEP) to result in differences in maternal cortisol production. Findings need to be replicated in larger samples of pregnant women, including those at risk for adverse maternal and neonatal outcomes, in order to further understand the links between SEP, cortisol, and maternal and infant health.

CONCLUSIONS

The present study provides evidence supporting an association between maternal SEP and HPA activity in the perinatal period and adds to the current literature by assessing this link among a variety of diurnal cortisol measures and across several periods of gestation, and by examining differences by fetal sex. Future research utilizing larger sample sizes is needed to explore the interactive effects of fetal sex, SEP, and maternal cortisol patterns, as well as pathways to adverse neonatal outcomes based on fetal sex and maternal SEP. These findings provide preliminary evidence for potential biomarkers that may serve as pathways to sex differences in adverse neonatal outcomes.

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CONFLICTS OF INTEREST
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REFERENCES


