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Diurnal Salivary Cortisol Patterns Prior to Pregnancy Predict Infant Birth Weight

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Objective: Elevated maternal psychosocial stress during pregnancy and accompanying changes in stress hormones may contribute to risk of adverse birth outcomes such as low birth weight and preterm birth. Relatedly, research on fetal programming demonstrates intriguing associations between maternal stress processes during pregnancy and outcomes in offspring that extend into adulthood. The purpose of this study was to test whether hypothalamic-pituitary-adrenal (HPA) patterns in mothers during the period between 2 pregnancies (i.e., the interpregnancy interval) and during the subsequent pregnancy predict infant birth weight, a key birth outcome. ***Method:*** This study sampled salivary cortisol before and during pregnancy in a diverse community sample of 142 women enrolled in the Community Child Health Network study. ***Results:*** Using multilevel modeling, we found that flatter diurnal cortisol slopes in mothers during the interval between one birth and a subsequent pregnancy predicted lower infant birth weight of the subsequent child. This interpregnancy cortisol pattern in mothers also correlated with significantly shorter interpregnancy intervals, such that women with flatter cortisol slopes had more closely spaced pregnancies. After adding demographic covariates of household income, cohabitation with partner, and maternal race to the model, these results were unchanged. For participants who provided both interpregnancy and pregnancy cortisol data ($n = 73$), we found that interpregnancy cortisol slopes predicted infant birth weight independent of pregnancy cortisol slopes. ***Conclusions:*** These novel findings on interpregnancy HPA axis function and subsequent pregnancy outcomes strongly support life course health approaches and underscore the importance of maternal stress physiology between pregnancies.

Keywords: pregnancy, cortisol, HPA axis, interpregnancy, birth

Theories of fetal programming propose that the prenatal environment shapes the development of the fetus and the offspring's health over the life course. For example, evidence confirms that maternal stress, trauma, alcohol use, malnutrition, and depression predispose the embryo and fetus to higher risk of developmental physical and mental health adversities (Barker, Eriksson, Forsén, & Osmond, 2002; Pies, Kotelchuck, & Lu, 2014). In studies testing the "fetal origins hypothesis," an infant's birth weight often served

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as a proxy for the quality of the intrauterine environment because it is easily measured, routinely recorded, and reflects key factors that affect fetal growth such as maternal health and undernutrition (Barker, Winter, Osmond, Margetts, & Simmonds, 1989). Low birth weight (<2,500 g) carries an increased risk of infant mortality and impaired neurodevelopment in infants who survive (McCormick, 1985; Paneth, 1995) and predicts health outcomes over the life course, including vulnerability to cardiovascular and metabolic disorders in adulthood (Barker et al., 2002). These findings present an important public health issue given that 8.2% of all babies in the United States are <2,500 g, a figure that increases to 13.6% among African-American babies (2009 data; Hamilton, Hoyert, Martin, Strobino, & Guyer, 2013).

Among the established medical and behavioral risk factors for low birth weight are maternal hypertension, malnutrition, and smoking (Kramer, 2003). A growing body of evidence has shown that maternal stress during pregnancy also contributes to lower birth weight (Dunkel Schetter & Lobel, 2012). Although the biological mechanisms underlying this association are not well established, the maternal hypothalamic-pituitary-adrenal (HPA) axis, through the actions of one of its key hormonal products, cortisol, is one of several possible pathways (Sandman, Wadhwa, Chicz-Demet, Dunkel-Schetter, & Porto, 1997).

Maternal cortisol may influence birth weight through multiple mechanisms, one of which is a direct influence on intrauterine growth rate. Maternal cortisol acts directly on the fetus and plays a key role in fetal development, notably organ maturation and neural generation (Challis et al., 2001). During pregnancy, passage of maternal cortisol through the placenta is regulated by the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD2; Benediktsson, Calder, Edwards, & Seckl, 1997), which allows a portion of maternal cortisol to cross the placental barrier, accounting for approximately 30–40% of fetal cortisol concentrations (Gitau, Cameron, Fisk, & Glover, 1998). Fetal exposure to elevated cortisol results in processes that reduce blood flow to the fetus and compromise fetal growth by restricting delivery of oxygen and nutrients. As evidence, women who receive synthetic corticosteroid infusions during pregnancy are at increased risk of delivering infants with fetal growth restriction and low birth weight (Bloom, Sheffield, McIntire, & Leveno, 2001; French, Hagan, Evans, Godfrey, & Newnham, 1999).

Elevated cortisol may also contribute to lower birth weight indirectly through earlier delivery (i.e., shortened gestation). Cortisol stimulates the production and release of placental corticotrophin releasing hormone (pCRH; Sandman et al., 2006), which plays a central role in the physiological events involved in the onset of parturition (McLean & Smith, 2001). pCRH exerts direct effects on the uterus and cervix, supporting estrogen-initiated changes in these tissues (Wadhwa, Culhane, Rauh, & Barve, 2001). pCRH also interacts with prostaglandins and oxytocin, which are known mediators of uterine contractility (Challis, 2000).

Normal pregnancy is characterized by marked increases in maternal HPA products, including two- to fourfold increases in circulating cortisol levels over the course of gestation and notable changes in the feedback loops that regulate glucocorticoid secretion (Harville et al., 2007; Mastorakos & Ilias, 2003; Sandman et al., 2006). Despite these changes, some characteristics of human HPA activity are preserved during pregnancy. For example, the circadian rhythm of cortisol remains intact and generally follows a diurnal pattern characterized by peak levels 30–45 min after awakening, followed by a gradual decline over the course of the day (Entringer, Buss, Andersen, Chicz-DeMet, & Wadhwa, 2011; Harville et al., 2007). However, there is individual variability in diurnal cortisol rhythms that may be attributable, in part, to psychological influences. For example, women who report greater distress during pregnancy tend to have flatter cortisol slopes (Kivlighan, DiPietro, Costigan, & Laudenslager, 2008; Obel et al., 2005; O'Connor et al., 2014), which parallels findings of flatter circadian cortisol rhythms in individuals experiencing chronic stress in nonpregnant samples (Abercrombie et al., 2004; Adam & Gunnar, 2001). Furthermore, although the maternal stress response is progressively dampened as pregnancy progresses (de Weerth & Buitelaar, 2005; Entringer et al., 2010), levels of cortisol and other HPA hormones are influenced by psychological stress through the second and third trimester (Entringer et al., 2011; Giesbrecht, Campbell, Letourneau, Kaplan, & the APrON Study Team, 2013; Nierop et al., 2006; Nierop, Wirtz, Bratsikas, Zimmermann, & Ehlert, 2008).

Most pregnancy studies involve convenience samples from prenatal care settings, often recruited after the critical early phases of embryonic and fetal development are over. Recent thinking is that risk factors for adverse birth outcomes could be better addressed if identified and managed before conception (Floyd et al., 2013; Johnson et al., 2006). The hypothesis that a woman's health and life experiences before pregnancy potentially shape the development of the fetus and pregnancy outcomes parallels life-course models in maternal-child health (Lu & Halfon, 2003; Misra, Guyer, & Allston, 2003; Ramey et al., 2015). Studies examining prepregnancy health necessitate data collection efforts before a pregnancy is recognized, which may include the intervals between pregnancies. Large population-based studies using national registries have linked preconception maternal stress to lower birth weight in Denmark (Khashan et al., 2008) and the United States (Strutz et al., 2014). However, neither of these studies explored possible biological mechanisms through which prepregnancy stress influenced birth outcomes.

The Present Study

We used data collected by the Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD)-funded Community Child Health Network (CCHN) to examine diurnal cortisol patterns in mothers before and during a pregnancy and test relationships between these patterns and infant birth weight. Mothers were recruited after the birth of an "index" child and studied at regular intervals for 2 years. During this time, a subset of mothers who became pregnant again was studied during their "subsequent" pregnancy. This study design intentionally afforded the rare opportunity to collect data during the interpregnancy interval, defined as the length of time between the birth of a child and conception of a subsequent child. The first aim was to test whether diurnal cortisol patterns in mothers predict infant birth weight. On the basis of the literature previously described linking dysregulated maternal HPA axis activity to poorer birth outcomes, we hypothesized that flatter maternal cortisol slopes would be associated with lower infant birth weight. The second aim was to test the hypothesis that interpregnancy cortisol patterns predict infant birth weight over and above pregnancy cortisol patterns.

Method

Participants

CCHN is a five-site research network engaged in community-based participatory research methods in the process of planning and conducting a prospective longitudinal study to better understand disparities in maternal health and child development (Ramey et al., 2015). The full CCHN cohort includes 2,510 mothers and 1,436 fathers or coparenting partners. Eligibility criteria, recruitment procedures, and cohort demographic characteristics are described elsewhere (Dunkel Schetter et al., 2013; Ramey et al., 2015). In brief, mothers were recruited just after the birth of a child in one of five study sites: Washington, DC; Baltimore, MD; Los Angeles County, CA; Lake County, IL; and eastern North Carolina. The study catchment areas were predominantly low income. CCHN sampled only African-American (54%), Latina (24%), and non-Hispanic White women (22%) and oversampled women who had delivered preterm infants.

Eighty-three percent of the mothers in the full CCHN cohort completed at least one of five possible follow-up study visits held at 6-month intervals between 6 months and 2 years after the birth of the index child (n = 2,089). During at least one of these visits, 372 participants (18%) reported that they were currently pregnant. Participants were also asked to contact study staff if they became pregnant again between study visits, and an additional 44 subsequent pregnancies were identified in this manner for a total of 416 subsequent pregnancies during the follow-up period. Most participants (n = 343, 82%) consented to continued participation in the subsequent pregnancy follow-up study and completed at least one study visit during or shortly after the subsequent pregnancy. A majority of the remaining 73 subsequent pregnancies were among women lost to follow-up (n = 64). A few women withdrew from the study for reasons such as moving out of the study catchment area (n = 2), death of the index child (n = 2), miscarriage (n = 3), and lack of time/interest (n = 2). There were no differences in terms of race/ethnicity or cohabitation status between women with subsequent pregnancies who withdrew or were lost to follow-up and those who were in this sample, except participants had a higher mean per capita household income ($10,407 vs. $14,816).

Neonatal hospital charts with birth weight data were available for 194 (57%) of the 343 subsequent pregnancies. All participants were invited to participate in the saliva sampling portion of the study at all time points; however, some participants did not return the saliva sampling kits, and only participants who provided saliva samples at least once during the interpregnancy interval or subsequent pregnancy and for whom we were able to obtain newborn medical charts were included in the multilevel analyses (n = 142 women). Study sample characteristics are presented in Table 1. Compared with women with subsequent pregnancies who were excluded because of missing birth data, participants were significantly more likely to be Latina (34% of participants vs. 18% of those excluded) or White (34% vs. 21%) and less likely to be African American (32% vs. 60%). Participants also had a significantly higher per capita household income (mean $15,221 vs. $10,304). There were no significant differences between included and excluded participants in cohabitation status.

Table 1
Descriptive Statistics (N = 142)

Descriptive variables	*n*	%
Race/ethnicity		
African American/Black	45	31.7
White/Caucasian	49	34.5
Hispanic/Latina	48	33.8
Cohabitating with baby's father	111	78.2
Recruitment site		
Baltimore, MD	25	17.6
Lake County, IL	84	59.2
Los Angeles County	6	4.2
Eastern North Carolina	9	6.3
Washington, DC	18	12.7
Cortisol samples provided		
T2 (6 months postpartum)	109	76.7
T3 (12 months postpartum)	93	65.5
T5 (24 months postpartum)	30	21.1
P1 (2nd trimester)	79	55.6
P2 (3rd trimester)	83	58.5
Total cortisol sampling days		
1	27	19.0
2	34	23.9
3	32	22.5
4	42	29.6
5	7	4.9

	M	(*SD*)	Range
Household income ($)	15,221	(24,224)	0–40,180
Infant birth weight (g)	3,278	(556.35)	1,090–4,750
Interpregnancy interval (days)	455.46	(233.22)	80–1,363
Interpregnancy diurnal cortisol			
Cortisol at wake (nmol/L)	5.50	(4.94)	0.10–42.0
Cortisol at wake + 30 (nmol/L)	5.69	(4.75)	0.10–39.0
Cortisol at bedtime (nmol/L)	2.23	(4.30)	0.10–25.0
Pregnancy diurnal cortisol			
Cortisol at wake (nmol/L)	6.59	(4.79)	0.10–42.0
Cortisol at wake + 30 (nmol/L)	7.08	(4.71)	0.20–39.0
Cortisol at bedtime (nmol/L)	2.78	(2.77)	0.20–19.5

Note. Interpregnancy diurnal cortisol descriptives reflect a total of 152 sampling days across 98 participants. Pregnancy diurnal cortisol descriptives reflect a total of 242 sampling days across 126 participants. All cortisol values reflect raw values before log transformation.

Procedures

CCHN study visits occurred after a birth when index children were approximately 1 month (T1), 6 months (T2), 12 months (T3), and 24 months (T5) of age with an additional telephone interview at 18 months (T4). Mothers who became pregnant again during this study period were interviewed during the second (P1) and third (P2) trimesters of their subsequent pregnancies and then 1 month after the birth of the subsequent child (P3). Biomarkers collected at the T2, T3, T5, P1, and P2 visits were examined in the present study. In addition, some women were pregnant at the T-series visits and if so, their visits were considered pregnancy visits. The beginning of the pregnancy was dated using the first day of the last menstrual period (LMP) or ultrasound dating. We used this information to identify interpregnancy versus pregnancy sampling days and to determine the trimester of pregnancy.

Salivary cortisol. During the study visits, research staff provided saliva sampling kits and verbal and written instructions on procedures for collecting saliva at three times over the course of

the sampling day (upon waking, 30 min after waking, and bedtime), completed a practice sample with the participant, and answered questions. The kits included vials, labels, and straws for "passive drool" collection of saliva. The kits also included morning and bedtime diaries that were completed by participants on the sampling day and used to extract time of sampling and related variables such as shift work and cigarettes smoked, which were included in preliminary analyses but were not significant predictors of cortisol and did not affect study results. On the day after the study visit, participants were asked to self-collect samples by expelling saliva through straws into sterile 2- or 5-ml cryogenic vials and to record the sampling time on accompanying labels. Completed materials were mailed back to each study office and stored at −80°C. Saliva samples were subsequently shipped to ZRT Laboratories on dry ice (Beaverton, OR) and assayed for cortisol by a competitive luminescence immunoassay (IBL-America, Minneapolis, MN) with reported detection limits of 0.015 μg/dl. The intra- and interassay coefficients of variance were 5.5% and 7.6%, respectively.

Infant birth weight. Research staff extracted birth weight from birth records/neonatal charts. Birth weight was treated as a continuous outcome and was divided by the standard deviation so that in interpreting results each one-unit change reflects a standard deviation.

Data Analysis

Raw cortisol values were examined for extreme outliers because they can bias the results. We took a conservative approach to outliers using a two-step strategy as follows. First, all values >3 *SD* from the sample mean were dropped, a common approach when cortisol values are extremely skewed (Dettling, Gunnar, & Donzella, 1999). Several outliers remained after truncation; therefore, we then recalculated the sample mean and standard deviation and winsorized any values >3 *SD* above the mean by transforming them into the mean + 3 *SD*. Altogether, 59 values were dropped or winsorized, <1% of the full sample of >8,000 samples. Finally, because significant skew remained (skewness = 3.47/*SE* = .03), we natural log-transformed all cortisol values.

To test diurnal slope, or the effect of time of day on cortisol levels, multilevel modeling (HLM 7.0; Raudenbush et al., 2011) was used to test a three-level model with cortisol levels as the outcome and sampling time as a predictor variable. This statistical approach is well suited for data that have a nested structure, such as cortisol sampling occasions within days within participants. It can adjust for saliva sample collection times, when these vary within and across participants, and it allows for inclusion of all participants when some data are missing at the within-person level (Singer & Willett, 2003). Our Level 1 (sample-level) predictors included time and a dummy variable to reflect the cortisol awakening rise (CAR), coded as 1 for the wake + 30 sample or 0 for the other samples (Adam, Hawkley, Kudielka, & Cacioppo, 2006). For further precision, we added one additional covariate at Level 1, which was the laboratory report of whether the sample was clear or discolored (dichotomously coded), which might indicate food or other contamination.

All available days from all participants were included in our final model. The intercept term was allowed to vary randomly and other effects were fixed. Restricted maximum likelihood estimation was used. At Level 2 (the day level) of the full model, we modeled pregnancy trimester on the sampling day, coded as 0 for interpregnancy, 1 for first trimester, 2 for second trimester, and 3 for third trimester sampling days. Finally, at Level 3 (the person level) we modeled infant birth weight. Race (coded as 1 = African American; 0 = non-African American), household income adjusted for cost of living, cohabitation with the father of the index child during the first year of the child's life, and interpregnancy interval (number of days between the index child's birth and the first day of the subsequent pregnancy) were included as Level 3 covariates in the fully controlled model.[1]

Because we hypothesized that interpregnancy cortisol might be predictive of subsequent birth outcomes above and beyond the effects of pregnancy cortisol, we conducted a series of follow-up analyses to compare interpregnancy and pregnancy diurnal slopes to each other. First, we extracted Empirical Bayes (EB) coefficients from the HLM analyses for the separate pregnancy and interpregnancy models by running these analyses without additional Level 2 and 3 covariates and then saving the residual files. EB coefficients are analogous to regression coefficients; therefore, the EB coefficient for the effect of sampling time of day on cortisol can be treated similar to an estimate of the diurnal slope (Raudenbush, Bryk, Cheong, & Congdon, 2004). These models included all available pregnancy and interpregnancy days such that if women contributed multiple cortisol sampling days, the EB coefficients would reflect the effect of time of day on cortisol across all available sampling days for the given period of time (pregnancy or interpregnancy).

Results

Table 1 shows descriptive statistics for the study sample and for cortisol at waking, 30 min after waking, and bedtime for interpregnancy and pregnancy time periods. Cortisol values were obtained from 394 sampling days and 1,127 cortisol sampling occasions. On average, women completed 2.67 sampling days (range = 1–5, *SD* = 1.19; median = 3 sampling days). Ninety-one women completed at least one interpregnancy sampling day, and 119 women completed at least one pregnancy sampling day. Seventy-three women (51.4%) completed an interpregnancy and a pregnancy sampling day. A more detailed breakdown of the number of participants who completed saliva sampling days at each time point is provided in Table 1. Because HLM is able to handle missing and unevenly spaced data, all 142 women with available birth weight who contributed at least 1 cortisol sampling day were included in the multilevel models of diurnal salivary cortisol. However, only the 73 women who contributed interpregnancy and pregnancy sampling days were used in the follow-up regression analysis.

[1] Of note, these multilevel models testing the effect of diurnal cortisol slope on infant birth weight included cortisol as the "outcome" because there were multiple measures of cortisol over multiple days for each participant and only one measure of birth weight. Although this modeling approach was necessary given the nested structure of the cortisol data to test our hypothesis, treating cortisol as the dependent variable does not imply a direction of causality but rather the effect of using nested data in which birth weight is at a different level of nesting than cortisol.

Table 2
Three-Level Model Showing Associations Among Infant Birth Weight, Interpregnancy Interval, and Diurnal Cortisol Slope Sampled Before and During Pregnancy: Fixed Effects With Robust Standard Errors and Additional Covariates (n = 142)

Fixed effects	Estimate	(*SE*)	*t* ratio	*df*	*p*
Cortisol intercept (morning)	1.67	.06	28.66	136	**<.001**
Level 2 covariates					
Pregnancy trimester	0.22	.03	7.55	251	**<.001**
Level 3 covariates	0				
Infants' birth weight	0.03	.04	0.65	136	.518
Interpregnancy interval	0.0001	.0002	0.54	136	.594
Household income	0.000004	.000002	1.71	136	.090
Cohabitation	−0.06	.11	−0.51	136	.612
African American	−0.39	.10	−3.73	136	**.001**
Cortisol slope (time)	−0.08	.00	−25.99	638	<.001
Level 2 covariates	0				
Pregnancy trimester	0.01	.003	3.23	638	**.001**
Level 3 covariates	0				
Infants' birth weight	−0.01	.003	−3.05	638	**.002**
Interpregnancy interval	−0.00003	.00001	−2.27	638	**.023**
Household income	−0.000000	.000000	−2.13	638	**.033**
Cohabitation	−0.01	.01	–0.78	638	.434
African American	.07	.007	10.62	638	**<.001**
CAR	.16	.05	3.53	638	**<.001**
Sample clarity	.06	.05	1.20	638	.233

Note. Pregnancy trimester coded as 0 for preconception study days, 1 for first trimester, 2 for second trimester, and 3 for third trimester. Interpregnancy interval calculated as difference between birth of index child and LMP. Sampling time is centered around wake time = 5:00 a.m. Household income is adjusted for cost of living differences across study site. Variable names for Level 1 indices (intercept, slope, CAR, and sample clarity) are presented in bold font.

Multilevel Models of Diurnal Salivary Cortisol

First, we tested a model that included interpregnancy and pregnancy saliva sampling days with the following variables included as Level 1 predictors: time, CAR, and a dichotomous variable indicating whether the sample was clear or discolored. Pregnancy trimester (which was coded as 0 for interpregnancy sampling days) was included as a Level 2 covariate. Table 2 shows the full model with race, income, and cohabitation status added as additional covariates at Level 3. Longer interpregnancy intervals, greater per capita household income, and higher birth weight were all associated with significantly steeper cortisol slopes. In addition, African-American mothers had significantly lower morning cortisol and a smaller decline across the day. Pregnancy trimester was associated with higher morning values and flatter diurnal slopes, such that women who were later in pregnancy had higher, flatter cortisol patterns than women who were earlier in pregnancy or not pregnant.

We retested the model separately for interpregnancy and pregnancy cortisol samples to establish whether associations with birth weight differed as a function of time relative to conception. We did not include a Level 2 covariate for pregnancy trimester in the interpregnancy model as we did in the full model. In the pregnancy-only model, we included a covariate for number of days pregnant to use a more sensitive measure of pregnancy stage. As expected, being later in pregnancy was associated with a significantly higher cortisol intercept and flatter diurnal slope. Whether or not the interpregnancy interval was included as an additional Level 3 covariate, birth weight remained significantly associated with the diurnal decline of cortisol in both models. As Table 3 shows, when we added the demographic variables of income, cohabitation status, and race, birth weight remained significantly associated with diurnal slope in the interpregnancy model and in the pregnancy model.

Finally, we extracted EB coefficients from the HLM analyses for the separate pregnancy and interpregnancy models. Visual inspection of plotted slopes revealed one outlier interpregnancy value (slope of .27, 5 *SD*s beyond the mean), which we dropped from subsequent analyses. Consistent with the overall negative effect of time of day on cortisol, these coefficients were, on average, negative (M for pregnancy cortisol = −.07, SD = .05, range = −.19 to .02, and M for interpregnancy cortisol = −.10, SD = .05, range = −.20 to .03).

Consistent with the HLM results, zero-order correlations indicated that diurnal slope coefficients were negatively associated with birth weight such that steeper slopes were linked with higher birth weights ($r(90) = -.36$, $p = .001$ for the interpregnancy model; $r(118) = -.23$, $p = .021$ for the pregnancy model). Interpregnancy and pregnancy diurnal slopes were moderately positively correlated with each other, $r(72) = .58$, $p = .001$), suggesting some stability across time periods. To compare the effects of interpregnancy and pregnancy cortisol slopes on birth weight, we included only women who provided cortisol samples on at least one interpregnancy and one pregnancy day in a regression analysis with both slopes as predictors of birth weight. The effect of pregnancy diurnal cortisol slope on birth weight became nonsignificant (b (70, 2) = −.03, $t = -.19$, $p = .85$), whereas the interpregnancy diurnal cortisol slope remained a significant predictor of birth weight (b (70, 2) = −.39, $t = -2.92$, $p = .005$). As

Table 3
Three-Level Model Showing Associations Between Infant Birth Weight, Interpregnancy Interval, and Diurnal Cortisol Slope Sampled During Interpregnancy or Pregnancy: Fixed Effects With Robust Standard Errors

	Model for interpregnancy cortisol (n = 99)					Model for pregnancy cortisol (n = 114)				
Fixed effects	Estimate	(*SE*)	*t* ratio	*df*	*p*	Estimate	(*SE*)	*t* ratio	*df*	*p*
Cortisol intercept (morning)	1.34	.11	11.73	93	**<.001**	1.51	.11	14.06	108	**<.001**
Level 2 covariates										
Days gestation	—	—	—	—	—	.002	.001	3.65	110	**<.001**
Level 3 covariates										
Infants' birth weight	−0.03	.06	−0.54	93	.588	.05	.06	0.90	108	.370
Interpregnancy interval	−0.00003	.00032	−0.10	93	.920	.0006	.0003	2.39	108	**.019**
Household income	0.000001	.000002	0.58	93	.561	.00001	.00000	2.72	108	**.008**
Cohabitation	−0.04	.17	−0.22	93	.826	−.10	.12	−0.82	108	.415
African American	−0.61	.16	−3.80	93	**<.001**	−.31	.12	−2.63	108	**.010**
Cortisol slope (time)	−0.09	.01	−16.70	201	**<.001**	−.10	.01	−13.10	327	**<.001**
Level 2 covariates										
Days gestation	—	—	—	—	—	.0002	.0000	4.30	327	**<.001**
Level 3 covariates										
Infants' birth weight	−0.010	.004	−2.23	201	**.027**	−.008	.004	−2.15	327	**.032**
Interpregnancy interval	0.00005	.00003	1.80	201	**.074**	−.00004	.00002	−2.63	327	**.009**
Household income	0.000000	.000000	−0.83	201	.408	.000000	.000000	−1.34	327	.182
Cohabitation	−0.02	.01	−1.68	201	.094	.004	.008	0.49	327	.628
African American	0.10	.01	7.71	201	**<.001**	.064	.008	7.98	327	**<.001**
CAR	0.16	.08	1.96	201	.051	.16	.05	3.14	327	**.002**
Sample clarity	0.21	.11	1.87	201	.063	.01	.06	0.18	327	.858

Note. Pregnancy trimester coded as 0 for preconception study days, 1 for first trimester, 2 for second trimester, and 3 for third trimester. Interpregnancy interval calculated as difference between birth of index child and LMP. Sampling time is centered around wake time = 5:00 a.m. Household income is adjusted for cost of living differences across study sites. Variable names for Level 1 indices (intercept, slope, CAR, and sample clarity) are presented in bold font.

shown in Table 4, when we added the original HLM covariates (household income, cohabitation status, African-American race, interpregnancy interval) to this regression analysis, interpregnancy diurnal cortisol slope continued to predict birth weight, but all other coefficients were nonsignificant (all p values $>$ .27).

Discussion

Repeated diurnal assessments of maternal salivary cortisol collected during the interval between delivery of one child and onset of the next pregnancy allowed us to examine the impact of both interpregnancy and prenatal diurnal slopes on infant birth weight. The results show that mothers who had a longer interpregnancy interval and who delivered heavier babies had steeper diurnal declines in cortisol before and during pregnancy. In contrast, a flatter slope of diurnal cortisol, which has previously been associated with greater chronic stress burden, more maladaptive relationship functioning, and poorer health outcomes (Adam & Gunnar, 2001; Saxbe, Repetti, & Nishina, 2008; Sephton, Sapolsky, Kraemer, & Spiegel, 2000), was associated with lower infant birth weight in the full model that included interpregnancy and pregnancy cortisol values as well as in further analyses that tested for separate effects of interpregnancy and pregnancy cortisol patterns. These results persisted when demographic covariates including race, household income, and cohabitation status were controlled. In follow-up analyses, interpregnancy cortisol slopes predicted infant birth weight independent of pregnancy cortisol slopes and demographic covariates. Thus, a particularly robust effect was found for cortisol slopes before the infant's conception, which is notable given that these measurements were less proximal to the pregnancy and birth of the subsequent child than the pregnancy cortisol readings.

Table 4
Regression Model Predicting Infant Birth Weight From EB Coefficients for Interpregnancy and Pregnancy Slope (n = 73)

Predictor	B	(*SE*)	*t* ratio	*p*
Interpregnancy slope	−5.39	2.44	−2.21	.03
Pregnancy slope	−1.14	2.87	−0.40	.69
Interpregnancy interval	−0.00	0.00	−1.12	.27
Household income	0.00	0.00	−0.09	.93
Cohabitation	0.10	0.23	0.45	.65
African American	−0.13	0.27	−0.49	.27
Constant	5.67	0.47	12.17	.00

Note. Total adjusted R^2 = .12.

By examining cortisol in the interpregnancy interval, we provide the first prospective evidence that maternal cortisol patterns before a woman conceives a child may influence the growth and weight of her next child. This study is particularly novel in its measurement of cortisol during the interpregnancy period. Previously, researchers conducting longitudinal studies have not been in a position to study women during this time before conception. In addition to being the first study to examine interpregnancy/preconception biology, this is the largest sample to our knowledge on diurnal salivary cortisol patterns in pregnancy and infant birth weight. Three prior investigations that collected maternal salivary cortisol during pregnancy reported that dysregulated diurnal patterns during pregnancy were linked to lower infant birth weight, but each had fewer than 100 participants (Bolten et al., 2011;

D'Anna-Hernandez et al., 2012; Hompes et al., 2012) and none had interpregnancy data.

Stress hormones produced by the HPA axis are integrally involved in normal pregnancy and parturition. Our results support the hypothesis that dysregulation of this system before conception may contribute to adverse birth outcomes, specifically risk of reduced fetal growth. Maternal diurnal cortisol patterns may serve as a marker of broader dysregulation across multiple physiological systems that support fetal growth and, ultimately, influence birth weight. These findings could potentially have several interpretations. First, a mother's life conditions may lead to HPA dysregulation that influences physiology of pregnancy and fetal growth directly. That is, maternal cortisol dysregulation is secondary to other risk factors and ongoing stress that adversely affect the fetus. For example, if the flattened cortisol slopes are an overall marker of poor adaptation to stress, they might be a result of adverse environmental factors and risky health behaviors during pregnancy. Second, HPA dysregulation is comorbid with inflammation (Chrousos, 1995; Miller, Cohen, & Ritchey, 2002; Silverman & Sternberg, 2012) and other processes that may more directly influence fetal growth (Challis et al., 2009; Redman, Sacks, & Sargent, 1999). Beyond these physiological mechanisms, flattened cortisol may reveal something about the overall stress burden or the mother's coping or resiliency that we did not explicitly model in these analyses. Clearly, the processes influencing fetal growth are complex and involve preconception as well as prenatal biological and psychosocial factors which necessitates further research and theoretical models.

Elevated maternal cortisol during pregnancy has been associated with greater behavioral and physiological stress reactivity in fetuses, infants, and children (Davis et al., 2007; Matthews, 2000); decreased cognitive ability in infants (Davis & Sandman, 2010; Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003); and increased affective problems and larger amygdala volumes in young girls (Buss et al., 2012). There also is some evidence that programming of the fetal HPA axis mediates long-term health consequences of low birth weight (Phillips et al., 1998; van Montfoort, Finken, le Cessie, Dekker, & Wit, 2005). These findings highlight the need for a better understanding of neuroendocrine processes across the life course of mothers and children. An in-progress follow-up study of the CCHN cohort is examining this in the mothers and subsequent children over the first 5 years of life.

Flatter slopes were also independently associated with a shorter interpregnancy interval, such that women with more closely spaced pregnancies had flatter cortisol slopes. Short interpregnancy intervals are defined as less than 18 months between the birth of a child and the beginning of a subsequent pregnancy and have been associated with adverse outcomes for the mother and child, including preterm birth, low birth weight, and preeclampsia (Conde-Agudelo, Rosas-Bermúdez, & Kafury-Goeta, 2006; Klerman, Cliver, & Goldenberg, 1998). Investigation of additional maternal health conditions related to cortisol patterns during the interpregnancy period and/or infant birth weight would be valuable now that we have demonstrated the potential importance of maternal diurnal cortisol patterns during the interpregnancy period.

A strength of this study is the large, diverse community sample of women studied over a relatively large reproductive time period. Our statistical approach, a three-level hierarchical linear model, added precision to analyses. However, cortisol was collected on only 1 day at each time point, and published guidelines for ambulatory cortisol research typically recommend a minimum of 2 days with at least 3–6 samples per day to calculate diurnal slope (Saxbe, 2008). We used a 1-day collection plan because community feedback emphasized the many life demands often at work and at home in this sample of low-income mothers of infants. Therefore, we developed a protocol that weighed the need for scientific rigor against participant burden and risk of noncompliance (Adam & Kumari, 2009). This issue limits the reliability of our slope estimates, although we attempted to control for some sources of error by controlling for shift work schedules and samples collected on different days (results not shown); even with controls, the results remained significant. Moreover, many participants contributed more than 1 cortisol sampling day, including multiple interpregnancy and pregnancy days, allowing us to explore the effects of pregnancy on cortisol patterns within participants. A limitation in the exploratory follow-up regression analyses is the sample size ($n = 73$), but it is rare to have study data on pregnancy and interpregnancy biomarkers and the sample was sufficient if not ideal. In addition, it was not possible to control for gestational age at time of sampling in these exploratory regression analyses because all available collection days were used to estimate EB coefficients.

In summary, this study is consistent with a life course approach in examining how processes before conception and during pregnancy each influence later pregnancy outcomes (Lu & Halfon, 2003; Misra et al., 2003; Ramey et al., 2015). The results suggest that maternal cortisol patterns may play an important predictive role starting before pregnancy. Our results are consistent with the premise that maternal physiology before conception is relevant to birth outcomes and they add to emerging evidence suggesting that birth outcomes are shaped by maternal experiences and health before and during pregnancy.

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