Original Research Article

Preterm Delivery as a Predictor of Diurnal Cortisol Profiles in Adulthood: Evidence from Cebu, Philippines

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Objectives: Fetal exposure to elevated maternal cortisol can permanently modify hypothalamic–pituitary–adrenal (HPA) axis function, and thereby have long-term health impacts. Maternal cortisol steadily increases throughout normal pregnancy, but is abnormally high in preterm deliveries (<37 weeks). Prematurity remains a widespread public health problem, yet little is known about its potential long-term effects on adult HPA function. Here we test the hypothesis that diurnal cortisol profiles measured in young adulthood will vary based upon an individual's preterm status.

Methods: Diurnal salivary cortisol profiles, a marker of HPA-axis function, were measured in 1,403 young adults (ages 21–23 years) participating in the Cebu Longitudinal Health and Nutrition Survey, located in Metropolitan Cebu City, Philippines.

Results: Males who had been born preterm exhibited lower morning cortisol and non-significantly elevated evening cortisol, resulting in a more adverse, flatter rate of decline across the day. In contrast, there were no significant differences by preterm status in cortisol measured at any time of day in females.

Conclusions: These findings point to potential long-term effects of having been born preterm on adult HPA-axis function, and add to evidence from this and other populations for sex differences in the biological and health impacts of prenatal stress exposure. Am. J. Hum. Biol. 26:598–602, 2014.

INTRODUCTION

There is much evidence that prenatal stress can "program" durable changes in metabolism, endocrine regulation, and other characteristics that influence health later in life (Chadio et al., 2007; Clark, 1998). The stress hormone cortisol is the major output of the hypothalamic–pituitary–adrenal (HPA) axis, and fetal exposure to maternal circulating cortisol is a prime candidate for such programming effects (Diego et al., 2006; Seckl and Meaney, 2004; Thayer et al., 2012). The developing fetus is normally buffered from elevated maternal cortisol by the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which converts active cortisol into inactive cortisone (Seckl and Holmes, 2007). However, abnormally high maternal cortisol levels resulting from stress experienced during pregnancy can overwhelm this barrier, leading to increased fetal cortisol exposure (Alexander et al., 2012; Diego et al., 2006; Glover et al., 2010). Excess fetal exposure to cortisol has been shown to result in preterm birth (Demendi et al., 2012; Wadhwa et al., 2004), as well as intrauterine growth restriction (IUGR), and low birth weight (LBW) (Marsit et al., 2012; Pike, 2005).

In addition to impacting birth outcomes, changes in prenatal cortisol exposure can also alter or "program" HPA-axis function and lead to other health consequences over the life course of the offspring. Consistent with this perspective, a growing body of research has linked prematurity status, independent of birth weight, to increased risk of hypertension and cardiovascular disease (CVD) in adulthood (Cooper et al., 2009; Crump et al., 2011; Dalziel et al., 2007; Irving et al., 2000; Rotteveel et al., 2008). If being born premature leads to durable changes in adult HPA function, this could modify adult health, and might also alter fetal exposure to cortisol in the grandoffspring generation, perpetuating an intergenerational pattern of undesirable health outcomes (Drake and Walker, 2004; Kuzawa and Sweet, 2009).

Although altered HPA activity is a plausible pathway linking preterm delivery with later health outcomes, relatively few human studies have evaluated short- and long-term effects of preterm status on cortisol profiles or HPA function. A small German study of 8- to 14-year-old children reported that individuals born preterm had higher cortisol upon waking and blunted HPA reactivity (Buske-Kirschbaum et al., 2007). Brummelte et al. (2011) examined the salivary cortisol response in prematurely born infants after a cognitive challenge and mother–infant interaction. Infants born at extremely low gestational age (ELGA) (between 24 and 28 weeks) had higher morning basal cortisol and blunted HPA reactivity compared with infants born at very low gestational age (VLGA) (between 29 and 32 weeks) and full-term infants. Similarly, 18-month-old infants born ELGA had significantly higher basal cortisol compared with full-term infants (Grunau et al., 2007). In the only study of adult subjects that we are aware of, IUGR, rather than prematurity, was found to predict higher cortisol metabolite excretion in females from Scotland, while the premature group (without

Contract grant sponsor: Interdisciplinary Obesity Center; Contract grant sponsor: the Center for Environmental Health and Susceptibility; Contract grant number: ES10126; project 7-2004-E; Contract grant sponsor: the National Institute for Child Health and Human Development (NIH); Contract grant number: R01 HD054501.

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Received 31 December 2013; Revision received 22 April 2014; Accepted 16 May 2014

DOI: 10.1002/ajhb.22569
Published online 4 June 2014 in Wiley Online Library (wileyonlinelibrary.com).

TABLE 1. Characteristics of CLHNS mothers and index children[a]

	Male (n = 802)		Female (n = 601)	
	Term male (n = 669)	Preterm male (n = 133)	Term female (n = 519)	Preterm female (n = 82)
Mother (1983)				
Age (years)	26.4 (5.8)	27.4 (6.6)∼	26.7 (5.8)	27.0 (6.7)
Highest grade achieved	7.5 (3.7)	7.5 (3.7)	7.7 (3.7)	6.9 (3.3)∼
Household income (pesos)	297 (625)	252 (269)	276 (366)	285 (316)
Offspring at birth (1983–1984)				
Birth weight (g)	3066 (400)	2838 (531)*	3038 (396)	2820 (468)*
Gestational age (weeks)	39.4 (1.4)	35.3 (1.4)*	39.6 (1.5)	35.4 (1.3)*
Adult offspring (2005)				
Age (years)	21.5 (0.3)	21.5 (0.3)	21.5 (0.1)	21.5 (0.3)
Height (cm)	163.2 (5.7)	162.0 (6.8)*	151.4 (5.5)	150.7 (5.6)
BMI[b] (kg/m^2)	21.0 (2.9)	21.2 (3.0)	20.3 (3.1)	20.3 (3.5)
Highest grade achieved	10.5 (3.9)	10.1 (3.9)	11.8 (3.2)	11.0 (3.7)*
Household income (pesos)	552 (623)	544 (1472)	621 (884)	547 (891)
Offspring cortisol (2005)				
Waking cortisol (mmol/L)	7.2 (4.5)	6.4 (3.3)*	7.8 (3.8)	7.7 (3.9)
30 minutes after waking cortisol (mmol/L)	9.2 (5.4)	8.9 (4.3)	10.0 (5.0)	9.9 (5.9)
Evening cortisol (mmol/L)	2.2 (2.7)	2.3 (2.4)	1.9 (2.2)	2.4 (2.7)∼
Cortisol awakening response (mmol/L)	2.0 (4.8)	2.5 (4.2)	2.2 (5.0)	2.2 (5.5)
Slope of diurnal cortisol decline (mmol/L/hours)	−0.32 (0.31)	−0.26 (0.26)*	−0.37 (0.25)	−0.35 (0.26)

[a]Mean (SD) for continuous variables.
[b]Body mass index.
[c]Gestational age at birth less than 37 weeks.
$\sim P < 0.1$; $^*P < 0.05$ term versus pre-term (two-tailed T-test).

IUGR) showed lower than normal cortisol metabolite excretion (Walker et al., 2002).

Here we seek to clarify the possible impact of preterm delivery on adult HPA-axis function. Data were gathered from young adult participants in the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a study that has followed a birth cohort living in Metropolitan Cebu City, Philippines from birth into adulthood. We describe diurnal cortisol patterns, and the cortisol awakening response, and evaluate whether they vary according to preterm status. Prior studies report evidence for sex differences in the effects of poor birth outcomes on HPA function (Grunau et al., 2010; Walker et al., 2002), and we have previously reported evidence for sex differences in the effect of maternal cortisol on offspring fetal growth rate in this population (Thayer et al. 2012). Thus, we also evaluated whether any relationships between prematurity and adult HPA function varied among males and females.

METHODS

Study population

Data come from the CLHNS, a longitudinal survey of 3,080 singletons whose mothers were recruited during pregnancy between 1983 and 1984 in Metropolitan Cebu City, Philippines (Adair et al., 2011). The present analysis focuses on samples and data collected in 2005 among the adult offspring of these pregnancies. Individuals with abnormal sleep–wake cycles, such as shift workers, often have altered diurnal cortisol rhythms (Weibel et al., 1996). To avoid confounding by abnormal sleep cycles, we defined locally relevant exclusion criteria based upon the distributions of wake times, bedtimes, and total hours of sleep, and choosing cut points that (a) were logically outside the bounds of typical wake times and bedtimes and (b) did not include large numbers of observations, thereby confirming that these particular sleep patterns were unusual. Following from this analysis, our sample was limited to participants reporting waking between 3 am and 3 pm, going to sleep between 4 pm and 4 am, sleeping for at least 4 hours, and staying awake for at least 8 hours. Women who reported being pregnant during the 2005 interview, and those who retrospectively were deemed to be pregnant in 2005 (using 2007 reproductive histories), were excluded due to pregnancy-related hormonal changes known to affect cortisol profiles. The final analysis sample included 1,403 male and female offspring (802 and 600, respectively) of the original cohort. This research was conducted under conditions of written informed consent, and with approval of the Institutional Review Boards of the University of North Carolina (Chapel Hill), Northwestern University (Evanston, Illinois), and the Office of Population Studies Foundation (Cebu, Philippines).

Anthropometric measurements, such as height and weight, were obtained using standard techniques. Gestational age was estimated based upon the day of the mother's last menstrual period in the baseline survey, and trained nurses performed Ballard maturational assessments if pregnancy complications occurred or if the infant's birth weight was lower than 2.5 kg. Preterm birth was defined as delivery before 37 weeks of gestation. Although maternal cortisol levels during pregnancy are of interest with regard to preterm birth and fetal programming, as evidenced by the findings reviewed above, maternal pregnancy cortisol measures were not obtained during the baseline survey in 1983, and thus are not available for this analysis.

Questionnaires were used to collect data on other individual, household, and community variables during in-home interviews. Household crowding score was defined as the number of people living in the household divided by the number of rooms. A household assets scale was

TABLE 2. Regression models with preterm status as a predictor of diurnal cortisol measurements in males

	Unadjusted model[a]		Adjusted model[b]		Adjusted + BW model[c]	
	β (SE)	*P*-value	β (SE)	*P*-value	β (SE)	*P*-value
Waking cortisol (mmol/L)	−0.10 (0.06)	0.122	−0.11 (0.06)	0.072	−0.11 (0.06)	0.094
Evening cortisol (mmol/L)	0.11 (0.09)	0.192	0.11 (0.09)	0.216	0.13 (0.09)	0.144
Cortisol awakening response (mmol/L)	0.57 (0.45)	0.202	0.52 (0.45)	0.247	0.46 (0.46)	0.313
Diurnal cortisol slope (mmol/L/hours)	0.06 (0.03)	0.035	0.06 (0.03)	0.032	0.07 (0.03)	0.026

[a]Adjusted only for times of cortisol measurement.
[b]Adjusted for times of cortisol measurement, current BMI, height, household income, assets, crowding, and self-reported stress on day of saliva collection.
[c]Adjusted model + individual's birth weight.

TABLE 3. Regression models with preterm status as a predictor of diurnal cortisol measurements in females

	Unadjusted model[a]		Adjusted model[b]		Adjusted + BW model[c]	
	β (SE)	*P*-value	β (SE)	*P*-value	β (SE)	*P*-value
Waking cortisol (mmol/L)	−0.02 (0.06)	0.719	−0.01 (0.06)	0.821	−0.01 (0.06)	0.905
Evening cortisol (mmol/L)	0.15 (0.11)	0.174	0.12 (0.11)	0.287	0.13 (0.11)	0.255
Cortisol awakening response (mmol/L)	−0.003 (0.60)	0.996	0.13 (0.61)	0.829	−0.06 (0.61)	0.918
Diurnal cortisol slope (mmol/L/hours)	0.02 (0.03)	0.537	0.01 (0.03)	0.722	0.003 (0.03)	0.912

[a]Adjusted only for times of cortisol measurement.
[b]Adjusted for times of cortisol measurement, current BMI, height, household income, assets, crowding, and self-reported stress on day of saliva collection.
[c]Adjusted model + individual's birth weight.

defined based on whether the family had electricity, owned their own home, had an air conditioner, refrigerator, TV, a vehicle, or other appliances (Adair et al., 2011). Self-reported stress level was collected at the time of saliva collection using a Likert scale ranging from 1 to 5.

Cortisol measurement

Three saliva samples were collected from each participant: before bed, immediately upon waking the following morning, and 30 minutes after waking. Participants were instructed not to eat, drink, or brush their teeth for at least 30 minutes before sample collection. Cortisol was measured in duplicate by a laboratory in Trier, Germany, using a time-resolved immunoassay with fluorometric detection (DELFIA). The intra- and inter-assay coefficients of variation (CVs) were between 4.0% and 6.7%, and 7.1% to 9.0%, respectively. Samples with CVs over 12% were rerun. The slope of the diurnal decline in cortisol was defined as the difference in cortisol measurements at waking and evening, divided by the elapsed time. Cortisol awakening response (CAR) was defined as the difference in cortisol level between the waking and 30 minutes after waking samples (Adam and Kumari, 2009).

Statistical analysis

All statistical analyses were conducted using Stata 12.0 (College Station, TX). Differences between preterm and term individuals were first analyzed separately for males and females using one-tailed *T*-tests. We subsequently evaluated whether prematurity status predicted cortisol outcomes using a series of regression models (Tables 2 and 3). Analyses began with a base model relating prematurity to each cortisol outcome (waking cortisol, evening cortisol, CAR, and diurnal cortisol slope) and were only adjusted for time of saliva collection. Household income, assets, crowding score, and self-reported stress at the time of cortisol measurement were added to evaluate potential confounding influences. In addition, because cortisol is a metabolic hormone that has been shown to relate to current nutritional status and measures of developmental nutrition (Power et al., 2006), we also considered the potential confounding influence of recent and chronic nutritional status as indexed using standing height and the uncorrelated measure of body mass index (BMI). Finally, to clarify if the relationship between prematurity and adult cortisol was due to small birth size, rather than term status, birth weight was added to the adjusted model.

RESULTS

Characteristics of CLHNS mothers and their offspring are reported in Table 1. Males born premature were significantly shorter as adults than those born full term. Mothers of preterm males were, on average, about a year older than mothers of term-born males, while females born preterm had completed fewer years of school (both $P < 0.1$).

Diurnal cortisol profiles for both males and females showed the expected pattern of a high waking value and a rise during the 30 minutes after waking, before declining across the day (Table 1). Prematurely born males had significantly lower waking cortisol ($P < 0.039$) and attenuated diurnal cortisol decline from waking to bedtime ($P < 0.035$) compared to term-born males. In contrast, the only difference in unadjusted cortisol measures among females was borderline elevated evening cortisol in preterm compared to term-born females ($P < 0.096$).

A series of regression models considering potential confounding influences and pathways were used to evaluate whether prematurity predicted adult cortisol patterns (Tables 2 and 3). After accounting for saliva collection time, it was found that, among males, being born premature was borderline significantly associated with lower waking cortisol ($P < 0.072$) and non-significantly elevated evening cortisol, yielding a significantly attenuated slope of diurnal cortisol decline ($P < 0.032$). These relationships were not substantially changed after further adjusting for birth weight. In females, there were no significant or borderline significant differences in adult HPA measures by

preterm status, with or without adjustment for potential confounding influences or for birth weight.

DISCUSSION

We hypothesized that individuals born preterm, who as a result likely experienced altered cortisol exposure *in utero*, would have altered circadian cortisol dynamics in adulthood. The evidence reported here supports such an effect, but only among male participants. Following adjustment for potential confounding factors, the diurnal cortisol slope was significantly flatter among males born preterm. The altered diurnal cortisol profile in preterm males suggests that preterm delivery could have durable effects on HPA-axis function, potentially affecting health outcomes over the life course. These findings are similar to those of another prospective cohort study demonstrating that individuals born premature or with extremely LBW had elevated evening and total cortisol levels (Gustafsson et al., 2010).

The findings reported here add to evidence that prenatal conditions, as indexed indirectly by preterm birth, can have sex-specific effects on adult HPA function and health. Although prior studies of the long-term effects of prematurity status on HPA function have been few, one small study reported evidence for more pronounced effects of adverse birth outcomes on HPA-axis function in adult females (Walker et al., 2002). In contrast, a study in Canada found evidence for lower cortisol reactivity to immunization in individuals born preterm, but with effects only significant for males (Grunau et al., 2010). At Cebu, we have previously reported evidence for greater prenatal sensitivity, and long-term biological and health effects of early environments, among males. For instance, we recently reported that women with higher evening cortisol in adulthood tend to give birth to lower birth weight offspring, with effects roughly twice as strong in male offspring (Thayer et al., 2012). These findings, along with evidence for a stronger male than female relationship between lower birth weight and adult CVD risk factors in Cebu (e.g., Adair et al., 2001; Kuzawa and Adair, 2003), help paint a consistent picture in which males are more sensitive to prenatal stress, which manifests as more pronounced long-term changes in endocrine regulation and CVD risk. Enhanced male sensitivity to environmental conditions has also been reported in research in comparative and evolutionary biology (Lindström, 1999), and may reflect sex differences in developmental sensitivity tracing to differences in sexual size dimorphism or life history strategy (see Kuzawa 2005, 2007; Stinson, 1985; Sheldon et al., 1998). From an applied perspective, these findings may indicate that more variability in male adult health outcomes ultimately traces to prenatal conditions. In addition, if the stress of prematurity has relatively attenuated long-term effects on adult phenotypes in females, this may indicate a reduced tendency for preterm-delivery to influence the intergenerational transmission of health disparities through the gestational environment in this population (e.g., Drake and Walker, 2004; Kuzawa and Sweet, 2009). However, prenatally programmed differences in maternal cortisol reactivity during pregnancy or other epigenetic modifications, which we did not evaluate here, could still contribute to such effects (Matthews and Phillips, 2012).

There were several limitations to our study. Notably, cortisol values at each time of day were measured by a single sample, whereas collecting samples across multiple days and using average values would enhance measurement reliability. This limitation in measurement reliability, however, was offset by a large sample size, which greatly exceeds that of most studies in other populations. Nonetheless, it is possible that some of the relationships that were borderline or that trended toward significance, such as the marginally higher evening cortisol among preterm males, would have reached statistical significance had we measured cortisol across multiple days. Because none of the relationships approached significance in females, it seems unlikely that our finding of no differences by preterm status among females would be altered by enhanced measurement reliability.

In sum, we found that males born preterm have altered circadian cortisol profiles in adulthood compared with term-born males, as reflected in lower morning values and a flatter diurnal slope. Flatter diurnal cortisol profiles have been associated with various negative health outcomes, such as metabolic syndrome, hypertension, CVD, cognitive and psychiatric conditions, immune suppression, impaired executive function, and physical performance (Blair et al., 2005; Gardner et al., 2011; Kumari et al., 2011; Sephton et al., 2000; Shirtcliff and Essex, 2008; Spiegel, 2011), underscoring the need to identify the developmental antecedents of these patterns. Our findings point to prematurity as a potential cause of altered diurnal HPA rhythms in adulthood, with more pronounced impacts on male biology and health.

ACKNOWLEDGMENTS

We thank Linda Adair and the researchers at the Office of Population Studies, University of San Carlos, Cebu, Philippines, for their role in study design and data collection, and study participants, who generously provided their time. Elizabeth Quinn, Jeff Huang, Katy Sharrock, Iram Azam, Divya Mallampati, Brian Dubin, Laura Rogers helped with lab work. Amy DeSantis helped with lab work and statistical analysis. Emma Adam advised on sample collection design. Funding: NIH (R01 HD054501/NICHD; RR20649; ES10126; project 7-2004-E).

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