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Tsimane' Amazonian Panel Study Working Paper # 77

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Abstract: Despite a significant literature exploring the relationships between prenatal stress and the developmental origins of adult health and disease, there is a dearth of data exploring the variation in HPA dynamics in healthy pregnancies. Even less is known about maternal stress hormones in a nonwestern context in ecologies characterized by high infectious disease burdens and marginal energy balance. To that end, cross-sectional data from the Tsimane', a population of semi-nomadic foragers in the Bolivian Amazon are used to provide the first insight into the HPA dynamics of pregnancy and lactation among 56 women. Specifically, the goals of this chapter are to 1) document variation in diurnal cortisol rhythms among pregnant, lactating, and nonpregnant nonlactating Tsimane' women; 2) to explore differential cortisol responses to infectious symptoms in these groups as a proxy for stress reactivity; and 3) to document the association between breastfeeding and HPA activity. Controlling for BMI, parity, and fat reserves, pregnant women exhibit significantly elevated diurnal cortisol rhythms compared to nonpregnant women. Subjective morbidity was not associated with a dampened cortisol response, while duration of lactation was associated was positively associated with morning cortisol concentration. This study is among the first to document diurnal cortisol rhythms in healthy pregnancies in a small scale horticulturalist society, and to clarify the role the HPA axis in navigating the liked physiological transition of pregnancy, birth, and lactation.

Considerable interest exists in understanding the health impacts of maternal stress on infant health and maternal postpartum well being (Kuzawa and Sweet, 2009; Seckl and Holmes, 2006; Sloboda et al., 2005; Sloboda et al., 2009; Wadhwa, 2005). Despite this attention to prenatal stress and the developmental origins of adult health and disease, however, research exploring the range of variation in HPA dynamics in healthy pregnancies has remained limited (Nyberg, 2012; Pike, 2005; Thayer and Kuzawa, 2011; Worthman and Kuzara, 2005). Even less is known about maternal stress hormones in a nonwestern context in ecologies characterized by high infectious disease burdens and marginal energy balance. Among anthropoid primate pregnancies, glucocorticoids typically increase over the course of pregnancy (Power and Schulkin 2006; Smith et al., 1999), with the placenta buffering a significant portion of maternal stress hormones from the fetus, and contributing to reduced maternal stress reactivity through the inactivation of cortisol by the enzyme 11-βHDS2 (Benediktsson et al, 1997; de Vries et al., 2007; deWeerth and Buitelaar, 2005; Rutherford, 2009; Schulkin and Power, 2006; Schulte et al., 1990; Su et al., 1990; Sun et al., 1999; Windle et al.,2012).

In humans, this marked elevation in GC release is hypothesized to play a critical role in coordinating the timing of parturition and accelerating fetal pulmonary and tissue maturation, facilitating developmental timing in a species with secondarily altricial births (Challis et al., 2001; Ellison 2001, Laatikainen et al., 1988; Liggins and Thorburn, 1994; Martin, 1996; Power and Schulkin, 2006; Pike, 2005; Smith et al., 2001). Rarely has the literature on maternal stress considered whether childbirth itself serves as a biological

stressor, in both a metabolic and mechanical capacity, even under ideal circumstances (Bergant et al., 1998; Ellison, 2001; Martin, 2007; Nyberg, In press; Valeggia and Ellison, 2009). With few exceptions (Bergant et al., 1998), the linked transitions between pregnancy, parturition, and lactation have also been lacking, yet shifts in HPA function are an integral part of mobilizing energy reserves and restoring allostasis during reproduction (Dallman et al., 1993; Kuzawa and Sweet, 2010; Linden et al., 1997; Nyberg, 2012a; Worthman and Kuzara, 2005). Moreover, prosocial neuropeptides such as oxytocin and prolactin expressed during lactation have been implicated in dampening maternal cortisol levels (Carter, 2003; Heinrichs et al., 2003; Heinrichs et al., 2001; Levine et al., 2007). These reductions in HPA function are thought to both reduce risk for postpartum depression and may also provide an important bridging mechanism between maternal behavior and the regulation of offspring stress physiology, at least until the negative feedback circuitry of the infant HPA is established (Bloch et al., 2003; Carter et al., 2001; Feldman et al., 2007; Flykt al., 2010; Hinde, 2010; Kammerer et al. 2006; Kuzawa and Quinn, 2009).

Given the paucity of data addressing variation in HPA function among pregnant women in a nonwestern setting, the primary goal of this study is to provide cross sectional documentation of diurnal cortisol rhythms among pregnant, lactating, and nonpregnant nonlactating women in a small scale foraging and horticulturalist society in the Bolivian Amazon, the Tsimane'. First, based on the established premise that the basal maternal HPA activity is elevated throughout pregnancy (Nyberg, In press; Power and Schulkin, 2006), we test whether there are significant differences in the diurnal rhythm of pregnant versus nonpregnant and lactating Tsimane' women. Second, we evaluate the hypothesis that the

reactive scope is dampened during pregnancy and lactation, with an expectation that cortisol responsiveness to infectious morbidity will be diminished among pregnant women compared to nonpregnant women. In the interest of exploring lactation as a physiological mechanism to facilitate postpartum restoration of the maternal HPA axis, it is hypothesized that lactating women will have comparatively lower cortisol profiles than pregnant women, with increased duration of lactation being inversely associated with cortisol profiles.

Methods

Data Collection TAPS Participants

Participants for this study were enrolled in conjunction with the Tsimane' Amazonian Panel Study (TAPS), as part of a study collecting data on market, stress, and health (Godoy et al., 2009; Leonard and Godoy, 2008). Thorough descriptions of TAPS are available at http://www.tsimane.org/index.html, and excellent ethnographic overviews of the Tsimane' are provided by Reyes-Garcia et al. (2003; 2010) and Huanca (2006). Data presented here are derived from a subsample of 362 salivary cortisol samples from 65 Tsimane women (7 pregnant, 29 lactating, 29 nonpregnant nonlactating).

To emphasize the assessment of the person-specific basal diurnal rhythm, salivary cortisol samples were collected twice a day over three days for a maximum of 6 samples per person. In an effort to capture the maximum cortisol decline across the day, participants were asked to fill the 2mL polypropylene collection vials immediately upon waking, "as soon as you open your eyes and before your feet hit the ground", and immediately before bed or "right before you close your eyes" (Adam and Kumari, 2009; Nyberg, 2012). The nature of this

collection protocol allowed for the adjustment of the morning waking and bedtime values to each individual's circadian rhythm (Adam and Gunnar, 2001; de Kloet and Sarabdjitigh, 2008).

After the collection of saliva samples was completed in each study community, the vials were stored in the TAPS refrigeration unit in San Borja, Bolivia within seven days of initial collection. Once manually transported back to the United States, the samples were stored at -30C at the Northwestern University Laboratory for Human Biology Research. Subsequently, the samples were placed on dry ice and express shipped to the University of Trier, Germany, where samples were assayed in duplicate using a competitive solid phase time-resolved fluorescence immunoassay with fluorometric endpoint detection (DELFIA). The mean inter-assay coefficient of variation was 6.7%, and no significant correlations were detected between cortisol concentrations and a) the duration (in days) between time of collection and storage in the project refrigerator in San Borja ($r=0.008$, n.s.), or b) the duration between collection time and assay completion at the University of Trier, Germany ($r=0.009$, n.s.) (Nyberg, 2012).

Standard anthropometric techniques utilized in previous TAPS studies (Foster et al., 2005; Godoy et al., 2005; Leonard and Godoy, 2008; Tanner et al., 2009; Lohman et al., 1988; Nyberg et al., Accepted) were used to assess maternal nutritional status. Stature and weight were used to calculated body mass index (BMI) as $(kg)/(height\ (m))^2$. Lange skinfold calipers were used to measure subcutaneous fat, and the variable sum of four skinfolds was comprised of the sum of biceps, triceps, subscapular, and suprailiac measures. A brief survey on health and self-reported illness was administered, and a dummy variable was constructed to

represent whether the participant had experienced illness in the week prior to the saliva collection, an important potential correlate of cortisol levels. Additional covariates include age, parity, and duration of breastfeeding in months.

Statistical analyses were performed in Stata version 10 (Stata Corp., College Station, TX). Cortisol and BMI were log transformed to improve the normality of the distributions for the multilevel analyses. Values for hierarchical models are centered at +8 hours, with morning waking cortisol values represent +0 hours postwaking, and the bedtime values represent +16 hours. Slope values were obtained by estimating a best fit line though the multiple measures of morning and evening cortisol using hierarchical linear regression according to Adam and Kumari (2009) and Hruschka et al. (2005). To preserve statistical power, dummy variables representing pregnant and lactating females were included in the full multilevel regression model, and interaction terms were constructed to assess the impact of infectious symptoms on cortisol in pregnant and lactating women.

The protocol employed in this study were approved by the Institutional Review Board at Northwestern University. In addition, in accordance with established TAPS protocol, the Gran Consejo Tsimane', the primary Tsimane' governing body, also granted permission to the project.

Results

Previous reports have presented the general characteristics of the broader sample of salivary cortisol by gender across the lifespan (Nyberg, 2012), and have demonstrated that cortisol profiles increased with age, with females demonstrating elevated cortisol compared to

their age matched male counterparts emerging in childhood and widening into adulthood. General anthropometric and health characteristics of this sample of adult females are presented in Table 1. Pregnant women displayed dramatically elevated morning cortisol concentrations (t=-4.82; df=163; p=0.000) and a heightened all times mean output (t=-4.88; df=359; p=0.000) compared to both nonpregnant and lactating females. Bedtime cortisol did not differ between pregnant and nonpregnant women (t=-0.91; df=136; p=0.42). Among lactating women, morning cortisol (t=0.47; df=153; p=0.63) and evening cortisol values (t=0.90; df=316; p=0.36) were not significantly different compared to nonpregnant nonlactating females. The differential cortisol rhythms of these subgroups are illustrated in Figure 1.

A hierarchical regression model (Table 2) was used to fit diurnal slopes according to time of collection, and centered at +8 hours postwaking, with the cortisol measures across the three days linked by individual subject identifier. Before adjusting for control variables, time of collection accounted for 51% of the within-person variation in the diurnal women in this sample. The average intercept at midday was -0.18 ug/dL, and exhibited a decline of 7% per hour. On average, pregnant females demonstrated a 101% increase in midday compared to nonpregnant women (p=0.000), although the maximum morning cortisol value among pregnant women exceeded the nonpregnant morning average by 352%. On the other hand, lactating women did not differ significantly in their diurnal rhythm from nonpregnant nonlactating women. Among lactating women, each additional month of breastfeeding predicts a 3% increase in midday cortisol (p<0.000), contrary to our expectations. Additional robust regression analyses predicting morning cortisol indicate that duration of breastfeeding

is more strongly related to reductions in morning compared to evening cortisol (AM cortisol β=0.01, $p<0.000$, R^2=0.24; PM cortisol β=0.004, $p<0.05$ R^2=0.10), a relationship that is depicted in Figure 3. The coefficients for age, BMI, subcutaneous fat reserves, and parity were not significantly associated with differential patterns of HPA activity across the day.

Hierarchical regression analyses reveal that the presence of morbidity symptoms was positively, but insignificantly related to elevated cortisol concentrations among nonpregnant women (β=0.24; p=0.78). The interaction term for lactating women experiencing morbidity was also positive, but insignificantly related to cortisol concentrations (β=0.05; p=0.59). Contrary to expectation, illness was not significantly associated with diminished cortisol among pregnant women, and in fact, exhibited a small positive coefficient (β=0.07, p=0.48). The adjusted coefficients for the predicted impact of infectious symptoms on midday cortisol are presented in Figure 4, and report that nonpregnant nonlactating women display the greatest increase in cortisol responsivity compared to women who were pregnant or lactating.

Discussion

These findings provide the first documentation of variation in diurnal cortisol rhythms among pregnant, lactating, and nonpregnant women in a foraging and horticultural society in the Bolivian Amazon. Consistent with our hypothesis (Kivlighan et al., 2008), pregnant women had significantly elevated cortisol rhythms compared to nonpregnant women. Among lactating women, reductions in HPA activity were most evident immediately following parturition. While we cannot distinguish correlation from causation within the current sample,

a broad body of literature implicates breastfeeding, and its concomitant release of oxytocin and vasopressin as potent HPA dampeners (Carter, 2003; Chatterton et al., 2000; Feldman et al., 2007). These findings, while confirming the relationship between HPA activity and lactation do not facilitate an inquiry into the broader dynamics of cortisol release within individuals across the course of lactation. An alternative possibility involves the expulsion of the placenta following birth, which itself is a major source of GCs and may contribute to the feed-forward elevation of the maternal HPA axis (Lightman et al., 2001; McLean and Smith, 2001; Milligan and Hinde, 2011; Rutherford, 2009).

Interpretations of the cortisol response to illness remain less clear, as the elevated cortisol measures among nonpregnant women were notably higher than the more marginal responses exhibited among pregnant and lactating women, but nonetheless statistically insignificant. The use of self-reported morbidity as a proxy of illness may be an imperfect measure, inadequately reflecting the objective immune response to infection. Several limitations should also be addressed. For instance, due to the cross-sectional nature of this data, few generalizations can be made about individual variation in GC trajectories across pregnancy though parturition and subsequently, across lactation. As these findings are preliminary and are derived from a small sample in a unique ecological setting, more extensive comparative data are needed from a range of populations across different contexts to map variation in HPA function in healthy pregnancies. Integrating comparative data on maternal cortisol rhythms will help elucidate the thresholds at which maternal stress buffering is exceeded, and more clearly delineate the developmental risks of fetal GC exposure.

Greater attention to GCs as not just a marker of psychosocial stress, but as a major metabolic indicator may also provide key insights into the shifts in developmental timing of human pregnancy in a broader evolutionary context (Challis et al., 2001 Crespi and Denver, 2005; Nyberg, In press; Worthman and Kuzara, 2005). Stress hormones not only coordinate organismal-wide synchrony of the *milieu interior* in response to environmental conditions, but at directly on the genome, altering transcription factors that promote placental development, influence fetal brain development, and calibrate maternal metabolic load (Lupien et al., 2009; Power and Schulkin, 2005; Rutherford 2009; Sloboda et al., 2005). During lactation, GCs command yet another major shift in energy reallocation, by mobilizing gluteofemoral fat reserves to fuel lactogenesis (Butte et al., 1984; Ellison, 2001; McNamara, 1995; Rebuffe-Scrive et al., 1985).

Although these findings provide preliminary insight into the HPA dynamics of reproduction, these analyses are just as critical for the questions they raise. For instance, how does psychosocial stress potentiate a process that is inherently metabolically stressful (Bergant et al., 1998; Nyberg, 2012)? And, if human pregnancy is comparatively physiologically expensive, does increased risk for maternal postpartum depression or reduced affect (‘baby blues’) represent an underrecognized cost of this transition (Carter et al., 2001; Tronick and Reck, 2009)? To what extent is the interaction between the HPA and HPG axes a central driver of the human pattern of altricial births (Brummelte and Galea, 2010; Clancy, 2012; Ellison, 2005; Nepomnaschy et al., 2006)? How does the HPA axis navigate trade-offs between provisioning offspring via lactation and restoring maternal GC homeostasis?

This study may represent the beginning of an inquiry into maternal immunoenergetics across diverse ecological and cultural contexts (Clancy et al. 2012; Hinde et al. 2012; Nepomnaschy et al. 2012; Piperata, 2010; Vitzthum, 2009). Evolutionarily-informed public health interventions designed to reduce maternal stress during pregnancy would benefit greatly from a more nuanced understanding of variation in HPA activity during pregnancy and lactation. Postpartum depression is increasingly recognized as a major health condition affecting nearly 20% of mothers, and in its subclinical form, baby blues may be experienced by up to half of all mothers (Beck, 1995; Brummelte and Galea, 2010; Tronick and Reck, 2009). In this respect, elevated maternal cortisol and dysregulated HPA feedback may not only impact maternal affect and well-being, but may also hold downstream consequences for infant health via transmission to offspring as GCs in breastmilk (Block 2003; Groer et al., 2002; Hinde 2010; Sullivan et al., 2010, Tu et al., 2006). Moreover, through behavioral and epigenetic pathways, maternal experience promotes alteration of GR expression and entrainment of the offspring stress response (Albers et al., 2008; Champagne and Meaney, 2001; Devlin et al., 2012; Meaney, 2010), particularly until the hippocampus has developed the capacity to invoke the inhibitory negative feedback (Anacker et al., 2010; Lupien et al., 2009; Tottenham and Sheridan, 2010). Clarifying the relationships between maternal stress and postpartum depression represents a prominent, yet understudied public health challenge, with implications for maternal and fetal health, as well as the developmental origins of health and disease (Wadhwa et al., 2009).

Table 1. Descriptive Statistics

	Pregnant	Lactating	Nonpregnant
n (samples)	8 (38)	29 (165)	29 (159)
Samples/person	5.3	5.7	5.5
Age	31.9	28.5	33.9
AM Cortisol (+0 hrs)	0.42 (0.24)	0.21(0.17)	0.22 (0.15)
PM Cortisol (+16 hrs)	0.12 (0.09)	0.09 (0.09)	0.09 (0.10)
Slope (SE)	-0.09 (0.01)	-0.07 (0.00)	-0.07 (0.00)
BMI	26.7 (3.12)	26.7 (3.2)	23.9 (3.1)
Sum of four skinfolds	53.2 (14)	60.7 (16.0)	64.5 (20.7)
Parity	3.6 (2.3)	4.6 (3.7)	3.7 (3.3)

Table 2. Multilevel predictors of log cortisol (165 samples from 65 women)

Fixed Effect	Coefficient (SE)	p-value
Intercept (+8 hrs)	-1.03 (2.24)	0.00
Time since waking	-0.07 (0.01)	0.00
Age	0.01 (0.01)	0.45

Pregnant	0.75 (0.24)	0.00
Lactating	-0.51 (0.32)	0.41
Duration lactation (months)	0.03 (0.01)	0.00
Total offspring	0.02 (0.04)	0.55
Log BMI	-0.49 (0.37)	0.76
Sum 4 skinfolds (mm)	0.00 (0.00)	0.81
Morbidity	0.24 (0.23)	0.78
Preg x Morb	0.07 (0.11)	0.48
Lact x Morb	0.05 (0.00)	0.59
Random Effect	Variance (SD)	p-value
Level 2 Intercept	0.11 (0.05)	0.00
Time slope	0.001 (0.03)	0.00
Level 1	0.43 (0.04)	

Figure 3. Adjusted Percentage Change in mean Cortisol During Illness

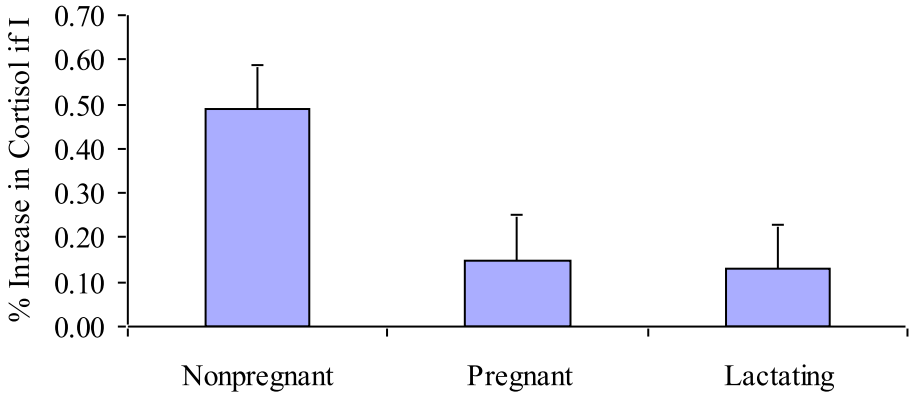


Figure 4. Relationship Between Duration of Lactation and Morning Cortisol

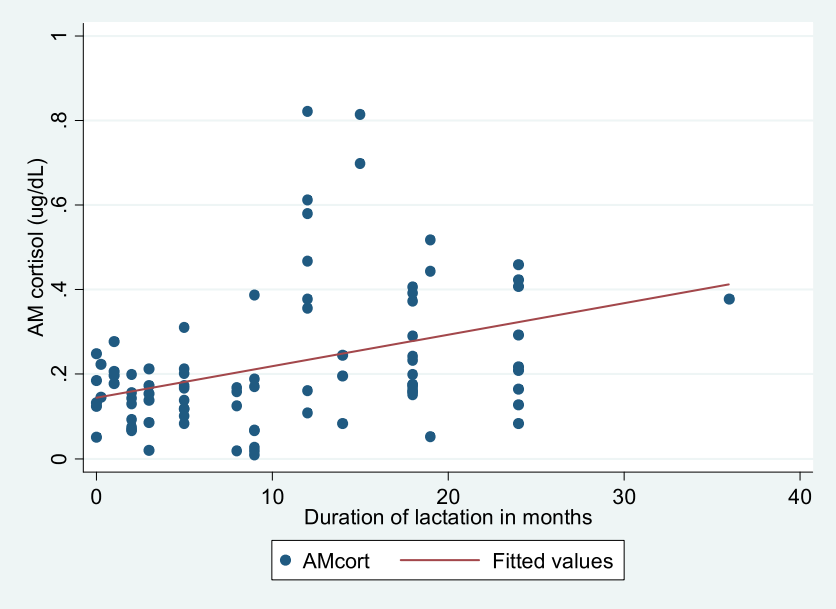
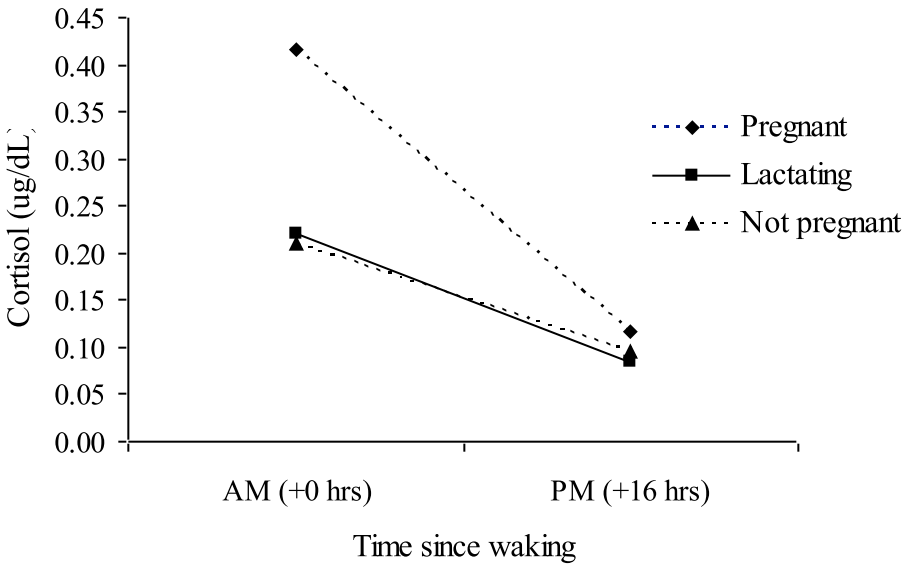


Figure 2. Diurnal Rhythms Vary By Pregnancy Status



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