Received: 25 February 2019 | Revised: 9 July 2019 | Accepted: 15 August 2019

DOI: 10.1002/ajhb.23315

ORIGINAL RESEARCH ARTICLE

American Journal of Human Biology WILEY

Steroid hormone concentrations in milk predict sex-specific offspring growth in a nonhuman primate

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Funding information
National Center for Research Resources, Grant/Award Numbers: P51RR000169, R24RR019970; National Institutes of Health, Grant/Award Numbers: P51OD011107, R24OD010962; National Science Foundation, Grant/Award Number: BCS-0921978; Stony Brook University; California National Primate Research Center

Abstract

Objectives: In humans and other mammals, maternal hormones are transferred to offspring during lactation via milk and may regulate postnatal development, including the pace of early growth. Here, we used a nonhuman primate model to test the hypotheses that milk cortisol and dehydroepiandrosterone-sulfate (DHEAS) concentrations reflect maternal characteristics, and that changes in these hormones across lactation are associated with early postnatal growth rates.

Methods: Demographic information, morphometrics, and milk samples were collected from rhesus macaque mothers and their infants at the California National Primate Research Center in Davis, California. Using linear models, we examined the relationship between maternal traits and milk hormone concentrations (N = 104 females) and explored the effect of milk hormones on the rate of offspring growth (N = 72 mother-infant dyads), controlling for available milk energy.

Results: Contrary to previous studies, we found that milk cortisol concentrations were categorically higher in multiparous females than in primiparous females. However, milk DHEAS concentrations decreased with maternal parity. Neither milk cortisol nor DHEAS were related to maternal rank. Finally, changes in milk hormones predicted offspring growth in a sex-specific and temporal manner: increases in cortisol from peak to late lactation predicted faster female growth, and increases in DHEAS concentrations from early to peak and peak to late lactation predicted faster male growth.

Conclusions: Our findings shed light on how hormonal components of milk have sex-specific effects on offspring growth during early postnatal life with varying temporal windows of sensitivity.

1 | INTRODUCTION

Mammalian offspring receive maternal physiological input through both prenatal and postnatal pathways. Postnatally, females transfer maternal-origin bioactives to offspring via milk during lactation, an adaptation that evolved approximately 250 million years ago (Lefèvre, Sharp, & Nicholas, 2010; Oftedal, 2012). Studies on humans, nonhuman primates, and rodents have explored the effects of maternal milk components on a number of infant developmental systems, including cognition, body composition, and temperament (Allen-Blevins, Sela, & Hinde, 2015; Bernstein & Hinde, 2016; Catalani, Alemà, Cinque, Zuena, & Casolini, 2011; Dettmer et al., 2017; Fields et al., 2017; Hinde et al., 2015; Hollanders, Heijboer, van der Voorn, Rotteveel, & Finken, 2017; Sullivan, Hinde, Mendoza, & Capitanio, 2011). One aspect of infant development that is of particular interest to both clinical and evolutionary research is the pace

of early postnatal growth. Accelerated early growth has been linked to trade-offs in multiple developmental systems (Berghänel, Heistermann, Schülke, & Ostner, 2016; Berghänel, Schülke, & Ostner, 2015; Fisher, Nager, Monaghan, Osmond, & Barker, 2006; Lee, Monaghan, & Metcalfe, 2012) as well as adult cardiovascular and metabolic disease (Barker, 2004; Eriksson et al., 1999; Falkner, Hulman, Kushner, Barker, & Karlberg, 1998; Oken & Gillman, 2003), suggesting that prioritizing early growth over other developmental systems and tissues may improve early life survival at the expense of health during later life (Stearns, 2010).

In humans, the rate of early postnatal growth is organized, in part, by milk nutritional components such as fat and protein (Prentice et al., 2016), as well as microbiota, which regulate nutrient absorption and energy balance in the infant gut (Thompson, 2012). In addition, hormones such as glucocorticoids (GCs) can modulate both intestinal transport (Pácha, 2000) and infant metabolic priorities, thereby regulating the energy available to sustain growth. GCs, including cortisol, are one class of metabolic steroid hormones recently linked to offspring growth in several mammalian species, including humans (Hahn-Holbrook, Le, Chung, Davis, & Glynn, 2016), macaques (Berghänel et al., 2016; Hinde et al., 2015), and red squirrels (Dantzer et al., 2013). Cortisol is produced in the zona fasciculata of the adrenal cortex, mediates the production of energy by catecholamines (Sapolsky, Romero, & Munck, 2000) and regulates glucose metabolism. It is also the end product of the hypothalamic-pituitary-adrenal axis, which regulates the body's physiological response to metabolic, immunological, and psychosocial challenges.

In infants, GC production is relatively high across early postnatal life. During this time, infants not only produce endogenous GCs, but also receive exogenous GCs from mother's milk. Experimental studies on rodents have shown that maternal-origin milk GCs readily cross the gastrointestinal barrier of pups, reaching circulation and the brain (Angelucci et al., 1985; Pundir et al., 2017). The expression of GC receptors in the pup's gut peaks from birth to 2 weeks of age, before decreasing to adult levels during weaning, suggesting that pups are highly receptive to milk GCs and are actively binding maternal cortisol during lactation (Pácha, 2000).

However, recent studies on the relationship between milk cortisol and postnatal growth have found mixed effects. While research in humans has consistently found that exposure to maternal gestational GCs during prenatal life is linked to poor fetal growth (Diego et al., 2006), some research on other mammals has documented a positive relationship between prenatal maternal GCs and postnatal offspring growth (Berghänel et al., 2016; Berghänel, Heistermann, Schülke, & Ostner, 2017; Dantzer et al., 2013). Furthermore, recent studies on the relationship between milk cortisol and postnatal growth have found a negative relationship (humans: Hahn-Holbrook et al., 2016) or mixed effects depending on the developmental time point at which growth was investigated (rhesus macaques: Hinde et al., 2015).

The inconsistent relationships found between maternal GCs and postnatal growth may suggest that the presence, magnitude, and direction of GC effects are mediated by maternal and offspring characteristics. For example, milk production and quality in rhesus macaques vary with maternal parity and offspring sex (Hinde, 2009), and mothers rearing daughters produced milk with higher calcium content (Hinde et al., 2013). Additionally, even when milk synthesis does not seem to differ between sons and daughters, the magnitude and windows of sensitivity to milk constituents can differ between sons and daughters (Hinde, Carpenter, Clay, & Bradford, 2014). Sex differences may therefore extend to milk hormones and their effects on the pace of early postnatal growth. Indeed, the effects of milk GCs on other offspring outcomes such as temperament (Grey, Davis, Sandman, & Glynn, 2013; Hinde et al., 2014; Sullivan et al., 2011) and social and cognitive functioning (Dettmer et al., 2017) have been found to vary as a function of infant sex.

Beyond the effects of GCs, research on humans suggests that the steroid hormone dehydroepiandrosterone-sulfate (DHEAS) may also be associated with variation in the pace of early offspring growth. DHEAS is the sulfated form of dehydroepiandrosterone (DHEA), which is produced in the zona reticularis of the adrenal cortex. In humans and other primates, DHEAS is the most abundant steroid hormone in circulation (Longcope, 1996; Muehlenbein et al., 2003) and has both metabolic and neurobiological actions (Maninger, Wolkowitz, Reus, Epel, & Mellon, 2009). Like GCs, DHEAS is produced following the release of adrenocorticotropic hormone and elevates in response to acute stress. However, rather than attenuating in response to chronic stress as GCs do (Maninger, Capitanio, Mason, Ruys, & Mendoza, 2010), DHEAS concentrations remain elevated for a longer duration, and may thus better capture exposure to metabolic or psychosocial challenges than do short-term measures of GCs. Importantly, DHEAS can be reconverted into DHEA through removal of the sulfate group by the enzyme steroid sulfatase. At this stage, DHEA can be converted further to both anabolic androgens (eg, testosterone and dihydrotestosterone [DHT]) and estrogens, and can bind to both androgen and estrogen receptors, thus there are multiple binding pathways that can link DHEAS to developmental outcomes. For example, if DHEAS is reconverted to DHEA, it may promote anabolic activity to fuel growth through the production of testosterone and DHT (Labrie et al., 2006; Luci, Valenti, & Maggio, 2010). In support of an association between DHEAS and early growth, low birth weight and "small for gestational age" human infants had higher childhood DHEAS levels linked to accelerated "catch-up growth" than

those characterized by typical fetal and birth mass (Ibáñez, Lopez-Bermejo, Diaz, & de Zegher, 2011; Ibáñez, Potau, Marcos, & de Zegher, 1999; Veening, Van Weissenbruch, & Delemarre-Van De Waal, 2002). However, in a recent study on captive nonhuman primates, neither maternal nor fetal DHEAS concentrations were correlated with neonatal body mass (Petrullo & Lu, 2019). Still, elevated circulating DHEAS concentrations during adolescence have been associated with accelerated catch-up growth in humans (Estourgie-van Burk, Bartels, & Boomsma, 2015). Such an association suggests that apart from fetal and neonatal body mass, the pace of early postnatal growth may be driven, at least in part, by DHEAS.

In the present study, we explored associations among maternal characteristics, cortisol and DHEAS concentrations in milk, and rate of offspring growth in captive rhesus macaque (*Macaca mulatta*) mother-infant dyads housed at the California National Primate Research Center (CNPRC) in Davis, CA. Rhesus macaques are Old World monkeys that live in multimale multifemale social groups and have been repeatedly used as standard models of mother-infant dynamics and development in humans and other mammals (Bardi, Shimizu, & Borgognini-Tarli, 2003; Berman, 1980; Hinde & Spencer-Booth, 1971; Machado, 2013). Female rhesus macaques form nepotistic and despotic matrilineal hierarchies and display high rates of agonism, making them particularly suitable for studies of hormones that are activated with response to social stress (Mendoza, 2017). Previous studies on this population found that first-time mothers produced milk of lower volume and lower energy density (Hinde, Power, & Oftedal, 2009), and that lower parity mothers produced milk with higher concentrations of cortisol (Hinde et al., 2015). Combined with data showing that higher cortisol was associated with faster infant growth, Hinde et al. (2015) suggested that milk cortisol concentrations might underlie the prioritization of milk energy for growth over behavioral activity in infants of low parity mothers (Hinde et al., 2015; Nuñez, Grote, Wechsler, Allen-Blevins, & Hinde, 2015). Similar mechanisms to prioritize growth may exist for females of low social rank who, in human and nonhuman primate societies, often experience greater energetic, immunological, and/or psychosocial stress and exhibit increased concentrations of GCs (Hoffman, Ayala, Mas-Rivera, & Maestripieri, 2009). Here, we used a larger data set to revisit this hypothesis, evaluating how parity and maternal social status influence milk cortisol and DHEAS, and how these hormones in turn are associated with postnatal growth. Because cortisol and DHEAS both respond to challenge and are expected to promote growth, we predicted that lower parity females would produce milk with greater concentrations of cortisol and DHEAS than higher parity females. Additionally, we predicted elevated concentrations of milk cortisol and DHEAS in low-ranking females, who we expected were exposed to greater rates of psychosocial stress from conspecifics (Abbott et al., 2003; Hoffman et al., 2009; Silk, 2003). In terms of the rate of early infant growth, we predicted that both cortisol and DHEAS across lactation would be positively associated with infant growth rates, controlling for available milk energy (AME). Finally, because previous studies have documented varying degrees of sex differences in infant sensitivity to milk cortisol (Grey et al., 2013; Hahn-Holbrook et al., 2016; Hinde et al., 2015; Sullivan et al., 2011), we predicted that cortisol would be associated with infant growth and may exhibit sex-specific sensitivities, but made no specific predictions about directionality. We also hypothesized that there would be sex differences in the effect of milk DHEAS on growth, but made no specific predictions for males versus females.

2 | MATERIALS AND METHODS

2.1 | Study site and subjects

All animal use procedures for this study were approved by the Institutional Animal Care and Use Committee at UC Davis and complied with the US National Research Council's Guide for the Care and Use of Laboratory Animals, the US Public Health Service's Policy on Humane Care and Use of Laboratory Animals, and Guide for the Care and Use of Laboratory Animals. Data for this study were collected at the CNPRC in Davis, CA. Mother-infant dyads were recruited from the outdoor colony during three birth seasons (2010, 2011, and 2012). Social groups were housed in 0.2-ha corrals with climbing structures and multiple feeding stations. Subjects were housed with kin and nonkin in groups similar in composition to those found in wild populations (Hinde & Capitanio, 2010). Adult females ranged in parity from 1 to 16 pregnancies, including N = 22 primiparous females. Subjects were provisioned twice daily with a commercial monkey chow (Purina Monkey Chow) and were supplemented with fresh produce provided on a semiweekly basis. Linear dominance hierarchies were generated by the CNPRC behavioral management division using methods described elsewhere (McCowan, Anderson, Heagarty, & Cameron, 2008). For the present study, maternal rank was split into categorical groups representing the top ("high"), middle ("middle"), and bottom ("low") third of the hierarchy. In the event that the tertile split categorized individuals into ranks that differed from that of their matriline, they were assigned the rank that corresponded to the majority of their matriline (Hinde et al., 2015).

2.2 | Milk collection

Milk was collected from subjects at three lactation time points: early (~1 month postpartum), peak (3-4 months postpartum),

and late (5-6 months postpartum), resulting in a total of 319 milk samples from 104 females (age: mean = 7.9 years, range = 3.8-18.9 years). Standardized milk collection methods were used (Hinde et al., 2009; Hinde & Capitanio, 2010), which involved moving mother-infant pairs from outdoor corrals into indoor temporary housing spaces between 7:30 and 9:00 AM. Mesh jackets were then placed on mothers to prevent nursing by the infant while allowing for mother-infant contact over the ~4-hour milk accumulation period. Following the accumulation period, mothers were sedated with 5-10 mg/kg of ketamine hydrochloride and given a 0.1-mL/kg dose of oxytocin (both administered intramuscularly) to stimulate milk letdown. Milk was then collected manually until mammary glands were fully evacuated to prevent sampling bias. Samples were placed immediately on ice, vortexed for 5 seconds, aliquoted into cryovials, and frozen at −80°C. In August of 2016, samples were shipped to Stony Brook University, where they were stored at −20°C for less than 30 days before being assayed for cortisol and DHEAS.

2.3 | Available milk energy

An aggregate index of AME was calculated as the product of milk energy density (kcal/g) and milk yield (g) for each milk sample across the three lactation time points (Hinde et al., 2009; Hinde & Capitanio, 2010). This index accounts for individual variation in the amount of milk produced as well as the nutritional composition of milk across mothers. When examining the effects of nonnutritional milk components on infant development, it is critical to control for AME as milk yield and quality directly influence infant outcomes such as growth (Hinde et al., 2015). Nutritional components in milk were measured using a MIRIS milk analyzer (Miller et al., 2013) calibrated for rhesus macaque milk in the Comparative Lactation Laboratory at Harvard University. Samples were assayed in duplicate. Milk yield was calculated by the total sample in grams obtained after full evacuation from both mammary glands following the milk accumulation period. These measures of milk quality and quantity have previously been associated with infant growth in this population (Hinde, 2009; Hinde et al., 2009; Pittet, Johnson, & Hinde, 2017) and were not correlated with milk cortisol and DHEAS in this study.

2.4 | Hormone analyses

Milk samples were thawed to room temperature and centrifuged at 3000 rpm for 10 minutes to separate the lipid layer from the aqueous portion, which has been previously shown to contain 81% of whole milk hormone values (Sullivan et al., 2011). Aqueous milk was assayed in duplicate using a commercial radioimmunoassay designed for human serum and modified for the present study to measure milk steroid hormones (Corti-Cote radioimmunoassay (RIA) and DHEAS-coated tube RIA; MP Biomedicals, Los Angeles, CA). Cross-reactivities for the cortisol antibody were 94.1% for prednisolone, 1.2% for corticosterone, and < 1% for cortisone. Cross-reactivities for the DHEAS antibody were 100% for DHEA, 6% for androstenedione, and < 1% for cortisol, estrone, and testosterone.

Assay protocols followed kit protocols with the following modifications to optimize the assays: Aqueous milk samples for cortisol were run at 100 μL of a 1:4 dilution, which served to minimize potential interference between components of milk and the assay. Standard volumes were also adjusted to 100 μL by adding 75 μL of distilled water to the 25 μL suggested volume to obtain consistent volumes across tubes and standard concentrations were adjusted accordingly. Aqueous milk samples for DHEAS were run at 400 μL of a 1:4 dilution. Standards volumes were adjusted accordingly by adding 375 μL of distilled water to the 25 μL suggested volume. Samples and tracer were incubated in coated tubes following kit protocols for 45 minutes (cortisol) and 1 hour (DHEAS) before aspirating the supernatant and reading on a gamma counter.

Assay parallelism was tested using serial dilutions of pooled aqueous milk. For both cortisol and DHEAS, pooled samples were diluted in parallel to the standard curves. Accuracy was performed by spiking standards with a pooled sample of low hormone concentration and determining recovery across the range of the assay curve. Average recovery for the DHEAS assay was 107 ± 6.5% (SD) (N = 7), and average recovery for the cortisol assay was 106 ± 2.8% (SD) (N = 7). Pooled samples and high/low controls (Liquichek, Bio-Rad Laboratories Inc., Hercules, CA) were included on all assays for quality control. For the cortisol assay, the mean interassay coefficient of variation (CV) was 2.8% and 11% for high and low Liquicheck controls, and 10.5% and 12.2% for high and low pooled controls. For the DHEAS assay, the mean interassay CV was 4.8% and 8.6% for high and low Liquicheck controls, and 9.7% and 8% for high and low pooled controls. Intraassay CVs were 7.9% for cortisol (N = 4), and 9% for DHEAS (N = 4).

2.5 | Statistical analyses

2.5.1 | Milk components and maternal characteristics

With our full data set of 319 milk samples from 104 females, we constructed three separate linear mixed models to examine the effect of maternal and offspring characteristics (parity, rank, and offspring sex) on milk cortisol, DHEAS, and AME. Residuals in all three models were not normally distributed after evaluation with a Shapiro-Wilk test; therefore, dependent variables were log-transformed to achieve normality. We included parity both as a categorical

(primiparous vs multiparous) and a continuous predictor in all models. We chose to include parity both ways because, while categorical divisions of parity are argued to better capture physiological differences associated with young motherhood (eg., somatic resource availability and mammary gland development), we also wanted to replicate a previous study that examined parity as a continuous variable (Nuñez et al., 2015). Finally, in all three models, lactation time point (early, peak, and late) was included as an additional fixed effect, while maternal ID was included as a random factor.

2.5.2 | Predictors of offspring growth rate

Previous studies on this population have found that AME is highly correlated with infant growth (Hinde, 2009; Hinde et al., 2009; Pittet et al., 2017), thus AME should be included as a covariate in any study seeking to evaluate the independent effects of hormones on growth. Therefore, for models of offspring growth rate, we excluded a subset of samples (and thus individual infants) in which measures of AME could not be obtained, resulting in a data set of N = 72 infants (37 females, 35 males) with complete milk sample data (AME, cortisol, and DHEAS) and complete body mass data at all three lactation time points. As early growth is linear in this population (Nuñez et al., 2015), growth rates were calculated as the change in mass in kilograms per day from the early to late lactation time point, capturing the period of maternal nutritional dependence. Rates were log-transformed to achieve normality in residuals prior to regression analyses. Female (N = 37) and male (N = 35) growth models were run separately to retain power as daily growth rates in this population are sex specific (Nuñez et al., 2015). We tested the effects of milk hormone concentrations on the dependent variable of infant growth rate using linear models, controlling for the effects of offspring mass at 1 month, absolute hormone concentrations at 1 month, and AME. We used dynamic (from early to peak and peak to late) rather than static measures of hormone concentrations, as a previous study on this population found that offspring were sensitive to dynamic changes in milk components (rather than values at any specific time point) across lactation (Hinde et al., 2015). As this set of models initially included a large number of predictors, we used Akaike Information Criterion corrected (AICc) for finite sample sizes to construct final models that included the smallest number of parameters that substantially captured variation in growth rates with the lowest AICc values (Akaike, 1974; Dettmer et al., 2017; Hinde et al., 2015). All analyses were performed in R version 3.2.3 (R Core Team, 2015). Mixed models were performed using the lme4 and lmerTest packages and partial residual plots were created using the package visreg (Breheny & Burchett, 2017). Significance was set at $P \leq .05$.

3 | RESULTS

3.1 | Hormone concentrations across lactation

Concentrations of both cortisol and DHEAS in milk were highly variable among females within each lactation time point, with average concentrations of cortisol and DHEAS comparable across samples (Table 1). Concentrations of milk cortisol did not significantly differ among the three time points (Table 2A). However, concentrations of DHEAS in milk were significantly higher at late lactation than at early or peak lactation (estimate $\pm$ SE = 0.29 ± 0.07, $t = 4.32$, $P = <.0001$, N = 104; Table 2B).

3.2 | Maternal characteristics and milk hormone concentrations

Primiparous females produced milk with significantly lower cortisol concentrations than multiparous females (estimate $\pm$ SE = -0.28 ± 0.12, $t = -2.26$, $P = .03$, N = 104; Table 2A), and maternal parity as a continuous variable negatively predicted milk DHEAS concentrations (estimate $\pm$ SE = -0.04 ± 0.02, $t = -2.18$, $P = .03$, N = 104; Table 2B), with milk DHEAS decreasing with successive births. Maternal parity was also positively associated with AME (estimate $\pm$ SE = 0.03 ± 0.01, $t = 3.35$, $P < .01$, N = 104; Table 2C). Maternal social rank and offspring sex were not significantly associated with milk cortisol, DHEAS, or AME.

TABLE 1 Descriptive statistics of cortisol, DHEAS, and AME in milk samples from females at early, peak, and late lactation (N = 104 females)

Time point	Mean	SD	Range
Cortisol (ng/mL)			
Early	49.20	3.11	9.76-133.10
Peak	57.48	3.55	2.84-199.06
Late	54.93	3.58	2.52-161.99
DHEAS (ng/mL)			
Early	48.80	39.77	7.77-263.41
Peak	54.06	41.56	2.32-246.44
Late	64.53	63.27	8.74-517.35
AME			
Early	15.08	7.61	7.06-47.74
Peak	20.74	11.38	7.53-70.10
Late	36.28	17.59	17.49-135.70

Abbreviations: AME, available milk energy; DHEAS, dehydroepiandrosterone-sulfate.

TABLE 2 Linear mixed models examining the relationship between milk hormone concentrations and female growth rate with maternal ID as a random factor

Predictors	Estimate	SE	*t*	*P* > |*t*|
A. Dependent variable: cortisol concentration (ng/mL) logged (N = 104)				
Intercept	3.74	0.17	22.10	<.0001
Infant sex (male)	0.01	0.10	0.11	.91
Primiparity	−0.28	0.12	−2.26	<.05
Maternal rank	0.00	0.08	0.03	.97
Time point (late)	0.09	0.08	1.08	.28
Time point (peak)	0.14	0.08	1.71	.09
B. Dependent variable: DHEAS concentration (ng/mL) logged (N = 104)				
Intercept	4.02	0.19	21.22	<.0001
Infant sex (male)	0.08	0.10	0.85	.39
Maternal parity	−0.04	0.02	−2.18	<.05
Maternal rank	−0.14	0.07	−1.94	.06
Time point (late)	0.29	0.07	4.32	<.0001
Time point (peak)	0.10	0.07	1.59	.11
C. Dependent variable: AME logged (N = 104)				
Intercept	2.39	0.10	23.61	<.0001
Infant sex (male)	0.05	0.05	0.98	.33
Maternal parity	0.03	0.01	3.35	<.01
Maternal rank	−0.03	0.04	−0.68	.50
Time point (late)	0.96	0.04	27.0	<.0001
Time point (peak)	0.37	0.03	10.48	<.0001

Abbreviations: AME, available milk energy; DHEAS, dehydroepiandrosterone-sulfate.

3.3 | Offspring growth rates

The rate of offspring growth during the first 6 months of life was positively associated with offspring mass at 1 month of age in both female and male infants (females: estimate ± SE = 1.70 ± 0.42, $t = 4.07$, $P < .001$, N = 37; males: estimate ± SE = 1.19 ± 0.28, $t = 4.17$, $P < 0.001$, N = 35). Hormone concentrations significantly predicted offspring growth in a sex-specific manner. Female growth rates were associated with increases in milk cortisol concentrations from peak to late lactation (estimate ± SE = 0.16 ± 0.05, $t = 3.18$, $P < .01$, N = 37; Table 3A, Figure 1), which together with mass at 1 month of age explained 36% of the total variance. In males, growth rates were associated with increases in milk DHEAS from early to peak lactation (estimate ± SE = 0.10 ± 0.05, $t = 2.23$, $P = .03$, N = 35; Table 3B, Figure 2) as well as peak to late lactation (estimate ± SE = 0.12 ± 0.06, $t = 2.16$, $P = .03$, N = 35; Table 3B, Figure 3) and absolute concentrations of DHEAS at early lactation (estimate ± SE = 0.09 ± 0.04, $t = 2.14$, $P = .04$, N = 35; Table 3B), which together with mass at 1 month of age explained 48% of the total variance.

TABLE 3 Final multiple regression models examining the relationship between milk hormone concentrations and offspring growth rate by sex

Predictors	Estimate	SE	*t*	*P* > |*t*|
A. Dependent variable: female growth rate (kg/day) (N = 37)				
Intercept	−6.72	0.36	−18.56	<.0001
Mass at 1 month	1.70	0.42	4.07	<.001
Early DHEAS	0.08	0.06	1.29	.21
Peak to late Δ cortisol	0.16	0.05	3.18	<.01
Model adjusted $R^2 = .36$		$F = 7.45$ $P < .001$		
B. Dependent variable: male growth rate (kg/day) (N = 35)				
Intercept	−6.58	0.24	−27.02	<.0001
Mass at 1 month	1.19	0.28	4.17	<.001
Early DHEAS	0.09	0.04	2.14	<.05
Early to peak Δ DHEAS	0.10	0.05	2.23	<.05
Peak to late Δ DHEAS	0.12	0.06	2.16	<.05
Early to peak Δ AME	0.002	0.002	0.77	.45
Peak to late Δ AME	0.005	0.003	1.88	.07
Model adjusted $R^2 = 0.48$		$F = 6.19$ $P < .0001$		

Abbreviations: AME, available milk energy; DHEAS, dehydroepiandrosterone-sulfate.

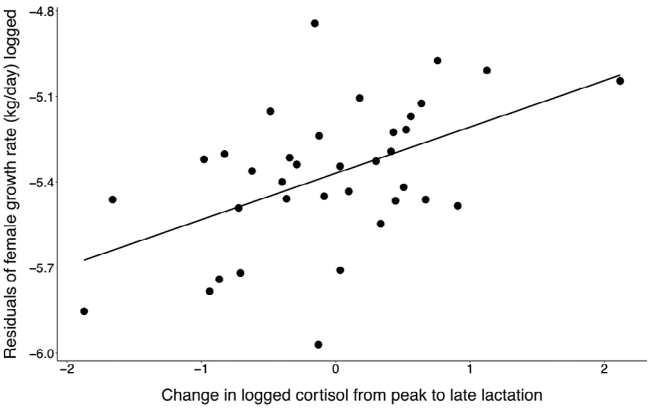

FIGURE 1 Partial residual plot showing the relationship between female growth rate (log [kg/day]) and change in logged cortisol concentrations from peak to late lactation

4 | DISCUSSION

Our study sought to explore how concentrations of milk cortisol and DHEAS are associated with maternal characteristics, and how these hormones contribute to sex-differentiated offspring growth rates in a nonhuman primate.

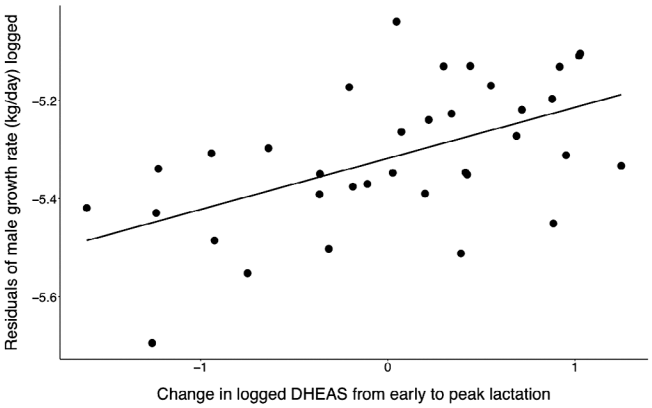

FIGURE 2 Partial residual plot showing the relationship between male growth rate (log [kg/day]) and change in logged DHEAS concentrations from early to peak lactation. DHEAS, dehydroepiandrosterone-sulfate

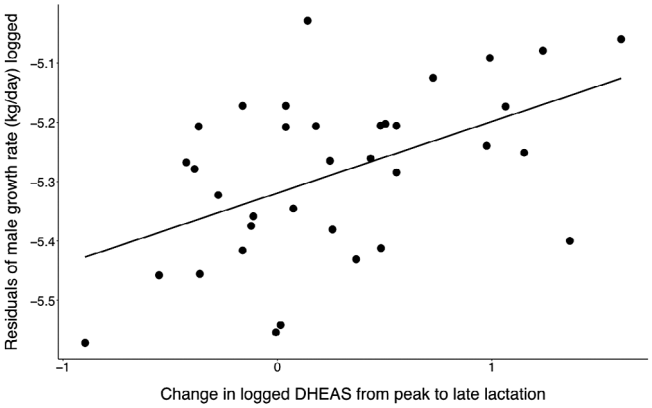

FIGURE 3 Partial residual plot showing the relationship between male growth rate (log [kg/day]) and change in logged DHEAS concentrations from peak to late lactation. DHEAS, dehydroepiandrosterone-sulfate

In the present study, we found that primiparous females produced milk lower in cortisol than multiparous females, a finding that differs from previously published research. Contrary to theoretical expectations regarding social rank, but consistent with previous research in rhesus monkeys, we found no effect of maternal rank on milk GCs. Concentrations of maternal-origin GC and DHEAS in milk exhibited sex-specific and temporal associations with postnatal offspring growth, such that female growth was sensitive to increases in cortisol concentrations from peak to late lactation, and male growth was sensitive to increases in milk DHEAS concentrations across lactation. Taken together, our findings contribute to a growing body of literature on the programming effects of milk on offspring outcomes and suggest a novel and sex-specific association between maternal-origin milk DHEAS and early postnatal growth.

4.1 | Hormone concentrations across lactation

Although we found no significant difference in cortisol concentrations among early, peak, and late lactation, we did find that DHEAS concentrations were significantly higher at late lactation than at any other time point (Table 2). This increase in milk DHEAS concentrations at late lactation may reflect increases in maternal circulating DHEAS as a result of reproductive state shifts and changes to maternal metabolism. This is, however, speculative and requires a better characterization of the hormonal correlates of maternal metabolic changes during lactation and toward the resumption of cycling. Surprisingly, we also found that concentrations of cortisol and DHEAS in milk were relatively equivalent. In both nonhuman primates and humans, DHEAS exists at much higher concentrations than other hormones in circulation (Longcope, 1996; Muehlenbein et al., 2003; Orentreich, Brind, Rizer, & Vogelman, 1984; Takeshita, Huffman, Bercovitch, Mouri, & Shimizu, 2013). Because it has been assumed that circulating hormones are incorporated into milk via passive diffusion at the mammary gland, hormone concentrations in milk are expected to be found at absolutely lower but similar ratios as they are found in circulation. Most previous studies examining passive diffusion from circulation to the mammary gland, however, have focused on the incorporation of pharmaceutical drugs into milk (O'Brien, 1974) rather than endogenous molecules, which may be subjected to different mechanisms of transfer. Our finding of comparable concentrations of cortisol and DHEAS within milk may therefore imply a potential decoupling of circulating hormones and milk hormones. In other words, equal concentrations of cortisol and DHEAS in milk may suggest that the mammary gland can selectively uptake or even independently synthesize hormones and immune factors (Gaiani, Chiesa, Mattioli, Nannetti, & Galeati, 1984; Pierce & Feinstein, 1965). Selective uptake or de novo synthesis of hormones at the mammary gland would imply that mothers have more control than previously assumed over the biochemical signals to offspring. Testing these possibilities necessitates, at minimum, comparing hormones in matched plasma and milk samples or, ideally, tracing the passage of radiolabeled hormone from circulation into milk.

4.2 | Maternal characteristics and milk hormone concentrations

Despite our general finding that maternal parity predicted concentrations of cortisol and DHEAS, we found that primiparous females produced milk with lower, rather than higher, milk cortisol concentrations, a finding that contradicted our predictions and the findings of many previous studies (eg, Hinde et al., 2015; Pawluski, Charlier, Lieblich, Hammond, & Galea, 2009; Vleugels, Eling, Rolland, & de Graaf, 1986). We had hypothesized that low parity females

would produce higher concentrations of milk cortisol in part due to their lower milk volumes and lower milk energy density (Hinde et al., 2009; Miller et al., 2006). Previous data deriving from a comparable data set (108 subjects and 37 primipara) in the same population also showed that milk cortisol at early and peak lactation decreased with increasing parity up to nine births, stabilizing thereafter (Hinde et al., 2015). Our study, which included a late lactation time point (and more total samples, N = 319) but slightly fewer adult females and primipara (n = 22), found that multiparous females had categorically higher GC concentrations in milk and no continuous relationship between the two variables.

Although age-associated decreases in cortisol (Dettmer, Novak, Meyer, & Suomi, 2014; Sapolsky & Altmann, 1991; Van Cauter, Leproult, & Kupfer, 1996) may obscure or overwhelm parity effects, we think this explanation is unlikely given that contrasting results were found in the same population, and on overlapping females. A more likely explanation for these differences is that the methodological criteria used in the current study biased our sample against primiparous females that produced the lowest volumes of milk, which are the same females that would be expected to compensate for poor maternal energy with higher milk cortisol. To facilitate our ability to examine AME as well as concentrations of both cortisol and DHEAS, we included only females with large enough milk production to allow for the analysis of all three measures in our growth models, likely skewing our results toward incorporating females that did not have to compensate for poor maternal condition with increased cortisol concentrations. These methodological circumstances suggest that the parity patterns found previously by Hinde et al. (2015) may better reflect an averaged and nonbiased biological effect.

In contrast to our results for cortisol, maternal parity negatively predicted milk DHEAS concentrations, although this held true only when parity was analyzed as a continuous variable. This relationship likely reflects an age-associated decline in circulating DHEAS concentrations, as DHEAS levels are known to decrease with age in humans and nonhuman primates (Muehlenbein et al., 2003; Parker, 1999; Sapolsky, Vogelman, Orentreich, & Altmann, 1993) and maternal parity and age are strongly and consistently correlated in this population (Hinde et al., 2015). That there was no relationship between parity as a categorical variable and DHEAS suggests that milk DHEAS concentrations are not sensitive to primiparity and the developmental parameters that typically accompany it (eg, first-time mothers are generally still developing themselves) (Nuñez et al., 2015).

Also contrary to our predictions, but similar to previous studies on the same species in captivity (Dettmer et al., 2017; Hinde et al., 2015), we found no effect of maternal rank on concentrations of cortisol or DHEAS in milk. The absence of a rank effect in captive rhesus macaques may not be surprising. Although individuals of low social rank are often expected to exhibit higher cortisol concentrations than higher ranking individuals, this trend is not universal, even within the same species (Creel, 2005). A recent review on humans, for instance, found that only 7 out of 21 studies examining the relationship between socioeconomic class and cortisol found higher cortisol concentrations in low-status individuals, while an almost equal number found no relationship between the two variables (Dowd, Simanek, & Aiello, 2009). In nonhuman primates, a study on serum cortisol found that low-ranking females exhibited higher cortisol concentrations than high ranking females (Hoffman et al., 2009), but studies on milk cortisol concentrations in nonhuman primates have found no effects of rank (Hinde, 2009; Hinde et al., 2015). These inconsistencies are perhaps unsurprising given the variety of factors that modulate rank effects on individual stress physiology, including variation in mating systems (Creel, 2005), social stability, personality, and access to social support (Abbott et al., 2003; Goymann & Wingfield, 2004).

4.3 | Offspring growth and milk hormone concentrations

We found that growth rates among females during the first 6 months of life were positively associated with increases in milk cortisol concentrations from peak to late lactation. Conversely, among males, growth was not predicted by cortisol but rather positively predicted by DHEAS concentrations at early lactation and by increases in milk DHEAS concentrations from early to peak and peak to late lactation. These results contribute to the growing body of evidence for sex-differentiated mechanisms underlying physiological processes during early development in other animals (Badyaev, 2002; Brummelte, Lieblich, & Galea, 2012; Carpenter, Grecian, & Reynolds, 2017; Galante et al., 2018). For example, among rhesus macaques in this population, the quantity and quality of milk differs by offspring sex (Hinde, 2009), and male and female offspring differ in sensitivity to maternal milk cortisol in relation to temperament (Hinde et al., 2015).

The exact mechanism by which milk cortisol and DHEAS influence growth remains unknown. One possibility is that milk hormones promote growth by binding to receptors located in the offspring gut, therefore modulating intestinal transport and regulating the absorption of nutrients. The gut houses the greatest density of GC receptors in the body during infancy (Pácha, 2000), and elevated GCs are known to increase intestinal permeability (Meddings & Swain, 2000; Vanuytsel et al., 2014), potentially promoting growth; however, nothing is presently known about the action of DHEAS in the gut. Alternatively, sex-specific cortisol sensitivities may also be explained by differences in offspring

enzymatic activity, which can modulate the degree to which maternal bioactives such as cortisol can impact offspring. Enzymes that are active in utero, such as 11-beta hydroxysteroid dehydrogenase type 2 (11B-HSD2), can inactivate maternal cortisol through enzymatic conversion to cortisone at the placenta. Recent research on prenatal sex differences has found that female fetuses show reduced 11B-HSD2 activity (and thus greater exposure to maternal GCs) (Mericq et al., 2009) coupled with higher sensitivity to late gestational maternal GCs (Carbone, Zuloaga, Lacagnina, McGivern, & Handa, 2012), suggesting a greater role for maternal cortisol in female offspring development. Importantly, 11B-HSD2 is also active in infant salivary glands (Smith et al., 1996) as well as in the ileum and colon (Pácha, 2000), potentially allowing for sex-specific modification of milk cortisol activity at multiple locations during suckling. This possibility should be investigated in future research.

Regarding the growth-promoting effects of milk DHEAS among males, one potential proximate mechanism underlying this relationship may be steroidal reconversion of DHEAS to anabolic androgens. Human salivary glands contain the enzyme steroid sulfatase, which can promote local conversion of DHEAS into DHEA and subsequently into testosterone and DHT (Spaan et al., 2009). Milk DHEAS may therefore drive growth through the anabolic activity of androgens that result from steroidal conversion in offspring saliva during suckling. Whether male offspring produce more steroid sulfatase than females is unknown, but may explain why growth in female rhesus macaque infants was not predicted by changes in DHEAS. More generally, sex differences in a number of mechanisms, including DHEAS conversion as well as the binding and actions of DHEAS in the gut, might also explain differential growth sensitivities to milk DHEAS among male and female offspring. Future research on sex-specific DHEAS conversion and activity will help clarify how ingested milk DHEAS contributes to DHEAS-driven developmental trajectories.

4.4 | Limitations and future directions

Overall, our findings contribute to emerging research linking maternal-origin bioactives to sex-specific postnatal development, specifically as it relates to the rate of early postnatal growth. Importantly, our study was limited in several ways. As previously stated, due to sampling constraints, our data set excluded primiparous females that produced the lowest volumes of milk, potentially biasing our sample and preventing us from examining milk concentrations of cortisol and DHEAS in those females. Similarly, the concurrent sampling of plasma was logistically untenable in consideration of other funded research priorities; as such, the relationship between milk and circulating DHEAS remains to be explored in the future. Additionally, we were unable to examine potential physiological mechanisms underlying parent-offspring conflict during this critical period, particularly those mechanisms that may allow offspring to modulate maternal input during lactation. We hypothesize that a combination of such mechanisms—particularly, the actions of the enzymes 11B-HSD2 and steroid sulfatase in offspring—can modulate the strength and efficacy of maternal hormonal signals during lactation. In doing so, components of milk that may reflect maternal reproductive and/or life history strategies are likely subject to modifying forces once assimilated by offspring.

ACKNOWLEDGMENTS

The authors thank John Capitanio for CNPRC research facilitation and Amy Skibiel, Michelle Wechsler, Danielle Rendina, Chase Nuñez, Amanda Vogel, and Alison Foster for contributions to milk collection and proximate nutritional analysis. We also would like to thank A. Koenig, C. Borries, and A.C. Markham, who provided helpful comments on earlier drafts of the manuscript. The authors would also like to thank three anonymous reviewers for their helpful feedback on earlier versions of this manuscript.

AUTHOR CONTRIBUTIONS

K.H. collected the data and samples, and L.P. and A.L. performed the laboratory analysis of hormone concentrations. K.H., L.P., and A.L. wrote the manuscript.

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How to cite this article: Petrullo L, Hinde K, Lu A. Steroid hormone concentrations in milk predict sex-specific offspring growth in a nonhuman primate. *Am J Hum Biol*. 2019;31:e23315. https://doi.org/10.1002/ajhb.23315