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RESEARCH ARTICLE

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Natural variation in fetal cortisol exposure is associated with neonatal body mass in captive vervet monkeys (*Chlorocebus aethiops*)

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Poor maternal condition during gestation is commonly associated with impaired fetal growth in humans and other animals. Although elevated maternal glucocorticoids (GCs) are often implicated as the mechanism of intrauterine growth stunting, the direct contribution of maternal GCs remains unclear because enzymatic conversion of GCs at the placenta may limit the ability of maternal hormones to reach the fetus. Further, because previous studies on gestational stress have often employed synthetic GCs, which cross the placenta unobstructed, it remains unknown whether naturalistic endogenous GC elevations will have similar effects. Here, we use an unmanipulated colony of captive vervet monkeys (N = 18 mother–offspring dyads) to examine how maternal condition predicts maternal gestational hormones, and how these in turn predict neonatal body mass, especially in comparison with total prenatal hormone exposure as measured from neonatal hair. We focused on GCs and dehydroepiandrosterone-sulfate (DHEAS), an additional steroid suspected to influence growth. We found that measures of poor maternal condition (low body mass and low parity) were not associated with elevations in maternal GCs or DHEAS. Furthermore, only fetal GC exposure predicted neonatal body mass, while neither maternal GCs, nor maternal or fetal DHEAS, had any effect. Surprisingly, neonates exposed to higher gestational GCs were larger, rather than smaller at birth. Taken together, these results suggest that GC concentrations within a more naturalistic range may be positively rather than negatively associated with neonatal body mass. Further, the effect of maternal gestational GCs on neonatal mass may be modulated by placental control of GC exposure.

KEYWORDS
birth weight, cortisol, DHEAS, fetal growth, gestation

1 | INTRODUCTION

The maternal gestational environment is widely known to influence offspring prenatal and postnatal development. In particular, poor maternal condition during gestation has been linked to impaired offspring metabolic function, altered brain development, and stunted fetal growth in humans and nonhuman primates (Antonow-Schlorke et al., 2011; Bai, Wong, Bauman, & Mohsin, 2002; Buss et al., 2012; Khashan & Kenny, 2009; Mi et al., 2000). These effects are mediated by fetal exposure to a number of hormones, including cortisol. Cortisol

is the predominant glucocorticoid (GC) steroid hormone found in mammals and is produced in the adrenal cortex as an end-product of the hypothalamic–pituitary–adrenal (HPA) axis (Sapolsky, Romero, & Munck, 2000). Although GCs are best known for their central role in the stress response, they are also important regulators of energy and basic metabolic processes (Sapolsky et al., 2000).

In humans, endogenous maternal cortisol production increases during late gestation (Carr, Madden, MacDonald, & Porter, 1981), and variation in this production has been previously associated with maternal condition. In humans and rodents, reduced food intake and maternal undernutrition consistently leads to elevated circulating concentrations of maternal GCs (Seckl, 2004; Welberg & Seckl, 2008). Because of this relationship, low parity mothers are commonly assumed to produce higher GCs because they face the compounded energetic costs of finishing somatic growth while simultaneously fueling reproduction. Empirical data, however, have failed to consistently support the proposed parity–GC relationship. While a number of studies across multiple species have found that lower parity females exhibit higher GCs (humans: Bleker, Roseboom, Vrijkotte, Reynolds, & de Rooij, 2017; Vleugels, Eling, Rolland, & de Graaf, 1986; rodents: Pawluski, Charlier, Lieblich, Hammond, & Galea, 2009; nonhuman primates: Bales, French, Hostetler, & Dietz, 2005; Dettmer, Rosenberg, Suomi, Meyer, & Novak, 2015; Hinde et al., 2015), other studies have found no relationship (humans: Bolten et al., 2011; nonhuman primates: Altmann, Lynch, Nguyen, Alberts, & Gesquiere, 2004; Kapoor, Lubach, Hedman, Ziegler, & Coe, 2014; Nguyen, Gesquiere, Wango, Alberts, & Altmann, 2008; Starling, Charpentier, Fitzpatrick, Scordato, & Drea, 2010; other mammals: Metrione & Harder, 2011).

Importantly, elevated maternal gestational GCs can reach the developing fetus by crossing the placenta (Seckl, 2001). However, the placenta restricts the amount of GCs that reach the fetal compartment through the actions of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), an enzyme which converts cortisol into the biologically inactive cortisone, resulting in only 10–20% of maternal cortisol reaching the fetal compartment (Murphy, Clark, Donald, Pinsky, & Vedady, 1974). In both humans and nonhuman primates, placental 11β-HSD2 activity increases in parallel with maternal GCs across gestation, potentially neutralizing the effects of increasing maternal GCs (Pepe, Babischkin, Burch, Leavitt, & Albrecht, 1996; Schoof et al., 2001). By limiting the passage of maternal cortisol, placental 11β-HSD2 can prevent two potentially detrimental processes: maternally induced down-regulation of GC production by the fetal adrenal, which can result in impaired organ growth and maturation (Campbell & Murphy, 1977), and fetal GC overexposure, which can result in restricted fetal growth and altered offspring HPA axis function (Bolten et al., 2011; Seckl, 2004).

Further, outside of humans (Field, Diego, & Hernandez-Reif, 2006; Thayer, Feranil, & Kuzawa, 2012), some studies supporting the link between maternal GCs and fetal growth restriction have relied on exogenously administered synthetic GCs (e.g., dexamethasone, betamethasone), which frequently exceed naturally occurring levels of endogenous hormone and can pass across the placenta unobstructed (e.g., Jobe, Newnham, Willet, Sly, & Ikegami, 1998; reviewed in Seckl, 2004). Thus, the growth effects established by these studies may exaggerate the role of endogenous maternal cortisol on neonatal body mass among typical gestations. In support of this hypothesis, two studies on unmanipulated callitrichids found either no relationship (Mustoe, Birnie, Korgan, Santo, & French, 2012) or a positive relationship (Bales, French, & Dietz, 2002) between endogenous maternal gestational GCs and offspring body mass index (BMI) shortly after birth. However, both of these studies considered only maternal GC production and did not measure fetal exposure directly. As some research suggests that the ability of GCs to restrict fetal growth during late gestation is contingent only upon elevated maternal—but not fetal—GCs (Moss, Nitsos, Harding, & Newnham, 2003), direct measurement of fetal GC exposure is critical to determining the relative effects of maternal versus fetal GC production.

Beyond cortisol, the hormone dehydroepiandrosterone-sulfate (DHEAS), the sulfated form of dehydroepiandrosterone (DHEA), may also mediate maternal effects on fetal growth. DHEAS is produced in the adrenal cortex and is a precursor to anabolic androgenic steroids, which drive organ and tissue growth (Longcope, 1996). In the fetus, DHEAS is the primary hormone secreted by the fetal zone of the fetal adrenals (Mesiano & Jaffe, 1997). While fetal DHEAS production increases across gestation and peaks during late gestation (Oh et al., 2006), maternal production of DHEAS decreases across gestation and reaches its lowest point during late gestation, with plasma levels subsequently doubling at parturition (Peter, Dörr, & Sippell, 1994). The degree to which maternal and fetal DHEAS can together or independently drive fetal development is poorly understood, however, as there has been no prior research on transplacental passage of maternal-origin DHEAS to the fetal compartment. Nevertheless, in humans, DHEAS has been implicated in faster postnatal growth in humans (Estourgie-van Burk, Bartels, & Boomsma, 2015; Ibáñez, Potau, Marcos, & de Zegher, 1999). Yet DHEAS is also thought to have a number of anti-GC properties, potentially counter-acting
GC-mediated effects (Kalimi, Shafagoj, Loria, Padgett, & Regelson, 1994; Muller, Hennebert, & Morfin, 2006), including effects on growth. These potentially contradictory effects provide strong arguments for measuring GCs and DHEAS in tandem in hopes of gaining a more comprehensive, "net-effect" interpretation of the relationship between GCs and developmental outcomes (de Bruin et al., 2002; Mocking et al., 2015).

In this study, we aim to address the role of maternal gestational GCs and DHEAS as drivers of fetal growth by measuring hormones in hair collected shortly after parturition from 18 mother–offspring dyads in a breeding colony of captive, socially housed vervet monkeys *(Chlorocebus aethiops)*. Prior studies on this population have utilized hair hormone concentrations to explore developmental patterns of endocrine function (Laudenslager, Jorgensen, & Fairbanks, 2012) and stress-related changes in HPA axis function (Fairbanks et al., 2011). Unlike samples such as blood and saliva, which capture acute changes in endocrine function, hair sampling represents a more integrated measure, as hormones are slowly incorporated into hair over an

extended period of time (Russell, Koren, Rieder, & Van Uum, 2012). Furthermore, because fetal monkey hair begins growing approximately 2 months prior to parturition (Schultz, 1937), neonatal hair hormones represent a cumulative a measure of hormone exposure (including maternal and fetal sources) during late gestation (Kapoor et al., 2014).

Our study has several aims. First, we investigate whether maternal characteristics (specifically, body mass and parity) in female vervets are associated with concentrations of maternal hair cortisol. We predict that lighter and lower parity females will exhibit higher concentrations of hair cortisol. Next, we compare maternal and neonatal hair cortisol concentrations and determine which is predictive of neonatal body mass. If maternal hormones are driving variation in neonatal body mass, we expect that maternal hormone production will correlate with fetal hormone exposure, and that maternal hormones, in addition to neonatal hair hormone concentrations, will predict neonatal mass. However, if fetal physiological strategies (endogenous hormone production and placental conversion) are important modulators of the effects of maternal GCs on neonatal mass, maternal hair GCs may not predict fetal hair GCs, and fetal GC exposure is expected to be the sole driver of neonatal mass. Following previous studies, we predict specifically that elevated neonatal hair cortisol restricts fetal growth as measured by neonatal body mass. Given the apparent growth-promoting and anti-GC properties of DHEAS, we hypothesize that DHEAS will also be associated with maternal characteristics and neonatal body mass, but make no specific predictions about directionality.

2 | METHODS

2.1 | Study site and population

Subjects were 18 vervet monkey mother–offspring dyads housed at the Vervet Research Colony (VRC) at the Wake Forest Primate Center in Winston-Salem, North Carolina. Vervet monkeys are highly social Old World monkeys that give birth to single offspring and breed annually (Else, Eley, Wangula, Worthman, & Lequin, 1986). Subjects were from eight matrilineal social groups living in enclosures with access to both indoor and outdoor areas. Social groups at the VRC resemble vervet social groups in the wild, with all offspring raised by their mothers, and all females remaining in their natal groups for life. In both captivity and in the wild, vervet monkeys exhibit strict matrilineal dominance hierarchies where high ranking individuals have priority of access to both space and resources (Fairbanks, 1980; Whitten, 1983). The adult females in our cohort ranged in body mass from 3.7 to 7.0 kg (mean ± SE = 5.1 ± 0.21 kg), ranged in parity from giving birth to their 1st through 9th offspring during the current study, and ranged in age from 3.6 to 19.1 years (mean ± SE = 9.6 ± 0.99 years; Table 1). All females gave birth through unassisted vaginal deliveries between June 18, 2017 and August 27, 2017 after approximately 5.5 months long gestations. Neonates ranged in body mass from 0.28 to 0.43 kg (mean ± SE = 0.35 ± 0.04 kg).

2.2 | Hair sampling and body mass measurements

The research presented in this manuscript adhered to the American Society of Primatologists Principles for the Ethical Treatment of Non-Human Primates. All animal use procedures for this study were approved by the Institutional Animal Care and Use Committee of each institution.

Hair and body mass measurements were collected from both mothers and offspring from May 2017 to November 2017, during routine veterinary examinations that took place within 2–5 days after parturition (mean = 3.78 days). Adult females and their offspring were temporarily removed from their social groups for sampling. Adult females were lightly sedated with 8–10 mg/kg ketamine hydrochloride administered intramuscularly and offspring were briefly separated from their mothers for sampling. Body mass measurements from adult females and offspring were then collected. From adults, the entire length (mean ± SE: 4.59 ± 0.19 cm, range = 3.11–6.58 cm) of hair was shaved using commercial electric clippers from a 4 × 4 cm patch on the upper back between the shoulder blades. From offspring, the entire length (mean ± SE: 1.19 ± 0.07 cm, range = 0.75–1.69 cm) of hair was shaved from a 2 × 2 cm patch at the posterior vertex region behind the neck. After the procedure, females recovered together with their infants in individual cages before being returned to their social group. Adult females were subject to an additional hair sampling at 4 months postpartum as part of another study, in which the same patch of hair was shaved from 14 of the originally sampled adult females to determine average hair growth rate. Four females were not resampled as they were not included in the second study. Hair samples were placed into small aluminum foil pouches inside of individual plastic bags and stored at room temperature before being shipped to Stony Brook University for analysis.

2.3 | Hormone assays

To capture maternal hormone production over the last 2 months of gestation, which parallels the period of time fetal monkey hair begins to grow (Schultz, 1937), maternal hair was trimmed such that only 1.8 cm of hair from the proximate end of the shaft (representing the last ~2 months of gestation) was retained for further analysis. This was based on the average monthly hair growth rate calculated for adult females (0.90 cm/month, $N = 14$, range = 0.63–1.26 cm), a method commonly used in studies of hair hormones in humans (Stalder et al., 2012; Massey et al., 2016; Romero-Gonzalez, Caparraos-Gonzalez,

TABLE 1 Descriptive statistics relating to maternal and neonatal metadata

	Mean	SE	Range
Parity	4.94	2.29	1–9
Maternal age (years)	9.57	0.99	3.6–19.1
Maternal mass (kg)	5.12	0.21	3.7–7.00
Neonatal mass (kg)	0.35	0.04	0.28–0.43

Gonzalez-Perez, Delgado-Puertas, & Peralta-Ramirez, 2018). Processing of hair samples for both hormones followed a previously published protocol for the extraction of cortisol from small samples (Meyer, Novak, Hamel, & Rosenberg, 2014). First, hair was washed twice in isopropanol (>99% purity) to remove any external contaminants and left to dry for a minimum of 4 days. Dried hair was then placed into a reinforced microcentrifuge tube along with three 3.2 mm chrome steel beads and ground using a bead beater (Mini Beadbeater-1, BioSpec Products, Inc.) at 4,200 rpm for 3 min. Once ground, 1.5 ml of methanol (>99% purity) was added to the tube and the sample was left to incubate on a shaker with gentle rotation at 160 rpm for 24 h. At the end of the incubation, the tube was centrifuged at 10,000 rpm for 5 min to pellet the powdered hair. The supernatant (methanol containing extracted hormone) was then transferred to a new tube and frozen at −80 °C. On the day of the assay, samples were removed from the freezer, transferred to glass culture tubes (200 µl for cortisol, 250 µl for DHEAS), and dried down under nitrogen gas in a 37 °C water bath. Dried samples were then reconstituted in buffer (250 µl for cortisol, 250 µl for DHEAS; Salimetrics, LLC) before being run in duplicate on assay (25 µl cortisol, 100 µl DHEAS).

Serial dilutions of pooled hair extract were parallel to the standard curves for both cortisol and DHEAS assays. Accuracy was evaluated by spiking the kit standards with a pooled sample of low hormone concentration and running these spiked standards in quadruplicate to determine recovery. Average recovery for the spiked cortisol and DHEAS were 97 ± 6.61% ($N = 6$) and 96 ± 2.2% ($N = 5$), respectively. Pooled samples were included as controls in addition to those provided by commercial kits. The inter-assay coefficients of variation (CVs) for the cortisol assay ($N = 4$) were 3.8% (high pool), 1.6% (low pool), 1.2% (high control), and 3.5% (low control). For the DHEAS assay ($N = 4$), the inter-assay CVs were 9.0% (high pool), 1.9% (low pool), 0.3% (high control), and 1.7% (low control). The mean intra-assay CV was 5.4% for the cortisol assay ($N = 4$) and 7.1% for the DHEAS assay ($N = 4$).

2.4 | Statistical analyses

Hair hormone concentrations are presented here as pg/mg of hair (Davenport, Tiefenbacher, Lutz, Novak, & Meyer, 2006). Hormone concentrations and neonatal body mass were normally distributed upon evaluation with Shapiro–Wilk tests and so remained untransformed for linear modeling. First, two linear regressions were used to examine the relationship between maternal characteristics and maternal hair hormone concentrations. Maternal parity and body mass were included as predictor variables in both models, with hair cortisol as the dependent variable in the first model and DHEAS as the dependent variable in the second. Maternal parity and maternal age were strongly correlated ($R = 0.77$, $p < 0.001$), thus to avoid multicollinearity, parity rather than age was included in linear models as it is a more comprehensive measure of reproductive experience than age per se. Next, correlations between maternal and neonatal hair hormone concentrations were tested using the Pearson's correlation coefficient for continuous data. Finally, to examine the independent effects of maternal and neonatal hormone concentrations on neonatal body mass, two linear regressions were performed: the first included maternal hormone concentrations as predictor variables and neonatal body mass as the dependent variable, and the second included neonatal hormone concentrations as predictor variables and neonatal body mass as the dependent variable. Maternal and infant hair hormones were included in separate models to retain power. Both models included neonatal age in days as an additional variable to control for potential differences in body mass based on sampling date. Two individuals were excluded from the body mass models as they had very low birth weights. However, these data points were included in corresponding plots as it is unclear whether their outlier status reflects methodological error or biologically relevant differences. All analyses were performed in R v. 3.2.3 (R Core Team, 2015) using the base package with significance set at $p \leq 0.05$. Effect sizes for linear models were computed using Cohen's f^2 (Selya, Rose, Dierker, Hedeker, & Mermelstein, 2012). Residual plots were generated using the package visreg (Breheny & Burchett, 2016).

3 | RESULTS

Maternal body mass was not associated with maternal hair cortisol concentrations, while parity was positively, rather than negatively associated with maternal hair cortisol (estimate ± SE: −8.72 ± 7.29, $p < 0.05$, $N = 18$, $f^2 = 0.35$, Figure 1). Neither parity nor body mass predicted maternal hair DHEAS concentrations. Maternal hair cortisol was not correlated with neonatal hair cortisol ($R = 0.16$, p = ns; Figure 2). However, concentrations of maternal hair DHEAS and neonatal hair DHEAS were correlated ($R = 0.50$, $p < 0.05$; Figure 2).

We also found no relationship between maternal concentrations of either hormone and neonatal body mass. Neonatal hair cortisol concentrations positively predicted neonatal body mass (estimate ± SE: 1.02e-04 ± 4.24e-05, $p < 0.05$, $N = 16$, $f^2 = 0.71$; Figure 3). Finally, there was no relationship between neonatal DHEAS and neonatal body mass.

4 | DISCUSSION

Our results represent some of the first data on how unmanipulated variation in maternal condition predicts maternal gestational GCs and how maternal gestational GCs in turn predict fetal GC exposure and fetal growth. Although we predicted that low parity and low body mass mothers would have the highest hair GC concentrations, we found no relationship between maternal body mass and GCs, and a positive rather than negative relationship between parity and GCs. We also found that maternal GCs were unassociated with neonatal hair GCs or neonatal body mass; however, neonatal hair GCs were positively predictive of neonatal body mass. These results are consistent with the hypothesis that prenatal GC exposure contributes to fetal growth, but raise questions about the consistency of body mass and parity as mediators of maternal GCs, the contribution of maternal GCs to

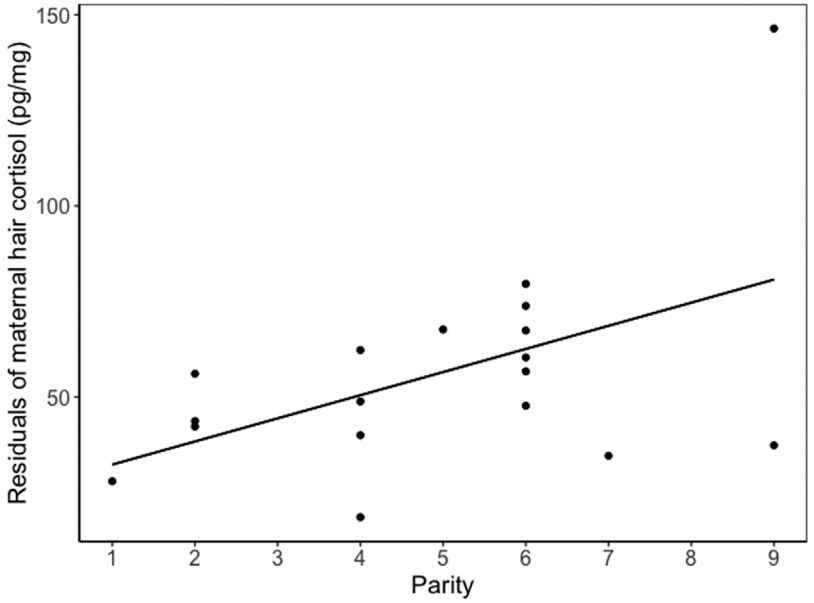

FIGURE 1 Relationship between parity and maternal hair cortisol concentrations (pg/mg) (points = individual data; line = linear regression line between the variables in question; $R^2 = 0.23$)

neonatal GC exposure, and the directionality of the relationship between prenatal GCs and growth. In terms of DHEAS, we found that maternal and neonatal hair DHEAS concentrations were positively correlated, but there was no relationship between DHEAS and maternal characteristics or neonatal body mass. Thus, despite being correlated with maternal DHEAS, fetal DHEAS exposure appears uninvolved in fetal growth during late gestation.

4.1 | Cortisol and maternal condition

Our finding that maternal cortisol was unrelated to maternal body mass may be explained by stable nutritional conditions associated with captivity. Although previous research has shown that food restriction increases GC production in humans and rodents (Seckl, 2004; Welberg & Seckl, 2008), variation in body mass may have been too small among our study subjects to capture a significant relationship. Indeed, none of

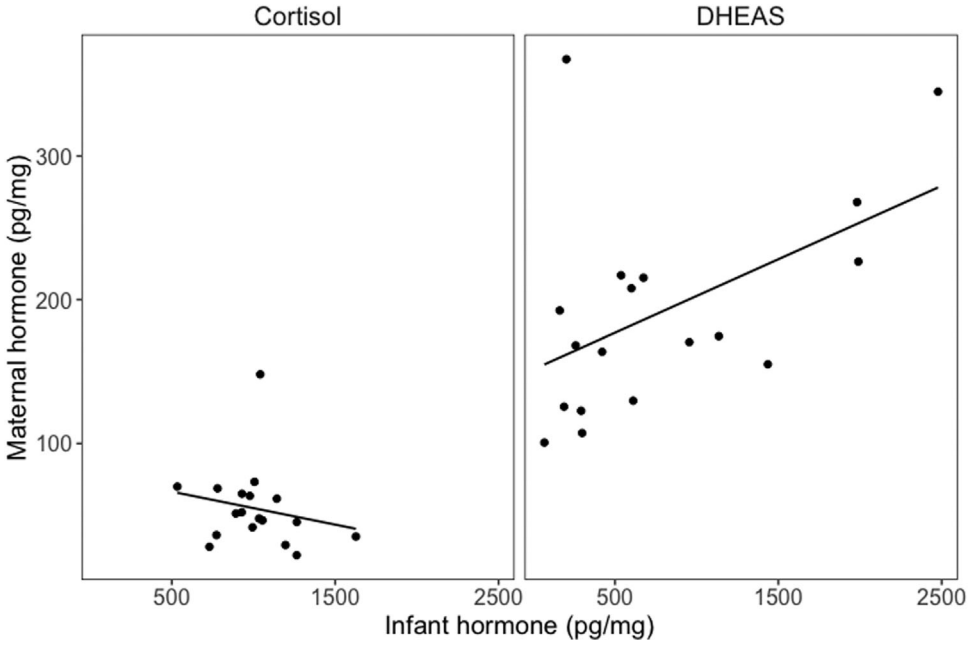

FIGURE 2 Relationship between maternal and neonatal hair hormone concentrations (pg/mg) (points = individual data; line = linear regression line between the variables in question; cortisol $R = 0.16$; DHEAS $R = 0.50$)

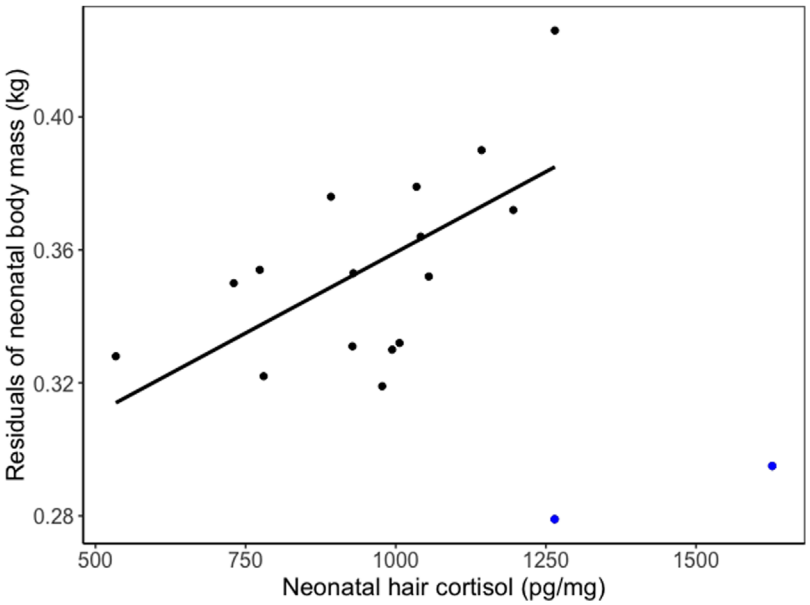

FIGURE 3 Relationship between neonatal hair cortisol concentrations (pg/mg) and neonatal body mass (kg) (points = individual data; line = linear regression line between the variables in question; blue points = outliers not included in linear regression model; $R^2 = 0.48$)

our subjects were categorized as clinically undernourished or overweight and thus may not exhibit phenotypes as extreme as those characterized in prior studies (e.g., Seckl, 2004; Welberg & Seckl, 2008). It is therefore possible that maternal body mass effects on GCs only become pronounced when undernourishment extends beyond a critical threshold (e.g., Romero & Wikelski, 2010).

Our finding that lower parity females exhibited lower, rather than higher, hair GCs may also warrant further explanation. On the one hand, these results may suggest that low parity is not consistently associated with greater maternal physiological stress (e.g., Altmann et al., 2004; Kapoor et al., 2014). However, our finding of a positive relationship rather than no relationship between the two variables may suggest other influences. First, because we examined maternal parity as a continuous rather than a categorical variable (primiparous vs. multiparous), our study may be less likely to account for the differences in energetic and social stress faced by experienced versus inexperienced, particularly first-time, mothers. For example, Dettmer et al. (2015) found that multiparous females, including second-time mothers, had lower GC concentrations than primiparous females (but see Hinde et al., 2015 for continuous relationship). Unfortunately, we were unable to dichotomize parity because our sample included only one primiparous female. Second, because parity was positively correlated with age in the present study, our results may largely reflect age- rather than parity-related GC patterns. In both humans (Lupien et al., 1998; Lupien et al., 1994) and nonhuman primates (Dettmer, Novak, Meyer, & Suomi, 2014; Fourie, Jolly, Phillips-Conroy, Brown, & Bernstein, 2015; Laudenslager et al., 2012; Sapolsky & Altmann, 1991), adult cortisol concentrations become significantly higher during later life, a transition which occurs around at ~12 years of age in baboons (Fourie et al., 2015), and ~15 years of age in macaques (Dettmer et al., 2014), comparable to the age of older females in the present study. Thus age-related increases in GCs associated with senescence (Sapolsky & Altmann 1991) may indeed explain our findings.

4.2 | Mother–offspring cortisol concentrations and fetal growth

Despite a number of studies that have examined the role of maternal GCs on offspring development, we found a lack of correlation between maternal hair GCs during the third trimester of pregnancy and neonatal hair GCs, a result that is consistent with two other studies in humans (Hoffman, D'Anna-Hernandez, Benitez, Ross, & Laudenslager, 2017; Romero-Gonzalez et al., 2018). Collectively, these studies suggest that maternal cortisol production does not directly correlate with offspring cortisol exposure. Given that fetal and maternal tissue together contribute to the placenta, the local conversion of maternal-origin cortisol to biologically inactive cortisone by placental 11β hydroxysteroid dehydrogenase type 2 (11β-HSD2) may be one mechanism by which fetuses exert some control over prenatal GC exposure and its potential downstream effects.

Despite the lack of correlation between maternal and offspring hair GCs, we found that infant hair GCs positively predicted neonatal body size. This pattern runs counter to observational studies on humans (Thayer et al., 2012; Field et al., 2006), as well as experimental research investigating the influence of synthetic GCs on neonatal body mass (Jobe et al., 1998). Although results from such studies likely reflect extreme types of physiological stress (associated with modern human lifestyles or captive environments), experimental studies are particularly problematic because synthetic GCs are often administered at exaggerated dosage levels and can pass unrestricted across the placenta. Within this magnified range of synthetic GC administration, GCs appear to have a negative relationship with neonatal mass. By

contrast, most of the data in our study may represent the lower end of GC variation, which appears to have a positive, rather than a negative relationship with fetal growth. Similar results have been found in unmanipulated studies of wild lion tamarins (Bales et al., 2002), suggesting that the GC–growth relationship may vary depending on the range of hormone concentration in question.

Intriguingly, the two individuals in our study who were excluded from the neonatal body mass model were characterized by very low body mass as well as the highest hair cortisol concentrations (Figure 3). These data may suggest that past a particular threshold, the positive, growth-promoting effects of gestational GC exposure begin to restrict growth. In support of this hypothesis, a number of GC-mediated effects are known to follow similar inverted U-shaped curves (Joëls, 2006; Mateo, 2008; Sapolsky, 2015; Schilling et al., 2013), where too little or too much GC exposure have similar effects. We hypothesize that the effects of fetal GC exposure on fetal growth during late gestation may be yet another example of a U-shaped relationship. Future studies that examine neonatal body mass in relation to a larger range of GC concentrations will be necessary to test this hypothesis.

4.3 | DHEAS, maternal characteristics, and fetal growth

Similar to our prediction for maternal GCs, we expected to find an effect of maternal condition on DHEAS concentrations. However, we found no relationship between the two variables, suggesting that maternal DHEAS production may be buffered against variations in maternal mass and is independent of prior reproductive experience and/or age. Interestingly however, maternal and neonatal hair DHEAS were positively correlated, indicating perhaps that placental DHEAS permeability is high. However, this hypothesis is purely speculative as there has been no previous research on the transfer of maternal-origin DHEAS across the placenta. Furthermore, because the fetus produces approximately 60% of late gestation DHEAS (Chatelain, Dupouy, & Allaume, 1980; Sinha, Halasz, Choi, McGivern, & Redei, 1997), it is possible that the positive correlation we found between maternal and fetal DHEAS was driven by fetal, not maternal production.

Finally, we found no relationship between maternal DHEAS, fetal DHEAS exposure, or neonatal body mass, suggesting that DHEAS is not a significant contributor to fetal growth during late gestation. Notably, late gestation DHEAS (of which 60% is of fetal origin) is largely converted to estrogen by the placenta in order to facilitate parturition (Kaludjerovic & Ward, 2012; Walsh, Stanczyk, & Novy, 1984). Thus the placenta rather than the fetus may be the target of the majority of DHEAS action during this time. Given research documenting a role of DHEAS in accelerated postnatal growth (Estourgie-van Burk et al., 2015), it is possible that the effects of DHEAS on growth are greater during postnatal rather than prenatal life. Nevertheless, because data on non-GC hormones and their potential effects of offspring prenatal development remain rare, we encourage more research on the potential role of DHEAS, particularly within the range of natural variation in maternal and fetal production.

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