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Differential Relationships Between Chronic Hormone Profiles in Pregnancy and Maternal Investment in Rhesus Monkey Mothers With Hair Loss in the Neonatal Period

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Abstract

Hair loss is commonly used as an indicator of well being in primate facilities, yet it has been shown to also occur in otherwise healthy pregnant and postpartum females. There is significant variability in the incidence of hair loss during these important developmental periods, reasons for which remain unclear. We studied female rhesus monkeys (*Macaca mulatta*, $n = 47$) with and without hair loss in pregnancy/postpartum. We hypothesized that, similar to previously published reports, pregnancy would result in an increased likelihood of hair loss, and that hair loss would be correlated with higher hair cortisol concentrations (HCCs). We further hypothesized that hair loss among pregnant females is related to differential maternal investment. We studied a subset of monkeys ($n = 26$) from mid-to-late pregnancy through peak lactation, some of which exhibited hair loss in the perinatal period ($n = 15$), and some of which did not ($n = 11$). We examined fetal measurements, infant birth weight, infant growth rate, and milk yield volume (MYV) in the first 30 days as indices of investment. We found that pregnant monkeys showed a greater incidence of hair loss across the study year ($\chi^2_{(2)} = 6.55$, $P = 0.038$), and that mothers with hair loss had significantly higher HCCs in pregnancy than those without ($F_{(2,28)} = 3.8$, $P = 0.017$, $hp^2 = 0.21$). HCCs in pregnancy were correlated with severity of hair loss in the neonatal period ($r_{(37)} = 0.42$, $P = 0.008$). Moreover, HCCs in pregnancy were positively correlated with infant birth weight ($r_{(12)} = 0.56$, $P = 0.038$), infant growth rate ($r_{(12)} = 0.64$, $P = 0.014$), and MYV ($r_{(11)} = 0.85$, $P < 0.001$) for alopecic but not non-alopecic mothers. These mothers did not differ in fetal measurements, infant birth weight/growth rate, or MYV. Our results suggest that hair loss in some monkeys, especially during the birthing season, may be a signal of greater physiological stress during pregnancy and differential investment by mothers to their offspring. *Am. J. Primatol.* 79:e22489, 2017.

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Keywords

hair loss; alopecia; pregnancy; infant growth; maternal investment

INTRODUCTION

Hair loss is common in rhesus monkeys (*Macaca mulatta*) in the time surrounding the birthing season, and it is known that pregnant monkeys are at an increased risk for alopecia [Beisner & Isbell, 2009; Vessey & Morrison, 1970]. Hair loss during the birthing season in free-ranging monkeys is described as “seasonal molt” [Vessey & Morrison, 1970], but this type of hair loss differs from that observed in pregnant monkeys in captivity. Our laboratory reported on marked hair loss in rhesus monkey mothers in the period immediately surrounding parturition [Davis & Suomi, 2006; Novak & Meyer, 2009], whereby some mothers show near-complete hair loss near the time of their infant’s birth and regrow full coats of hair over the next few months. However, this pregnancy-related hair loss does not occur in all monkey mothers, reasons for which remain unclear.

Hair loss in the perinatal period is also common in women, with about 30–50% of women experiencing postpartum hair loss [Dawber & Connor, 1971]. The earliest documentations of postpartum hair loss reported the cause as a significant decrease in the percentage of anagen (growing) hairs from 2 to 5 months postpartum [Lynfield, 1960; Schiff & Kern, 1963]. A later study documented telogen effluvium (shedding) as the cause for some women [Murray, 1990]. One study in humans reported that the incidence of postpartum hair loss gradually increased from 2% at 1 month postpartum to 20% at 6 months, then declined [Gjerdingen et al., 1993]. Not every woman experiences this kind of hair loss. Like in non-human primates, the reasons for the large observed individual variability in this phenomenon remain largely unknown.

Because hair loss in captive primates is often used as an indicator of well being [Novak et al., 2015, this issue; Novak & Meyer, 2009], it is of particular interest that in critical periods, such as pregnancy and lactation, some individuals develop hair loss whereas others do not. Given that hair cortisol concentrations (HCCs) have proven to be reliable biomarkers for other indices of well being in both human and non-human primates [Meyer & Novak, 2012; Russell et al., 2012; Staufenbiel et al., 2013], we tested the hypothesis that HCCs were related to hair loss in pregnant rhesus monkeys. Specifically, we predicted that pregnant monkeys with hair loss would exhibit higher HCCs. Additionally, because the marked hair loss around the time of parturition that we previously observed [Davis & Suomi, 2006; Novak & Meyer, 2009] was not present in all mothers, we tested the hypothesis that hair loss during the peripartum period was reflective of differential maternal investment (e.g., differential fetal or postnatal growth, milk production). One possible reason for the observed hair loss in mothers in the neonatal period may be that she is diverting resources toward their infants that would otherwise go toward hair growth/regrowth. We sought to perform exploratory analyses linking hair loss to prenatal (fetal growth as measured by ultrasound) and postnatal (milk yield values and infant growth) measures of maternal investment.

METHODS

All procedures were approved by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Animal Care and Use Committee. This research adhered to the American Society of Primatologists principles for the ethical treatment of animals.

Subjects and Housing

Adult female rhesus macaques ($n = 47$, $\text{mean} \pm \text{SEM} = 8.3 \pm 0.5$ years, range = 5–19) born and reared at the Laboratory of Comparative Ethology at the NIH Animal Center in Poolesville, MD, were studied throughout pregnancy and 3–6 months post-partum in 2013. These monkeys represented our breeding colony of adult female rhesus monkeys, and as such all had the potential to become pregnant; thus, they were included in the current study. Six monkeys were not pregnant, and average parity among the 41 pregnant monkeys was 3.3 ± 0.5 (mean $\pm$ SEM). The 41 pregnant monkeys, 26 kept their infants in the social, mother-peer-reared condition whereas the other infants were nursery reared (see Dettmer et al., 2012, for rearing conditions).

Of the 26 monkeys that reared their infants, 15 were classified as alopecic ($>10\%$ hair loss) and 11 as non-alopecic ($<10\%$ hair loss) near the time of parturition (see “Hair loss,” below). These groups of monkeys did not differ in age (9.1 ± 0.9 vs. 7.8 ± 0.8 years, respectively; $t_{(1)} = 1.04$, $P = 0.32$), or in parity (3.7 ± 0.9 vs. 3.1 ± 0.8 infants, respectively; $t_{(1)} = 0.25$, $P = 0.62$).

All monkeys for this study were socially housed in large indoor/outdoor enclosures with 10–12 other monkeys according to previously published methods for this laboratory [Dettmer et al., 2014], and were fed twice/day (Purina Monkey Chow #5038, St. Louis, MO), with water available ad libitum. Fruits, seeds, and nuts were provided daily for added foraging and nutrition.

All measures recorded during pregnancy (hair loss, hair cortisol, fetal measurements) as well as infant birth weight were used for all pregnant monkeys ($n = 41$). Postnatal measures (infant growth rate, milk yield volume [MYV]) were used only for mothers who reared their infants ($n = 26$). Detailed methods of each measure are described below.

Hair Loss

Photographs were taken of monkeys during routine health exams in April, July, and October 2013 to quantify hair loss. Monkeys were photographed although laying on their left and right sides, as well as in the prone position to obtain a picture of the back of the animal's body. These photographs were rated by two independent experimenters at a separate facility who were blinded to the animals' IDs as well as to the hypotheses for this study. For each monkey, raters scored hair loss as “No” ($<10\%$ hair loss), “Yes” ($10\text{--}50\%$ hair loss), or “Extreme” ($>50\%$ hair loss) based on visual assessment of all three photos. Thus, alopecic monkeys were those that exhibited $>10\%$ hair loss, and non-alopecic monkeys were those that exhibited $<10\%$ hair loss. Inter-rater reliability was achieved at $>90\%$.

Hair Sampling and Cortisol Assay

Hair samples were collected by shaving the nape of the neck using commercially available pet grooming clippers. Two-square inch samples were collected at the same time photographs were taken, with the same sampling area shaved at each time point. Thus, cortisol concentrations in these samples reflected chronic steroid deposition over the previous time period (specifically three months in the case of the July and October samples; and 3–6 months for the April sample, as the monkeys were shaved in October 2012 and in April, July, and October 2013) [Davenport et al., 2006]. Rhesus monkey gestation is approximately 165 days, though in our colony average gestation is closer to 170 days (unpublished data). In rhesus monkeys, peak lactation occurs between 3 and 4 postnatal months and tapers significantly by 6 months, with full weaning usually occurring by 1 year of age when the next sibling is born [Fooden, 2000; Hinde et al., 2009].

By the July health exam, all pregnant monkeys had delivered their infants, though some had just delivered days before the exam. Based on the birth date of the infant, for the pregnant monkeys, the April samples were collected on average in mid-to-late gestation (“pregnancy”; range: 46–182 gestational days; mean $\pm$ SEM = 124.7 ± 5.8 gestational days), the July samples were collected on average around 2 months postpartum (“perinatal”; range: 144–287 gestational days; mean $\pm$ SEM = 230.2 ± 5.8 gestational or mean $\pm$ SEM 60.1 ± 8.7 postnatal days), and the October samples were collected on average during peak/late lactation (“lactation”; range: 80–221 postnatal days; mean $\pm$ SEM 158.9 ± 5.8 postnatal days).

Hair samples were stored in a freezer (-20 or -80°C) in aluminum foil pouches until processing according to previously published methods [Davenport et al., 2006; Meyer et al., 2014]. Briefly, hair samples were weighed and washed twice with 5 mL of isopropanol to remove external contaminants, then air dried in a fume hood. Once completely dry, each sample was ground to a fine powder using a Retsch ball mill (model MM200). Powdered hair was weighed and placed into a 2.0 mL Eppendorf microcentrifuge tube for extraction.

Methanol (1 mL) was added to the powdered hair and the tubes were slowly rotated for 18–24 hr. Samples were centrifuged for 1.5 min at 14,000 RPM in a microcentrifuge to pellet the powder, and 0.6 mL of the methanol extract was placed into a 1.5 mL Eppendorf tube, after which the methanol was evaporated using a Savant Speedvac with refrigerated vapor trap. The cortisol was reconstituted with 0.4 mL diluent from the assay kit. Extracts were either placed in freezer or assayed immediately. Extracts were analyzed in duplicate for cortisol by enzyme immunoassay (Salimetrics, State College, PA) to determine HCCs. The intra-assay coefficient of variation was 1.4% and inter-assay coefficient of variation was 5.7%.

Fetal Measurements

Routine ultrasounds were performed at a mean $\pm$ SEM 81.4 ± 2.1 days gestation (range: 65–130) during monthly exams to confirm pregnancy by the veterinarian in January and February. The veterinarian estimated gestational age based on ultra-sound measurements of

the fetus. For this study, biparietal distance and femur length were used as indices of fetal growth.

Milk Yield Volume

Neonatal assessments routinely occurred on postnatal days 7, 14, 21, and 30, and mothers were randomly assigned to have milk samples collected on postnatal days 7 and 21 ($n = 11$ mothers), or 14 and 30 ($n = 15$ mothers). Infants and mothers were temporarily removed from their social group at 1100 hr, and infants were temporarily removed from their mothers at 1115 hr for the neonatal assessment [Dettmer et al., 2015; Schneider & Suomi, 1992]. Mothers were sedated to allow for removal of the infant and were outfitted with soft woven jackets at 1130 hr. This jacket remained on the mother until 1400 hr to allow for contact comfort between the mothers and infants, which were reunited at 1230 hr, without allowing the infants to nurse. Milk collection began between 1345 and 1400 hr, thus allowing for at least 2.5 hr of milk accumulation in the mammary gland [Hinde, 2007; Hinde et al., 2009]. Mothers were given a light sedative (4–5 mg/kg ketamine HCl, IM) to allow milk collection to be performed. According to previously published procedures [Hinde, 2007; Hinde et al., 2009], mothers' nipples were wiped clean with alcohol swabs, and mothers were then given 0.05 mL/kg oxytocin to stimulate milk letdown. Milk collection began immediately by manually mimicking natural neonatal nursing using the thumb and index finger combined with gentle squeezing [Hinde et al., 2009]. Milk was collected directly into 15 mL collection tubes until both mammary glands were fully evacuated. Samples were quickly centrifuged, aliquoted into 2 mL cryotubes, and frozen at -80°C for later analysis.

To calculate MYV, we weighed the collection tubes before and after milk collection and calculated the difference in weight. This weight in grams is a reliable measure of milk yield [Hinde et al., 2009]. For this study, average MYV across the two collection times (i.e., days 7/21 and 14/30) were used for analysis.

Infant Growth

Infant growth was assessed by routine weigh-ins at or within 3 days of birth and during the neonatal assessments on days 14 and 30. For this study, growth rate was determined by calculating the difference between day 30 weight and birth weight, in grams, and dividing by the number of days in between the two measures to yield a growth rate in grams/day.

Data Analysis

Analyses for all monkeys

Photos were available for 32 of the 47 monkeys in April 2013; 3 of 6 non-pregnant females did not have photos available and 12 of 41 pregnant females did not have photos available. Of the pregnant females missing photos in April, three had infants that were nursery reared and the other nine kept their infants (Table I). Photos for all monkeys were available in July and October. Fetal measurements were available for all 41 infants.

Because only 4 monkeys were categorized with “severe” alopecia in April 2013, and only one was “severe” in October 2013, for analyses “yes” and “severe” were combined such that

hair loss was coded simply as “yes” (alopecia) or “no” (control). χ^2 were performed for pregnant and non-pregnant monkeys separately to determine whether the proportion of monkeys with and without hair loss differed across the year based on pregnancy status.

HCCs were available for all monkeys at all time points. These values were log transformed to meet assumptions of normality. We used multivariate ANOVA to analyze HCCs at each time point for alopecia and control pregnant monkeys, as this test allowed us to control for gestational age at sampling. Partial correlation was used to determine the relation between HCCs and severity of hair loss at each time point although controlling for gestational age at hair sampling (for this measure, the original “no,” “yes,” “severe” ratings were retained). Controlling for gestational age at ultrasound, we used multivariate ANOVA to determine whether alopecic and non-alopecic monkeys in pregnancy differed on fetal measurements, since these measurements were taken closest to the pregnancy time point.

Analyses for mothers keeping their infants

For these 26 monkeys, independent samples t tests were employed to examine whether alopecic and non-alopecic monkeys (based on hair status at the perinatal time point) differed in infant birth weight, infant growth rate, and MYV. The perinatal hair ratings were calculated closest to these dependent measures.

The aim of this study was to determine whether maternal HCCs were related to MYV and infant growth rate for mothers with and without hair loss in the perinatal period. Thus, we excluded nursery-reared monkeys owing to their lack of dependence on mother’s milk. We compared alopecic and nonalopecic monkeys based on the ratings at the perinatal time point, as the dependent variables were taken closest to this time and also because by this time, the greatest proportion of mothers showed alopecia. Indeed, 6 mothers that did not show hair loss in pregnancy went on to develop it by the perinatal period, and all 6 of these gave birth between these two time points, thus supporting the notion that hair loss in pregnant monkeys develops closer to parturition. We tested the hypothesis that mothers with hair loss have higher HCCs in pregnancy, which in turn is associated with differential investment. Thus, controlling for gestational age at the time of hair sampling, partial correlations were used to determine whether alopecic and nonalopecic differed in the relationship between HCCs in pregnancy and MYV, infant birth weight, and infant growth rate.

IBM SPSS v22 was used for all analyses, with $P < 0.05$ considered statistically significant. Wherever significant effects were revealed for ANOVAs or t tests, effect sizes are also reported.

RESULTS

Rates of Hair Loss Across Pregnancy and Lactation

As expected, pregnant monkeys exhibited significant changes in hair loss across the study period, with more monkeys having hair loss in the perinatal period ($\chi^2_{(2)} = 6.55$, $P = 0.038$; Fig. 1), whereas non-pregnant monkeys showed no change in the proportion of animals with hair loss over the study period ($\chi^2_{(2)} = 2.5$, $P > 0.2$; Fig. 1).

The rates of hair loss from the pregnancy to perinatal periods were fairly consistent. Two of the three non-pregnant females that had photos in April showed no change in the July, whereas one changed from “no” to “yes” for hair loss. For pregnant females, six changed from “no” to “yes,” and five changed from “yes” to “no” (and these all gave birth soon after the pregnancy sampling period [April], thus having sufficient time for hair regrowth by the perinatal period [July]. Eighteen pregnant females showed no change (seven retained their “no” hair loss status, and 11 retained their “yes” status).

HCCs and Hair Loss in Pregnant Monkeys

Pregnant monkeys with alopecia had significantly higher HCCs than non-alopecic monkeys in pregnancy ($F_{(1,28)} = 3.8$, $P = 0.017$, $h_p^2 = 0.21$; Fig. 2). No significant differences were revealed for other time points. HCCs in pregnancy were positively correlated with severity of hair loss in pregnancy ($r_{(25)} = 0.44$, $P = 0.021$) and in the perinatal period ($r_{(37)} = 0.42$, $P = 0.008$; Fig. 3). No other significant correlations were revealed.

Fetal Measurements, MYV, and Infant Measures

Alopecic ($n = 15$) and non-alopecic ($n = 11$) mothers in pregnancy did not differ on fetal measurements of biparietal distance ($F_{(1,29)} = 1.78$, $P > 0.10$) or femur length ($F_{(1,29)} = 1.11$, $P > 0.10$). They also did not differ in MYV ($F_{(1,23)} = 0.14$, $P > 0.10$), birthweight ($F_{(1,23)} = 0.01$, $P > 0.10$), or infant growth rate ($F_{(1,23)} = 0.02$, $P > 0.10$).

HCCs, MYV, Infant Birth Weight, and Infant Growth Rate

Only alopecic mothers showed significant correlations between HCCs in pregnancy and infant birth weight ($r_{(12)} = 0.56$, $P = 0.038$), infant growth rate ($r_{(12)} = 0.64$, $P = 0.014$), and MYV ($r_{(11)} = 0.85$, $P < 0.001$). Non-alopecic mothers showed no significant correlations between these measures (birth weight: $r_{(7)} = 0.22$, $P > 0.10$; growth rate: $r_{(6)} = 0.16$, $P > 0.10$; MYV: $r_{(7)} = -0.001$, $P > 0.10$).

DISCUSSION

This study examined the change in hair loss across pregnancy and lactation in rhesus monkeys and associated changes in HCCs, with further exploration into the relationships between long-term HPA axis activity during pregnancy and indices of maternal investment in monkeys with and without hair loss. Our study yielded several novel findings of particular interest that may in part explain some of the individual variability in hair loss during pregnancy and the postpartum period in captive primates.

We found that the incidence of hair loss increased significantly in the weeks immediately postpartum, as has been reported previously for both monkeys [Davis & Suomi, 2006] and humans [Dawber & Connor, 1971; Gjerdengen et al., 1993]. Although photos/ratings were not available for 12 of the 41 pregnant monkeys in pregnancy, we can be certain that pregnancy results in an increased incidence of hair loss as inspection of the data on a case-by-case basis revealed that 6 pregnant females changed from no hair loss (<10% hair loss) to alopecia (>10% hair loss) between the pregnancy (April) and perinatal (July) periods, and the 5 females that changed from alopecia to no hair loss between these periods all gave birth

soon after the pregnancy time point. Thus, they likely had ample time to regrow hair by the perinatal time point. As seems to be common in about one-third to one-half of human pregnancies [Dawber & Connor, 1971], our rhesus monkeys show increased incidence of hair loss at or immediately following parturition.

We also found that monkeys that exhibited hair loss in the perinatal period had higher HCCs in pregnancy. These findings suggest that high circulating levels of glucocorticoids may play a part in subsequent hair loss in pregnant females, a notion that is supported by evidence of hair loss in individuals with hyperadrenocorticism (i.e., Cushing syndrome; Frank, 2006; Kimura, 2004; Peterson & Kintzer, 1997).

Notably, only about half of our monkeys exhibited hair loss in both pregnancy and the perinatal period. To examine a possible mechanism for the individual variability observed in hair loss among pregnant monkeys, we examined whether hair loss in mothers is correlated with differential investment in fetal and infant growth. We found no differences in any of these measures when simply comparing alopecia and non-alopecic groups. However, we did find significant relationships between HCCs and indices of postnatal maternal investment for alopecic monkeys only, such that mothers with alopecia and higher HCCs in pregnancy also had infants that were born heavier and grew faster. Remarkably, these mothers also produced more milk than alopecic mothers with lower HCCs. However, alopecic and non-alopecic mothers did not differ in measures of fetal growth, and HCCs in pregnancy were not correlated with fetal measurements (data not shown). Thus, it appears that many mothers with hair loss in the perinatal period may be diverting resources to their newborns especially in the first month of life to encourage infant growth, and this differential investment may be the cause for the observed hair loss in these mothers. Furthermore, HCCs in pregnancy may be driving this differential investment, as HCCs in pregnancy were significantly correlated with the severity of hair loss in the perinatal period.

These findings support the notion of prenatal cortisol programming [Glover, 2015; Glover et al., 2010; Welberg & Seckl, 2001], and are in agreement with studies in rodents showing that glucocorticoids are necessary for lactogenesis [Feng et al., 1995; Neville et al., 2002], although they contradict the majority of human studies that show that higher prenatal cortisol levels are associated with poorer infant birth weight and cognition, among other measures [Bergman et al., 2010; De Weerth et al., 2003; Diego et al., 2006]. However, other non-human primates have shown a positive correlation between maternal cortisol in infant birth weight [Bales et al., 2002]. A major difference between the human studies and the present one is sampling method: other studies relied on “point” samples of cortisol, that is, mother’s blood plasma or amniotic cortisol, whereas we relied on maternal HCCs, a long-term measure. Although it is known that maternal plasma cortisol is at least moderately correlated with amniotic cortisol [Murphy et al., 1975], it remains to be determined whether maternal HCCs are actually indicative of fetal exposure to cortisol. The maternal HCCs studied here may simply not reflect fetal or placental sources of glucocorticoid secretion that the growing fetus is exposed to, and clearly validation of this relationship is warranted. Additionally, the higher HCCs in our alopecic mothers may not correspond to the deleteriously high levels of plasma or amniotic cortisol associated with low birth weight in

the human studies. Instead, it is possible that these mothers are within a higher range of normal, although this too remains to be determined.

Maternal HCCs in pregnancy reflect the long-term hormonal secretions of the mother, and perhaps it is these secretions rather than in utero cortisol exposure per se, that program certain downstream aspects of maternal investment, such as milk production and infant growth. Why mothers with hair loss do not appear to invest in fetal growth, but instead invest in their infants after birth, is still unknown. Yet our findings of higher HCCs in alopecic mothers in mid-to-late gestation suggest that signaling for this investment begins before birth, as the hair samples taken in pregnancy reflect accumulated cortisol secretion from the time of conception to mid/late pregnancy.

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Fig. 1.
Pregnant monkeys (right) showed significant changes in rates of hair loss across the study period. * $P < 0.05$.

Fig. 2.

Pregnant monkeys with hair loss had higher hair cortisol concentrations (HCCs) than pregnant monkeys without hair loss in mid-to-late pregnancy. * $P < 0.05$. Note: These results are based on hair loss status in the perinatal period.

Fig. 3. Correlations between hair cortisol concentrations (HCCs) in mid-to-late pregnancy and severity of alopecia in pregnancy (left) and the perinatal period (right).

TABLE I.

Total Numbers of Sample Types Available at Each Time Point

	April (pregnancy)	July (perinatal)	October (lactation)
Photos	32 (3, 29 [*])	47 (6, 41)	47 (6, 41)
Hair samples	47 (6, 41)	47 (6, 41)	47 (6, 41)
Fetal measurements	41 (-, 41)	41 (-, 41)	41 (-, 41)

Numbers in parentheses indicate sample sizes for (non-pregnant, pregnant) female monkeys. -, samples not collected for non-pregnant monkeys.

^{*} 12/41 photos for pregnant monkeys were missing in April; 3 of these offspring were nursery reared and 9 of these offspring were mother reared, thus contributing to the dataset for fetal and infant measurements.