Maternal constraint on fetal growth patterns in the rhesus monkey (Macaca mulatta): the intergenerational link between mothers and daughters

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The gestational experience of a mother can influence the intrauterine environment she provides her own offspring, allowing prenatal events to affect pregnancy outcomes across several generations. Using a multigenerational database, we determined the reproductive consequences for rhesus monkeys descended from small-for-date and large-for-date birth weight matrilines. Both the maternal half-brothers and -sisters of large-for-date infants exhibited enhanced fetal growth, but for small-for-date probands, only the maternal half-sisters experienced significant intrauterine growth constraint. In addition, the growth-restricted females were at higher risk of poor reproductive outcomes in adulthood, and they perpetuated the maternal birth weight pattern by selectively constraining the fetal development of their daughters. Collectively, these findings suggest a mechanism for the intergenerational persistence of suboptimal pregnancy outcomes.

Key words: birth weight/intergenerational trends/intrauterine constraint/Macaca mulatta/reproductive health

Introduction

The relationship between birth weight and subsequent disease in adulthood suggests that the uterine environment can initiate events that last well beyond the fetal period (Barker et al., 1993; Barker, 1994). Maternal undernutrition and exposure to high concentrations of corticosteroid hormones in utero, two factors known to restrict prenatal growth, have been postulated to alter the regulatory set points of the fetal neuroendocrine system and predispose the individual to certain diseases in adulthood (Reinisch et al., 1978; Edwards et al., 1993; Barker, 1994; Langley-Evans et al., 1996; Seckl, 1997). This concept of ‘programming’ also extends to reproductive health, as the mother’s own prenatal experience may influence the uterine environment she provides her offspring, thereby creating a link between her fetal development and the health of the next generation (Hackman et al., 1983; Klebanoff et al., 1984; Emanuel, 1997; Lumey and Stein, 1997; Skjærven et al., 1997). Though the importance of intergenerational factors on infant outcome has been recognized for decades, establishing the association between a woman’s own prenatal environment and her reproductive performance is difficult given the complexity of population-based studies in humans. To improve the characterization of the relationship between fetal development and pregnancy outcome, we examined reproductive data collected from a population of rhesus monkeys (Macaca mulatta) over five generations in captivity.

This primate population is unique in that detailed birth and pedigree records have been compiled on every animal born to this closed breeding colony since it was founded over 40 years ago. Based on these archives, we discovered that the birth weights of rhesus monkeys, like humans, followed a matrilineal transmission pattern, with an infant’s weight being highly associated with those of its mother and its maternal relatives across several generations (Price et al., 1999). Because the care and nutrition provided under laboratory conditions has remained fairly uniform, the observed trends within matrilines were more probably attributable to intrauterine factors characterizing the lineage than to lifestyle differences between families, a confounding factor that often complicates human studies of familial birth weight patterns. Further, we found that improved resource availability in the laboratory versus the feral environment led to larger infants in association with increased maternal pregravid weight and pregnancy weight gain, suggesting that gestational processes may govern the rate of prenatal development by monitoring maternal energy balance. Even more striking, the increase in birth weight was considerably larger for the female offspring and essentially eliminated the typical sexual dimorphism in infant birth weight within four generations. As the daughters provide the uterine milieu for the next generation, a mechanism that adjusts the growth of female fetuses in response to local resources may offer an efficient means for selection toward the optimal birth weight sustainable by the environment.

For our earlier analyses we considered only the data derived from average-for-date (AFD) births. However, women who deliver a large- or small-for-gestational age infant are more likely to produce another such birth and those who were themselves born small-for-date are at greater risk of poor pregnancy outcomes (Bakketeig et al., 1979; Hackman et al., 1983; Klebanoff et al., 1984; Magnus et al., 1997; Skjærven et al., 1997). Thus, we have now extended our analyses to focus on the inheritance patterns and reproductive consequences for small-for-date (SFD) and large-for-date (LFD) monkeys. In addition, as nearly all the first-degree descendants within a lineage were half, rather than full, siblings, we had a novel opportunity to distinguish the maternal from the paternal contributions to the familial birth weight patterns.
Materials and methods

Subjects and housing

The rhesus monkey (Macaca mulatta) is widely used to model human reproductive processes because of its long gestation (5.5 months), predominantly singleton births, and many similarities with human placental and endocrine physiology (Stolte, 1975). Our breeding colony at the University of Wisconsin Primate Laboratory originated in the 1950s with animals imported from India as young adults, although a small chimp group was integrated in the 1970s. The Laboratory is dedicated to studies of non-human primates, and the current colony comprises over 500 rhesus monkeys. Comprehensive breeding, birth, and body weight records have been maintained on every animal, providing extensive information on the dates of conception and birth, pregnancy outcome, parentage, sex, and birth weight for each infant. In recent years, our breeding program has produced 100 infants annually, of which 93% survive beyond the first week. Only singleton infants were included in the analyses (twinning occurs approximately 1:600 births). Viable pregnancies in our sample varied in length from 146 to 184 days, with 90% of all pregnancies ranging between 160 and 177 days with a mean duration of 168.6 ± 0.2 days.

Experimental design (see Figure 1)

Female monkeys were time-mated by housing them with a breeder male during a 4-day period at the time of ovulation. Once conception occurred, females were typically housed individually in stainless steel cages (0.8×0.8×0.8 m) for the remainder of pregnancy. The neonates were first observed between 06.00–07.00 hours, and most (>75%) were weighed on the day of birth. Because infants lost and then regained ~5% of their body weight over the first week of life, birth weights taken beyond the first day were adjusted according to the formula: birth weight = 0.174 x^4 − 3.27 x^3 + 17.786 x^2 − 27.118 x, where x = the number of days after birth that the weight was first recorded. This formula was derived by fitting a polynomial function to the birth weights that were recorded between days 1 and 7 of life. Neonates not weighed within the first week of life (<1%) were excluded from the analyses. These elimination criteria yielded a multigenerational database on 2354 singleton infants (2170 live born, 184 stillborn) born during the last 40 years.

The live-born infants were separated by sex, then categorized according to their gestational ages: ~159, 160–162, 163–165, 166–168, 169–171, 172–174, 175–177, and ≥178 days. We then selected probands with birth weights >1.64 standard deviation units from the mean of their gestational-age-by-sex grouping (i.e. ~lower and upper 5th percentiles). The birth weight of the mothers, fathers, and all known live-born maternal and paternal half-siblings for each proband were identified through pedigree records. The birth weights of the remaining 382 live-born animals and their parents (243 mothers, 81 fathers) were used as the average-for-date (AFD) comparison groups. To evaluate the impact of maternal birth weight on later reproductive performance, the birth weights and infant outcomes of all offspring born to the index females (75 SFD, 255 AFD, and 73 LFD) were compared (i.e. live-born and stillborn). It should be noted that because the siblings of the probands were half, rather than full siblings, there were many cases where an animal was the maternal half-sibling on one proband and the paternal half-sibling of another. Thus their birth weights were represented in more than one sibling group. However, animals selected for the AFD comparison group had no LFD or SFD family members and were therefore entirely independent for statistical purposes.

Figure 1. Schematic diagram outlining the study design. Infants with birth weights more than 1.64 standard deviation units from the means for their gestational-age-by-sex category were assigned to the proband groups [88 small-for-date (SFD), 91 large-for-date (LFD)]. The birth weights of the mothers (54 SFD, 74 LFD), fathers (61 SFD, 51 LFD), and all known live-born maternal (306 SFD, 327 LFD) and paternal (978 SFD, 838 LFD) half-siblings for each proband were identified through pedigree records. The birth weights of the remaining 382 live-born animals and their parents (243 mothers, 81 fathers) were used as the average-for-date (AFD) comparison groups. To evaluate the impact of maternal birth weight on later reproductive performance, the birth weights and infant outcomes of all offspring born to the index females (75 SFD, 255 AFD, and 73 LFD) were compared (i.e. live-born and stillborn). It should be noted that because the siblings of the probands were half, rather than full siblings, there were many cases where an animal was the maternal half-sibling on one proband and the paternal half-sibling of another. Thus their birth weights were represented in more than one sibling group. However, animals selected for the AFD comparison group had no LFD or SFD family members and were therefore entirely independent for statistical purposes.

Statistics

All statistical tests were conducted using procedures in the Statistical Package for the Social Sciences, Version 8.0 (SPSS Inc., Chicago, IL, USA). For the index infants and their offspring, the main effects of proband grouping and sex on birth weight were assessed by two-way analysis of variance (ANOVA), with Scheffé’s tests used for pairwise comparisons by group and gender (significance established at P < 0.05). The birth weights of the probands’ relatives were compared with those of the corresponding AFD using independent
Figure 2. Mean birth weights (± SEM) of index infants by sex. Dashed lines represent the population mean ± 2 SD (mean = 488.9 ± 49.9 g) as a reference point for the magnitude of growth restriction and enhancement displayed by proband animals. Birth weights differed significantly at *P < 0.05 and §P < 0.001 for male versus female birth weights.

Results

As expected, the weights of index infants differed dramatically between the three birth categories (F2553 = 738.38, P < 0.001). Further, the gestational ages were equivalent across the three weight categories (P > 0.50), confirming that the differences in birth weight were due to variance in fetal growth rate. While male infants weighed more than females overall (F1553 = 11.60, P < 0.001), post-hoc analyses revealed that the typical sexual dimorphism in birth weight was exhibited by the LFD and AFD infants only (P < 0.05 and P < 0.001 respectively; Figure 2); the weights of SFD probands did not vary by sex.

The birth weights of the infants’ first-degree relatives were examined to assess the familial contribution to the observed prenatal growth trends. The birth weight patterns of the mothers mirrored those of their infants, with the mothers of LFD infants heavier (P < 0.005), and those of SFD probands lighter (P < 0.01), than the mothers of AFD controls at their own births (Figure 3A). In contrast, the birth weights of the fathers of LFD and SFD probands appeared to be lower than, but not significantly different from, those of the fathers of AFD control monkeys (P > 0.05 for fathers and P > 0.025 for SFD fathers). These observations concurred with a modest, but statistically significant bivariate association between the birth weights of the index infants and their mothers (r = 0.24, P < 0.001), but not their fathers (r = 0.06, P > 0.60).

Similarly, the maternal half-siblings had birth weights that differed dramatically from the AFD control group, with LFD half-siblings heavier and SFD half-siblings lighter by comparison (P < 0.001 in both cases; Figure 3B). Moreover, in keeping with the marginal contribution of the father, the birth weights of the paternal half-siblings did not differ significantly from those of AFD control infants (P > 0.05 for both comparisons).

Next, we evaluated the persistence of the birth weight patterns into the next maternal generation by comparing the weights of the live-born progeny of the female index animals. Because the incidence of preterm birth was higher among infants born to SFD mothers (see below), the effect of gestational age on birth weight was controlled by entering it as a covariate into the analyses. The birth weights of the second-generation infants varied by maternal birth category (F2352 = 4.25; P < 0.02, after controlling for gestation length). This difference was due solely to the reduced birth weights of
Matrilineal birth weight trends and reproductive outcomes

Table 1. Odds ratios (95% confidence intervals) for reproductive outcomes by maternal birth weight category using mothers born AFD (with 255 infants from 56 mothers) as the reference group

<table>
<thead>
<tr>
<th>Infant outcome</th>
<th>Maternal birth weight category</th>
<th>Mothers born small-for-date (75 infants from 13 mothers)</th>
<th>Mothers born large-for-date (73 infants from 15 mothers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth(^a)</td>
<td></td>
<td>3.40 (1.47, 7.86)*</td>
<td>0.69 (0.15, 3.22)</td>
</tr>
<tr>
<td>Daughters</td>
<td></td>
<td>4.27 (1.52,11.95)*</td>
<td>0.77 (0.71, 0.83)</td>
</tr>
<tr>
<td>Sons</td>
<td></td>
<td>2.35 (0.55,10.03)</td>
<td>0.65 (0.20, 2.10)</td>
</tr>
<tr>
<td>Preterm birth(^b)</td>
<td></td>
<td>5.95 (1.80,19.69)*</td>
<td>3.01 (0.66, 13.87)</td>
</tr>
<tr>
<td>Daughters</td>
<td></td>
<td>5.41 (1.62,18.05)*</td>
<td>0.64 (0.20, 2.06)</td>
</tr>
<tr>
<td>Sons</td>
<td>Not determined(^c)</td>
<td></td>
<td>0.18 (0.13, 0.27)</td>
</tr>
<tr>
<td>Small-for-date birth</td>
<td></td>
<td>4.08 (1.67, 9.94)*</td>
<td>1.31 (0.34, 5.07)</td>
</tr>
<tr>
<td>Large-for-date birth</td>
<td></td>
<td>1.09 (0.36, 3.27)</td>
<td>2.96 (1.12, 7.82)*</td>
</tr>
</tbody>
</table>

\(^*\) P < 0.05 (Fisher’s exact test), compared to infants from AFD reference group.
\(^a\) Includes neonatal deaths within the first week of life.
\(^b\) Live-born infants with gestational ages ≤160 days.
\(^c\) There were no preterm sons born to small-for-date (SFD) or average-for-date (AFD) mothers.

infants born to SFD mothers (P = 0.005 compared to infants of AFD mothers); the infants of LFD mothers had birth weights that were similar to those born to AFD mothers. Further post-hoc analyses revealed a sex by category interaction, as only the daughters of SFD mothers had reduced birth weights (P < 0.005 compared with the daughters of AFD mothers; Figure 3C). The birth weights of the sons were similar across the maternal birth categories.

The influence of birth weight in females extended to other aspects of their reproductive functioning. Females born SFD were significantly older than other mothers when giving birth to their first infant (6.03 ± 0.32 versus 5.07 ± 0.17 years; P < 0.01). They also experienced a higher rate of neonatal mortality and were at greater risk of delivering preterm and SFD infants, particularly among the female progeny (P < 0.05 in all cases; Table 1). Despite the lower birth weights and poorer outcomes of their offspring, females born SFD still had pregravid weights comparable to those of AFD-born mothers (6.21± 0.16 versus 6.42 ± 0.08 kg for SFD and AFD females respectively), suggesting they were neither of small stature nor in poor health. In contrast, females born LFD had higher pregravid weights (6.91 ± 0.21 versus 6.42 ± 0.08 kg; P < 0.05) and were more likely to produce LFD infants (P < 0.05) than AFD mothers. Moreover, the incidence of aberrant pregnancy outcomes (specifically, stillbirth and prematurity) for LFD-born females did not differ from control pregnancies.

To further characterize the interaction between prenatal growth patterns and infant sex, the birth weights of the index infants’ half-brothers and -sisters were analysed separately. For the maternal siblings, the half-brothers and -sisters of LFD probands showed comparable rates of intrauterine growth acceleration, with both weighing significantly more than AFD males and females respectively (P < 0.001 for both comparisons; Figure 4A). However, consistent with other findings for the SFD, the maternal half-sisters of SFD probands experienced greater growth restriction than their half-brothers: the birth weights of the half-sisters, but not the half-brothers, were significantly lower than those of AFD controls (P < 0.001 for the sisters; Figure 4B). In contrast, the birth weights of the paternal half-brothers and -sisters were similar to those of the AFD males and females respectively, again emphasizing the

Figure 4. Mean birth weights (± SEM) of large-for-date (LFD) (A) and small-for-date (SFD) (B) half-brothers and -sisters illustrated in Figure 3B. The birth weights of male and female average-for-date (AFD) controls are indicated by horizontal dotted lines and by ❄ and • respectively. §Birth weights differ at P < 0.001 for proband half-siblings versus AFD controls.
Discussion

The present study demonstrates that female family members overwhelmingly account for the intergenerational transmission of birth weight in monkeys. Cross-breeding studies with horses were among the first to propose that uterine mechanisms might modulate the rate of fetal growth to produce matrilineal patterns in birth weight (Walton and Hammond, 1938). Reciprocal matings between Shetland ponies and Shire horses produced heterozygous offspring with birth weights similar to those of the pure-bred progeny of the maternal strain, despite the nearly four-fold size difference in stature between the two breeds. In human populations, the maternal, but not paternal, relatives of SFD infants have significantly lower birth weights than those of AFD offspring. At the other extreme, heritable factors from both parents appeared to contribute to the growth acceleration observed in LFD infants (Ounsted and Ounsted, 1968; Ounsted et al., 1986). These observations suggest that uterine processes may operate differently at opposite ends of the birth weight continuum: at lower birth weights, maternal constraint is prepotent, whereas other factors, such as infant sex, take up more of the variance in birth weight for heavier infants.

Our data from the rhesus monkey confirm and extend earlier human studies: the birth weights of maternal relatives followed that of the proband, with the mothers and maternal half-siblings of LFD and SFD infants respectively heavier or lighter than AFD controls at birth. Conversely, the mean birth weights of the probands’ paternal relatives did not differ from those of AFD infants, suggesting that the maternal influence was more pervasive for both SFD and LFD fetal growth patterns in this species. In human studies, assortive mating may contribute to the increased birth weight observed among paternal family members of LFD infants, but in our monkey colony the breeding of half- rather than full-siblings eliminated this potential confounding factor from our analyses. Accordingly, these findings concur with an early report in humans that detected a significant association between birth weights of maternal, but not paternal, half-siblings (Morton, 1955).

Beyond the matrilineal constraint, birth weight varied by infant sex in a predictable manner. Though males weighed more at birth than females overall, the SFD infants did not exhibit this typical male–female dimorphism. The absence of this difference among SFD probands supports the assertion that maternal constraint overrides the influence of other variables, such as infant sex, at the lower end of the birth weight distribution. As dramatic was the finding that the consequences of maternal constraint were much more pervasive for female descendants within the SFD matriline. The daughters and maternal half-sisters of the SFD probands weighed significantly less than AFD females and their daughters at birth, whereas the birth weights of their half-brothers and sons, while apparently somewhat reduced, were not different from the AFD males. In contrast, the operation of other factors in promoting fetal growth is evident at the upper end of the birth weight continuum: in addition to the expression of the male-female dimorphism in birth weight of LFD probands, both the maternal half-brothers and -sisters showed a similar degree of growth acceleration when compared to AFD controls.

Our presentation of transgenerational patterns in birth weight indicates that one pregnancy should not be viewed as an independent event, but as a manifestation of the reproductive health of a female’s lineage overall. As described for women (Hackman et al., 1983; Klebanoff et al., 1984; Coutinho et al., 1997; Skjærven et al., 1997), a female monkey’s birth weight had important consequences for her later reproductive performance. In addition to selectively restricting the prenatal growth of their daughters, females born SFD were nearly a year older than other monkeys at the birth of their first infant, and they were at greater risk for delivering a stillbirth and for bearing live infants that were either SFD or premature, particularly if the offspring was a daughter. While females born LFD were more likely to produce LFD infants, they did not experience such adverse reproductive consequences. Given the finding that a mother’s own intrauterine experience can directly influence her daughters’ fetal development (and subsequently, their reproductive performance), it could take several generations to ameliorate the impact of a poor pregnancy outcome within a family. If similar mechanisms operate in humans, these uterine-mediated, intergenerational factors might help to clarify the persistence of low birth weight births among high-risk populations, despite the initiation of prenatal interventions aimed at improving pregnancy outcomes (Raine et al., 1994; Coutinho et al., 1997).

Some advocate that birth weight is a marker for events occurring both before and after birth, as the social and environmental conditions that produce low birth weight infants are likely to continue operating on the child postnatally (Bartely et al., 1994; Paneth, 1994). While of potential significance in humans, this observation is particularly relevant in the context of the matriarchal social organization of the rhesus monkey. Daughters remain in the troop and are destined to occupy the social position of their mothers, whereas the status of the dispersing sons that emigrate from the group is more labile (Berman, 1988). Though the postnatal rearing environment clearly directs the learning of complex social behaviours, uterine factors operating prenatally could facilitate the process of rank acquisition. Accordingly, in environments where female-biased philopatry (and consequently, female/female resource competition) prevails, daughters of low-ranking mothers may benefit more than sons from a mechanism that restricts fetal growth and programmes the endocrine and metabolic axes in utero to acclimatize to a poorer quality of life. Yet, even in a laboratory environment that provided all essential resources, SFD mothers and their daughters experienced higher perinatal mortality and impaired reproductive performance, indicating that any survival advantages conferred to the neonate by intrauterine programming might come at the cost of reduced fecundity in adulthood.

Though the term ‘maternal constraint’ may be taken to imply that the mother is physically incapable of carrying a fetus too large for her to bear, our data are consistent with human studies demonstrating that maternal pregravid weight does not differ significantly between SFD and AFD mothers.
(Ounsted et al., 1986). Thus, maternal stature, as reflected by her weight at the time of fertile mating, was not sufficient to account for the restricted fetal development experienced by the daughters of SFD mothers. Rather, intrauterine constraint more probably reflects altered maternal metabolic processes or uterine/placental transport mechanisms that limit the provision of nutrients to the fetus. Studies in both rodents (Pollard, 1986; Pinto and Shetty, 1995) and humans (Skjærven et al., 1997) have suggested that prenatal stress and undernutrition can lead to deviant fetal and infant growth patterns that persist for several generations. Our findings extend these conclusions to suggest that they may be mediated through a special relationship between mothers and daughters by means of a gestational imprinting that takes place during fetal development.

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