# ARTICLES

# Growth Trajectory Evident at Birth Affects Age of First Delivery in Female Monkeys

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# ABSTRACT

Growth trajectories established early in life have proven to be important determinants of metabolism, health in adulthood, and ultimate mortality. The age of sexual maturation may also be set early in development, perhaps etched *in utero*. The following study used growth curve modeling to investigate the degree to which birth weight and weight gain before sexual maturation constrained the timing of reproduction in 147 female rhesus monkeys living under standardized social and nutritional conditions. Although size at birth by itself did not determine age of reproductive maturation, it was strongly associated with the subsequent developmental growth trajectory, which in turn predicted age at first offspring. In contrast to human studies indicating that small birth size is followed by a postnatal "catch-up" growth phase that accelerates menarche, growth trajectories remained distinctive in small and large infant monkeys. Thus, it was the sustained and stable disparity in size already evident at birth and amplified through development that accounted for variation in the age of adult sexual maturity. (*Pediatr Res* 55: 914–920, 2004)

#### Abbreviations

FI, factor invariance
M, mean
NFI, normed fit index
NNFI, nonnormed fit index
CFI, comparative fit index
RMSEA, root mean square error of approximation
LBW, low birth weight

Whereas variation in age at puberty was once thought to be due primarily to individual differences in weight, stature, and activity levels in the preadolescent period (1-6), there is now extensive evidence that the timing is constrained by events much earlier in development. The important influence of reduced prenatal growth and LBW was highlighted by Barker (7-10) in relation to a wide variety of metabolic diseases and conditions, but fetal growth also appears to influence the timing of puberty (11, 12) and later reproductive success (13). LBW has been reported to be a risk factor for early maturation (14-17), and girls who experience a precocious pubarche (18-20) or early menarche (21) were often of low weight at birth. Normal birth weight girls appear to be protected in part

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from such early maturation by progressing more slowly through the pubertal transition, but LBW girls often develop more rapidly once they show the initial bodily signs of hormone activation (21). These observations differ from studies in animals that indicate optimal growth from birth onward accelerates the attainment of adult maturity and frequently endows the individual with greater reproductive success (22, 23). Therefore, we re-examined birth and development in female monkeys to provide a cross-species comparison and potentially to add greater credence to several discrepant reports in humans that found higher birth weight was associated with an earlier puberty in normal (24) and growth-restricted girls (25).

Further resolution of discrepancies in the literature may be achieved by considering whether the pattern of postnatal growth remains consonant with birth weight. LBW can be associated with slow growth from infancy through childhood (25–31) such that approximately 15–20% of children remain of small stature through adolescence (32, 33). Adair (12) argued that it is only when LBW girls show "catch-up" growth (26, 34), especially those who were long and lean at birth, that they evince an early puberty (see also 35, 36). It should be noted further that when LBW girls catch up in weight, it is often not

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manifest in their final adult height (21), with 20% LBW girls being overweight and 15% obese at age 20 (34). This finding would appear to be in keeping with Barker's hypothesis about the effects of *in utero* growth restriction and postnatal sufficiency (9). Any potential for accelerated growth would be predicated on a small baby being exposed subsequently to abundant nutritional resources in the rearing environment (35– 37). On the other end of the spectrum, big babies who just sustain their enhanced growth could be as predisposed for an early puberty, a finding that concurs with the traditional views about larger stature and maturity (6, 11, 12, 15, 38, but see 39). Although it is not feasible to design a prospective study of pregnant women that controls environmental conditions and standardizes nutrition, it is possible achieve this type of experimental rigor in a breeding colony of monkeys.

Given that growth is commonly theorized to be a mechanism linking birth weight with age at puberty, we also found it a little surprising that the analytic strategies have not usually used modeling techniques that treat postnatal weight gain as a change measure, albeit with some notable exceptions (12, 40). Further, some studies opted to statistically control for weight, and found that weight in childhood was an independent predictor of pubertal timing (e.g. 11, 12, 15, 24). This approach potentially underestimates the importance of individual differences in growth trajectories, and places the emphasis primarily on the between-group difference in weight (41). In the present study, growth curve modeling (42) was used to characterize individual differences in birth weight and growth across the first 3 y of the female monkey's life. This age span captures the prepubertal period of maturation in the rhesus monkey, as menarche typically occurs between 2.5 and 3.5 y of age (43). Birth weight and growth were then used to predict differences in the age at first successful delivery of a baby. This method of parameterizing individual differences is optimal because (a) growth is modeled as a change from birth weight, rather than by weight at any specific time point; (b) the influence of birth weight and growth are examined in the same model; (c) unsystematic error variance is partitioned out of the "true" score of weight and growth; (d) individual differences in birth weight and growth are statistically tested; and (e) the predictive values of birth weight and growth are examined in the same model, thereby partialling out the effects of each parameter (42, 44-46).

Previous studies of birth weight patterns in this monkey colony have indicated that the predisposition for large or small babies is a heritable tendency passed from mother to daughter, and that fetal growth and birth weight were strongly associated with the amount of maternal weight gain during pregnancy (47, 48). These new analyses provided an opportunity to assess whether there might also be more sustained consequences for reproductive success persisting into adulthood. Specifically, the modeling was designed to test the following three hypotheses: (a) birth weight would be associated with growth during the prepubertal period and subsequently with age at first delivery; (b) larger size and faster growth would be related to an earlier puberty; and, finally, (c) LBW might be linked with a distinct growth trajectory that delayed the attainment of adult maturity and birth of first offspring.

## **METHODS**

#### Subjects

The data were generated from clinical records on a large breeding colony of rhesus monkeys (Macaca mulatta) maintained under standardized conditions at the University of Wisconsin since the 1960s (47, 48). The current analyses were based on the third-through-fifth generation descendants of animals that originated in India. Information on 147 female monkeys, born between August 1979 and October 1997, and their first offspring, born an average 4.6 y later (SD = 0.8), was summarized. Inclusion criteria included: (a) birth weight recorded within 3 d of parturition (M = 0.6, SD = 0.9 d); (b) complete weight records through the first 3 y of age; and (c) successful delivery of a live baby before the age of 7 y. Exclusion criteria included: (a) housing or experimental conditions that restricted normal breeding; (b) sustained or recurrent ill health, such as gastrointestinal infections; or (c) relocation to another facility before reproductive age.

### Housing and Rearing Conditions

This monkey colony typically generates between 50 and 100 infants per year, which are reared normally by their mothers through 6-12 mo of age. Thereafter, they are transferred to small juvenile groups or mixed-age groups where they remain through the birth of their first offspring. The rhesus monkey typically reaches menarche at 2.5 y, begins ovulatory cycles at approximately 3.5 y (43), then has a 169-d gestation before giving birth to her first offspring. Environmental and housing conditions were standardized. Water was available ad libitum, a fixed quantity of commercial monkey biscuits was provided in the early morning (from the same vendor, Purina, for the last two decades), and fruit supplements were given in the afternoon. The light-dark schedule was 14:10, with lights on at 0600, which largely overrode the seasonal breeding tendency of this species.<sup>1</sup> Ambient room temperature was constant at 21°C. All breeding and research procedures described here in have been approved by the institutional Animal Care and Use Committee.

### Measures

**Birth.** The date of birth, sex of infant, and its weight have been recorded routinely for several decades. For inclusion in the present study, all infants had to be weighed within 3 d of parturition. Mean weights taken on d 1–3 (n = 62) did not differ from those weights recorded on the day of birth (n = 85),  $F_{3,143} = 1.68$ , p = 0.17, pairwise comparison ps > 0.29. Weights recorded 4 d after birth (M = 441 g, SD = 44), however, were significantly lower than neonatal weights recorded on the day of birth (M = 500 g, SD = 60), and hence

<sup>&</sup>lt;sup>1</sup> Retrospective analyses based on birth dates indicated that 60% of the fertile matings occurred during the months of October through January. This estimate is significantly less than the seasonality effects observed by Terasawa (41) in which 80% of first ovulatory cycles in the rhesus monkey occurred within these 4 mo, p < 0.0001, but it is also greater than would be expected by chance (33%, p < 0.0001). Off-season mating did not affect birth weight,  $F_{1,135} = 0.83$ , birth category,  $\chi^2_2$  (n = 147) = 0.55, nor the growth trajectory category,  $\chi^2_2$  (n = 147) = 0.15, ps > 0.61.

any later weighings were not included in the present study, even though monkey infants typically return to their birth weight by 1 wk of age.

The reported weights represent the normal range for this species because infants born premature or extremely small are less likely to survive without human intervention, and only mother-reared babies were included. A previous article has characterized small-for-date monkeys in our colony as weighing <380 g (47, 48). In the current data analysis, only one monkey was included that weighed <380 g or was 2 SD below the mean [a standard clinical cutoff for LBW (33, 34)].

Three groups based on percentile birth weight scores were created to determine whether babies born small or large exhibited different growth trajectories (*i.e.* to test for catch-up growth). Small (lower 25%; range, 370–460 g, n = 37) and large babies (upper 25%; range, 525–755 g, n = 37) were compared with their average counterparts (mid 50%; range, 460–520 g, n = 73).

*Growth.* Complete clinical and experimental records were maintained on all animals, including regular weights. For analyses, weights were summarized at annual intervals through the typical age for menarche, which is between 2.5 and 3.5 y of age (43). For descriptive purposes, three additional groupings were also created on the basis of percentile growth scores (lower 25%, mid 50%, and upper 25%) to evaluate the effects of slow, average, or fast growth (which overlapped, but was not necessarily identical to the birth weight categorization).

**Reproductive success.** The age at delivery of the first viable offspring was the primary outcome variable. Inclusion criteria required that the female was maintained in social housing conditions conducive to reproducing, and had given birth to at least one baby before 7 y of age (*i.e.* within 3 y of even a late menarche). This inclusion criterion was set because any further delays in reproducing might have been indicative of a gynecological basis for the infertility.

## **Analytical Strategy**

Growth curve modeling with maximum likelihood estimation was used to evaluate birth weight and growth (Fig. 1). This strategy used latent factors to assess individual differences in the level (birth weight) and slope (growth from birth to 3 y of age). The level and slope were modeled initially at the individual level (49). After it was found that variation around the mean level and slope was systematic, the capacity of level and slope to predict individual differences in age at first delivery was considered (50). Slope across 3 y was linearized to incorporate the faster growth in the first year of life compared with the second and third years (42, see also 51). The  $\chi^2$  goodness of fit and indices of practical fit were used to assess the fit of the model (52).

The growth curve model was examined initially for all subjects; then, FI procedures (53–55) were used to determine whether growth and age at delivery were similar in infant monkeys that were low, average, or large birth weight using a multiple group approach (56, 57). With the exception of birth weight and level, which were different by definition of the grouping factor, the reduction in the fit of the model, when the parameters were constrained to be equal across groups, estimates the size of differences between small, average, and large babies. Obtaining strict FI would allow one to conclude that the model operated similarly in babies of low, average, or large birth weight and would rule out the possibility that small or large babies had different growth functions than babies of average birth weight (52, 53).

#### RESULTS

The birth weights and growth patterns observed in this colony were typical for the species and representative of female maturation in other colonies (Table 1) (58). At birth, these full-term monkey babies exhibited a wide variation in size, between 370 and 755 g, and then underwent fairly rapid

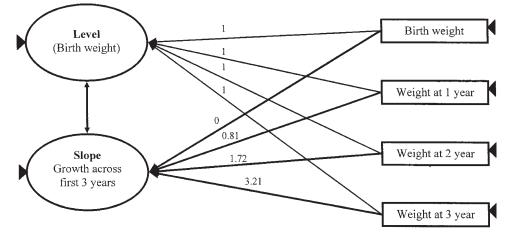


Figure 1. Growth curve model for birth weight and growth across 3 y. Manifest (measured) items are denoted with *squares*, and latent factors derived for level and slope are denoted with *circles. Arrowheads* refer to unique error terms. The slope for weights was linearized to adjust for faster initial growth. Instead of setting the slope regression time points according to year (0, 1, 2, and 3), the y-1 weight was set earlier because monkeys achieved their first year linear growth by 0.81 y (9.7 mo), their y-2 linear growth at 1.72 y (20.6 mo), and their y-3 linear growth at 3.21 y (38.5 mo).

 Table 1. Mean (SD) birth weight and growth (in grams) for female rhesus monkeys during first 3 y of life, and age at delivery of their first offspring

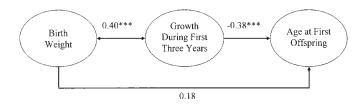
	Birth weight category						
	Small $(n = 37)$		Average $(n = 73)$		Large $(n = 37)$		
	Mean	SD	Mean	SD	Mean	SD	
Birth weight	428.4	20.2	490.0†	18.3	560.0‡	46.3	
Weight at 1 y	1910.1	179.1	2023.3†	205.8	2088.7‡	185.6	
Weight at 2 y	2979.7	316.1	3138.0†	365.0	3273.7‡	399.3	
Weight at 3 y	4159.5	563.3	4463.0†	578.4	4679.1‡	620.0	
Age at parity	4.8	0.7	4.6	0.8	4.7	0.9	

Birth weight continues to be related to size across 3 y, ps < 0.01. Age at parity was not significantly different by birth weight when considered as a broad category; however, it was related to the overall difference in size across 3 y of growth (Fig. 3). The symbol  $\dagger$  is used when the small group differs from the average group and  $\ddagger$  denotes when the small group differs from the large group.

growth by 1 y of age (range, 1.5-2.7 kg, mean change = 1.5 kg, SD = 0.2). By this point, the infant was eating independently, and based on our normal husbandry practice was rehoused with other juveniles. Weight increased at a slightly slower rate through 2 y (range, 2.1-4.1 kg, mean change = 1.3 kg, SD = 0.4), and continued through 3 y of age (range, 3.2-6.1 kg, mean change = 1.1 kg, SD = 0.3), which is the typical age of menarche. Correlations of individual weights across years were highly significant, suggestive of stability in the growth trajectories (*rs* range, 0.41-0.71, *ps* < 0.0001).

Growth curve modeling was then used to examine the slope or change in weight from birth through 3 y of age (42). The fit of the basic model was excellent when growth was linearized to account for the accelerated growth in the first year of life,  $\chi^2_3 = 1.99$ , p = 0.57, NFI = 0.99, NNFI = 1.01, CFI = 1.00, and RMSEA = 0.001, indicating that the model accurately captured the structure of the data. Variance estimates for level, 1850, t = 2.22, p = 0.06, slope, 24753, t = 6.86, p < 0.0001, and age at birth of first offspring, 79858, t = 8.95, p < 0.0001, were highly significant, demonstrating that there were sufficient individual differences in these measures to be considered acceptable independent and dependent variables. Larger females at birth grew faster across the first three years of life, r = 0.40, p < 0.01.

When age at first delivery was included in the model, the fit was adequate,  $\chi^2_5 = 9.12$ , p = 0.10, NFI = 0.95, NNFI = 0.96, CFI = 0.98, and RMSEA = 0.08. Birth weight by itself was not associated with age at first offspring, r = 0.18, p = 0.40, but the slope of growth was inversely associated with age at first offspring, r = -0.38, p < 0.001 (Fig. 2). Quartiles based on growth trajectories demonstrated that females with the slowest growth trajectory (bottom 25%) gave birth to their first offspring, on average, at 4.81 (SD = 0.78) y of age,



**Figure 2.** Relationship between birth weight, growth during first 3 y, and age at birth of first offspring. Birth weight was indirectly related to age at first offspring. Monkey infants that were larger at birth grew faster and, in turn, had offspring earlier.

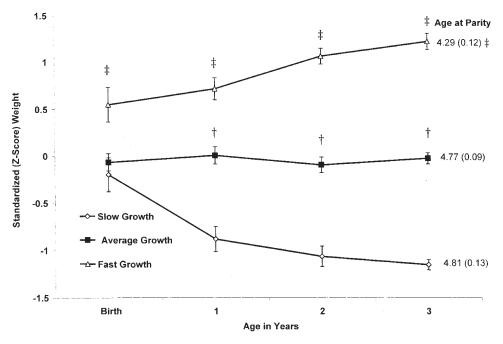
whereas females with the fastest growth trajectory (top 25%) gave birth an average of five months earlier (M = 4.29 y, SD = 0.76),  $F_{2.144} = 5.18$ , p = 0.007 (Fig. 3).

Three groups were then created to represent monkeys born small, average, or large, to test the hypothesis that the growth trajectories and age at first delivery were affected by birth size. FI procedures demonstrated that strict FI did not substantially reduce the fit of the model (Table 2). Thus, the association between level and slope and the prediction of age at birth of first offspring were similar in all three groups. This indicated that, with the exception of birth weight, the model parameters-variance, covariance, regression weights, and beta weights -were similar in monkeys of small, average, and large birth weight (Table 2). Babies who were born small were 10.4 times more likely to have a slow growth trajectory compared with babies born big. Only 11% of babies born small evinced a fast growth trajectory, in contrast to 43% of babies born big, providing further support that big babies tended to grow faster,  $\chi^2_4 = 12.03, p = 0.02$ . Further, there was no evidence that the LBW females had a more rapid initial growth trajectory than did the average or large infants (*i.e.* they did not show signs of postnatal catch-up growth).

### DISCUSSION

These analyses have confirmed that growth patterns starting very early in life have a strong influence on maturational processes related to the attainment of adult reproductive status. Although birth weight by itself did not determine the timing of adult reproduction, the size of the neonate was an important component of the developmental growth trajectory, which in turn had a significant effect on the female monkey's age at first delivery. The findings highlight the importance of considering the association between both pre- and postnatal growth in studies on the effects of LBW (12, 40). Because birth weight reflects the earlier processes of fetal growth (7, 8), it is likely that critical events related to age of sexual maturation are initiated in utero (11-17), and then are substantiated through growth processes during the prepubertal period (11, 12, 15, 24, 26, 40, 59). Consistent with other nonhuman primate research and a number of human studies, bigger babies remained larger and attained sexual maturity earlier than did the smaller and slower-growing offspring (22, 24, 25). Further, the profile of the growth trajectory was relatively stable across monkeys of

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**Figure 3.** Standardized weight scores during the first 3 y of life in slow-growing (bottom 25%), average-growing (mid 50%), and fast-growing (top 25%) offspring. Monkeys that grew quickly were more likely to be bigger at birth and, subsequently, had offspring at an earlier age than average or slow-growing monkeys. Monkeys that grew slowly across the first 3 y of life were more similar to the average-growing monkeys in birth weight and age at parity. The symbol  $\dagger$  denotes when the small group differs from the average group, and  $\ddagger$  denotes when the small group differs from the large group.

**Table 2.** Chi-square goodness of fit  $(\chi^2)$  and degrees of freedom (DF) for models testing whether the growth curve model is similar for small, average, and large birth weight babies

Model	DF	$\chi^2$	$\Delta \mathrm{DF}$	$\Delta \chi^2$	p Value
Unconstrained (a)	15	22.46			
Strict Factor Invariance (b)	25	28.35	10	5.89	0.9
Association between level and slope	27	31.85	12a	9.39	0.9
_			2b	1.70	0.6
Association with age at first offspring	31	38.34	16a	15.88	0.8
			4b	6.49	0.2

Strict FI, constraining the regression weights, means, and unique variance estimates to be equal in small, average, and large birth weight babies, did not substantially reduce the fit of the model. Change in degrees of freedom ( $\Delta DF$ ) and chi-square ( $\Delta \chi^2$ ) demonstrates the reduction in the fit of the constrained model when compared to the unconstrained (a) and strict factor invariance (b) model.

different sizes, providing little evidence for postnatal catch-up growth in the smaller infants, but instead demonstrating sustained and stable developmental advantage for larger infants (2, 3). Even when a small portion of the LBW monkeys did show some enhanced growth in the postnatal period, they typically entered only the average growth group, and did not cross over to the fastest growing category. Similarly, it was rare for an infant monkey born large to shift all the way to the slow profile of postnatal growth, and if they changed at all, it was just to regress toward the average rate of growth.

Based on these findings, it would appear that growth processes already evident at birth are the primary mediators of the relationship between preterm factors and sexual maturation (12, 40). The value of growth curve modeling was that it allowed us to consider birth weight as one point on this continuum, reflecting *in utero* processes, which then gained additional significance as the growth trajectory extended through postnatal development. Dos Santos Silva and colleagues (40) found that LBW in humans was associated with an early puberty, which is consistent with the majority of the literature. However, when they controlled for growth in infancy as a change measure, high birth weight was associated with early puberty. Similar to our findings in the monkey, when they also controlled for growth in childhood, postnatal growth mediated the relationship between birth weight and puberty. Thus, postnatal growth has the potential to clarify whether small or large babies are at risk for early maturation. Just as pre- and postnatal growth are conceptually important in studies of birth weight and maturation, analyzing growth in the right statistical manner is equally crucial to the interpretation of findings on LBW babies.

There are several possible reasons why we failed to find evidence for either LBW or postnatal catch-up growth as risk factors for early maturation. This project was designed to examine birth weight that was in the normal range for this species, in contrast to our earlier survey of 1321 babies over 25 y, which specifically identified a different cohort of LBW monkeys <380 g (47, 48). Although some studies in humans have demonstrated that small size within the normal range accelerated puberty (11, 12, 40), the most compelling evidence comes from reports on girls born moderately or extremely LBW (14–16). These types of infants were not included in our analyses because our inclusion criteria also required maternal rearing without human intervention: very small or sickly monkeys would be less likely to survive through the birth process and neonatal period (60-63). In addition, catch-up growth does not seem to be as common in babies on the lower end of the normal range as it is in LBW babies (24, 35). It appears that the coincidence of a period of malnourishment during pregnancy followed by a more benevolent postnatal rearing environment is the critical factor in changing the timing of puberty (59), just as it appears to accentuate the relationship between LBW and adult disease (9, 36). For example in a sheep model, when the placental transfer of nutrients was purposefully restricted only during pregnancy, it resulted in LBW lambs, but their subsequent postnatal growth on a controlled diet was then enhanced, resulting in an accelerated puberty (21). In our case, gravid females were maintained on a standardized and sufficient diet, which was sustained through both the nursing and prepubertal phases, fostering a more normative growth profile and perhaps maximizing the likelihood of stable growth trends in the majority of offspring. To fully understand the relationship between growth in LBW babies and an accelerated puberty, it thus seems that a consideration of the combined effect

of intrauterine growth restriction and postnatal diet is required. Our findings concur with placing greater emphasis on the prenatal period when considering influences on age at menarche, because it appears that the growth trajectory begun during fetal life is the primary constraint. In monkeys, this conclusion becomes even more evident after experimental manipulations that cause radical departures in growth from the norm. For example, when female fetal monkeys were exposed to androgens in utero, it both shifted their growth to a masculine pattern and delayed their menarche until the age when male monkeys normally reach puberty (64). Conversely, when the established growth trajectory was experimentally altered at 1.5 y of age in female monkeys, by lesions in the lateral hypothalamus, the onset of menarche was markedly advanced (65). These observations highlight the fact that both radical and modest manipulations of the pre- and postnatal environment can have long-term effects on the timing of sexual maturation, which are amplified through growth. Taking this extended developmental perspective is of value for evaluating the significance of birth weight when it is used as the primary outcome measure in a pregnancy study (66). Similarly, a modeling of trajectory can also be of value for interpreting observations on shifts in the timing of puberty due to seemingly discrete events that occur during childhood (67).

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