

Maternal determinants of gestation length in the rhesus monkey

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ABSTRACT

A gestation length of normal duration and natural delivery at term are considered to be important indicators of a healthy pregnancy, especially given the potentially adverse consequences for neonates of being born premature. While many have assessed the factors influencing gestation length in humans, and there has been considerable interest in the pregnancy duration of domesticated farm animals, this topic has not been re-assessed recently in rhesus monkeys, the most commonly used primate in biomedical research. In older articles, it's gestation length was typically reported to be 165 days, although most authors acknowledged that viable pregnancies could occur out to 180 days. Predicting the normal range of acceptable due dates has important veterinary implications for when to intervene in a prolonged pregnancy. Using archival records from a large, established breeding program, gestation lengths and infant birthweights were analyzed for 408 pregnancies across a 25-year period. The potential influence of maternal factors, including age and parity, was assessed. Familial concordance in gestation length within mother-daughter matriline was examined, as well as similarity in length across repeat pregnancies for 84 multiparous females. Mean duration from mating to delivery was 168.8 days, longer than reported in most but not all previous articles. Many females birthed successfully at a longer duration that might have prompted consideration of a caesarian delivery. Gestation length for an individual female was fairly

stable and significantly correlated across multiple pregnancies. There was not a pronounced transgenerational influence on gestation length even though familial propensities for birthing small and large infants were evident in the female descendants. Typical pregnancy lengths and birthweights are provided as reference norms to assist other breeding programs and to enhance our understanding of the natural reproduction of rhesus macaques that still live in many forested and urban locations across South Asia.

KEYWORDS: pregnancy, gestation length, rhesus monkey, birth weight, parity.

INTRODUCTION

Although gestation length is an important metric of a healthy pregnancy, it is well known that there is significant variation around the typical duration [1]. For that reason, the predicted due date is usually considered to be just an estimate. Clinical concerns have focused primarily on the risks associated with premature births [2, 3], but it is also the case that 1 in 10 pregnant women deliver later than anticipated [4]. In addition to the synergistic effects of many endogenous processes, including maternal and placental hormones, the length of pregnancy and infant birthweight can also be influenced by the mother's age, parity, and stress, as well as by some heritable factors [5]. For example, epidemiological analyses have documented that women under 18 years or older than 35 years of age are more likely to have an atypical gestation length, which most studies found to be shorter [1, 6] although others reported prolonged pregnancies can also be more

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frequent [7]. When examining large national samples, it has been possible to discern a familial influence, with moderately-sized positive correlations in gestation length between mothers and daughters as well as between sisters [8-11]. Given the consequences of gestational age at term for both mother and infant, it continues to be of interest to determine if additional insights can be gained by considering pregnancy characteristics and natal outcomes of other animals.

The pregnancy length of domesticated farm animals has attracted a lot of agribusiness attention because term deliveries and the weight of the offspring at birth reflect a herd's wellbeing, and the infant's growth rate has economic consequences for farmers and breeders. For example, among cattle, the father's adult size is important because he has more of an influence on birthweight than is evident in humans. A larger bull can sire a fetus with a faster growth rate, which in turn is a stimulus for parturition and a determinant of the calf's postnatal growth [12]. In contrast, among primate species, including humans, the father's prenatal history, including his gestational age and weight at birth as well as his adult size appear to have little influence on either pregnancy duration or the birthweights of his offspring [11]. Maternal attributes in primates are the primary factors that govern fetal growth, including her own birthweight and the amount of weight she will gain when pregnant [13-15]. The extent of this maternal influence may contribute to the individual variation in gestation length between females, which has been found to vary between 1.5-to-5% of the species-typical gestation length in mammals [16, 17]. Therefore, while it is possible to calculate a modal length for each species, the normative range for a whole population may actually be as informative and reflects many endogenous and extrinsic factors. One of our aims was to provide a more comprehensive characterization of gestation length in the rhesus monkey, given the continued need to generate monkeys for biomedical research. Large breeding programs depend on normative data about pregnancy to guide veterinary care and husbandry practices, including for making clinical decisions about if and when to intervene in a prolonged pregnancy.

The first publication stating the rhesus monkey had a 165-day gestation is typically cited to Hartman,

although his conclusion in 1928 was based on only 3 pregnancies with a range of 159-174 days [18]. Later analyses of breeding in rhesus monkeys often reported a similar mean length in their colonies [19]. However, most authors acknowledged that there was a wide normative range [20, 21]. For example, one analysis calculated a mean of 166.5 days for 708 pregnancies, but stated that 80% of births occurred between 160-175 days, with the full distribution of live births extending from 133-182 days [22]. Moreover, a few articles reported a longer mean length of 169 days [23, 24], as well as found that the diet consumed by female monkeys during pregnancy affected gestation length [21]. Some detected an influence of maternal age and parity, whereas other analyses concluded that neither maternal factor exerted an overt effect. When sex of the fetus was considered, one analysis concluded that gravid monkeys had a shorter pregnancy when gestating a male [22], while others found the opposite effect with males born as much as 5 days later than female infants [21]. These findings provided the foundation for our study aims, which included an examination of the potential influence of maternal age and parity, as well as considered if the sex of the fetus affected gestation length. In addition, we evaluated the stability of gestational length across multiple pregnancies, as well as the possibility of a familial influence on gestation length within matriline. The overarching goals were to determine the prevalence of short and long gestations, the capacity of females to birth live infants if parturition was delayed beyond the typical due date, and to quantify the connection between gestation length and infant birthweight for pregnancies of different durations.

MATERIALS AND METHODS

Subjects

The reproductive records and birth histories of rhesus monkeys (*Macaca mulatta*) in a long-established, large breeding colony were summarized for these analyses. The data derive from 408 singleton pregnancies across a 25-year period from 1997-2022. Information on gestation length and birthweights was acquired from the pregnancies of 324 different females. Eighty-four of these females had these two key variables quantified for multiple pregnancies, which allowed us to determine the stability in

gestation length across 2-4 pregnancies. The unique historical span of these records also enabled us to conduct a 2- and 3-generation analysis for the descendants of 53 females (i.e., comparing the gestation length of the ‘grandmothers’ and their 123 daughters, who in turn had gestated and birthed 277 female and male infants). During this 25-year period of time, the colony composition typically had >25 adult breeder males, over 150 adult females, and birthed 80-100 infants annually [15, 25]. However, for the current analysis, data on pregnancy were included only if the likely date of conception was known and the infant was weighed within the first week of life.

Procedures

Husbandry and breeding practices have been described previously [15, 25]. Some breeding occurs spontaneously in social groups at our facility, especially in the case of younger, nulliparous females, but for the current analysis of gestation length, the focus was on older adult females bred with a standardized timed-mating protocol. The menstrual bleeding of these females was monitored, and then they were moved to a breeder male’s cage when optimally fertile at mid-cycle. Following the practice of previous papers on primate reproduction [22, 26], date of conception was estimated as occurring on the first day a female was introduced into the male’s cage during her periovulatory phase. Gestation length was calculated from that date to the birth of the infant. Pregnancy durations and infant birth weights were included only if there was a live birth *via* vaginal delivery, excluding caesarian deliveries, and only if the infant was weighed within the first week after birth. Most infant weights were obtained by Day 3 postpartum. For this report, paternal attributes were not considered because previous analyses had unequivocally indicated that maternal characteristics predominantly affect gestational outcomes in the rhesus monkey [13, 14].

Prevalence of short and long gestations

In addition to analyzing gestation length in numerical days as a parametric variable, it was also considered as a categorical variable by creating 5 categories: 1) Preterm (< 160 d), 2) Short (161-164 d), 3) Normal (165-173 d), 4) Long (174-177 d), and 5) Postterm (>178 d). The Normal range was calculated on the

basis of the grand mean of 168.8 days and 1 SD (+/- 4.2 days) calculated from the 408 pregnancies. The shortest viable birth occurred at 147 days and the longest quantified gestation was 182 days.

Data analysis

Statistical comparisons were conducted primarily with two-factor analyses of variance (ANOVA). Sex of the fetus was included as one factor in the ANOVA to determine if it interacted with other variables. The influence of maternal age and parity was assessed in separate tests. Given the 25-year span of the records, we also examined if there had been a temporal shift in gestation length over time. The analysis was conducted by categorizing the pregnancy and birth data into five 5-year quintiles from 1997-2022 (see Table 1). This temporal evaluation confirmed there had not been a change in pregnancy duration, which allowed us to consider data from the entire cohort together. An initial conclusion that neither maternal age or parity influenced gestation length was tested again and affirmed in a follow-up analysis of multiple pregnancies for the subgroup of 84 females with data from 2-4 pregnancies. Finally, an analysis of transgenerational trends was conducted by identifying 53 monkeys who had 123 daughters that went on to birth their own infants. In the 3rd generation, there were a total of 277 descendants, including female and male offspring from pregnancies of known gestational age and with birthweights at delivery. Associations between variables, including the key correlations between gestation lengths and birthweights, were evaluated with the Pearson’s *r* test. Statistical significance was set at $\alpha < 0.05$, but in a few instances a positive trend that attained a $p < 0.09$ is reported for informational purposes only.

RESULTS

Descriptive results

Table 1 provides summary statistics on the primary factors considered to be potential mediators or moderators of gestation length. Overall, the mean gestation length for the 408 pregnancies was 168.8 days (SD: 4.2 days; SE: 0.21 days). A comparison of gestation length across the 25-year period indicated there had not been a significant shift in the duration of pregnancy across the five 5-year quintiles. Similarly, there was not a significant

Table 1. Descriptive statistics for variables evaluated as potential modifiers of gestation length in the rhesus monkey, including birth year, maternal age and maternal parity. Mean (S.E.) gestation lengths are shown separately for female and male infants.

	Female	Male	P*
Temporal stability			
1998-2002	168.1 (.8)	169.1 (.6)	Time: NS
2003-2007	168.3 (.6)	168.4 (.6)	Sex: p<.05
2008-2012	168.2 (.5)	169.9 (.8)	
2013-2017	168.4 (.5)	169.5 (.5)	
2018-2022	169.3 (.5)	169.5 (.4)	
Maternal Age (yr)			
4-5	168.9 (.8)	169.5 (.5)	Age: NS
6-10	167.9 (.4)	169.2 (.5)	Sex: p=.066
11-15	168.8 (.5)	169.7 (.6)	
16-20	166.8 (1.6)	168.3 (.9)	
Maternal Parity			
Primiparous	169.2 (.8)	169.6 (.7)	Parity: NS
Multiparous +1	168.6 (.7)	168.9 (.8)	Sex: p=.051
Multiparous +2-3	168.0 (.5)	169.7 (.6)	
Multiparous >4	168.3 (.5)	169.0 (.5)	

*Statistical comparisons were conducted with 2-factor analyses of variance. Significance is shown for the main factor and if there was a significant difference related to whether a female or male fetus was being gestated. While less than a 1 day different, mean gestation length for all 240 female infants was 168.4 days (SD = 4.3) compared to 169.3 days (SD = 3.9) for all males ($F[1,406] = 4.70$, $p < 0.03$).

influence of maternal age or parity on gestation length when examining all 408 pregnancies. This conclusion about a lack of influence of age or parity was also confirmed when considering the repeat pregnancies of the 84 females that were the source of data on 2-4 pregnancies as they grew older and had subsequent conceptions. The effect of fetal sex on pregnancy length was small, but several of the analyses summarized in Table 1 indicated the gestation of a female fetus was often shorter, with an average difference of 1 day. Mean gestation length for all female infants was 168.4 days (SD = 4.3), whereas for all males, it averaged 169.3 days (SD = 3.9) ($F[1,406] = 4.70$, $p < 0.03$). While maternal age did not affect gestation length, a parallel analysis of the effect of a dam's age on infant birthweight revealed there was a progressive increase in the size of the infant across a female's

reproductive life. Birthweights increased incrementally upward from a mean 494.1 g (8.3 g) in the offspring of 4-5 year old mothers to 530.9 g (15.4 g) for the infants from older mothers who were 16-20 years of age. Similarly, while the effect of fetal sex on gestation length was small—just 1 day—the sex difference in neonatal weight was large and statistically significant (492.3 g [4.3] vs. 523.3 g [4.8], female vs. male, respectively, $F[3, 386] = 16.15$, $p < 0.0001$).

Prevalence of short and long gestations

The percent of the 408 pregnancies that would be considered to be outside of the typical gestation range is shown in Figure 1, both for shorter and longer durations. While 11% were shorter than Normal, only 3% of the live births were in the Preterm category, less than 160 days. Similarly, while 38.2%

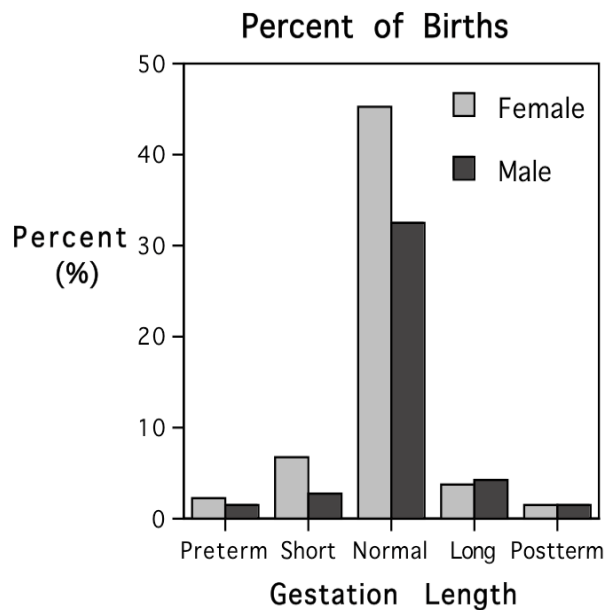


Figure 1. Prevalence of gestation lengths for 408 singleton rhesus monkey pregnancies. The Normal length category was based on the overall mean of 168.8 days (± 1 SD of 4.2 days), and included 317 pregnancies. Female and male infants were represented in each category. The birthweights of infants after pregnancies of shorter duration were significantly less than those born at an older gestational age ($F[4,403] = 244.6$, $p = 0.0001$).

were longer than 173 days, only 2% went beyond 178 days. Because the duration of each category was predefined, the ANOVA confirmed that the gestation lengths of the 5 categories differed significantly ($F(4, 398) = 213.9$, $p < 0.0001$). Similarly, as would be expected, there was a significant difference in the birthweight of infants across the 5 length categories ($F[4, 398] = 8.22$, $p < 0.0001$). Infants in the Preterm category weighed only a mean 450.9 g, smaller than the typical birthweight of 505.6 g for a Normal length gestation. The premature infants were over 100 g smaller than the much larger average birthweight of 569.3 g for infants designated as Postterm. Male infants were larger in four of the gestation categories at delivery. Overall, the mean birthweight for male infants was 523.3 g ($n = 168$), larger than the mean 491.8 g for female infants ($n = 240$). However, because the Premature male infants weighed less than the Premature females, the ANOVA examining the 5 length categories indicated there was significant interaction between Pregnancy Duration and Fetal

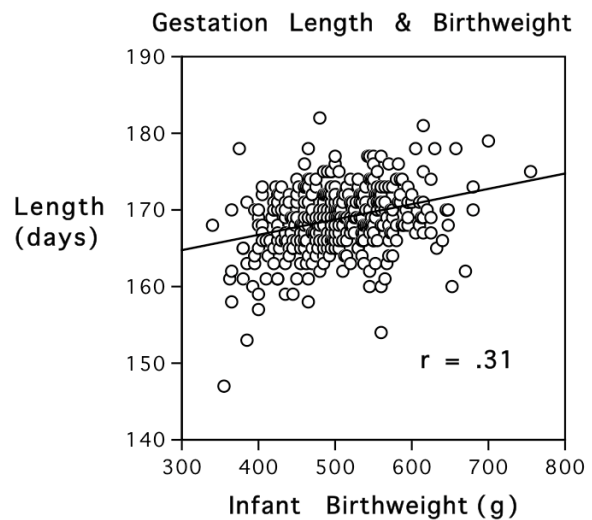


Figure 2. Correlation between gestation length and infant birthweights for 408 rhesus monkey pregnancies. Pregnancy duration and birthweight were significantly correlated ($r = 0.31$, $p < 0.001$). The linear curve fit reflected the overall distribution, but its predictive accuracy was better for shorter and normal length gestations than for those of long duration. For infants in the Long and Postterm categories, the formula underestimated the actual quantified weights of the neonates when they were weighed during the first week of life.

Sex, rather than a simple main effect with male infants always being larger than females. Age of the mother was not predictive of a shift in the prevalence of Preterm or Postterm births. But because of a propensity for more female infants to be birthed when the gravid dam was older than 10 years of age, there were more female than male infants born in the Preterm, Long and Postterm categories to the older mothers.

Association of gestation length and infant birthweight

As expected, there was significant correlation between gestation length and infant birthweight ($r = 0.317$, $p < 0.0001$). Figure 2 illustrates that infants born earlier than the Normal range tended to be smaller, whereas those born beyond the Normal gestational age (>173 days) were heavier. Linear curve fitting sensitively captured the relation between gestation length and birthweight, but the formula for this regression line performed more accurately for gestations of short and normal lengths. For longer gestations beyond Day 173, the

regression formula would underestimate the actual neonatal birthweight by as much as 200 g. This discrepancy likely reflects the rapid pace of fetal growth in the final days of gestation. Even though the gestation lengths of female and male infants were generally similar, the female infants were consistently smaller than males at birth. This sex difference in birthweight was larger than could be explained solely by the tendency for female infants to be born 1 day earlier.

Gestation lengths across multiple pregnancies

It was also possible to assess the stability of gestation length from the data available on 84 females with multiple time-mated pregnancies and infants weighed after delivery. The correlations in

gestation length across their 2-4 repeat pregnancies are illustrated in Figure 3. The panels show that there were significant associations in gestation lengths between the first pregnancy and subsequent pregnancies in later years. In addition to revealing a general stability in gestation length, this analysis across repeat pregnancies affirmed the conclusion from the cross-sectional analysis that neither increasing maternal age or parity significantly affected the gestation length. There was not a clear trend for a shortening or lengthening of pregnancy duration as these multiparous females became older and had subsequent pregnancies. In keeping with the stability in gestation length across a female's reproductive life, the birthweight of her infants tended to be correlated as well.

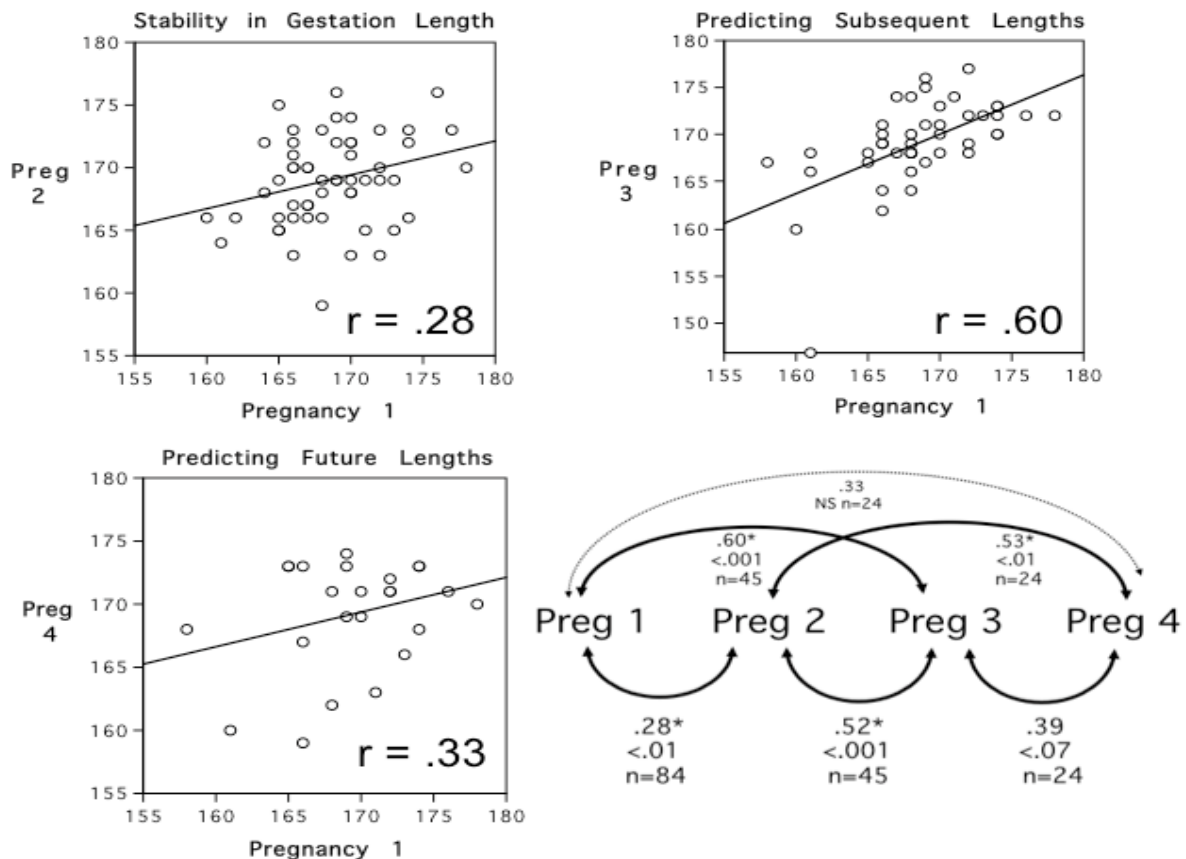


Figure 3. Association of gestation lengths across 2-4 repeat pregnancies for 84 females. This analysis was based on each female's first time-mated pregnancy with a quantified gestation length and infant birthweight, and then successive pregnancies in subsequent years. There were 84 females with 2 quantified pregnancies; 45 of these females had data for a third pregnancy, and 24 had information from a 4th pregnancy. The 3 panels illustrate correlations between the first and second pregnancy, followed by Pregnancies 1 and 3, and then Pregnancies 1 and 4. A summary diagram shows the positive correlations among all 4 pregnancies.

The birthweights of infants from the first pregnancy were significantly correlated with the birthweights of their half-siblings from the second pregnancy ($r[84] = 0.22$, $p = 0.047$). The magnitude of the association with infant birthweights for the third and fourth pregnancies was similar ($r[45] = 0.24$, $r[24] = 0.37$, respectively). However, due to the smaller sample size available for later pregnancies, these positive correlations no longer attained statistical significance.

Transgenerational influence on gestation length

A final analysis assessed whether there was a confluence in gestation length within a female matriline. It was based on 53 females that birthed 123 daughters who subsequently become pregnant as adults with a third generation of offspring. The gestation length of the first generation of females (i.e., reflecting the prenatal experiences of the 'grandmothers') proved to not be correlated with the gestation lengths of her descendants in the future, at least not beyond one generation. This familial analysis revealed only a nonsignificant trend for a transgenerational association between the gestation age at birth for the 123 daughters and their own pregnancy lengths as adults when gestating their own offspring ($r = 0.16$, $p = 0.085$). Even this trend was not as pronounced as the transgenerational similarity in birthweights between these same dams and their offspring ($r = 0.20$, $p < 0.05$).

DISCUSSION

This analysis of 408 pregnancies in the rhesus monkey indicated that the average gestation length was longer than the 165 days commonly reported in the literature [19, 22]. The mean length of 168.8 days in our colony is more in keeping with the reports that concluded the modal length for this primate species is 169 days [23, 24]. While the discrepancy may seem small, the difference has significant implications for the attending veterinarian who relies on this information to make clinical decisions about whether to induce with oxytocin and prostaglandins, or to operate and deliver by caesarian section. For those basing their clinical decisions on the frequently cited length of 165 days, it is not uncommon to become concerned about a pregnancy that goes longer than 170 days. Using that cutoff would have impacted 139 or 34% of the pregnancies in our colony.

As highlighted in the Introduction, the mean gestation length does not fully capture the extensive variation in pregnancy duration that occurs normally in a population. Prior analyses across mammalian species have indicated that the intra-specific variation can range from 1.5-5.0% of the species-typical length [17]. One analysis of variation in pregnancy length across primate species concluded further that the temporal variation may be even larger for monkeys and apes than for prosimians [16]. It is possible to estimate typical population variation in our dataset by considering gestation lengths out to two standard deviations from the mean. Then the variation around the mean would be 4.98%, a variance on the upper end when compared to other mammals. It is also important to reiterate that even the authors who reported a mean gestation length of 165 days for the rhesus monkey acknowledged that viable births could occur from 160 to 180 days [22]. It is not known why the modal length seems to vary by several days across different colonies, but it likely reflects differences in husbandry practices, including diet, and the type of research being conducted at that facility. For example, there is evidence that nutrition, exposure to reproductive hormones, consumption of alcohol, and infectious pathogens can affect gestation length and birthweight in the rhesus monkey [26-30].

It is also likely that some heritable factors account for differences in the reproductive profiles across different primate breeding programs. Our rhesus monkey colony is descendant from a founder population derived originally from India over 50 years ago. It has been closed to new animals for over 3 decades. Thus, the data used in the current analysis spanned a 25-year period when the genetics of the colony and husbandry practices were stable. As reported in the Results section, there wasn't a significant change in gestation length over this time period. We also did not detect an influence of maternal age or parity, in spite of evaluating pregnancies across a female monkey's entire reproductive life history, from 4-20 years of age. Previous reports of an effect of maternal age and parity have not been consistently replicated [21]. Similarly, the conclusions about an effect of the sex of the fetus on gestation length have been equivocal. One study found that gestation length was shorter if the fetus was male [22], whereas

our data would agree with the report that found pregnancies could be longer when gestating a male [21]. Here it may be important to consider one other variable, which was the trend for more female infants to be born when the mother was older than 10 years of age. Overall our dataset included more female than male infants, in part because many of the breeding monkeys tended to birth more female infants when they were 10-20 years of age.

Less equivocal was the very clear association between gestation length and birthweight. The longer the pregnancy lasted, the larger the infant. In fact, when the pregnancy extended beyond 170 days, the actual birthweight of the neonate at delivery would typically be even heavier than the weight predicted from the regression line shown for the entire population in Figure 2. Although gestation length and birthweight were significantly correlated, it should be highlighted that this relation was only of moderate strength at just 0.31. It would indicate that pregnancy duration is only one determinant of infant birthweight. If one considers the amount of the variance in birthweight explained by gestational age at term, which can be estimated by calculating the *r*-squared value, it would be just 9.6% of the variation. This conceptual perspective is important for a number of reasons. For example we had demonstrated previously that the gestational weight gain of a gravid female is another major determinant of an infant's birthweight [13, 14]. Maternal adiposity and infant size at birth have additional implications for a daughter's postnatal growth and age at menarche [31]. In addition, even when birthed at a similar gestational age, males were born significantly heavier than females. In the current analysis, males were heavier on average in 4 of the 5 gestation length categories, with the one exception of Premature births, when they tended to be smaller. There was also another interesting discrepancy in the linkage between gestation length and birthweight. While maternal age and parity did not significantly affect gestation length, the weight of both female and male infants born to older females progressively increased with the mother's age and parity. Finally, we have published previously on the extent to which maternal factors influence infant birthweights, including the degree to which there are transgenerational, maternal factors that constrain

infant birthweight within a female matriline [15]. In contrast, in the current analyses, we did not detect a comparable transgenerational trend for the gestation lengths to be similar among female descendants. The length of a female's pregnancy remained surprisingly stable across repeat pregnancies within her own life, and did not appear to be strongly affected by the prenatal experiences of her female ancestors. Many analyses of gestational length and birthweights in humans have reached the same conclusions. Specifically, heritable and familial factors have a much larger influence on birthweight than on the length of pregnancy [8].

Notwithstanding the uniqueness of these data and findings, a number of limitations should be acknowledged. While gestation length was quantified for each pregnancy after a controlled timed-mating, it was based on an estimated date of conception, assuming a fertile female conceived on the first day she could mate with an adult male. If conception actually occurred a few days later, it would have contributed to our conclusion that gestation length was longer than reported by others. However, this methodological issue would still not explain the longer gestation lengths that extended out to 180 days. Estimating date of conception based on the start of mating opportunities has been the approach employed by other primate researchers [21, 26]. It is also important to acknowledge that the 408 pregnancies included a subset of repeat pregnancies for 84 females. However, there were still 324 different females in these analyses. In addition, the majority of the 84 females provided data for only 2 pregnancies. Our decision to summarize all information together was based on several considerations, including that the repeat pregnancies occurred at least one year later, the sire was different so the next fetus was a half-sibling not a full sibling, the sex of the fetus was often different, and preliminary analyses indicated a female's age and parity would not influence the overall conclusions. Nevertheless, in light of finding that gestation length was fairly stable across a female's successive pregnancies, it is important to be cautious when including data from multiple pregnancies within this type of analysis. For that reason, several key findings were retested a second time with just the females that had repeat pregnancies, as well as with the female descendants

within a matriline. The primary take home messages remained the same with data derived from only one pregnancy or multiple pregnancies.

CONCLUSION

In summary, perhaps the most significant finding is that the typical pregnancy length of the rhesus monkey may be several days longer than the commonly reported length of 165 days. It is also important to highlight that all authors agree that there is extensive variation in gestation length across females. The variance for just the typical pregnancy lengths in our dataset was about 5%, which is high, but not beyond what has been found in some other mammalian species. In addition to the relevance for a veterinary decision about if and when to intervene in a prolonged pregnancy, there are other implications of gestational age at delivery. For example, it is known that some neuromotor reflexes are more mature at delivery if a neonate has been gestated longer [32]. Moreover, there can be cascading husbandry considerations if a caesarian section is performed, because of the likelihood that a surgically delivered infant will be rejected by the parturient female and require human care in a nursery setting. While some facilities have developed behavioral strategies to increase the willingness of a birth mother to accept an infant from an assisted delivery [33], it is not uncommon for a monkey to be unresponsive to her infant upon return, unless birthed vaginally. In other analyses, we have also demonstrated that with each additional day of pregnancy, more maternal antibody and maternal iron are being transferred across the placenta to the term infant [34]. Thus, accurate knowledge about pregnancy parameters, including gestation length, is essential for optimizing maternal and infant wellbeing and for ensuring the success of breeding programs.

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CONFLICT OF INTEREST STATEMENT

Neither author has any COI to disclose.

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