Comparative Medicine
Copyright 2008
by the American Association for Laboratory Animal Science

Vol 58, No 6
December 2008
Pages 597–603

Effects of Maternal and Infant Characteristics on Birth Weight and Gestation Length in a Colony of Rhesus Macaques (*Macaca mulatta)*

Kelly J Hopper,[1,*] Denise K Capozzi,[2] and Joseph T Newsome[2]

A retrospective study using maternal and birth statistics from an open, captive rhesus macaque colony was done to determine the effects of parity, exposure to simian retrovirus (SRV), housing, maternal parity, and maternal birth weight on infant birth weight, viability and gestation length. Retrospective colony statistics for a 23-y period indicated that birth weight, but not gestation length, differed between genders. Adjusted mean birth weights were higher in nonviable infants. Mothers positive for SRV had shorter gestations, but SRV exposure did not affect neonatal birth weights or viability. Infants born in cages had longer gestations than did those born in pens, but neither birth weight nor viability differed between these groups. Maternal birth weight did not correlate with infant birth weight but positively correlated with gestation length. Parity was correlated with birth weight and decreased viability. Increased parity of the mother was associated with higher birth weight of the infant. A transgenerational trend toward increasing birth weight was noted. The birth statistics of this colony were consistent with those of other macaque colonies. Unlike findings for humans, maternal birth weight had little predictive value for infant outcomes in rhesus macaques. Nonviable rhesus infants had higher birth weights, unlike their human counterparts, perhaps due to gestational diabetes occurring in a sedentary caged population. Similar to the situation for humans, multiparity had a protective effect on infant viability in rhesus macaques.

Abbreviations: ANCOVA, analysis of covariance; PRL, Primate Research Laboratory; SRV, simian retrovirus.

The rhesus macaque (*Macaca mulatta*) is a useful animal model for human female reproduction studies because the comparative physiology between the 2 species is nearly identical.[1,5,49] Some factors that affect birth weight and neonatal viability in both humans and macaques include maternal birth weight, maternal age, maternal parity, and the presence of underlying maternal disease. Even experimentally induced simulated human lifestyle factors can affect neonatal outcome.[10,16,17,25,44]

In humans, maternal birth weight correlates with infant birth weight such that low birth weight mothers themselves have low birth weight infants.[8,19,28,30] A similar association has been shown in the macaque.[38,39] Because low birth weight is associated with increased neonatal mortality in humans and in macaques, this correlation, if present, may have important predictive value.[11,20,21,32,45,47,53] One objective of this study was to establish whether maternal birth weight correlated with neonatal birth weight and viability in this colony of rhesus macaques.

The relationship between parity, age, and birth outcomes in humans is controversial because multiparous and grand multiparous women tend to be of lower socioeconomic status, older, and have many confounding lifestyle factors.[2,24,27,56] In macaques, low parity and young age are associated with reproductive failure.[50] In pigtailed macaques (*Macaca nemestrina*), increased parity was associated with decreased neonatal viability but increased birth weight. Despite their lower parity, younger mothers in the colony of pigtailed macaques produced lower birth-weight infants, but more viable infants, compared with those of older mothers.[17] The positive correlation between birth weight and viability merits further investigation in rhesus macaques. One objective of the current study was to determine whether maternal parity and age affected birth weight and neonatal viability in our rhesus macaque colony.

The lifestyle factors of alcohol consumption, cigarettes, caffeine, drug use, diabetes and exercise have all been shown to influence birth weight and gestation length in humans and macaques.[4,7,15,22,26,35,40,42,44,51,55] Captive animals can become obese and develop insulin-resistant diabetes, which prolongs gestation and produces oversized infants that are less healthy.[21,46,51] Because exercise is a preventative lifestyle factor for obesity and diabetes, it would be useful to compare active animals with sedentary ones.[30] Previous retrospective colony studies in pigtail macaques show that cage type, location, and social housing have significant effects on birth weight and birth outcome.[18,19] Another objective of the current study was to determine whether housing in cages (sedentary animals) or group pens (active animals) influenced gestation length, birth weight, and viability in our rhesus macaques.

Another factor in birth outcome is the disease status of the mother. Viral infections, particularly of adenoviruses and immunosuppressive retroviruses, are associated with low birth weight and infant mortality in humans and nonhuman primates.[13,21,25,33,34,52,53] A previous report describes maternal transmission of simian retrovirus in a colony of pigtailed macaques with concurrent immunosuppression, low birth weight, and increased infant mortal-

Received: 10 Jan 2008. Revision requested: 17 Mar 2008. Accepted: 03 Jun 2008.
[1]Research Resources, The Mannheimer Foundation, Homestead, Florida; [2]Division of Laboratory Animal Resources, University of Pittsburgh, Pittsburgh, Pennsylvania.
[*]Corresponding author. Email: khopper@mannheimerfoundation.org

ity in viremic mothers.[33] However, some evidence suggests that lentiviral antibodies in amniotic fluid may protect against in utero infection.[23] Further confounding the effects of retroviruses on reproductive outcome, animals infected horizontally can be viremic but serologically negative, and animals with sufficient, detectable immune responses may have provirus latent in their tissues.[33] Because simian retrovirus (SRV) was endemic in the subject rhesus colony and most data were retrospective thus preventing confirmation of viremia, another objective was to determine whether seropositivity of the dam was associated with neonatal viability, gestation length, and infant birth weight.

Materials and Methods

Data collection. Retrospective birth data were obtained from investigator breeding records and colony medical health records at the Primate Research Laboratory (PRL; Division of Laboratory Animal Resources, University of Pittsburgh, PA). All animals were on animal protocols that were reviewed and approved by the Institutional Animal Care and Use Committee at the University of Pittsburgh. All breeders and their offspring were used strictly for reproduction and familial behavior studies, which involved no manipulations other than what was dictated by medical necessity. Animals in the data set included those that lived in, were born or imported into, the facility from March 1979 through March 2003 for the reproductive research facility. This colony was an open colony in that some animals were imported, some lived their entire lives in the colony, and some left the colony. Some information on animal origin was missing from records of deceased animals prior to 1990. This colony was a mixed-source population of Indian-origin rhesus macaques. Only animals seropositive for SIV, with questionable tuberculosis status, or that cultured positive for enteric pathogens were excluded from entering the colony. Animals known to reside within the United States for less than 1 y were quarantined for 90 d; all others had a 30-d standard quarantine before joining the colony.

Because SRV was endemic in this colony, there was interest in the effect of viral exposure, if any, on reproduction. Seropositive animals were not culled or restricted from entering the colony. Exposure to SRV was determined serologically by a commercial laboratory. Because the bulk of the data was from animals that were deceased or no longer in the breeding colony, confirmation for presence of virus was not included because so few of the animals had the confirmatory test or were available to be tested. If female macaques seroconverted to positive status between births, subsequent births were included in the SRV-positive category.

Infant information gathered included gender, birth date, birth weight, gestation length, and infant viability. Only birth weights known to be taken within 24 h of birth were included. A nonviable infant was one that did not survive for 1 mo after birth due to natural disease or euthanasia because of illness. Maternal information collected included birth date, birth weight, age at each birth, parity at each birth, SRV serology status, and delivery in a gang pen or a cage. Subject selection criteria included infant or maternal birth at the PRL and maternal delivery at the PRL or both. Imported females that had been bred and delivered infants at the PRL were included in the maternal data. Birth weights of mothers that were imported or purchased were included in the maternal data. Gestations of these imported mothers before their arrival at the PRL were included in parity calculations, but infant data previous to joining the colony were not included. Information from 101 female macaques was included in the data set; male information was scarce and therefore not included. Because this study was retrospective, not all information was available for all animals, so group sizes in the different analyses vary. This weakness is typical of retrospective data; however, significance values were applied consistently across the study.

Animal facilities and environment. Female monkeys in the breeding colony delivered infants either in single-housed caging or in indoor group pens. All single-housed mothers had breeding dates, whereas only group-housed mothers that were cage-bred had definite breeding dates. Female macaques were bred every year. Although controlled timed breeding is successful through exogenous progesterone administration, in this colony animals were bred on natural cycles only, as is common practice in other nonhuman primate breeding programs.[6,21,37] Single-housed females and those that were single-housed before moving to a pen had their menstrual cycles continuously monitored to target the right time for breeding. Those female macaques that did not produce infants at least every 3 y were removed from the breeding protocol and program. However, the animals in pens were maintained in their social groups regardless of fertility in order to maintain established family groups.

When they were known to be in estrus, based on condition of sex skin and cycle history, cage-bred female macaques were placed with a male macaque in his home cage. Male and female macaques were left together for 3 to 5 d. The breeding date was considered to be the first day of cohabitation, because during monitoring for compatibility, pairs generally were seen to breed on the first or second day. The female macaque then was placed back in her home cage or introduced to a new group in a pen. Pen animals were housed within a family group, at least 1 of which was an adult, sexually active male, therefore breeding date could not be estimated. Therefore, only cage-bred pen animals were included in gestation length data. Palpation, ultrasonography, or both were used to diagnose pregnancy according to known breeding dates of cage-bred animals. Pen-bred female macaques had no definite breeding date and were palpated or had transabdominal ultrasonography (or both) to confirm pregnancy and estimate parturition date when they appeared to have abdominal distention; these births were included for outcomes other than gestation length.

Infants were left with their mothers for a minimum of 6 mo unless they were rejected or the mother died. Rejected infants were fostered when possible, otherwise they were hand-reared. Caesarian sections were performed on any female macaque with a known breeding date for whom parturition had not occurred by 175 d or when the fetus was too large, as determined by biparietal diameter, or too mature by abdominal ultrasonography for a live natural birth.

All animals were housed indoors on a 12:12-h light:dark schedule; the temperature fluctuated between 20.0 and 22.2 °C. Cages were standard stainless-steel primate cages. Enrichment included cage toys, food puzzles, mirrors, and novel complex food treats. Radios and televisions were provided in the rooms for added enrichment. Cage pans were scraped daily, and cages were sanitized every 2 wk, whereas pens were changed and sanitized every 2 wk. Group pens were of sealed concrete block and chainlink walls (9 ft high, 12 ft long, 6 ft wide), with woodchip floor bedding over poured concrete. Animals were not overcrowded and were housed according to The *Guide for the Care and Use of Labora-*

tory Animals.[36] Roof sky lights provided natural light. Pen enrichment included various swings and climbing fixtures as well as toys. All monkeys were fed a standard pelleted diet (Monkey Chow/Purina #5, Nestlé Purina PetCare, St Louis, MO) that was supplemented with seasonally available fresh fruits, nuts, and vegetables and food enrichment of varying consistency, flavor and complexity. Fresh water was provided through an automatic watering system that was flushed when cages and pens were sanitized.

Statistical analyses. All statistical analyses were done using SAS statistical software (version 8e; SAS Institute, Cary, NC). Frequencies were generated for SRV status, birth housing, parity and viability. Colony means and SEMs for birth weight and gestation length were generated. The Shapiro–Wilkes constant was calculated to determine whether continuous data were normally distributed (that is, a Shapiro–Wilkes constant of 1.0).[8] Simple *t* tests were applied to assess the difference between 2 means; ANOVA was applied when more than 2 means were compared. The Scheffe posthoc test was used to adjust for the *P* value in the comparison of several means. Analysis of covariance (ANCOVA) was applied to 2 or means to adjust for possible correlation between variables for the difference between 2 or more means. In this way, ANCOVA removed or adjusted for any existing correlations and gave a more representative comparison of those means, also known as adjusted means. A Pearson correlation matrix was constructed to examine the magnitude and direction of correlations among continuous variables. Odds ratios were calculated as estimates of relative risk and were determined by the case control contingency table method with 95% confidence limits. Logistic regression including all maternal factors was done to determine if parity predisposed mothers to having lower birth weight infants by providing an estimated risk (odds ratio). Because ours was a retrospective case control study, the odds ratio estimates the relative risk for a certain factors or variables to result in a particular outcome, such as death or low birth weight, in this data set. Significance was set at a *P* value of 0.05 or less for differences in means and correlation coefficients or any odds ratio confidence limit that did not contain 1. Trends were defined as associations where $0.1 \geq P \geq 0.05$.

Results

Colony descriptive statistics. Birth weight and gestation length were both normally distributed according to the Shapiro-Wilkes test statistic (Table 1). Birth weight differed between genders, but gestation length did not (Table 2) (p=0.039). Viability frequency is summarized in Table 2. The total percentage of nonviable births in this data set was 11.23%. Correlations (Table 3) represent variables that change together; therefore, ANCOVA was used to adjust for covariations in comparing means. This analysis revealed a trend toward a difference in mean birth weights was seen between viable and nonviable infants (F = 2.12, *P* = 0.06, df = 7). Adjusted mean birth weights were higher in nonviable infants. The mean age of the dam at her first birth in this colony was 5.52 y (range, 3.5 to 11.87). Analysis of variance was done on mean birth weights across 4 generations (1 primate generation = 5.5 y, time from birth to reproductive ability in this colony). Means for transgenerational birth weight differed across those time periods (F= 3.57, *P* = 0.0152, df = 7, $r^2 = 0.0547$). Post hoc testing showed significant differences in birth weight between animals born before 1990 and those born from 1996 to 2000 and those born after 2000. In this colony, birth weight and gestation length were consistent with known values in rhesus macaques. The percentage of 5onviable infants in this colony is consistent with that of at least 1 other macaque colony.[15]

Table 1. Birth weight and gestation length distributions

	n	Mean	SD	Shapiro–Wilkes constant[a]
Overall birth weight (kg)	295	0.495	0.071	0.98
Male birth weight (kg)	157	0.506	0.074	0.97
Female birth weight (kg)	133	0.488	0.071	0.97
Overall length of gestation (d)[b]	202	167.2	5.4	0.97

[a]A Shapiro-Wilkes constant of 1 indicates a completely normal distribution.
[b]Gestation length was statistically the same for male and female macaques.

Table 2. Frequencies of discrete factors

	n
Total no. of births of known SRV status	335
SRV+ Births	287
SRV- Births	48
Total no. of births in pens or cages	365
Pen births	44
Cage births	321
Total no. of births of known viability	365
Viable	324
Nonviable	41
Parity (no. of births)	
Primiparous (1)	58
Multiparous (2 to 5)	141
Grand multiparous (6 or more)	61
Total no. of female macaques represented in data set	101

Discrete factors are 'either/or' and must be represented as a whole number.

Maternal SRV serologic status. Analysis of covariance showed no difference in mean birth weights between infants from SRV-positive and SRV-negative mothers. SRV serologic status had a significant effect on gestation length when ANCOVA corrected for other factors (F = 2.94, df = 5 *P* = 0.020; Table 4). After this adjustment, SRV-positive animals had a shorter gestation. The estimated relative risk (odds ratio) for an SRV-positive dam delivering a nonviable infant as compared with that of an SRV- negative mother was 3.41 (95% confidence interval, 0.794 to 14.793), but this was not significant. The average birth age of mothers that had not been tested for SRV was 6.84 y whereas the mean age of those that tested positive was 9.27 y, compared with 9.84 y for those that were SRV-negative. Of all deaths in this dataset, 90.2% were neonates from SRV-positive female macaques. Of all animals serologically tested, 85.7% were viral-antibody–positive. Three animals changed from negative or unknown to positive

Table 3. Correlation between maternal and infant factors

	Parity	Maternal birth age	Gestation length	Birth weight	Maternal birth weight
Parity		r = 0.80 *P* < 0.0001 n = 211	r = 0.092 *P* = 0.27 n = 146	r = 0.13 *P* = 0.061 n = 195	r=-0.09 *P* = 0.35 n = 99
Birth age	r = 0.79687 *P* < 0.0001 n = 211		r=-0.12 *P* = 0.90 n = 120	r = 0.084 *P* = 0.29 n = 163	r=-0.15 *P* = 0.15 n = 99
Gestation length	r = 0.09179 *P* = 0.2705 n = 146			r = 0.018 *P* = 0.85 n = 112	r = 0.38 *P* = 0.004 n = 55
Birth weight	r = 0.13427 *P* = 0.0613 n = 195				r = 0.42 *P* = 0.71 n = 79
Maternal birth weight	r=-0.0944 *P* = 0.3526 n = 99				

The Pearson Correlation Coefficient (r; range, 0 to 1) represents the probability that the interdependence between the two factors is actually greater than or equal to *r*.

Table 4. Adjusted means of birth weight and gestation length

	Adjusted mean birth weight	Adjusted mean gestation length
Pen	0.487 kg	161.94 d
Cage	0.512 kg	166.10 d
Housing F and *P* values	F = 1.42, df = 5 *P* = 0.225	F = 2.91, df = 5 *P* = 0.021[a]
SRV-positive	0.480	164.95 d
SRV-negative	0.505 kg	167.11 d
SRV status F and *P* values	F = 1.42, df = 5 *P* = 0.225	F = 2.94, df = 5 *P* = 0.020[a]
Viable	0.486 kg	165.85 d
Nonviable	0.596 kg	168.01 d
Viability F and *P* values	F = 2.30, df = 5 *P* = 0.042[a]	F = 2.49, df = 5 *P* = 0.036[a]

ANCOVA incorporated the additional variables of maternal age, maternal parity, and maternal birth weight.
[a] *P* < 0.05.

SRV status in this dataset, but none showed a difference in birth weight between positive and negative status. Positive SRV serologic status of the mother was associated with shorter gestation length but not lower infant birth weight.

Housing status. Housing in a pen instead of a cage was associated with a shorter gestation length; however, this difference was not apparent when ANCOVA was used to adjust for other maternal factors. Pen and cage mean birth ages were 6.01 y and 9.58 y, respectively, and these means were significantly different (F = 20.34, df = 7, *P* < 0.0001), so younger females gave birth in pens. The mean maternal birth weight of the mothers in the pens was significantly (T=-2.98, *P* = 0.0036) higher than that of the mothers in the cages. However, there was a preponderance of younger females delivering in the pen environment, and after adjusting for maternal age and maternal birth weight, infant viability did not differ between pen and cage environments.

When adjusting for all factors by ANCOVA, no differences were seen in mean infant birth weights between cage- and group-housed mothers. However, ANCOVA revealed a difference in gestation length between pen- and cage-born animals (F = 2.91, df = 5, *P* = 0.021 Table 4), such that cage-born infants had a longer gestation length. Pen birth lent a protective effect on the viability of neonates according to the odds ratio of 0.768 (95% confidence interval, 0.342 to 13.570).

Maternal birth weight and parity. Frequency within parity groups is described in Table 2. Most births were the second to the fifth birth of a dam. ANOVA revealed differences in mean birth weights across parities (F = 2.83, df = 7, *P* = 0.0072, Table 5), and mean birth weights of infants of multiparous mothers differed from that of dams of first births (F = 2.26, df = 7, *P* = 0.0093). A trend toward correlation between parity and birth weight (r = 0.135, *P* = 0.0613) was detected also (Table 3). Multiparous births produced larger infants. Parity of 6 or greater was associated with the highest birth weights. Low parity of mothers was associated with a significantly increased risk of low birth weight in neonates [β = –0.639; odds ratio = 0.528 (0.320, 0.871)]. First-parity deaths accounted for 19.5% of all neonatal deaths in this data set, whereas parity 6 and over (grand multiparous) contributed 43.9% of all neonatal deaths. The estimated relative risk for neonatal death at parity 6 and greater was elevated: 3.11 (1.96, 6.11). Maternal birth weight and gestation length were correlated (r = 0.382, *P* = 0.0040) but maternal birth weight and infant birth weight were not. (Table 3).

Discussion

Both birth weight and gestation length distributions were normal and means were consistent with known, published values for rhesus monkeys.[21,38,39,41,54] Female infants predictably had weights that were lower than male infants (Table 1). However, it did not follow in this study that birth weight and gestation length were correlated, because one would expect the smaller female macaques to have a shorter gestation. The neonatal death rate in the current study was similar to another report of 12% in a breeding colony of cynomologus macaques.[14] Average age at first birth was

Table 5. ANOVA: birth weight by parity

Parity	Mean birth weight (kg)	Rank
*1	0.472	8
*2	0.492	6
3	0.504	3
4	0.495	5
*5	0.487	7
6	0.500	4
*7	0.549	1
8 or more	0.506	2

Parity 7 was significantly different [F = 2.83, df = 7, $P = 0.0072$ (Scheffe's posthoc test)] from parities 1, 2, and 5

5.52 y, slightly older than the average reported in literature.[41,54] All of these animals are kept indoors in artificial environments, where breeding is controlled to a large extent. This practice may explain why the generation time in this colony is longer than what is reported.

Over several generations, rhesus infant birth weights increased in a closed colony,[38] similar to what appears to be emerging in our open colony. Because the majority of the animals included in the data set were from later generations, 1995 to 2003 (78.49%), an increased proportion of heavier animals was represented in the data set if the generational effect on birth weight is truly present. Birth weight increased across all generations, but this trend is distinct only in female neonates, and the sex disparity cannot be explained. This trend may be secondary to improved management practices incorporated over the 23 y of the data set. Similarly, the significance of the association between maternal birth weight and gestation length is unclear. Perhaps larger female infants mature as larger adults and larger adults tend to have longer gestation length.

Although seen in humans,[28,48] no correlation was found between infant and maternal birth weight among rhesus macaques. This lack may partially be explained by the trend in increasing birth weight over time. The preponderance of data from later generations represents a selection bias in data collection that may have contributed to the failure to detect any infant and maternal birth weight correlation. More animals in the data were from later generations, and those animals had heavier birth weights. The correlation function does not adjust for that temporal change. Parity and birth weight were correlated, and there were differences in mean birth weights across parities by ANOVA. This finding is consistent with a previous study in pigtailed macaques, where increased parity was associated with increased birth weight but decreased viability.[18]

Although simian retroviruses are known to cause decreased birth weights in infants,[21,53] we did not see an association between exposure or positive serologic status and decreased viability in our colony. A possible explanation is that so many of the infants were born to SRV-positive mothers (Table 2) that the entire mean birth weight for the colony represents a low average. Alternatively, seropositive status does not confirm the presence of disease, so birth weights may simply be normal because the mothers are not diseased.[33] In addition, the presence of protective maternal antibody may explain the lack of effect of virus on the fetus or newborn.[23] Some investigators report a 40-y overall average colony birth weight of 488 g,[39,38] but colony viral status is not discussed in either report in which they study genetic transmission of birth weight. It is also important to recall that in our study population, the average birth age of mothers that had not been tested for SRV and those that were tested positive or negative were significantly different. The SRV calculations involved many more older animals than younger animals, and this bias may have raised the birth weight means for the SRV-positive group. The presence of a positive SRV titer had a negative association with gestation length (Table 4), consistent with current literature that describes this group of viruses as causing low birth weight, preterm delivery, and acquired immune deficiency.[52]

In contrast to literature reports, no correlation was found between infant birth weight and gestation length among our rhesus macaques.[29,32] In human populations, birth weight, gestation length, and infant mortality are strongly correlated.[20,29,32,43] Another inconsistency from current literature is that in our study, infants with longer gestation lengths were more likely to be nonviable. In addition, nonviable infants had a higher mean birth weight than did viable infants (Table 4). These outcomes may reflect the effects of gestational diabetes and infant macrosomia, which are common in overweight women and caged female nonhuman primates.[12,46,47] Many of the macaque mothers were obese and had confirmed hyperglycemia at delivery. Diabetes, macrosomia, dystocia, and resulting neonatal death have been diagnosed causes of reproductive mortality in this colony.

Consistent with human literature, infants from multiparous macaque mothers were significantly larger, and increasing parity was associated with decreased viability. Infants from grand multiparous mothers (6 or more) had higher odds of death. Therefore, larger infants did not always thrive. In addition, a longer gestation length was associated with larger, nonviable infants. This result is completely opposite from findings in the current literature, which reports that longer gestation length is associated with higher birth weight and viable, healthy birth outcomes in nonhuman primates and humans.[9,21,28,29]

Our study yielded many unexpected outcomes. Some may be due to missing historical data, a common problem in retrospective studies that cover extended periods of time, particularly when scientific methodology is rapidly evolving. The high prevalence of SRV and the long time period over which data were included also may have influenced the results. Most of the births occurred in cages rather than a more natural environment, and cage breeding was highly controlled. All of these factors may have contributed to unexpected results. Colony managers should consider the parity, SRV serologic status, housing status, and age of the mother when planning a breeding program for nonhuman primates, because all of these factors potentially can have an effect on the survival of neonates. Analysis of detailed colony records as they pertain to maternal factors can be used as a tool to maximize fertility and infant survival.

Acknowledgments

We would like to thank Dr Tony Plant, Dr Anthony Zeleznik, and The Center for Reproductive Research (supported by grant HD 08610 from the National Institutes of Health) for use of their reproduction data; we also thank the staff at the Primate Research Laboratory (particularly Kate Guernsey, Lindsay Pulman, and Jennifer Dry-Hennich) for providing animal records for data collection. We thank Dr Roberta Ness (Chairman, Department of Epidemiology, University of Pittsburgh) for her assistance with statistics and study design. Dr Linda Waterman, Dr Norman Altman, Dr Julia Zaias, and Dr Eleni Kapsalis (University of

Miami) assisted with manuscript development. The Division of Laboratory Animal Resources, the University of Pittsburgh, provided internal funding for completion of this project.

References

1. **Alak BM, Wolf DP.** 1994. Rhesus monkey oocyte maturation and fertilization in vitro: roles of the menstrual cycle phase and of exogenous gonadotropins. Biol Reprod **51:**879–887.
2. **Bai J, Wong FW, Bauman A, Mohsin M.** 2002. Parity and pregnancy outcomes. Am J Obstet Gynecol **186:**274–278.
3. **Bagheri MM, Burd L, Martsolf JT, Klug MG.** 1998. Fetal alcohol syndrome: maternal and neonatal characteristics. J Perinat Med **26:**263–269.
4. **Bergmann A, Zygmunt M, Clapp JF 3rd.** 2004. Running throughout pregnancy: effect on placental villous vascular volume and cell proliferation. Placenta **25:**694–698.
5. **Brenner RM, Rudolph L, Mastrisian L, Slayden OD.** 1996. Nonhuman primate models: artificial menstrual cycles, endometrial matrix metalloproteinases and subcutaneous endometrial grafts. Hum Reprod **11 Suppl 2:**150–164.
6. **Cho F, Hiyaoka A, Suzuki MT, Honjo S.** 2002. Breeding of African green monkeys (*Cercopithecus aethiops*) under indoor individually caged conditions. Exp Anim **51:**343–351.
7. **Clausson B, Granath F, Ekbom A, Lundgren S, Nordmark A, Signorello LB, Cnattingius S.** 2002. Effect of caffeine exposure during pregnancy on birth weight and gestational age. Am J Epidemiol **155:**429–436.
8. **Cody RP, Smith JK.** 1997. Applied Statistics and the SAS Programming Language, 4th Edition. Prentice Hall, Inc.
9. **Coutinho R, David RJ, Collins JW.** 1997. Relation of parental birth weights to infant birth weight among African Americans and whites in Illinois: a transgenerational study. Am J Epidemiol **146:**804–809.
10. **Davison BB, Cogswell FB, Baskin GB, Falkstein KP, Henson EW, Tarantal AF, Krogstad DJ.** 1998. *Plasmodium coatneyi* infection in the rhesus monkey (*Macaca mulatta*) as a model of malaria in pregnancy. Am J Trop Med Hyg **59:**189–201.
11. **Dettmer AM, Houser LA, Ruppenthal GC, Capuono S, Hewitson L.** 2007. Growth and development outcomes of three high-risk infant rhesus macaques (*Macaca mulatta*). Am J Primatol **69:**503–518.
12. **Divon MY.** Prolonged pregnancy. 2002. Gabbe SG, Niebyl JR, Simpson JL, editors. Obstetrics—normal and problem pregnancies, 4th ed. Oxford (UK): Churchill Livingstone.
13. **Friis H, Gomo E, Nyazema N, Ndhlovu P, Krarup H, Kaestel P, Michaelson KF.** 2004. Maternal body composition, HIV infection and other predictors of gestation length and birth size in Zimbabwe. Br J Nutr **92:**833–840.
14. **Gardin JF, Jerome CP, Jayo MJ, Weaver DS.** 1989. Maternal factors affecting reproduction in a breeding colony of cynomologus macaques (*Macaca fasicularis*). Lab Anim Sci **39:**205–212.
15. **Gilbert SG, Rice DC, Reuhl KR, Stavric B.** 1988. Adverse pregnancy outcome in the monkey (*Macaca fasicularis*) after chronic caffeine exposure. J Pharmacol Exp Ther **245:**1048–1053.
16. **Golub MS, Gershwin ME, Hurley LS, Baly DL, Hendrickx AG.** 1984. Studies of marginal zinc deprivation in rhesus monkeys: II. Pregnancy outcome. Am J Clin Nutr **39:**879–887.
17. **Golub MS, Hogrefe CE, Tarantal AF, German SL, Beard JL, Georgieff MK, Calatroni A, Lozoff B.** 2006. Diet-induced iron deficiency anemia and pregnancy outcome in rhesus monkeys. Am J Clin Nutr **83:**647–656.
18. **Ha JC, Robinette RL, Sackett GP.** 1999. Social housing and pregnancy outcome in captive pigtailed macaques. Am J Primatol **47:**153–163.
19. **Ha JC, Ha RR, Almasy L, Dyke B.** 2002. Genetics and caging type affect birth weight in captive pigtailed macaques (*Macaca nemestrina*). Am J Primatol **56:**207–213.
20. **Hackman E, Emanuel I, van Belle G, Daling J.** 1983. Maternal birth weight and subsequent pregnancy outcome. JAMA **250:**2016-2019.
21. **Hendrickx AG, Dukelow R.** 1995. Nonhuman primates in biomedical research: biology and management. First Edition. Academic Press, Inc. 147 p
22. **Janerich DT, Mayne ST.** 1990. Alcohol and pregnancy. An epidemiologic perspective. Ann Epidemiol **1:**179–185.
23. **Jaspan HB, Robinson JE, Amedee AM, Van Dyke RB, Garry RF.** 2004. Amniotic fluid has higher relative levels of lentivirus-specific antibodies than plasma and can contain neutralizing antibodies. J Clin Virol **31:**190–197.
24. **Juntunen KS, Laara EM, Kauppila AJ.** 1997. Grand grand multiparity and birth weight. Obstet Gynecol **90 4 Pt l:**495–499.
25. **Kalanda BF, van Buuren S, Verhoeff FH, Brabin BJ.** 2005. Anthropometry of fetal growth in rural Malawi in relation to maternal malaria and HIV status. Arch Dis Child Fetal Neonatal Ed **90:**F161–F165.
26. **Kemnitz JW, Eisele SG, Lindsay KA, Engle MJ, Perelman RH, Farrell PM.** 1984. Changes in food intake during menstrual cycles and pregnancy of normal and diabetic rhesus monkeys. Diabetologia **26:**60–64.
27. **Kiely JL, Paneth N, Susser M.** 1986. An assessment of the effects of maternal age and parity in different componenets of prenatal mortality. Am J Epidemiol **123:**444–454.
28. **Klebanoff MA, Graubard BI, Kessel SS, Berendes HW.** 1984. Low birth weight across generations. JAMA **252:**2423–2427.
29. **Klebanoff MA, Yip R.** 1987. Influence of maternal birth weight on rate of growth and duration of gestation. J Pediatr **111:**287–292.
30. **Laakso M.** 2005. Prevention of type 2 diabetes. Curr Mol Med **5:**365–374.
31. **Little RE.** 1987. Mother's and father's birth weight as predictors of infant birth weight. Paediatr Perinat Epidemiol **1:**19–31.
32. **Mathews TJ, Menacker F, MacDorman MF.** 2002. Infant mortality statistics from the 2000 period linked birth–death data set. National Center for Health Statistics.Natl Vital Stat Rep **50:**1-27.
33. **Moazed TC, Thouless ME.** 1993. Viral persistence of simian type D retrovirus (SRV-2/W) in naturally infected pigtailed macaques (*Macaca nemestrina*). J Med Primatol **22:**382–389.
34. **Mok J, Pembrey L, Tovo PA, Newell ML.** 2005. When does mother to child transmission of hepatitis C virus occur? European Paediatric Hepatitis C Virus Network. Arch Dis Child Fetal Neonatal Ed **90:**F156–F160.
35. **Morris SN, Johnson NR.** 2005. Exercise during pregnancy: a critical appraisal of the literature. J Reprod Med **50:**181–188.
36. **National Research Council. 1996.** Guide for the Care and Use of Laboratory Animals. National Academy Press, Washington, DC.
37. **Phillippi-Falkenstein K, Harrison RM.** 2003. Four-year study of controlled timed breeding of rhesus monkeys (*Macaca mulatta*). Am J Primatol **60:**23–28.
38. **Price KC, Coe CL.** 2000. Maternal constraint on fetal growth patterns in the rhesus monkey (*Macaca mulatta*): the intergenerational link between mothers and daughters. Hum Reprod **15:**452–457.
39. **Price KC, Hyde JS, Coe CL.** 1999. Matrilineal transmission of birth weight in the rhesus monkey (*Macaca mulatta*) across several generations. Obstet Gynecol **94:**128–134.
40. **Prager K, Malin H, Spiegler D, Van Natta P, Placek PJ.** 1984. Smoking and drinking behavior before and during pregnancy of married mothers of live- born infants and stillborn infants. Public Health Rep **99:**117–127.
41. **Ross C.** 1988. The intrinsic rate of natural increase and reproductive effort in primates. J Zool **214:**199–219.
42. **Ruijter I, Miller JM Jr.** 1999. Evaluation of low birthweight in African Americans. J Natl Med Assoc **91:**663–667.
43. **Sanderson M, Emanuel I, Holt VL.** 1995. The intergenerational relationship between mother's birthweight, infant birthweight and infant mortality in black and white mothers. Paediatr Perinat Epidemiol **9:**391–405.
44. **Schneider ML, Moore CF, Becker EF.** 2001. Timing of moderate alcohol exposure during pregnancy and neonatal outcome in rhesus monkeys (*Macaca Mulatta*). Alcohol Clin Exp Res. **25:**1238–1245.

45. **Schneider ML, Moore CF, Kraemer GW, Roberts AD, DeJesus OT.** 2002. The impact of prenatal stress, fetal alcohol exposure, or both on development: perspectives from a primate model. Psychoneuroendocrinology **27:**285–298.
46. **Schwartz R, Susa J.** 1980. Fetal macrosomia—animal models. Diabetes Care **3:**430–432.
47. **Shaughnessy PW, DiGiacomo RF, Martin DP, Valerio DA.** 1978. Prematurity and perinatal mortality in the rhesus macaque (*Macaca mulatta*): relationship to birth weight and gestational age. Biol Neonate **34:**129–145.
48. **Skjaerven R, Wilcox AJ, Oyen N, Magnus P.** 1997. Mother's birth weight and survival of their offspring: population based study. BMJ **314:**1376–1380.
49. **Slayden OD, Nayak NR, Burton KA, Chwalisz K, Cameron ST, Critchley HOD, Baird DT, Brenner RM.** 2001. Progesterone antagonists increase androgen receptor expression in the rhesus macaque and human endometrium. J Clin Endocrinol Metab **86:**2668–2679.
50. **Small MF.** 1982. Reproductive failure in macaques. Am J Primatol **2:**137–147.
51. **Susa JB, Neave C, Sehgal P, Singer DB, Zeller WP, Schwartz R.** 1984. Chronic hyperinsulinemia in the fetal rhesus monkey. Effects of physiologic hyperinsulinemia on fetal growth and composition. Diabetes **33:**656–660.
52. **Thorne C, Patel D, Newell ML.** 2004. Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. AIDS **18:**2337–2339.
53. **Tsai CC, Follis KE, Snyder K, Windsor S, Thouless ME, Kuller L, Morton WR.** 1990. Maternal transmission of Type D simian retrovirus (SRV-2) in pigtailed macaques. J Med Primatol **19:**203–216.
54. **Van Wagenen G.** 1972. Vital statistics from a breeding colony. Reproduction and pregnancy outcome in *Macaca mulatta*. J Med Primatol **1:**2–28.
55. **Wen SW, Goldenberg RL, Cutter GR, Hoffman HJ, Cliver SP, Davis RO, DuBard MB.** 1990. Smoking, maternal age, fetal growth, and gestational age at delivery. Am J Obstet Gynecol **162:**53–58.
56. **Wilcox MA, Chang AMZ, Johnson IR.** 1996. The effects of parity on birth weight using successive pregnancies. Acta Obstet Gynecol Scand **75:**459–463.