Published in final edited form as:

J Med Primatol. 2019 April ; 48(2): 90–98. doi:10.1111/jmp.12396.

Effect of maternal obesity on fetal and postnatal baboon (*Papio* species) early life phenotype

Cun Li^{1,2}, Susan Jenkins¹, McKenna M. Considine¹, Laura A. Cox^{2,3}, Kenneth G. Gerow⁴, Hillary F. Huber¹, and Peter W. Nathanielsz^{1,2}

¹Texas Pregnancy and Life-course Health Center, Department of Animal Sciences, University of Wyoming, Laramie, Wyoming, USA

²Southwest National Primate Research Center, Texas Biomedical Research Institute, San Antonio, Texas, USA

³Center for Precision Medicine, Department of Internal Medicine, Section on Molecular Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA

⁴Department of Statistics, University of Wyoming, Laramie, Wyoming, USA

Abstract

Background—Nonhuman primate models of developmental programming by maternal obesity (MO) are needed for translation to human programming outcomes. We present baboon offspring (F1) morphometry, blood cortisol, and ACTH from 0.9 gestation to 0–2 years.

Methods—Control mothers ate chow; MO mothers ate high-fat high-energy diet pre-pregnancy through lactation.

Results—MO mothers weighed more than controls pre-pregnancy. MO gestational weight gain was lower with no correlation with fetal or placenta weights. At 0.9 gestation, MO and control F1 morphometry and ACTH were similar. MO-F1 0.9 gestation male cortisol was lower, rising slower from 0–2 years vs control-F1. At birth, male MO-F1 and control-F1 weights were similar, but growth from 0–2 years was steeper in MO-F1; newborn female MO-F1 weighed more than control-F1 but growth from 0–2 years was similar. ACTH did not change in either sex.

Conclusions—MO produced sexually dimorphic fetal and postnatal growth and hormonal phenotypes.

Keywords

high fat diet; fructose; high energy diet; nonhuman primates; developmental programming; maternal nutrition; Baboon; Cortisol; ACTH

Correspondence Peter W. Nathanielsz, University of Wyoming, C/O Texas Biomedical Research Institute, P.O. Box 760549, San Antonio, Texas 78245-0549, peter.nathanielsz@uwyo.edu, Telephone: (210) 632-6749 .

Institution at Which Work Was Performed: Southwest National Primate Research Center, San Antonio, Texas, USA

Introduction

Obesity in women of reproductive years is now an epidemic. As a result there is considerable interest in developmental programming of offspring (F1) as a consequence of maternal obesity.¹ Developmental programming can be defined as *responses to challenges during critical time windows that alter development with persistent effects on phenotype that may not emerge until later life*. Maternal obesity is associated with multiple maternal complications, including preeclampsia, gestational diabetes, thromboembolic complications, infection, poor progress in labor, increased incidence of cesarean section, postpartum hemorrhage difficulties in delivery, and hypertension.^{2,3} In addition F1 of obese pregnant women experience more neonatal morbidity and mortality.^{4,5} Recently much interest has focused on the predisposition of F1 born to obese mothers to multiple chronic life course adverse health conditions, such as diabetes, hypertension, and themselves becoming obese.^{4,6–11} In animal models, maternal obesity has been shown to result in offspring hypertension, glucose metabolism dysregulation, and altered endocrine and reproductive function.¹²

Many rodent models have been extensively studied in multiple laboratories,^{13–16} but to date only two nonhuman primate models of maternal obesity have been reported: the Japanese macaque (*Macaca fuscata*)¹⁷ and baboon (*Papio* species).¹⁸ While data on maternal changes in pregnancy and F1 function in fetal life and postnatally have been published,^{19–21} the fetal and early life growth phenotype programmed by maternal obesity has not been established. To characterize early life programming consequences, we report here growth data from male and female offspring of control and obese mothers from 0.9 gestation (G) through the first two years of postnatal life in our baboon model. In this model, control mothers are fed normal primate center chow *ad libitum* while starting at least nine months before pregnancy obese mothers are fed a diet consisting of free access to both the control diet and a high fat, high-energy diet and high fructose beverages. We have demonstrated that this feeding regimen leads to higher maternal body fat content, higher waist-hip circumferences, and dyslipidemia (elevated LDL cholesterol and triglycerides), typical characteristics of an obesogenic phenotype.¹⁸ In preparation for an independent postnatal life, the fetal hypothalamo-pituitary-adrenal (HPA) axis plays a central role in balancing perinatal growth and terminal cellular differentiation in the second half of pregnancy and early life.²² We therefore measured serum adrenocorticotropin (ACTH) and cortisol levels in fetuses and offspring.

Materials and methods

Humane care guidelines

All procedures were approved by the Texas Biomedical Research Institute Institutional Animal Care and Use Committee and conducted in AAALAC approved facilities.²³

Animal management and housing

Female baboons were housed with a proven breeder male in custom-built group cages containing up to 16 females per cage and allowing normal physical and social interaction and environmental enrichment at Southwest National Primate Research Center (SNPRC).

Details of housing and breeding have been described previously.^{23,24} Animal health was supervised by SNPRC veterinarians. Females were randomly assigned prior to breeding to the control group (CTR) or the maternal obesity group (MO). CTR mothers ate *ad libitum* SNPRC biscuits (Purina Monkey Diet and Monkey Diet Jumbo, Purina LabDiets, St Louis, MO) containing 12% energy from fat, 0.29% from glucose, 0.32% from fructose, and a metabolizable energy content of 3.07 kcal/g. For at least 9 months prior to breeding, MO mothers ate *ad lib* CTR diet + *ad lib* Purina 5045–6 (Purina LabDiets, St Louis, MO, USA), a high fat and high energy diet containing 45% energy from fat, 4.6% from glucose, 5.6% from fructose, and a metabolizable energy content of 4.03 kcal/g; MO group also had continuous access to a high fructose beverage. The MO group was provided with both diets because animals ate more when both diets were available.¹⁸

In a subgroup of pregnant baboons, C-sections were performed^{24,25} at 0.9 G (N = 46). Details of c-section and postoperative care are published.²⁶ Briefly, mothers were premedicated with ketamine (10 mg/kg body weight) and c-section performed under general anesthesia (isoflurane 2%). Fetuses were euthanized by exsanguination to preserve tissues for histological studies. Maternal postoperative analgesia was buprenorphine SR (0.2 mg/kg IM). Thirty-nine mothers delivered live newborns by spontaneous vaginal delivery. Lactating mothers and their offspring remained on their pregnancy diets and continued to be housed in the same group cages until offspring were weaned onto SNPRC biscuits (Purina Monkey Diet, Purina LabDiets, St Louis, MO) at approximately 9 months of age. After weaning, offspring were separated into male and female juvenile groups. Since diet treatment was assigned before sex of offspring was known, we were unable to control the exact number of males and females in each group. Sex distribution between groups is shown in Table 1.

Morphometrics

Offspring of CTR and MO mothers were weighed and body dimensions measured at C-section, birth, and at 2, 3, 6, 9, 12, 18, and 24 months of age. Body weight was measured with a digital scale. Body length, head circumference, abdominal circumference, chest circumference, and hip circumference were assessed with a tape measure by trained and experienced personnel (Table 2). All measurements were taken three times and the means used as final values. We have demonstrated inter-observer reliability of these measurements.²⁷

Blood sampling

Fetal blood samples were taken at 0.9 G. Postnatal samples were taken at birth, and at 2, 3, 6, 9, 12, 18, and 24 months of age. Blood samples were taken from 8:00–10:00 am in the group cage area within 5 minutes of isolation and tranquilization with 10 mg/kg ketamine IM. We have shown that ketamine administration does not affect ACTH and cortisol levels within 10 minutes of administration.²⁷ Serum ACTH_{1–39} was measured by a two-site ELISA and cortisol by chemiluminescent immunoassay on an Immulite® 1000 Immunoassay System (Siemens Healthcare Diagnostics). The intra-/inter-assay CVs for ACTH were 4.8 / 7.2. The intra-/inter-assay CVs for cortisol were 5.6/8.4.²⁸

Statistical analyses

Linear regression was used to provide correlation and hence potential evidence of causative effects during pregnancy of the variables maternal gestational weight gain, fetal weight, and placenta weight. All ACTH and cortisol data were ln-transformed to attain normality. Fetal morphometric measurements and blood values for ACTH and cortisol were compared between CTR and MO at a single time point (0.9 G) using unpaired two-way Student's *t*-tests. Birth weight was also investigated with two-way *t*-tests. Postnatal morphometric variables, ACTH, and cortisol were regressed against age (0–24 months), then CTR and MO groups compared using F-test. Data are presented as mean $\pm$ standard error of the mean (SEM). Significance was set at $P = 0.05$.

Results

Relationships between maternal gestational weight gain, fetal weight, and placenta weight

At 0.9 G, fetal weight was correlated with placenta weight in CTR males and females, as well as MO males (Figure 1 A–B). Fetal weight was correlated with maternal gestational weight gain in CTR females but not CTR males or MO of either sex (Figure 1 C–D). Placenta weight was not correlated with maternal weight gain in MO or CTR males or females (Figure 1 E–F).

When baboons were allowed to deliver spontaneously, gestation length was similar between MO and CTR for both sexes of offspring. Baseline maternal weights were greater in the MO group than in CTR among mothers of both males and females. Weight gain during pregnancy, whether expressed in kg or as a % of baseline weight, was greater in the CTR mothers than MO among mothers of females, but not among mothers of males (Table 3).

Fetal morphometrics

At 0.9 G, the difference between CTR and MO hip circumference in male fetuses (Table 4 A) and chest circumference in female fetuses (Table 4 B) approached significance. There were no differences in fetal weight, length, BMI, or head circumference between CTR and MO groups in either male (Table 4 A) or female fetuses (Table 4 B).

Fetal ACTH and cortisol

At 0.9 G, fetal serum ACTH was similar between CTR and MO in both males and females (Figure 2 A). In males, cortisol was lower in the MO group than in CTR, $P = 0.04$ (Figure 2 B).

Postnatal morphometrics

Mean body weight values were numerically higher for MO than CTR in both males and females at most ages of measurement (Figure 3 A). At birth, MO females weighed 26% more (0.96 ± 0.04 kg) than CTR females (0.74 ± 0.04 kg, $P = 0.002$). Male MO weighed 10% more on average than (0.97 ± 0.04 kg) CTR (0.88 ± 0.05) at birth, although birth weights were statistically similar ($p = 0.19$). Birth weight was higher than 0.9 G weight in MO males ($P = 0.01$) and females ($P < 0.001$), but not CTR males ($P = 0.31$) or females ($P = 0.67$).

In males, the MO body weight regression slope ($Y = 0.28 * X + 0.87$; $R = 0.99$) was steeper than the CTR slope ($Y = 0.25 * X + 0.82$, $R = 0.99$) from birth through 2 years (Figure 3 A; $P < 0.0001$). In females, body weight slopes were similar (Figure 3 A; MO $Y = 0.26 * X + 0.92$, $R = 0.98$; CTR $Y = 0.25 * X + 0.67$, $R = 0.99$; $P = 0.26$). Male MO showed steeper growth slopes compared to CTR for circumferences of the head (MO $Y = 0.36 * X + 24.2$, $R = 0.87$; CTR $Y = 0.28 * X + 24.3$, $R = 0.84$; $P = 0.002$), chest (MO $Y = 0.93 * X + 20.3$, $R = 0.94$; CTR $Y = 0.82 * X + 19.9$, $R = 0.95$; $P = 0.02$), and hip (MO $Y = 0.73 * X + 15.0$, $R = 0.92$; CTR $Y = 0.60 * X + 15.1$, $R = 0.93$; $P = 0.002$); in each case, male MO and CTR started out similar in size, but by 2 years of age MO were larger (Figure 3 B). In females, MO and CTR regression slopes differed in the measurements body length (MO $Y = 1.65 * X + 42.9$, $R = 0.92$; CTR $Y = 1.99 * X + 40.1$, $R = 0.96$; $P = 0.006$) and chest circumference (MO $Y = 0.85 * X + 21.2$, $R = 0.93$; CTR $Y = 0.98 * X + 18.8$, $R = 0.97$; $P = 0.02$); female MO started out larger, with the difference between groups decreasing by 2 years of age (Figure 3 C).

During the first 2 years of life, growth appeared to be symmetric, as the head to abdominal circumference ratio slopes were similar between male MO and CTR (MO $Y = -0.02 * X + 1.3$, $R = 0.71$; CTR $Y = -0.02 * X + 1.4$, $R = 0.77$; $P = 0.41$), as well as between female MO and CTR (MO $Y = -0.03 * X + 1.3$, $R = 0.79$; CTR $Y = -0.03 * X + 1.4$, $R = 0.72$; $P = 1.0$).

Postnatal ACTH and cortisol

ACTH slopes were similar between CTR and MO in both males (Figure 4 A; $P = 0.65$) and females (Figure 4 B; $P = 0.33$) through the first two postnatal years.

Cortisol slopes differed between male MO ($Y = 0.96 * X + 40.0$, $R = 0.39$) and CTR ($Y = 1.64 * X + 29.2$, $R = 0.62$); cortisol started out higher in MO than in CTR but increased less than in CTR over the first two postnatal years ($P = 0.04$, Figure 4 C). Cortisol was similar throughout the period studied between female MO and CTR (Figure 4 D, $P = 0.20$).

Discussion

The morphometric data presented in this paper demonstrate that in a baboon model of MO, offspring growth was altered in a sexually dimorphic manner. At 0.9 G, MO and CTR were similar in body size in both sexes. However, by the time of birth treatment differences had appeared due to fetuses of MO mothers growing much more during the last 10% of gestation than fetuses of CTR mothers; F1 delivery weight was higher than 0.9 G weight in MO males (16% weight gain) and females (28.4% weight gain), but not CTR males (6.2 % weight gain) or females (-2.9% weight loss). By birth, MO females weighed 26% more than CTR females, while MO males weighed 10% more on average than CTR although male birth weights were statistically similar.

Postnatally, in males the difference in weight increased with age such that male MO showed a much steeper weight growth rate than male CTR. MO males also showed steeper growth than CTR in circumferences of the head, chest, and hips. In females there was a different pattern. Although MO females started out heavier, the overall difference in weight growth from birth to two years was similar between groups. Female MO showed different growth

than female CTR in body length and chest circumference; MO females started out larger, but by two years of age the difference between groups decreased. Thus, it appears that offspring macrosomia resulting from MO increased over the first two years of life in males but decreased over the first two years of life in females. Maternal obesity and infant and childhood macrosomia in humans are associated with increased risk of offspring obesity and metabolic syndrome in childhood and adolescence. Sex differences in maternal obesity induced outcomes in human neonates have received limited direct attention. Most studies use multivariate analysis modelling to control for sex differences but do not analyze sex effects in depth.^{6,7,10,11}

The morphometric differences occurred even though MO and CTR offspring ate the same diets from weaning at nine months of age until the last measurements were taken at two years of age. The finding that male MO and CTR were statistically similar in body weight at birth, but MO grew sharply heavier thereafter, provides yet another demonstration that birth weight alone is not an accurate indicator for effects of developmental programming. Although studies sometimes consider lack of change in birth weight as implying safety of a treatment,^{29,30} more investigators are beginning to recognize that developmental programming outcomes are highly variable across birth weights.^{31–33}

Male fetal cortisol was higher in CTR than MO at 0.9 G, while ACTH was similar between groups (Figure 2). Postnatally, although cortisol started out higher in MO males than in CTR, MO cortisol increased less steeply over the first two postnatal years, such that MO cortisol was eventually lower (Figure 4). This finding partly corresponds with the scant human literature. One study found a positive association between pregnancy weight gain (but not pre-pregnancy BMI) and fasting morning cortisol of preschool age children, with the relationship more pronounced in females.³⁴ Another study reported maternal truncal obesity was positively associated with elevated morning cortisol in 8.5-year-old children regardless of gender.³⁵ Studies in sheep have also demonstrated an association between maternal obesity and offspring elevated cortisol.^{36,37} Although the findings are distinct in each case, potentially due to differences in characterization and the precise cause of the obesity, demographics, and age at cortisol measurement, there is support for the view that cortisol is increased in offspring of obese mothers.

The HPA axis regulates basal circulating ACTH and cortisol concentrations as well as responding rapidly to environmental perturbations by increasing secretion of these key stress hormones.³⁸ Increases in ACTH secretion are driven by hypothalamic corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which stimulate release of ACTH, which then stimulates adrenal glucocorticoid secretion. Fetal adrenal function is relatively unresponsive to ACTH until late gestation when it increases dramatically.^{27,39,40} The overall physiological significance of circulating cortisol is complicated by the potential for local cortisol production in fetal tissues by the 11 β hydroxysteroid dehydrogenase (11 β HSD) system. The enzyme 11 β HSD1 increases cortisol levels by converting inactive cortisone to cortisol while 11 β HSD2 catalyzes the reverse reaction. Cortisol can be produced in fetal baboon liver and adipose tissue⁴¹ with potential local effects. 11 β HSD1 and 2 are both present in the baboon hypothalamus⁴² and can potentially affect negative feedback on the HPA system.

Both local and circulating cortisol regulate growth and differentiation of multiple organ systems. As mentioned above, in late gestation, cortisol plays a vital role in preparing the fetus for extrauterine life,⁴³ with maturational effects on major organs, including the thyroid, lungs, intestines, liver, kidney, and brain that favor cellular differentiation over proliferation.⁴³ We have reported that MO upregulates proteins associated with stress in the late gestation fetal frontal cortex,⁴⁴ increases oxidative stress in the frontal cortex⁴⁵ and pancreas,⁴⁶ and dysregulates key factors in pancreatic islet proliferation and differentiation.⁴⁷ It is thus clear that a variety of challenges to the normal developmental trajectory of the fetus are influenced by cortisol exposure, with both immediate and long-term consequences in terms of life course health.

In humans, MO is associated with higher birth weight,^{48,49} although there is a large degree of variability, including higher risk of fetal growth restriction⁵⁰ as well as higher fat mass in MO F1 with only a trend toward increase in weight.⁵¹ Study of MO in sheep has found increased body and organ weight at mid gestation,^{52,53} with similarity in weights by late gestation⁵² or birth⁵⁴ between MO and CTR. These findings indicate that MO does not always lead to statistically significant difference in birth weight between MO and CTR. This may be due to the high amount of variability in birth weight, since MO groups tend to weigh more on average but standard errors may lead to nonsignificant difference. In this study, CTR mothers gained more weight during pregnancy than did obese mothers regardless of offspring sex. On average, MO mothers lost weight during pregnancy, even though their offspring were similar in size to CTR at 0.9 G and tended to be heavier at birth. Since MO offspring grew without their mothers gaining weight, there was no correlation between gestational weight gain and fetal weight or placenta weight in MO mothers. Placenta weight was associated with fetal weight in all groups except MO females. CTR mothers showed gestational weight gain in positive association with fetal weight in mothers of females but not males. Among human mothers, gestational weight gain is typically associated with birth weight in both offspring sexes,^{3,9,10,55} and has also been positively associated with offspring BMI from ages 1–42 years.^{10,11} Human obese mothers often gain weight in excess of recommendations and complications for mother and offspring intensify with greater weight gain.^{56–58} For example, risk for preeclampsia, large for gestational age offspring (especially among males⁵⁹), and Cesarean section are increased in obese mothers, but risk is reduced with decreased gestational weight gain.⁵⁷ Therefore, the MO mothers and offspring in this study present with higher risk than CTR due to maternal obesity, but lower risk than if mothers had experienced excessive gestational weight gain. Despite the low gestational weight gain among obese mothers, their offspring still showed altered postnatal growth and hormonal phenotypes.

In summary, we have compared fetal and postnatal phenotype in the setting of maternal obesity during fetal and neonatal life. Numerous changes to pre- and post-natal offspring phenotype were observed, including sexually dimorphic alterations to body growth and cortisol levels indicative of increased life course risk of disease. Our findings will focus attention on critical periods of development and potential involvement of the HPA axis. MO is an ever-increasing complication of human pregnancy. NHP studies provide benefits such as the ability for multiple repetitive sampling in the same individual, even with minimally

invasive procedures like venipuncture. Studies in NHP are necessary to determine the mechanisms, origins, and outcomes of MO.

Acknowledgements

The baboon cohorts were funded by HD21350 and R24OD010916. We thank Karen Moore for administrative support. We are grateful to Martha Avila, Steve Rios, and Sam Vega for their work in animal husbandry and management.

Acknowledgement of Funding: This work was supported by HD21350 and R24OD010916.

References

1. Poston L, Caleyachetty R, Cnattingius S, Corvalán C, Uauy R, Herring S, Gillman MW. Preconceptional and maternal obesity: epidemiology and health consequences. *Lancet Diabetes Endocrinol* 2016;4(12):1025–1036. doi:10.1016/S2213-8587(16)30217-0. [PubMed: 27743975]
2. Oteng-Ntim E, Doyle P. Maternal outcomes in obese pregnancies. In: Gillman MW, Poston L, eds. *Maternal Obesity* New York, NY: Cambridge University Press; 2012:35–44.
3. Cedergren M Effects of gestational weight gain and body mass index on obstetric outcome in Sweden. *Int J Gynaecol Obstet* 2006;93(3):269–274. doi:10.1016/j.ijgo.2006.03.002. [PubMed: 16626716]
4. Fraser A, Lawlor DA. Long-term consequences of maternal obesity and gestational weight gain for offspring obesity and cardiovascular risk: Intrauterine or shared familial mechanisms. In: Gillman MW, Poston L, eds. *Maternal Obesity* New York, NY: Cambridge University Press; 2012:87–99.
5. Chu SY, Kim SY, Lau J, Schmid CH, Dietz PM, Callaghan WM, Curtis KM. Maternal obesity and risk of stillbirth: a metaanalysis. *American Journal of Obstetrics and Gynecology* 2007;197:223–228. [PubMed: 17826400]
6. Whitaker RC. Predicting preschooler obesity at birth: the role of maternal obesity in early pregnancy. *Pediatrics* 2004;114(1):e29–36. [PubMed: 15231970]
7. Martorell R, Stein AD, Schroeder DG. Early nutrition and later adiposity. *J Nutr* 2001;131(3):874S–880S. [PubMed: 11238778]
8. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics* 2005;115(3):e290–6. doi: 10.1542/peds.2004-1808. [PubMed: 15741354]
9. Catalano PM, Ehrenberg HM. Review article: The short- and long-term implications of maternal obesity on the mother and her offspring. *BJOG: An International Journal of Obstetrics & Gynaecology* 2006;113(10):1126–1133. doi:10.1111/j.1471-0528.2006.00989.x. [PubMed: 16827826]
10. Schack-Nielsen L, Michaelsen KF, Gamborg M, Mortensen EL, Sørensen TIA. Gestational weight gain in relation to offspring body mass index and obesity from infancy through adulthood. *Int J Obes (Lond)* 2010;34(1):67–74. doi:10.1038/ijo.2009.206. [PubMed: 19918246]
11. Curhan GC, Chertow GM, Willett WC, Spiegelman D, Colditz GA, Manson JE, Speizer FE, Stampfer MJ. Birth weight and adult hypertension and obesity in women. *Circulation* 1996;94(6): 1310–1315. [PubMed: 8822985]
12. Zambrano E, Nathanielsz PW. Mechanisms by which maternal obesity programs offspring for obesity: evidence from animal studies. *Nutrition reviews* 2013;71 Suppl 1:S42–54. doi:10.1111/nure.12068. [PubMed: 24147924]
13. Armitage JA, Khan IY, Taylor PD, Nathanielsz PW, Poston L. Developmental programming of the metabolic syndrome by maternal nutritional imbalance: how strong is the evidence from experimental models in mammals? *The Journal of physiology* 2004;561(Pt 2):355–377. doi: 10.1113/jphysiol.2004.072009. [PubMed: 15459241]
14. Armitage JA, Taylor PD, Poston L. Experimental models of developmental programming: consequences of exposure to an energy rich diet during development. *J Physiol (Lond)* 2005;565(Pt 1):3–8. doi:10.1113/jphysiol.2004.079756. [PubMed: 15695245]

15. Armitage JA, Poston L, Taylor PD. Developmental origins of obesity and the metabolic syndrome: the role of maternal obesity. *Front Horm Res* 2008;36:73–84. doi:10.1159/0000115355. [PubMed: 18230895]
16. Aiken CE, Ozanne SE. Breaking the cycle of intergenerational obesity. *J Physiol* 2017;595(5): 1443–1444. doi:10.1113/JP273821. [PubMed: 28012252]
17. Sullivan EL, Nousen EK, Chamlou KA, Grove KL. The Impact of Maternal High-Fat Diet Consumption on Neural Development and Behavior of Offspring. *Int J Obes Suppl* 2012;2:S7–S13. doi:10.1038/ijosup.2012.15. [PubMed: 26069734]
18. Nathanielsz PW, Yan J, Green R, Nijland M, Miller JW, Wu G, McDonald TJ, Caudill MA. Maternal obesity disrupts the methionine cycle in baboon pregnancy. *Physiological reports* 2015;3(11). doi:10.14814/phy2.12564.
19. McCurdy CE, Schenk S, Hetrick B, Houck J, Drew BG, Kaye S, Lashbrook M, Bergman BC, Takahashi DL, Dean TA, Nemkov T, Gertsman I, Hansen KC, Philp A, Hevener AL, Chicco AJ, Aagaard KM, Grove KL, Friedman JE. Maternal obesity reduces oxidative capacity in fetal skeletal muscle of Japanese macaques. *JCI Insight* 2016;1(16):e86612. doi:10.1172/jci.insight.86612. [PubMed: 27734025]
20. Roberts VHJ, Frias AE, Grove KL. Impact of maternal obesity on fetal programming of cardiovascular disease. *Physiology (Bethesda)* 2015;30(3):224–231. doi:10.1152/physiol.00021.2014. [PubMed: 25933822]
21. Suter MA, Sangi-Haghepykar H, Showalter L, Shope C, Hu M, Brown K, Williams S, Harris RA, Grove KL, Lane RH, Aagaard KM. Maternal High-Fat Diet Modulates the Fetal Thyroid Axis and Thyroid Gene Expression in a Nonhuman Primate Model. *Mol Endocrinol* 2012;26(12):2071–2080. doi:10.1210/me.2012-1214. [PubMed: 23015752]
22. Fowden AL, Giussani DA, Forhead AJ. Intrauterine programming of physiological systems: causes and consequences. *Physiology (Bethesda)* 2006;21:29–37. doi:10.1152/physiol.00050.2005. [PubMed: 16443820]
23. Schlambritz-Loutsevitch NE, Howell K, Rice K, Glover EJ, Nevill CH, Jenkins SL, Bill Cummins L, Frost PA, McDonald TJ, Nathanielsz PW. Development of a system for individual feeding of baboons maintained in an outdoor group social environment. *J Med Primatol* 2004;33(3):117–126. doi:10.1111/j.1600-0684.2004.00067.x. [PubMed: 15102068]
24. Li C, Levitz M, Hubbard GB, Jenkins SL, Han V, Ferry RJ, McDonald TJ, Nathanielsz PW, Schlambritz-Loutsevitch NE. The IGF axis in baboon pregnancy: placental and systemic responses to feeding 70% global ad libitum diet. *Placenta* 2007;28(11–12):1200–1210. doi:10.1016/j.placenta.2007.06.011. [PubMed: 17707905]
25. Schlambritz-Loutsevitch N, Ballesteros B, Dudley C, Jenkins S, Hubbard G, Burton GJ, Nathanielsz P. Moderate maternal nutrient restriction, but not glucocorticoid administration, leads to placental morphological changes in the baboon (*Papio* sp.). *Placenta* 2007;28(8–9):783–793. doi:10.1016/j.placenta.2006.11.012. [PubMed: 17382997]
26. Schlambritz-Loutsevitch NE, Hubbard GB, Dammann MJ, Jenkins SL, Frost PA, McDonald TJ, Nathanielsz PW. Normal concentrations of essential and toxic elements in pregnant baboons and fetuses (*Papio* species). *J Med Primatol* 2004;33(3):152–162. doi:10.1111/j.1600-0684.2004.00066.x. [PubMed: 15102072]
27. Li C, Jenkins S, Mattern V, Comuzzie AG, Cox LA, Huber HF, Nathanielsz PW. Effect of moderate, 30 percent global maternal nutrient reduction on fetal and postnatal baboon phenotype. *J Med Primatol* 2017. doi:10.1111/jmp.12290.
28. Li C, Ramahi E, Nijland MJ, Choi J, Myers DA, Nathanielsz PW, McDonald TJ. Up-regulation of the fetal baboon hypothalamo-pituitary-adrenal axis in intrauterine growth restriction: coincidence with hypothalamic glucocorticoid receptor insensitivity and leptin receptor down-regulation. *Endocrinology* 2013;154(7):2365–2373. doi:10.1210/en.2012-2111. [PubMed: 23625543]
29. Murphy VE, Zakar T, Smith R, Giles WB, Gibson PG, Clifton VL. Reduced 11 β -hydroxysteroid dehydrogenase type 2 activity is associated with decreased birth weight centile in pregnancies complicated by asthma. *J Clin Endocrinol Metab* 2002;87(4):1660–1668. doi:10.1210/jcem.87.4.8377. [PubMed: 11932298]

30. Mercado AB, Wilson RC, Cheng KC, Wei JQ, New MI. Prenatal treatment and diagnosis of congenital adrenal hyperplasia owing to steroid 21-hydroxylase deficiency. *J Clin Endocrinol Metab* 1995;80(7):2014–2020. doi:10.1210/jcem.80.7.7608248. [PubMed: 7608248]
31. Moritz KM, Singh RR, Probyn ME, Denton KM. Developmental programming of a reduced nephron endowment: more than just a baby's birth weight. *Am J Physiol Renal Physiol* 2009;296(1):F1–9. doi:10.1152/ajprenal.00049.2008. [PubMed: 18653482]
32. Barker DJP. Human growth and cardiovascular disease. *Nestle Nutr Workshop Ser Pediatr Program* 2008;61:21–38. doi:10.1159/000113163.
33. Gluckman PD, Hanson MA. The Developmental Origins of Health and Disease. In: Wintour EM, Owens JA, eds. *Early Life Origins of Health and Disease*. Vol 573. *Advances in Experimental Medicine and Biology* Boston, MA: Springer; 2006:1–7. doi:10.1007/0-387-32632-4_1.
34. Elhassan ME, Miller AL, Vazquez DM, Lumeng JC. Associations of prenatal and perinatal factors with cortisol diurnal pattern and reactivity to stress at preschool age among children living in poverty. *J Clin Res Pediatr Endocrinol* 2015;7(2):114–120. doi:10.4274/jcrpe.1685. [PubMed: 26316433]
35. Phillips DIW, Bennett FI, Wilks R, Thame M, Boyne M, Osmond C, Forrester TE. Maternal body composition, offspring blood pressure and the hypothalamic-pituitary-adrenal axis. *Paediatr Perinat Epidemiol* 2005;19(4):294–302. doi:10.1111/j.1365-3016.2005.00661.x. [PubMed: 15958152]
36. Ford SP, Zhang L, Zhu M, Miller MM, Smith DT, Hess BW, Moss GE, Nathanielsz PW, Nijland MJ. Maternal obesity accelerates fetal pancreatic beta-cell but not alpha-cell development in sheep: prenatal consequences. *Am J Physiol Regul Integr Comp Physiol* 2009;297(3):R835–843. doi:10.1152/ajpregu.00072.2009. [PubMed: 19605766]
37. Long NM, Ford SP, Nathanielsz PW. Maternal obesity eliminates the neonatal lamb plasma leptin peak. *J Physiol (Lond)* 2011;589(Pt 6):1455–1462. doi:10.1113/jphysiol.2010.201681. [PubMed: 21262878]
38. Sapolsky RM. Adrenocortical function, social rank, and personality among wild baboons. *Biol Psychiatry* 1990;28(10):862–878. [PubMed: 2268690]
39. Challis JR, Sloboda D, Matthews SG, Holloway A, Alfaidy N, Patel FA, Whittle W, Fraser M, Moss TJ, Newnham J. The fetal placental hypothalamic-pituitary-adrenal (HPA) axis, parturition and post natal health. *Mol Cell Endocrinol* 2001;185(1–2):135–144. [PubMed: 11738803]
40. Poore KR, Young IR, Canny BJ, Thorburn GD. Studies on the role of ACTH in the regulation of adrenal responsiveness and the timing of parturition in the ovine fetus. *J Endocrinol* 1998;158(2):161–171. [PubMed: 9771459]
41. Guo C, Li C, Myatt L, Nathanielsz PW, Sun K. Sexually dimorphic effects of maternal nutrient reduction on expression of genes regulating cortisol metabolism in fetal baboon adipose and liver tissues. *Diabetes* 2013;62(4):1175–1185. doi:10.2337/db12-0561. [PubMed: 23238295]
42. Yang S, Gerow KG, Huber HF, Considine MM, Li C, Mattern V, Comuzzie AG, Ford SP, Nathanielsz PW. A decline in female baboon hypothalamo-pituitary-adrenal axis activity anticipates aging. *Aging* 2017. doi:10.18632/aging.101235.
43. Liggins GC. The role of cortisol in preparing the fetus for birth. *Reprod Fertil Dev* 1994;6(2):141–150. [PubMed: 7991781]
44. Yang S, Nathanielsz PW, Li J, Li C. Maternal obesity (MO) up-regulates proteins associated with stress in the late gestation baboon fetal frontal cortex. *Reprod Sci* 2016;23(1 Suppl):93A.
45. Li C, Yang S, Xie D, Li J, Nathanielsz PW. Increased oxidative stress (OS) at 90% (0.9) of gestation (G) in the frontal cortex (FC) of fetuses of obese baboons on a high energy diet. *Reprod Sci* 2016;23(1 Suppl):145A.
46. Tuerxun A, Li C, Nathanielsz PW. Maternal obesity increases oxidative stress in the fetal baboon pancreas in late gestation (G). *Reprod Sci* 2016;23(1 Suppl):193A–194A.
47. Li C, Xie LY, Nathanielsz PW. Maternal obesity (MO) in baboon pregnancy decreases fetal pancreatic proliferation and differentiation at 0.9 gestation (G). *Reprod Sci* 2015;22(1 Suppl):265A–266A.

48. Ehrenberg HM, Mercer BM, Catalano PM. The influence of obesity and diabetes on the prevalence of macrosomia. *Am J Obstet Gynecol* 2004;191(3):964–968. doi:10.1016/j.ajog.2004.05.052. [PubMed: 15467573]
49. Sebire NJ, Jolly M, Harris JP, Wadsworth J, Joffe M, Beard RW, Regan L, Robinson S. Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London. *Int J Obes Relat Metab Disord* 2001;25(8):1175–1182. doi:10.1038/sj.ijo.0801670. [PubMed: 11477502]
50. McDonald SD, Han Z, Mulla S, Beyene J, Knowledge Synthesis Group. Overweight and obesity in mothers and risk of preterm birth and low birth weight infants: systematic review and meta-analyses. *BMJ* 2010;341:c3428. [PubMed: 20647282]
51. Sewell MF, Huston-Presley L, Super DM, Catalano P. Increased neonatal fat mass, not lean body mass, is associated with maternal obesity. *Am J Obstet Gynecol* 2006;195(4):1100–1103. doi:10.1016/j.ajog.2006.06.014. [PubMed: 16875645]
52. Tuersunjiang N, Odhiambo JF, Long NM, Shasa DR, Nathanielsz PW, Ford SP. Diet reduction to requirements in obese/overfed ewes from early gestation prevents glucose/insulin dysregulation and returns fetal adiposity and organ development to control levels. *Am J Physiol Endocrinol Metab* 2013;305(7):E868–878. doi:10.1152/ajpendo.00117.2013. [PubMed: 23921140]
53. George LA, Uthlaut AB, Long NM, Zhang L, Ma Y, Smith DT, Nathanielsz PW, Ford SP. Different levels of overnutrition and weight gain during pregnancy have differential effects on fetal growth and organ development. *Reprod Biol Endocrinol* 2010;8:75. doi:10.1186/1477-7827-8-75. [PubMed: 20576133]
54. Long NM, George LA, Uthlaut AB, Smith DT, Nijland MJ, Nathanielsz PW, Ford SP. Maternal obesity and increased nutrient intake before and during gestation in the ewe results in altered growth, adiposity, and glucose tolerance in adult offspring. *J Anim Sci* 2010;88(11):3546–3553. doi:10.2527/jas.2010-3083. [PubMed: 20622177]
55. Frederick IO, Williams MA, Sales AE, Martin DP, Killien M. Pre-pregnancy body mass index, gestational weight gain, and other maternal characteristics in relation to infant birth weight. *Matern Child Health J* 2008;12(5):557–567. doi:10.1007/s10995-007-0276-2. [PubMed: 17713848]
56. Guelinckx I, Devlieger R, Beckers K, Vansant G. Maternal obesity: pregnancy complications, gestational weight gain and nutrition. *Obes Rev* 2008;9(2):140–150. doi:10.1111/j.1467-789X.2007.00464.x. [PubMed: 18221480]
57. Kiel DW, Dodson EA, Artal R, Boehmer TK, Leet TL. Gestational weight gain and pregnancy outcomes in obese women: how much is enough? *Obstet Gynecol* 2007;110(4):752–758. doi:10.1097/01.AOG.0000278819.17190.87. [PubMed: 17906005]
58. Crane JMG, White J, Murphy P, Burrage L, Hutchens D. The effect of gestational weight gain by body mass index on maternal and neonatal outcomes. *J Obstet Gynaecol Can* 2009;31(1):28–35. [PubMed: 19208280]
59. Ehrenberg HM, Mercer BM, Catalano PM. The influence of obesity and diabetes on the prevalence of macrosomia. *American Journal of Obstetrics and Gynecology* 2004;191:964–968. [PubMed: 15467573]

Figure 1.

Linear regressions of CTR (open) and MO (filled) data in male (A, C, E) and female (B, D, F) baboons at 0.9 G. Significant linear relationships in CTR group are indicated by dotted line and in MO group by solid; only significant linear relationships are depicted with a regression line. Significant correlations: A) CTR $Y=1.78 \cdot X+438$, $R=0.66$, $P=0.02$; MO $Y=1.46 \cdot X+480$, $R=0.73$, $P=0.02$; B) CTR $Y=1.72 \cdot X+419$, $R=0.68$, $P=0.01$; D) CTR $Y=68.7 \cdot X+666$, $R=0.59$, $P=0.03$.

Figure 2. Fetal A) ACTH and B) cortisol at 0.9 G in CTR (open, N = 14 male, 13 female) and MO (filled, N = 10 male, 9 female) fetuses. Mean $\pm$ SEM; *P = 0.04 compared to CTR.

Figure 3.

Offspring morphometric measurements during the first 2 years of life in CTR (open with dotted line; $N = 9\text{--}10$ males, $2\text{--}7$ females) and MO (filled with solid line; $N = 8\text{--}12$ males, $7\text{--}10$ females). A) Male MO showed steeper growth slopes than male CTR in body weight (MO slope 0.28 vs CTR slope 0.25; $P < 0.0001$), while female MO and CTR had similar body weight slopes (0.26 vs 0.25; $P = 0.26$). B) Male MO showed steeper slopes than CTR in head circumference (0.36 vs 0.28; $P = 0.002$), chest circumference (0.93 vs 0.82; $P = 0.02$), and hip circumference (0.73 vs 0.60; $P = 0.002$). C) Female MO differed from CTR in growth in body length (1.65 vs 1.99 cm; $P = 0.006$) and chest circumference (0.85 vs 0.98 cm; $P = 0.02$).

Figure 4.

Regression of A) ACTH in male CTR (open, $N = 10$) and MO (filled, $N = 12$) and B) ACTH in female CTR ($N = 5$) and MO ($N = 10$). CTR and MO ACTH slopes were not different in either sex. Regression of C) cortisol in male CTR ($N = 10$) and MO ($N = 12$) and D) cortisol in female CTR ($N = 5$) and MO ($N = 10$). Cortisol slopes in males (C) were significantly different: CTR 1.64 ng/ml/month vs MO 0.96 ng/ml/month, $P = 0.04$.

Table 1.

Male and female group sizes at different ages.

Age	Sex	Maternal diet	N
0.9 G fetuses	F	CTR	13
	M	CTR	14
	F	MO	9
	M	MO	10
Postnatal (0–2 yrs) baboons studied	F	CTR	7
	M	CTR	10
	F	MO	10
	M	MO	12

Table 2.

Morphometric measurement methods.

Measurement	Method
Body length (cm)	measured from the back of the head at the intersection of the parietal and lambdoidal sutures to the rump at the largest protrusion of the coccyx to the heel of the right foot
Chest circumference (cm)	measured all the way around the chest at the level of the nipples
Head circumference (cm)	measured over the most prominent part on the back of the head (occiput) and just above the eyebrows (supraorbital ridges), i.e., the largest circumference of the head
Hip circumference (cm)	measured all the way around the hips at the level of the greatest protrusion of the innominate/pelvic bone (anterior superior iliac spine)
Abdominal circumference (cm)	measured all the way around the abdomen at the level of the umbilicus

Table 3.

Maternal delivery data comparing mothers of MO and CTR male and female fetuses.

F1 sex & treatment	Gestation duration (days)	Maternal pre-pregnancy weight (kg)	Maternal weight gain (kg)	Maternal weight gain (%)
CTR F	181.6	15.3	1.37	9.78
SEM	1.57	0.52	0.82	5.88
N	7	6	6	6
MO F	182.8	20.2	-0.53	-2.34
SEM	1.63	0.75	0.50	2.30
N	10	9	9	9
CTR M	181.9	16.2	0.86	5.57
SEM	2.74	0.64	0.33	2.06
N	10	6	6	6
MO M	184.0	20.7	-0.50	-2.01
SEM	1.95	0.68	0.94	4.57
N	12	6	6	6
Female CTR vs MO P value	0.61	<0.001	0.06	0.05
Male CTR vs MO P value	0.53	0.001	0.21	0.16

Table 4.

Fetal morphometrics at 0.9 G in A) male CTR (N = 14) and MO (N = 10), and B) female CTR (N = 13) and MO (N = 9). Mean $\pm$ SEM; $+0.05 < P < 0.10$ compared to CTR.

A							
Group	Weight (g)	Length (cm)	BMI (kg/m²)	Head circ. (cm)	Chest circ. (cm)	Abdomen circ. (cm)	Hip circ. (cm)
CTR	828.05 $\pm$ 27.19	38.89 $\pm$ 0.67	5.53 $\pm$ 0.21	22.49 $\pm$ 0.26	17.25 $\pm$ 0.27	14.71 $\pm$ 0.39	14.81 $\pm$ 0.71
MO	824.64 $\pm$ 26.49	38.06 $\pm$ 0.16	5.82 $\pm$ 0.16	22.20 $\pm$ 0.32	16.75 $\pm$ 0.17	14.75 $\pm$ 0.35	16.50 $\pm$ 0.46+
B							
Group	Weight (g)	Length (cm)	BMI (kg/m²)	Head circ. (cm)	Chest circ. (cm)	Abdomen circ. (cm)	Hip circ. (cm)
CTR	756.95 $\pm$ 30.00	36.81 $\pm$ 0.78	5.59 $\pm$ 0.16	21.62 $\pm$ 0.27	17.42 $\pm$ 0.41	14.79 $\pm$ 0.53	14.54 $\pm$ 0.53
Mo	720.29 $\pm$ 27.44	35.83 $\pm$ 0.74	5.64 $\pm$ 0.25	21.78 $\pm$ 0.36	16.44 $\pm$ 0.31+	14.11 $\pm$ 0.62	14.56 $\pm$ 0.67