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Reproductive Cycling in Adult Baboons (*Papio* species) that Were Intrauterine Growth Restricted at Birth Implies Normal Fertility but Increased Psychosocial Stress

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Abstract

We investigated menstrual cycles in intrauterine growth restricted (IUGR, 7–10 yrs, n=8) and age-matched control (n=10) baboons. Cycle duration and plasma anti-Mullerian hormone were similar. IUGR spent more days per cycle swollen and had elevated early morning fasted serum cortisol, suggesting normal fertility in the presence of increased psychosocial stress.

Keywords

maternal nutrition; menstruation; fertility; tumescence; animal model; developmental programming; IUGR

Introduction

Intrauterine growth restriction (IUGR) resulting from reduced maternal nutrition during pregnancy and lactation developmentally programs offspring organ structure and function, predisposing offspring to chronic diseases, such as hypertension, obesity, and diabetes.[1,2] Few data are available to evaluate female reproductive function in adulthood following IUGR. We developed a baboon model of offspring IUGR resulting from moderate maternal, 30% global nutrient reduction and investigated adult female menstrual cycle characteristics.

Studies in humans and other animals suggest reduced maternal nutrition does not always reduce total number of offspring produced.[3] In one study, women exposed as fetuses to the Dutch Hunger Winter produced more offspring, more twins, and reproduced at earlier ages.[4] In another study from the same cohort, famine-exposed women, compared to non-famine exposed, had similar numbers of infant deliveries, age at menarche, and age at first delivery, but experienced more stillbirths.[5] In marmosets, triplet litter mates have restricted prenatal nutrition compared to twins. Adult triplets experience greater pregnancy losses than twins; nevertheless, overall number of offspring produced remains similar.[6]

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Fertility by breeding has not been tested in the IUGR baboons because for programming studies we wish to keep parity in all animals at zero for as long as possible. Therefore, we tested reproductive capability by analyzing plasma anti-mullerian hormone (AMH), an indicator of ovarian reserve, and timing of the sex skin tumescence cycle, a visual indicator of baboon estrus.[7] In humans, AMH strongly predicts odds of live birth,[8] and longer cycles are associated with increased chances of pregnancy and delivery.[9] Considering prior studies of fertility in developmentally programmed cohorts indicate no change in total number of offspring produced, we hypothesized IUGR and control (CTR) would show similar AMH, cycle duration, and swelling duration. To measure stress we quantified serum cortisol, known to affect fertility.[10,11] We predicted higher cortisol in IUGR than CTR based on earlier reports of increased fetal cortisol[12,13] and juvenile aggression[14] among IUGR baboons. Cortisol and AMH can be tested with a single blood sample and tumescence estimated noninvasively, allowing baboon maintenance in social housing without the stresses of individual housing and repeated percutaneous blood sampling.

Materials & Methods

Humane care guidelines

All procedures were approved by Texas Biomedical Research Institute (TBRI) Institutional Animal Care and Use Committee, conducted in *Association for Assessment and Accreditation of Laboratory Animal Care* approved facilities, and in accordance with the United States Animal Welfare Act.

Animals & housing

Animals were housed in outdoor social groups (8–16 animals) at TBRI. Baboons were in good health at semi-annual veterinary exams and when studied. IUGR baboons were offspring of mothers who ate 70% feed eaten by *ad libitum* fed CTR mothers in pregnancy and lactation, adjusted for body weight. IUGR offspring had ~12% lower birthweight than age- and sex-matched controls.[13] There is no universally accepted clinical definition of IUGR. Different publications use ranges of less than the 3rd to 15th percentile of all birthweights. We therefore use the simple definition that growth restriction has occurred when neonates weigh statistically significantly less than appropriate contemporaneous controls.[15] Detailed methods and IUGR phenotypes are published.[13,14,16–22]

Data collection & analysis

Reproductive characteristics were investigated in adult female IUGR baboons (7–10 yrs) and age-matched CTR. Sex skin swelling was observed 3x/wk in IUGR (n=8) and CTR (n=10) and scored from 0 (no swelling) to 4 (max swelling)[7] for 8–10 full cycles by two observers blind to treatment. Fasting morning blood was drawn from 8:00–10:00 am within 10 minutes of ketamine sedation. Ketamine does not affect cortisol within 10 minutes of administration.[13] Plasma was assayed for AMH with Ultra-Sensitive AMH ELISA (Ansh Labs) and serum was assayed for cortisol with Immulite 1000 Cortisol (Siemens Healthcare Diagnostics) (n=8 CTR, 8 IUGR). Differences between IUGR and CTR in AMH, mean cycle duration, maximum swelling, zero swelling, and total swelling duration were evaluated by two-tailed t-tests. One-tailed t-test evaluated IUGR and CTR cortisol due to the one-directional

hypothesis and our previous data on the pituitary adrenal axis in IUGR.[12,13] Levene's test investigated homogeneity of variances. Analyses performed in SPSS 23.

Results

Compared to CTR, IUGR spent fewer days per cycle with zero swelling and more days swollen. Cortisol was elevated in IUGR. IUGR and CTR were similar in cycle duration, max swelling duration, and AMH. Variances were similar between IUGR and CTR in all measures (Table 1).

Discussion

IUGR adult females were similar to CTR in many measures of fertility. Their cycles were of similar mean lengths and they spent equivalent amounts of time at the maximum swelling level, the period corresponding with ovulation.[7] Ovarian reserve (measured by AMH) was similar between IUGR and CTR. Increased variance in cycle duration has been reported in perimenopausal women and aged baboons,[23] but IUGR did not show any difference in variance from CTR. This suggests IUGR are not experiencing accelerated reproductive senescence. However, IUGR spent more days per cycle swollen and had elevated serum cortisol. In another baboon study, lengthening of the swelling phase was associated with psychosocial stress instigated by moving females between their normal social groups and individual cages.[24] Among IUGR baboons, lengthening of the swelling phase and elevated cortisol may be related to the increased aggressive behavior previously reported, a potential source of psychosocial stress.[14] In two human studies, cortisol levels were not associated with several measures of fertility,[10,11] although women were less likely to conceive in months during which they reported psychosocial stress.[11] Thus, it is unclear whether the changes to cortisol and length of the swelling phase in IUGR will translate to reduced fertility.

Considering prior research demonstrating unchanged or improved fertility in marmosets[6] and humans[4,5] programmed by prenatal nutrient restriction, these findings indicate IUGR reproductive cycles are not suggestive of decreased fertility or reproductive senescence. However, three lines of evidence together imply elevated psychosocial stress, which may lead to decreased fertility:[11] increased cortisol,[12,13] swelling duration,[24] and aggressive behavior.[14] Additionally, these females are in their reproductive prime, and differences between IUGR and CTR may emerge or intensify with aging. When IUGR offspring reproduce, their offspring may show inter-generational programming effects. For example, in a mouse model, maternal undernutrition led to sperm methylome changes in grandsons, linked to transmission of metabolic syndrome.[25] Since IUGR females are likely able to produce offspring, but those offspring may be predisposed to chronic disease, future investigations in nonhuman primate models of developmental programming should explore inter-generational effects. Additionally, studies are necessary to determine the degree to which outcomes are due to various regulatory mechanisms, such as the hypothalamo-pituitary-adrenal axis (HPAA) and hypothalamo-pituitary-gonadal axis (HPGA). In conclusion, we show here in a unique group of IUGR adult nonhuman primates that the HPAA is increased; future studies will investigate HPAG involvement.

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Table 1

Cortisol, anti-Mullerian Hormone (AMH), and menstrual cycle timing in intrauterine growth restricted (IUGR) and control (CTR) baboons.

	Group	N	Mean	SEM	t	p
Cortisol (ug/dL)	CTR	8	41.2	2.86		
	IUGR	8	49.7	3.26	−1.97	0.03
AMH (ng/ml)	CTR	8	13.4	1.92		
	IUGR	8	14.6	2.91	−0.36	0.72
Cycle duration (days)	CTR	10	29.9	0.64		
	IUGR	8	31.0	0.81	−1.11	0.28
Max swelling duration (days)	CTR	10	8.84	0.82		
	IUGR	8	10.7	0.97	−1.50	0.15
Zero swelling duration (days)	CTR	10	12.9	0.59		
	IUGR	8	10.9	0.71	−2.25	0.04
Total swelling duration (days)	CTR	10	17.0	0.78		
	IUGR	8	20.1	1.05	−2.48	0.03

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