Lower Resting Energy Expenditure and Fat Oxidation in Native American and Hispanic Infants Born to Mothers with Diabetes

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Objective To determine whether exposure to diabetes in utero affects resting energy expenditure (REE) and fuel oxidation in infants.

Study design At 35 ± 5 days after birth, body composition and REE were measured in full-term offspring of Native American and Hispanic women with either well-controlled diabetes (13 girls, 11 boys) or normal healthy pregnancies (18 girls, 17 boys).

Results Control of dysglycemia during gestation in the women with diabetes mellitus met current clinical standards, shown by average glycated hemoglobin (5.9 ± 0.2%; 40.6 ± 2.3 mmol/mol). Infant body mass (offspring of women with diabetes: 4.78 ± 0.13, control offspring: 4.56 ± 0.08 kg) and body fatness (offspring of women with diabetes: 25.2 ± 0.6, control offspring: 24.2 ± 0.5 %) did not differ between groups. REE, adjusted for lean body mass, was 14% lower in offspring of women with diabetes (41.7 ± 2.3 kJ/h) than control offspring (48.6 ± 2.0, $P = .025$). Fat oxidation was 26% lower in offspring of women with diabetes (0.54 ± 0.05 g/h) than control offspring (0.76 ± 0.04, $P < .01$) but carbohydrate oxidation did not differ. Thus, fat oxidation accounted for a lower fraction of REE in the offspring of women with diabetes (49 ± 4%) than control offspring (60 ± 3%, $P = .022$). Mothers with diabetes were older and had higher prepregnancy body mass index than control mothers.

Conclusions Well-controlled maternal diabetes did not significantly affect body mass or composition of offspring at 1-month old. However, infants with mothers with diabetes had reduced REE and fat oxidation, which could contribute to adiposity and future disease risk. Further studies are needed to assess the impact differences in age and higher prepregnancy body mass index. *(J Pediatr 2015;166:884-9)*.

A mother's health and her lifestyle during pregnancy, including her nutrition, physical activity, smoking, or the presence of metabolic disease, can have both immediate and long-lasting effects on offspring.[1] Diabetes during pregnancy has a particularly important impact on offspring health as shown by the 10-fold higher rate of childhood obesity[2] and 4-fold higher risk of developing impaired glucose tolerance (prediabetes) during adolescence.[3] Cardiovascular risk factors are also increased in otherwise healthy children exposed to diabetes in utero compared with unexposed children.[4] All of those outcomes appear to be due, at least in part, to in utero exposure to maternal diabetes.[5] The risk for offspring to develop obesity and insulin resistance has been reported to increase in association with elevated maternal glucose in some studies,[6,7] suggesting that the maternal diabetes state per se is responsible, possibly through epigenetic programming in utero.[8,9] Although increased surveillance and more aggressive management of dysglycemia in pregnant women has substantially reduced neonatal morbidity, it remains to be shown whether such advances in prenatal care affect subsequent development of obesity, diabetes, and metabolic syndrome in offspring exposed to maternal diabetes.[5,10-12]

Low resting energy expenditure (REE) and rates of fat oxidation are positive predictors for future weight gain in adults.[13,14] Likewise, adults with type 2 diabetes have been shown to oxidize less fat and more carbohydrate while at rest (part of a phenotype called metabolic inflexibility) compared with people without diabetes, and this could contribute to the deposition of excess fat mass.[15] Whether these metabolic features are transmissible from mother to baby or are evident early in life is unclear. In the current study, we postulated that such metabolic alterations might be implicated in the subsequent development of obesity and/or diabetes, and may serve as markers for risk of future disease early in children born to mothers with diabetes during pregnancy. To test this we measured energy expenditure in 1-month-old offspring of Hispanic and Native American women, members of racial/ethnic groups at increased risk for diabetes and obesity.[2]

BMI	Body mass index
GDM	Gestational diabetes mellitus
HbA1c	Glycated hemoglobin
REE	Resting energy expenditure

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Methods

Self-declared Native American and Hispanic women experiencing a normal, uncomplicated pregnancy (control group, N = 34) or pregnancy accompanied by diabetes mellitus (gestational or pre-existing type 2 diabetes, diabetes group, N = 27) were recruited before the birth of their child. The current analyses are from a larger ongoing investigation of maternal diabetes on offspring. Native American mothers (N = 25 controls, N = 17 with diabetes) received the majority of their prenatal care and completed delivery at the Chickasaw Nation Medical Center (Ada, Oklahoma), the Choctaw Nation Healthcare Center (Talihina, Oklahoma), or the University of Oklahoma Medical Center (Oklahoma City, Oklahoma). Hispanic mothers (N = 9 controls, N = 10 with diabetes) received the majority of their prenatal care and completed delivery at the University of Oklahoma Medical Center (Oklahoma City, Oklahoma). All mothers provided informed consent for their child to participate in the study in accordance with the Institutional Review Boards of the Chickasaw Nation, Choctaw Nation of Oklahoma, and the University of Oklahoma Health Sciences Center, respectively, which approved the study. Control offspring and offspring of women with diabetes were excluded from the study if they were born prior to 37 weeks of gestation, or there was evidence of known or presumed congenital birth defects, including major physical malformations, severe persistent nervous system deficit, severe birth asphyxia (defined as 5-minute Apgar score of <6 or umbilical cord pH <7), or congenital infection, or metabolic or endocrine disease. Infants born to mothers with pre-eclampsia or other potentially confounding health conditions other than diabetes were also excluded from these analyses. The approaches used for diabetes management were insulin (11 mothers), glyburide (7 mothers), metformin (1 mother), both insulin and metformin (2 mothers), both insulin and glyburide (1 mother), and lifestyle/no medication (5 mothers).

Study personnel at each clinic site used standardized protocols to acquire estimates of gestational age, measurements of maternal health characteristics, and the weight and length of the baby at birth. All anthropometric, body composition, and metabolic measurements performed on the 1-month-old infants were conducted during a single visit to the Children's Medical Research Institute Pediatric Metabolic Research Center at the University of Oklahoma Health Sciences Center, Oklahoma City, when the infants were between 26 and 46 days old (mean ± SD = 35 ± 5 days). Previous experience in our center has shown that feeding infants within 30-60 minutes before performing body composition measurements helps keep them relaxed during testing and, therefore, increases data acquisition. Therefore, we did not restrict food intake of the infants prior to the measurements in this study. Because infants at this age eat frequently throughout the day, they are in a near-continuous postprandial state.

Body length (cm) was measured from crown to heal using a horizontal stadiometer, and body mass (kg) was measured using an infant scale. Ponderal index was calculated as body mass (kg)/height (m^3). Body mass was also expressed as a percentile on the age- and sex-specific growth charts available from the US Centers for Disease Control. Body composition was measured using dual energy X-ray absorptiometry (Lunar iDXA v11-30.062; GE-Healthcare, Fairfield, Connecticut) similar to the approach used by our group for 6-month-old babies.[16] Briefly, the infant, wearing only a disposable diaper, was swaddled in a light cotton blanket, the overhead lights were dimmed, and noise was minimized during the ~4-minute-long procedure. The fat and lean mass of the whole body (excluding the head), trunk, and appendicular regions was calculated using the pediatric whole body analysis enCore 2007 software package from the instrument manufacturer (GE-Healthcare). All measurements were performed and analyzed by the same investigator using standardized protocol that included daily calibration of the instrument.

REE and the relative portion of fat and carbohydrate oxidation were measured using an indirect calorimetry system with a flow-through canopy placed over the head while the baby was resting supine (TrueOne 2400; ParvoMedics, Sandy, Utah). Measurements were performed for approximately 20-25 minutes. Data were summarized each minute with the first 5 minutes excluded from analysis. Short time segments (1-2 minutes) were also excluded from analyses if the baby moved excessively. Tests in which the baby began to cry or engaged in continuous movement were also excluded from analyses. Rates of oxygen consumption and carbon dioxide production were used to calculate REE and fuel oxidation using the Weir equations.[17] Volumetric flow rate and gas concentration analyzers were calibrated daily, and ethanol burn tests were used to confirm optimal performance of the instrument.

Statistical Analyses

Summary statistics are presented as mean ± SEM. Student unpaired *t* tests were used to compare results between groups. Strength of association among selected variables was calculated using Pearson correlation coefficient. Covariate adjustment of REE and fuel oxidation results for lean body mass was performed as previously described.[18] Multivariate regression modeling, using stepwise approaches for variable entry and removal, was used to determine the best set of predictor variables for the REE and fuel oxidation outcomes in the infant. *P* value of <.05 was considered statistically significant for all analyses.

Results

Characteristics of the mothers during pregnancy and the offspring at birth are presented in **Table I**. The diabetes group was comprised of 9 women who had type 2 diabetes before becoming pregnant and 18 women diagnosed with gestational diabetes mellitus (GDM). Mothers with diabetes were older, had higher parity and prepregnancy body mass