Adiposity in Adolescent Offspring Born Prematurely to Mothers with Preeclampsia

Lisa Washburn, MD[1], Patricia Nixon, PhD[1,3], Gregory Russell, MS[2], Beverly M. Snively, PhD[2], and T. Michael O'Shea, MD, MPH[1,2]

Objective To evaluate the relationship between maternal preeclampsia resulting in premature delivery and adiposity in the offspring during adolescence.

Study design The 172 study participants were 14 years old and had very low birth weight. We compared height, weight, body mass index (BMI), percent fat, waist circumference, and triceps and subscapular skin fold thicknesses between those born prematurely secondary to preeclampsia (n = 51; 22 male) and those born prematurely after normotensive pregnancies (n = 121; 55 male). Multiple linear regression analysis was used to adjust for potential confounders (maternal BMI, antenatal steroid exposure, and race) and to evaluate potential explanatory variables (fetal, infancy, and childhood weight gain, and caloric intake, level of fitness, and physical activity at 14 years).

Results When adjusted for potential prenatal confounders (antenatal steroid exposure and race), adolescent male offspring of preeclamptic pregnancies had higher BMI (4.0 kg/m^2 [1.5, 6.6]) (mean difference [95% CI]), waist circumference (11.8 cm [3.8, 19.7]), triceps (4.6 mm [0.6, 8.6]) and subscapular skinfold thicknesses (6.2 mm [1.5, 10.9]), and percent body fat (4.1% [−0.1, 8.3]). Adjusting for infancy and childhood weight gain attenuated these group differences. There were no group differences among females.

Conclusion Male adolescent offspring born prematurely of women with preeclampsia have higher measures of adiposity than those born prematurely of normotensive pregnancies. *(J Pediatr 2013;162:912-7)*.

See editorial, p 889 and related article, p 906

Offspring of pregnancies complicated by preeclampsia are at increased risk for adverse cardiovascular outcomes.[1,2] Alterations in adiposity might contribute to this increased cardiovascular risk. A recent meta-analysis reported a modest but significant increase in body mass index (BMI) in the offspring of mothers with preeclampsia, compared with normotensive pregnancies.[3] Potential mechanisms linking maternal preeclampsia to later differences in offspring body composition include preeclampsia-induced alterations in the intrauterine environment, restricted fetal growth followed by rapid childhood weight gain, and genetic and environmental factors shared by the mother and her offspring that increase both maternal and offspring body size.

Children born very preterm have not been well represented in studies of whether preeclampsia predisposes the offspring to increased adiposity. Preeclampsia that leads to very preterm birth is likely to provide a different intrauterine exposure than preeclampsia resulting in a term or near term delivery.[4] Thus, infants born prematurely might be at particularly high risk for the potential programming effects of the intrauterine environment specific to preeclampsia. Although there is evidence that male and female fetuses respond differently to an adverse intrauterine environment,[5] most studies have not reported analyses stratified by sex.

Our objective was to evaluate the relationship between maternal preeclampsia resulting in premature delivery of a very low birth weight (VLBW; ≤1500 g) infant and adiposity in the offspring during adolescence and to determine if this relationship varies by sex. We studied a cohort of VLBW infants at 14 years of age and compared BMI, waist circumference, triceps and subscapular skin fold thicknesses, and percent body fat between those born prematurely secondary to preeclampsia and those born prematurely from normotensive pregnancies.

Methods

The study sample was derived from a cohort of consecutive VLBW births at the regional perinatal center in Forsyth County, North Carolina from January 1,

BMI	Body mass index
No HTN	Offspring of normotensive pregnancies
PreE	Offspring of preeclamptic pregnancies
VLBW	Very low birth weight

From the Departments of [1]Pediatrics, [2]Biostatistical Sciences, Wake Forest School of Medicine, [3]Department of Health and Exercise Science, Wake Forest University, Winston-Salem, NC

Funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (PO1 HD047584), the Clinical Research Unit of Wake Forest Baptist Medical Center (MO1-RR07122), Forsyth Medical Center, and the Wake Forest School of Medicine Department of Pediatrics research funds. The authors declare no conflicts of interest.

 http://dx.doi.org/10.1016/j.jpeds.2012.10.044

1992-June 30, 1996 (Figure; available at www.jpeds.com). Eligible infants (n = 479) were singleton at birth, had no major congenital malformation, and returned to the medical center for evaluation at 1-year corrected age. Among eligible children, 312 were located and 193 were studied at 14 years of age. Twenty-one participants were excluded from this analysis because of presence of maternal hypertension but not preeclampsia during pregnancy (16), twin gestation (2), chromosomal abnormality (1), polycystic kidney disease (1), and severe cerebral palsy (1).

This study was approved by the Wake Forest School of Medicine and the Forsyth Medical Center Institutional Review Boards. Informed consent was obtained from parents or legal guardians, and participants gave assent.

We reviewed medical records and delivery logs to identify participants whose mothers were diagnosed as having preeclampsia/eclampsia, pregnancy-induced hypertension, or chronic hypertension. When available, a first trimester ultrasound was used to estimate gestational age. Otherwise, we used, in order of priority, the mother's last menstrual period or a clinical assessment of the newborn infant. From infant medical records, we obtained birth weight and weight at 1 year of age adjusted for prematurity. As an index of fetal growth we used birth weight z score, calculated using US natality data.[6] Z scores for measurements made at 1 year of age corrected for prematurity, and at 14 years were derived using Epi Info (Centers for Disease Control, Atlanta, Georgia).[7] Race was categorized as black or non-black, based on participants' self-report. From information obtained up to 1 year corrected age, we calculated the social disadvantage score (1-3), by assigning 1 point each for maternal black race, single marital status, and completion of less than a high school education.[8] Maternal prepregnancy BMI was calculated from prepregnancy weight determined from medical record review and height obtained by maternal report at the follow-up visit. BMI percentile ≥85th to <95th was considered overweight, and BMI percentile ≥95th, obese.[9] Waist circumference percentiles were determined using US normative data.[10]

Measurements

Anthropometrics/Body Composition. Anthropometric measurements were made in triplicate with participants wearing light clothing and no shoes. Height was measured using a wall-mounted stadiometer. Weight was measured using a digital platform scale. Abdominal circumference was assessed with a measuring tape according to procedures of the third National Health and Nutrition Examination Survey.[11] Triceps, subscapular, and suprailiac skin fold thicknesses were measured using a Lange skinfold caliper.[12] Percent body fat and lean mass were assessed using a Delphi dual energy X-ray absorptiometer (Hologic, Bedford, Massachusetts) equipped with pediatric software.

Aerobic Fitness and Physical Activity. Aerobic fitness was determined from a graded exercise test to exhaustion on an electronically-braked cycle ergometer following the Godfrey Protocol.[13] Expired gases were analyzed using a Viasys Vmax Encore metabolic cart (CareFusion, Yorba Linda, California). Peak oxygen uptake was taken from the highest 20 seconds of exercise and expressed per kilogram body mass. Subjects were verbally encouraged to give a maximal effort. Habitual physical activity was assessed using Kriska's Modifiable Activity Questionnaire and expressed as average total hours of physical activity per week for the past year.[14]

Dietary Intake. Subjects were provided with standard measuring cups, spoons, and a ruler, and were instructed in the proper use of these items for measuring food portions by a registered dietician. The food record was completed for 3 days. Nutrient content was calculated using the Nutrition Data System for Research software developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, Minnesota.[15]

Statistical Analyses

Group means were compared by the 2-sample independent t test, and proportions were compared by the χ^2 or Fisher exact test. We defined potential confounders (birth weight, Cesarean delivery, race, sex, social disadvantage score, antenatal steroid treatment of the mother, and mother's prepregnancy BMI) as those factors associated with both maternal preeclampsia and an obesity-related outcome using a P value of ≤ 0.2. As we hypothesized sex differences, we stratified the analyses for evaluating the effects of maternal preeclampsia by sex of the child. Thus, for each outcome, there were 2 prespecified subgroups for analysis and twice the expectation of results reaching statistical significance on the basis of chance alone. Multiple linear regression was used to evaluate the relationship of maternal preeclampsia and the obesity-related outcomes adjusting for potential confounders. Similar results were obtained in models that adjusted for race or social disadvantage score; we report here only the results from models that included race. When associations were observed between maternal preeclampsia and obesity-related outcomes, we were interested in whether these associations might involve, in the causal pathway, weight gain during gestation (birth weight z score), infancy (weight z score at 1-year corrected age − birth weight z score), and childhood (weight z score at 14 years − weight z score at 1-year corrected age), estimated daily caloric intake at 14 years, aerobic fitness at 14 years, and physical activity at 14 years. We examined this possibility with regression models that adjusted for each of these factors. Statistical significance was defined as $P < .05$. No correction for multiple testing was applied to outcomes, as those selected for analysis were closely related and were used to evaluate consistency across findings. Analyses were performed using SAS for Windows v. 9.2 (SAS Institute Inc, Cary, North Carolina).

Results

The participants whose data are included in the study had slightly lower gestational age and higher birth weight z score