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Relation Between Birth Weight and Weight and Height at Age Two in Children Born Preterm

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Abstract

Objective—To evaluate associations between fetal growth and weight at two years in infants born preterm using a customized approach for birth weight.

Study Design—This is a secondary analysis of a multicenter trial that included a two year follow up of children born prematurely. Customized birth weight percentiles were calculated using the Gardosi model for a US population, and the relation between customized percentile and weight and height at two years (adjusted for gender using z score) was determined using regression analysis and by comparing z scores for children with birth weight <10th versus 10th percentile.

Results—Weight z score at two years was significantly lower in the <10th versus 10th percentile group (median [IQR]: −0.66 [−1.58, −0.01] vs −0.23 [−1.05, 0.55]; $p < 0.001$), and remained after adjusting for maternal education ($p < 0.001$). A similar relationship was noted for height z score between groups. (median [IQR]: −0.56 [−1.29, 0.19] vs −0.24 [−0.99, 0.37]; $p < 0.001$). Positive relationships between customized birth weight percentile and weight and height at two years were noted ($p < 0.001$ for both), but were not strong ($R^2 = 0.04$ and 0.02 , respectively).

Conclusions—Customized birth weight percentile is a minor determinant of weight at two years among children born preterm.

Keywords

preterm; fetal growth potential; customized birth weight

Introduction

Poor fetal growth resulting in low birth weight at the time of a term delivery is strongly associated with diminished health and well being from infancy through adulthood. McIntire et al demonstrated that perinatal mortality and morbidity in both term and preterm infants were increased for infants with a birth weight below the 3rd percentile for gestational age.(1) In addition, growth restricted infants are at increased risk for subsequent child, adolescent or adult obesity, cardiovascular disease, and altered neurologic development. (2–5) In the analysis of the Helsinki birth registry data, Barker et al identified increased rates of cardiovascular disease in boys with a birth weight 0.2 standard deviations below a mean birth weight of 3.4 kg.(5) The EPOCH study, a retrospective cohort analysis of term infants, demonstrated that infants who were small for gestational age (SGA) at birth, defined as birth weight for gestational age z score less than the 5th percentile, demonstrated significant “catch up growth” by 12 months of life. Further, their BMI at 27 months was comparable to infants whose weight was normal at birth (AGA) and went on to later develop a higher waist circumference, lower adiponectin and increased adiposity. (6) Available literature suggests the postnatal growth trajectory of preterm infants remains lower than the trajectory of term infants. Bocca-Tjeertes et al have shown for infants born at 32–35 6/7 weeks the weight (kg) for girls born preterm compared to girls born at term significantly differed (16.0 ± 2.4 vs 16.7 ± 3.05 ; $p < 0.01$) at 4 years of age. (7) They also reported substantially greater increases in BMI at 4 years of age for the large for gestational age (LGA) preterm infants when compared with both preterm and term infants. (8) However it is unclear if infants who are preterm and growth restricted will experience a similar “catch up growth” pattern noted

for the SGA term infants, and if this “catch up” will be accompanied by an increase in their BMI.

Traditionally, fetal growth has been assessed by comparing birth weight with population-based norms. (9,10) However, customized growth curves, using maternal and fetal characteristics to define a specific nomogram for each fetus, may improve the distinction between normal and abnormal growth as well as correlate with adverse neonatal outcomes better than population-based assessment of fetal growth. (11–15) Our objective was to evaluate the child weight at two years after preterm birth in relation to customized birth weight percentile. Our hypothesis is that the preterm infant born growth restricted will demonstrate increased postnatal growth demonstrated by an increased weight at two years of age compared with preterm infants not growth restricted at birth.

Materials and Methods

This was a secondary analysis of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network “Randomized Clinical Trial of the Beneficial Effects of Antenatal Magnesium Sulfate”, in which singleton or twin gestations between 24^{0/7} – 31^{6/7} weeks’ gestation at high risk for imminent preterm birth were randomized to receive either magnesium sulfate (MgSO₄) infusion or placebo. Full details of the methods and study design have been provided elsewhere (16), however a focus of the trial was reducing the risk of cerebral palsy. Given this focus, the trial involved extensive data collection of maternal and infant variables, including two follow up examinations of the children at 12 and 24–36 months. Available data included variables required for calculation of customized growth percentiles (maternal ethnicity, parity, height, weight, infant gender, birth weight) and weight and height at two years.

Children enrolled in the parent trial who had a two year follow up examination were included for the secondary analysis. The two year follow up was defined in the original trial as an exam any time between 24 months and 36 months of age. Excluded from this analysis were those from a twin gestation, delivery at 37 weeks’ gestational age, with a congenital malformation or genetic syndrome, and those with conditions that affect chronic feeding after initial newborn discharge (facial weakness, G-tube, tracheostomy, tracheal stenosis). Customized birth weight percentiles were calculated according to the Gardosi model which adjusts for maternal height, weight, ethnicity, parity, gestational age and fetal gender. Child weight and height at two years were used to generate z-scores standardized by gender and age using CDC reference data. (17,18)

Comparisons of demographic and two year exam results between those with birth weights <10th versus 10th percentile were based on chi-squared statistic (or Fisher’s exact test in the case of infrequent outcomes) for discrete variables, or the Wilcoxon Rank Sum test for continuous variables. The association between the two year exam results and birth weight percentile was assessed using linear regression adjusting for treatment group (magnesium sulfate or placebo) and maternal education level, with a natural log transformation of the birth weight percentile. Maternal age was not included as a covariate, since it was strongly

correlated with maternal parity, which is used to calculate the customized birth weight percentile. SAS software, version 9.3 (SAS Institute), was used for the analyses. All tests were two-tailed. $P < 0.05$ was used to define statistical significance, and no adjustments were made for multiple comparisons.

Results

A total of 2,241 women underwent randomization in the parent trial, 1,096 women (1,188 fetuses) were assigned to receive MgSO_4 while 1,145 women (1,256 fetuses) were assigned to receive placebo. From this cohort of 2,444 neonates, the following were excluded from this analysis: 406 twins, 65 delivered at ≤ 37 weeks gestation, 65 with congenital malformations, 17 with feeding difficulty, 136 deaths prior to two years, and 191 missing data necessary for calculation of the customized birth weight percentile using the Gardosi model. Within the randomized trial, children determined to be developmentally normal at the 12-month exam were not required to undergo examination at two years ($n = 410$). The 1,154 infants who had a two-year exam were born at a median of 30 weeks estimated gestational age, while, the 410 who did not undergo an examination were born on average 4 days later, were heavier at birth (average almost 100g more), and had higher customized birth weight centiles (average 2.3 points higher). The weight at two years of age in four children did not appear biologically plausible according to the WHO criteria and were also removed from the analysis. After all exclusions, 1,150 children were included in this analysis. Height was not measured in six of these children.

The maternal demographic and newborn data, divided into birth weight $<10^{\text{th}}$ and 10^{th} percentile strata are shown in Table 1. Significant differences were noted for maternal age ($p < 0.01$) and education ($p = 0.04$), in addition to factors used to compute the customized birth weight percentile (pre-pregnancy weight, height and ethnicity; all $p < 0.01$).

Overall anthropometric characteristics of this cohort of children at two years of age are shown in Table 2. In general, the children were of lower than expected weight (median z-score -0.32 ; interquartile range -1.17 to 0.43) and height (median z-score -0.30 ; interquartile range -1.06 to 0.34) at two years compared with age-matched US-born children. The weight z-score was significantly lower in the $<10^{\text{th}}$ versus 10^{th} birth weight percentile group (median [IQR]: -0.66 [$-1.58, -0.01$] vs -0.23 [$-1.05, 0.55$]; $p < 0.001$), and remained so even after correcting for maternal education and original study treatment group ($p < 0.001$). A similar relationship was seen with the height z-score (median [IQR]: -0.56 [$-1.29, 0.19$] vs -0.24 [$-0.99, 0.37$]; $p < 0.001$), and which also remained after correcting for maternal education and original study treatment group ($p < 0.001$). Furthermore, a weak but positive relationship was noted between customized birth weight percentile and weight ($R^2 = 0.04$; $p < 0.001$), as well as height ($R^2 = 0.02$; $p < 0.001$) at two years (Figure 1). Results for body mass index at two years were consistent with those found for weight alone.

Discussion

Contrary to our hypothesis, we did not find that children born both preterm and growth restricted were heavier at two years of age compared with those who were preterm and not

growth restricted. Instead, we found a positive association between birth weight, assessed using a customized approach, and weight at two years of age. Two year old children born preterm and growth restricted continue to weigh less and remain shorter in stature than the children that were premature but not growth restricted, but the difference is not as large as at birth. The children born preterm and growth restricted never reached a growth trajectory similar to preterm peers. Other studies have suggested higher levels of maternal education are associated with increased offspring height, birth weight and decreased rates of low birth weight. In addition, the influence of maternal education may vary by ethnicity and gender and the mechanisms for a direct or indirect influence are not clear. (19,20) This confounder was considered in the analysis and our findings remained significantly different after controlling for education. Pierrat et al have suggested a significant proportion of catch up growth for infants born at < 33 weeks occurs in the first six months of life. Nonetheless, nearly half of the children in their study with short stature at age two remained short at age five years. The incidence of short stature was increased for children born before 29 weeks gestational age and whose mother's stature was < 160 cm. Also of interest in this study is 9% of the infants categorized as normal weight at birth later appeared growth restricted. (21) Bocca-Tjeertes et al also identified a different pattern of infant growth in preterm infants (< 36 weeks) with LGA defined as a birth weight more than 1.6 standard deviations above the median for their reference group. By 4 years of age BMI for preterm LGA infants was similar to full term LGA and exceeded full term AGA infant growth. (8) Combined, these findings suggest mechanisms influencing growth restriction and subsequent growth may differ between preterm and term infants. Furthermore, these studies and the current analysis highlight the importance of identifying infants born small at birth in order to appropriately adjust the postnatal environment for optimal growth.

Many studies assessing fetal growth and birth weight use comparisons based upon population norms (9,10) which were developed from heterogeneous cohorts without addressing individual variability. In order to circumvent misrepresentations of growth inherent in population norms, a number of individualized or customized growth norms have been developed to predict optimal growth potential curves for individual pregnancies. Adjusting for physiologic characteristics pertaining to the pregnancy such as maternal weight, height, ethnicity/race, parity and infant gender allows for more precise individual assessment of expected growth and correlation with perinatal complications. (12,13) Several fetal growth curves are available, and vary in the characteristics used depending on the population tested or targeted outcome such as growth norm or prediction of perinatal morbidity. (22,23) The Gardosi customized growth norm was used for our analysis. (14,15) This customized growth norm assesses individualized and optimal fetal growth potential curves by incorporating physiological maternal and fetal variables: maternal weight at entry to care or pre-pregnancy, height, ethnicity/race, parity, and infant gender. The actual birth weight is compared to the optimal weight, and a measure of birth weight in relation to the optimal growth is calculated (birth weight centile). (24)

A strength of this study is the application of individualized birth weight assessment of prematurely born infants and comparisons with weight and height at two years of age. The Beneficial Effects of Antenatal Magnesium Sulfate "BEAM" trial (16) was designed to test the hypothesis that the administration of MgSO₄ before early preterm delivery would reduce

the risk of cerebral palsy. The primary analysis focused on the composite outcome of stillbirth or infant death by year one or moderate or severe cerebral palsy by age two or greater. As a result, the robust data collection for the primary analysis is also a strength for this secondary analysis. By contrast, detailed environmental data was not collected from birth to age two and could be considered a weakness. Further, two year outcomes were not assessed in a substantial number of infants with normal exams at one year or infants who may have expired from failure to thrive. Exclusion of these infants could potentially bias the relationship as those with normal growth are more likely to have normal neurologic outcomes. Additionally, infant death could be a confounding factor as poor growth is associated with higher mortality. If anything, lack of availability of these children for evaluation at two years would diminish the apparent association between low birth weight and smaller size at two years.

A positive association, not a negative one as expected, was noted using a customized approach. The difference in weight z score and BMI between the <10th versus 10th percentile groups was less at two years than at birth suggesting some “catch up” growth did occur in the growth restricted infant. However, whether this “catch up” growth can be related to a risk of metabolic and cardiovascular dysfunction later in life remains to be determined; the association appears to be weak, and explains a relatively small portion of the weight at two years. Our findings point to the presence of other influences (environmental, genetic, nutritional), beyond fetal growth in programming of weight in children born preterm and growth restricted.

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Appendix

In addition to the authors, other members of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network are as follows:

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Figure 1.

Distribution of weight and height z-scores at two years, according to Gardosi birth centile for each Gardosi birth centile category, the median (circle) and upper and lower quartiles (horizontal bars) are shown.

Table 1

Demographic characteristics by birth weight (BW) percentile.*

	BW <10th percentile (n=286)	BW 10th percentile (n=864)	p-value
Maternal pre-pregnancy weight (kg)	69.1 (59.1, 86.4)	63.6 (55.0, 78.6)	<0.001
Maternal height (cm)	162.6 (160.0, 170.2)	162.6 (157.5, 167.6)	<0.001
Maternal education (yr)	12 (11, 14)	12 (11, 13)	0.04
Maternal age (yr)	27 (22, 31)	25.5 (21, 30)	<0.01
Maternal race			
European	123 (43.0%)	311 (36.0%)	<0.01
African American	129 (45.1%)	378 (43.8%)	
Hispanic	30 (10.5%)	161 (18.6%)	
Other	4 (1.4%)	14 (1.6%)	
Parity			
0	48 (16.8%)	194 (22.5%)	0.26
1	75 (26.2%)	209 (24.2%)	
2	57 (19.9%)	172 (19.9%)	
3	43 (15.0%)	103 (11.9%)	
4+	63 (22.0%)	186 (21.5%)	
MgSO ₄ treatment	143 (50.0%)	430 (49.8%)	0.95
Birth gestational age (weeks)	29.9 (27.4, 31.4)	30.0 (27.6, 31.9)	0.29
Birth weight (gm)	1175.5 (816, 1419)	1490 (1080, 1840.5)	<0.001
Birth length (cm)	38 (34, 40.5)	40 (36.5, 43)	<0.001
Male	138 (48.3%)	461 (53.4%)	0.13

* Data presented as frequency (percentage) or median (interquartile range)

Table 2

Anthropometric characteristics of the cohort of children at the two year exam*.

	BW <10th percentile (n=286)	BW 10th percentile (n=864)
Age(months)	27.9 (26.8, 29.6)	27.9 (26.9, 29.9)
Weight (kg)	12.2 (11.0, 13.2)	12.7 (11.7, 13.8)
Height (cm)	87.0 (84.5, 90.5)	88.4 (86.0, 90.9)
Body Mass Index (kg/m ²)	15.9 (15.0, 16.9)	16.3 (15.3, 17.4)
Weight percentile**	25.6 (5.8, 49.8)	41.0 (14.7, 70.8)
Weight z-score**	-0.66 (-1.58, -0.01)	-0.23 (-1.05, 0.55)
Height percentile**	28.8 (9.9, 57.6)	40.6 (16.1, 64.3)
Height z-score**	-0.56 (-1.29, 0.19)	-0.24 (-0.99, 0.37)

* All p-values <0.001, except for age (months), with p=0.63. Data presented as median (interquartile range)

** Compared with age-matched data for US-born children (15)