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The association of cerebral palsy and death with small-for-gestational age birth weight in preterm neonates by individualized and population-based percentiles

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Abstract

OBJECTIVE—To determine whether an individualized growth standard (IS) improves identification of preterm small-for-gestational-age (SGA) neonates at risk of developing moderate/severe cerebral palsy (CP) or death.

STUDY DESIGN—Secondary analysis of data from a randomized trial of MgSO4 for prevention of CP or death among anticipated preterm births. Singleton non-anomalous liveborns delivered before 34 weeks' were classified as SGA (< 10th % for their GA) by a population standard (PS) or an IS (incorporating maternal age, height, weight, parity, race/ethnicity, and neonatal gender). The primary outcome was prediction of moderate or severe CP or death by age 2.

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The authors reports no conflict of interests

Use of an individualized growth standard for identification of SGA neonates does not improve prediction of cerebral palsy or death among preterm neonates.

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RESULTS—Of 1588 eligible newborns, 143 (9.4%) experienced CP (N=33) or death (N=110). Forty-four (2.8%) were SGA by the PS and 364 (22.9%) by the IS. All PS-SGA newborns also were identified as IS-SGA. SGA newborns by either standard had a similarly increased risk of CP or death (PS: RR 2.4, 95% CI 1.3–4.3 vs. IS: RR 1.8, 95% CI 1.3–2.5, respectively). The similarity of RRs remained after stratification by MgSO4 treatment group. The IS was more sensitive (36% vs. 6%, p <.001), but less specific (78% vs. 98%, p <.001) for CP or death. ROC curve analysis revealed a statistically lower AUC for the PS, although the ability of either method to predict which neonates would subsequently develop CP or death was poor (PS: 0.55, 95% CI 0.49–0.60 vs. IS: 0.59, 95% CI 0.54–0.64, p<.001).

CONCLUSION—An individualized SGA growth standard does not improve the association with, or prediction of, CP or death by age 2.

Keywords

small-for-gestational-age; cerebral palsy; death

Fetal growth restriction traditionally has been defined according to liveborn growth curves based on a population standard.[1] Some investigators have noted, however, that such a definition is suboptimal because it includes birth weights that result from both normal physiologic variation and pathologic states.[2] Consequently, the ability to identify those fetuses or newborns with truly abnormal growth, who are most at-risk for both short-term and long-term adverse outcomes, is compromised by the use of such a standard.

As a result, a definition of growth restriction based on an individualized standard has been proposed.[3] An individualized standard is based on the predicted growth potential of a given individual and therefore should improve the accuracy with which truly at-risk fetuses or newborns are identified. Indeed, several studies have suggested that certain perinatal morbidities are better identified using an individualized standard as opposed to a population standard. Gardosi and Francis, for example, found that threatened preterm labor, antepartum hemorrhage, pregnancy-induced hypertension, preeclampsia, stillbirth, and early neonatal death all were better identified using the individualized standard.[4]

The potential benefit of using individualized birthweight standards to help predict long-term neurodevelopmental adverse outcomes, however, is not known. While it is well established that adverse neurodevelopmental outcomes such as cerebral palsy (CP) are associated with fetal growth restriction,[5] many of those who are diagnosed with adverse neurodevelopmental outcomes based on population standards do not have evident growth abnormalities. If individualized standards could improve identification of those newborn who are pathologically growth restricted, and thereby the identification of those at risk for long-term disability, counseling and the targeting of early intervention could both be improved. Accordingly, the primary aim of this study was to determine whether an individualized growth standard, compared to a population-based standard, would improve identification of SGA neonates destined to develop moderate or severe CP or death by 2 years of age.

Materials and Methods

This is a secondary analysis of data from a randomized trial (i.e., the BEAM study) of magnesium sulfate for prevention of moderate/severe CP or death among infants born prematurely. Full details of this study have been described previously.[6] In brief, women judged to be at high risk for preterm birth prior to 32 weeks of gestation were randomized to either a magnesium sulfate or placebo infusion. After delivery, liveborn infants were

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followed for 2 years with detailed developmental assessments performed by trained examiners.

The present analysis includes all non-anomalous singleton liveborns in the BEAM study who delivered prior to 34 weeks of gestation. Each newborn's birth weight was used to determine whether it was small-for-gestational-age (SGA), defined as less than the 10th percentile, according to a population standard or an individualized standard. The population standard used was that proposed by Alexander et al, which is stratified according to neonatal gender and ethnicity.[7] Since the continuous values of the population standard were not available, the following approach was used to approximate these values: an Arc-Tan based transformation of birth weights (ArcTan((weight/1000)2)*2/π) was performed, and the corresponding continuous values of the population standard were calculated by a simple approximation method based on the linear connection of the 3rd, 10th, 50th and 90th percentiles, provided by Alexander et al., in the different race, infant gender, and gestational age groups.[8] The individualized standard used was that proposed by Gardosi et al, which takes into account maternal age, height, weight, parity, race/ethnicity, and neonatal gender.[3] The software GROW (Gestation Related Optimal Weight) at www.gestation.net was used to calculate the individualized standard.

The association of the primary outcome, moderate/severe CP or death by 2 years of age, with the diagnosis of SGA by each type of standard was presented as the relative risk with 95% confidence intervals. The ability of each type of standard to accurately classify newborns, based on their SGA status, according to whether they developed CP or death was assessed using sensitivity, specificity, and the area under the receiver operating characteristic curve (AUC-ROC).

Cerebral palsy was diagnosed by an annually-certified pediatrician or pediatric neurologist if two or more of the following three features were present: a delay of 30% or more in gross motor developmental milestones (e.g., inability to sit without arm support by 9.5 months or walk by 17 months of corrected age); abnormality in muscle tone (e.g., scissoring), 4+ or absent deep-tendon reflexes, or movement abnormality (e.g., posturing or gait asymmetry); or persistence of primitive reflexes or absence of protective reflexes. When CP was diagnosed, the Gross Motor Function Classification System (GMFCS) was used to assess severity.

In addition, the associations of the SGA diagnosis with secondary outcomes, including respiratory distress syndrome, necrotizing enterocolitis, grade 3 or 4 intraventricular hemorrhage, retinopathy of prematurity, seizures, or sepsis, were determined.

All analyses were performed with R (http://www.r-project.org/) and SAS (SAS Institute Inc, Cary, NC). $P < .05$ was used to define statistical significance, and all tests were two tailed. No adjustments were made for multiple comparisons. McNemar's test for classification agreement was used for the comparison of sensitivity or specificity.[9] A nonparametric statistical method was used for the comparison of the AUC-ROCs.[10] All analyses were repeated by treatment subgroups (placebo vs. magnesium sulfate). Institutional review board approval was obtained prior to the initiation of the study.

Results

One thousand five hundred and eighty-eight newborns met inclusion criteria. Characteristics of the study population are presented in Table 1. Of these, 364 (22.9%) were identified as SGA according to the individualized standard (IS) and 44 (2.8%) were identified as SGA according to the population standard (PS). Forty-four newborns met SGA criteria by both standards (i.e., all PS-SGA newborns also were identified as IS-SGA).

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One hundred and forty-three neonates (9.4%) developed either moderate or severe CP (n = 33, 2.2 %) or death (n = 110, 7.2%) by 2 years of age. Moderate or severe CP was seen in 14.4% of the infants defined as SGA by the IS and in 21.4% of the infants defined as SGA by the PS. Neonates defined as SGA by either the population standard or by the individual standard were significantly more likely to develop moderate/severe CP or death, although the magnitudes of the associations were similar for both types of standards (Table 2).

The test characteristics of the different growth standards for prediction of the primary outcome also are presented in Table 2. While the individualized standard had a significantly greater sensitivity for the primary outcome, its specificity was significantly lower. Although the AUC for prediction of the primary outcome was greater for the individualized standard, this difference was small and unlikely to have clinical relevance. Moreover, the AUC for either the individualized or population standard demonstrates that either standard is poorly predictive of CP or death.

The results were similar for prediction of the various secondary outcomes. While the individualized standard appeared to be better at predicting these outcomes, the difference was small in magnitude. In addition, the ability of either growth standard to predict any secondary outcome was repeatedly poor (Table 3). The AUC values indicate that prediction of these outcomes was at best barely better than chance.

Results did not vary by treatment group (data not shown).

Comment

In this study, we evaluated whether the use of an individualized growth standard would enhance the ability to identify preterm neonates who were most likely to develop moderate or severe CP or die. In addition, we evaluated whether an individualized growth standards could better predict other significant morbidities associated with preterm birth. Our results do not support the concept that the predictive ability of an individualized standard is clinically superior to that of a population standard.

These results stand in contrast to those of some investigators whose studies have suggested that use of an individualized standard could improve identification of pathologically grown neonates. For example, Gardosi and Francis demonstrated that the presence of a SGA neonate, as classified by an individualized standard as opposed to a population-based standard, was significantly more likely to be associated with pregnancies that had been complicated by threatened preterm labor, antepartum hemorrhage, pregnancy-induced hypertension, preeclampsia, stillbirth, and early neonatal death.[4] Others have reported that adverse outcomes subsequent to birth, such as Apgars < 4 at 5 minutes, long hospital stays, or neonatal death, were more strongly associated with SGA births classified according to the individualized standard.[11–13]

In contrast, other investigators, when examining antepartum or short-term neonatal outcomes, have not found that an individualized standard is superior. Hutcheon et al, studying over 780,000 births from a Swedish birth registry, found that an individualized birth weight standard had a similar ability to predict perinatal death as a population-based standard that did not adjust for maternal characteristics.[14] Larkin et al studied over 32,000 births from an American population and similarly found no significant difference in the ability of population-based or individualized standards to predict which women were more likely to have pregnancies complicated by perinatal morbidity.[15] Our work supports and extends the concept that outcomes are similar regardless of which type of growth standard is used. By focusing upon a preterm population only, we were able to assess immediate complications related to prematurity, as well as longer term complications, such CP or infant

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mortality. Regardless of which outcome was examined, associations and predictive abilities were similar between the two types of growth standards.

The population for this study was derived from a randomized trial that assessed whether magnesium sulfate was efficacious for prevention of moderate or severe CP, and was predominantly composed of neonates born after premature preterm rupture of the membranes. As such, further investigation will need to determine whether these findings are generalizable to all women, such as those with pregnancy complications characterized by chronic placental insufficiency (e.g., preeclampsia, chronic abruption), who deliver preterm.

The accurate prediction of which prematurely born neonates will die or develop CP would be of great value, as it would allow not only better counseling but offer the potential that early interventions in the neonatal period could reduce the frequency of these adverse events. Although neonates who are SGA according to population-based growth are at higher risk of death or CP, the predictive ability of the SGA designation for these outcomes has been poor. Unfortunately, designation of SGA status through the use of individualized standards does not appear to improve this predictive ability. In light of the additional work that is necessary to establish an individualized standard, these findings do not support their introduction into clinical practice at present, and suggest that further work will need to be done to establish whether their use is supported by enhancements in clinical outcomes.

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Appendix

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Table 1

Characteristics of the study population

Characteristic	N = 1588	
Weeks of gestation at randomization	28.2 ± 2.4	
Maternal age (years)	26.3 ± 6.3	
Maternal height (cm)	162.9 ± 7.5	
Maternal pre-pregnancy weight (kg)	69.5 ± 18.9	
Maternal pre-pregnancy BMI (kg/m^2)	26.2 ± 6.8	
Maternal race/ethnicity		
Black	719 (45.3%)	1.
White	598 (37.7%)	2.
Hispanic	235 (14.8%)	3.
Other	36 (2.3%)	4.
Married *	760 (48.0%)	5.
Nulliparous	567 (35.7%)	6.
Previous preterm delivery	450 (28.3%)	7.
Cigarette use during pregnancy	475 (29.9%)	

Data presented as mean ± standard deviation or n (%)

* Marital status unknown for 4 women

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Table 2

Association of small-for-gestational age status with moderate or severe cerebral palsy or death.

	Individualized standard	Population standard	P*
Relative risk (95% CI) **	1.8 (1.3 – 2.5)	2.4 (1.3 – 4.3)	--------
Sensitivity	36%	6%	<.001
Specificity	78%	98%	<.001
Area under the curve	0.59 (0.54–0.64)	0.55 (0.49–0.60)	<.001

* P-value based on McNemar's test for classification agreement (sensitivity/specificity) or non-parametric comparison of areas under the ROC curves.

** Referent = non-small-for-gestational-age neonates

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Table 3

Area under the curve of the receiver operating characteristic curve for secondary neonatal outcomes

	Individualized standard	Population standard	P*
RDS	0.52 (0.49 – 0.55)	0.43 (0.40 – 0.46)	<.001
Necrotizing enterocolitis	0.54 (0.49 – 0.58)	0.49 (0.45 – 0.54)	<.001
IVH, grade 3 or 4	0.44 (0.34 – 0.54)	0.38 (0.26 – 0.49)	0.04
ROP	0.56 (0.53 – 0.60)	0.48 (0.45 – 0.52)	<.001
Seizures	0.55 (0.46 – 0.64)	0.51 (0.40 – 0.61)	0.15
Sepsis	0.57 (0.54 – 0.61)	0.52 (0.49 – 0.56)	<.001

RDS = respiratory distress syndrome; IVH = intraventricular hemorrhage; ROP = retinopathy of prematurity

*P-value based on non-parametric comparisons for area under the ROC curves.