OBSTETRICS

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

William A. Grobman, MD, MBA; Yinglei Lai, PhD; Dwight J. Rouse, MD; Catherine Y. Spong, MD; Michael W. Varner, MD; Brian M. Mercer, MD; Kenneth J. Leveno, MD; Jay D. Iams, MD; Ronald J. Wapner, MD; Yoram Sorokin, MD; John M. Thorp Jr, MD; Susan M. Ramin, MD; Fergal D. Malone, MD; Mary J. O'Sullivan, MD; Gary D. V. Hankins, MD; Steve N. Caritis, MD; for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network

OBJECTIVE: The objective of the study was to determine whether an individualized growth standard (IS) improves the identification of preterm small-for-gestational-age (SGA) neonates at risk of developing moderate/severe cerebral palsy (CP) or death.

STUDY DESIGN: This study was a secondary analysis of data from a randomized trial of $MgSO_4$ for the prevention of CP or death among anticipated preterm births. Singleton nonanomalous liveborns delivered before 34 weeks' were classified as SGA (less than the 10th percentile for their gestational age) by a population standard (PS) or an IS (incorporating maternal age, height, weight, parity, race/ethnicity, and neonatal sex). The primary outcome was the prediction of moderate or severe CP or death by age 2 years.

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: relative risk [RR], 2.4, 95% confidence interval [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 the $MgSO_4$ treatment group. The IS was more sensitive (36% vs 6%, $P < .001$) but less specific (78% vs 98%, $P < .001$) for CP or death. The receiver operating characteristic curve analysis revealed a statistically lower area under the curve 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 years.

Key words: cerebral palsy, death, small for gestational age

Cite this article as: Grobman WA, Lai Y, Rouse DJ, et al. The association of cerebral palsy and death with small-for-gestational-age birthweight in preterm neonates by individualized and population-based percentiles. Am J Obstet Gynecol 2013;209:340.e1-5.

From the Departments of Obstetrics and Gynecology, Northwestern University, Chicago, IL (Dr Grobman); Brown University, Providence, RI (Dr Rouse); University of Utah Health Sciences Center, Salt Lake City, UT (Dr Varner); Case Western Reserve University–MetroHealth Medical Center, Cleveland, OH (Dr Mercer); University of Texas Southwestern Medical Center, Dallas, TX (Dr Leveno); The Ohio State University, Columbus, OH (Dr Iams); Thomas Jefferson University and Drexel University, Philadelphia, PA (Dr Wapner); Wayne State University, Detroit, MI (Dr Sorokin); University of North Carolina at Chapel Hill, Chapel Hill, NC (Dr Thorp); University of Texas Health Science Center at Houston–Children's Memorial Hermann Hospital, Houston, TX (Dr Ramin); Columbia University, New York, NY (Dr Malone); University of Miami, Miami, FL (Dr O'Sullivan); University of Texas Medical Branch, Galveston, TX (Dr Hankins); University of Pittsburgh, Pittsburgh, PA (Dr Caritis); George Washington University Biostatistics Center, Washington, DC (Dr Lai); and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD (Dr Spong). Participating subcommittee members and the other members of the Maternal-Fetal Medicine Units Network are listed in the Acknowledgments.

Received March 7, 2013; revised June 5, 2013; accepted June 6, 2013.

The views expressed herein are those of the authors do not necessarily represent the official views of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Institute of Neurological Disorders and Stroke, or the National Institutes of Health.

Supported by grants HD27869, HD34208, HD34116, HD40544, HD27915, HD34136, HD21414, HD27917, HD27860, HD40560, HD40545, HD40485, HD40500, HD27905, HD27861, HD34122, HD40512, HD53907, HD34210, HD21410, HD36801, and HD19897 from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; and grant M01-RR-000080 from the National Center for Research Resources, National Institutes of Health, Department of Health and Human Services, and the National Institute of Neurological Disorders and Stroke.

The authors report no conflict of interest.

Presented at the 32nd annual meeting of the Society for Maternal-Fetal Medicine, Dallas, TX, Feb. 6-11, 2012.

Reprints not available from the authors.

0002-9378/$36.00 • • http://dx.doi.org/10.1016/j.ajog.2013.06.007

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 birthweights that result from both normal physiological variation and pathological 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,[4] 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.

The potential benefit of using individualized birthweight standards to help predict long-term neurodevelopmental adverse outcomes, however, is not known. Although 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 with a population-based standard, would improve identification of small-for-gestational-age (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 (ie, the Beneficial Effects of Antenatal Magnesium Sulfate [BEAM] study) of magnesium sulfate for the 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 followed up for 2 years with detailed developmental assessments performed by trained examiners.

The present analysis includes all nonanomalous singleton liveborns in the BEAM study who delivered prior to 34 weeks of gestation. Each newborn's birthweight was used to determine whether it was 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,[7] which is stratified according to neonatal sex and ethnicity.

Because 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 birthweights (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 third, 10th, 50th, and 90th percentiles, provided by Alexander et al,[8] in the different race, infant sex, and gestational age groups.

The individualized standard used was that proposed by Gardosi et al, [3] which takes into account maternal age, height, weight, parity, race/ethnicity, and neonatal sex. The software GROW (Gestation Related Optimal Weight; 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 2 or more of the following 3 features were present: a delay of 30% or more in gross motor developmental milestones (eg, inability to sit without arm support by 9.5 months or walk by 17 months of corrected age); abnormality in muscle tone (eg, scissoring), 4 or more or absent deep-tendon reflexes, or movement abnormality (eg, posturing or gait asymmetry); or persistence of primitive reflexes or absence of protective reflexes. When CP was diagnosed, the Gross Motor Function Classification System 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 2 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 eighty-eight newborns met the inclusion criteria. Characteristics of the study population