The Influence of Fetal Growth Reference Standards on Assessment of Cognitive and Academic Outcomes of Very Preterm Children

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Objective To compare 3 methods of identifying small-for-gestational-age (SGA) status in very preterm children as related to cognitive function and academic outcome.

Study design There were 1038 singletons in the Epipage Study, born before 33 weeks in 1997 without severe neurosensory impairment, who were classified as SGA when birth weight was below the 10th percentile according to: (1) birth weight (bw) reference: SGA(bw)/appropriate for gestational age (AGA)(bw); (2) intrauterine (intraut) reference: SGA(intraut)/AGA(intraut); and (3) intrauterine reference customized (cust) according to individual characteristics: SGA(cust)/AGA(cust). Cognitive function was assessed by the mental processing composite (MPC) score of the Kaufman Assessment Battery for Children at age 5 and academic achievement by a parental questionnaire at age 8.

Results Of the children, 15% were SGA(bw), 38% were SGA(intraut), and 39% were SGA(cust). All children SGA(bw) were also SGA(intraut) and SGA(cust). MPC was <85 in 32% of children and 27% had low academic achievement. AGA(bw)/SGA(intraut) children had a significantly increased risk of MPC <85 (adjusted OR 1.74, 95% CI 1.22-2.28) or low academic achievement (adjusted OR 1.64, 95% CI 1.05-2.55) compared with AGA(bw)/AGA(intraut) children. The SGA(cust) group was only slightly different from the SGA(intraut) group.

Conclusions An intrauterine reference identified very preterm infants at risk of poor cognitive or academic outcomes better than a birth weight reference. Customization resulted in only slight modifications of the SGA group. *(J Pediatr 2012;161:1053-8)*.

Being born preterm or small for gestational age (SGA) is associated with neonatal mortality and morbidity, as well as developmental disabilities such as cognitive impairment and low academic achievement.[1,2] SGA newborns are usually defined as newborns whose birth weight is below the 10th percentile for their gestational age (GA). SGA is generally used as a proxy for fetal growth restriction (FGR), although these terms are not synonymous: SGA describes an anthropometric characteristic, and FGR is a pathologic condition characterized by an insufficient fetal growth.[3] FGR is significantly more frequent among preterm than term newborns, because they are not born after a normal pregnancy and are more likely to have been exposed before birth to medical conditions associated with an insufficient fetal growth.[4] For this reason, a reference based on the observed distribution of birth weights (bw) underestimates the true number of growth-restricted preterm newborns.[4,5] Intrauterine (intraut) references that used ultrasound measures to estimate fetal weight make it possible to describe the growth of normal fetuses in utero.[6] Their use instead of birth weight references may give better information on the actual incidence of FGR in preterm newborns.[5,7,8] Intrauterine references identify about 25%-30% of very preterm newborns SGA compared with 10% for birth weight references.[4,7,9,10] Customized (cust) references are weight-for-GA percentiles that have been individualized to account for physiological influences on fetal

AGA	Appropriate for gestational age
bw	Birth weight classification
(cust)	Customized classification
CP	Cerebral palsy
FGR	Fetal growth restriction
GA	Gestational age
(intraut)	Intrauterine classification
K-ABC	Kaufman Assessment Battery for Children
MPC	Mental processing composite
SGA	Small-for-gestational-age

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growth.[11] They have been designed to distinguish between newborns who are small but have reached their individual growth potential and those who have FGR. In studies of all births, approximately 5% of newborns change SGA status with the use of customized versus noncustomized intrauterine curves.[12] It remains controversial whether newborns newly classified SGA when using a customized curve had an increased risk of stillbirth or perinatal death compared with non-SGA newborns.[12,13]

When studying the influence of SGA on outcomes in preterm children, the classification bias is problematic if SGA is defined according to a birth weight reference.[3] Long-term cognitive or academic outcomes in preterm children according to intrauterine growth curves have not yet been studied, although these references may give better information about the association of FGR with neonatal morbidity in preterm newborns.[5,8] Moreover, the utility of customized references in evaluating the risk of mortality or neonatal morbidity has not been assessed for very preterm newborns.

We investigated the relation between SGA status and cognitive outcome at age 5 and academic achievement at age 8 in a population-based cohort of singleton children born before 33 weeks and free of severe neurosensory impairment using 3 different methods to define SGA: SGA(bw), SGA(intraut), and SGA(cust).

Methods

The population is part of the Epipage Cohort, which included all births before 33 weeks' gestation in all maternity units in 9 French regions in 1997. For this study, we were interested in singleton children born between 24 and 32 completed weeks, alive and eligible for follow-up at discharge, free of severe neurosensory impairment (nonambulatory cerebral palsy [CP] or CP walking with aid, severe auditory or visual impairment). At recruitment, parents were told about the study and given written information, and oral consent was provided. The study was approved by the French Commission Nationale de l'Informatique et des Libertés (the French data protection agency).

GA referred to completed weeks of amenorrhea, and the values reported are the best obstetric estimates on the basis of the date of the last menstrual period and a first trimester ultrasound, which is a universal practice in France. Data about pregnancy were collected by midwives in the delivery room. Pediatricians completed data about neonatal complications. The mother's age, parity, nationality, and educational level were collected during the neonatal hospitalization and completed at follow-up when missing. Educational level was classified into 3 categories: low (elementary school or lower secondary education), intermediate (upper secondary education), or high (university).

SGA Classifications

We categorized the child as SGA if his/her birth weight was <10th percentile or appropriate for GA (AGA) otherwise using 3 different references. We first used the French Association of Users of Computerized Files in Perinatology, Obstetrics and Gynecology[14] curves for each sex as a population birth weight reference. This led to a birth weight (bw) classification as SGA(bw) or AGA(bw).

An intrauterine growth standard was then considered, using Hadlock et al [6] proportional growth curves modified by Gardosi et al.[15] The growth trajectory of the fetus was modeled as a proportion of the average birth weight of boys and girls at 40 weeks, which was estimated from a combination of the French perinatal surveys conducted in 1998 and 2003 (3504 g for boys and 3346 g for girls).[16] For each GA, the estimated fetal weight was expressed as a percentage of the weight at 40 weeks[3]:

$$\%\ \text{Weight}/40\ \text{weeks} = 299.1 - (31.85 * \text{GA}) + (1.094 * \text{GA}^2) + (1.01055 * \text{GA}^3)$$

The SD was assumed to be equal to 11% of the mean at each GA.[15] Each child was then classified as SGA(intraut) or AGA(intraut) at birth, when his/her birth weight was plotted on such an intrauterine curve.

Last, we classified the children according to a customized standard as defined by Gardosi et al.[11] The birth weight norms of Gardosi et al incorporate information about maternal height, weight, parity, and ethnic origin. The coefficients from a linear regression model make it possible to calculate the average weight of a fetus at 40 weeks given its sex and its mother's characteristics. Hadlock's et al modified formula was then used to derive the optimal adjustable weight at each GA.[6,15] We used the same sample from the French perinatal surveys to determine the coefficients for the variables in Gardosi's et al model. The calculation of the regression coefficients was done taking smoking into account, but the optimal fetal weight was predicted assuming that all women were nonsmokers. We did not model ethnic origin, because these data were not available in France. Each child was classified SGA(cust) or AGA(cust), where cust indicates customized.

Outcomes

At 5 years of age, the mental processing composite (MPC) scale, which is considered to be equivalent to IQ, was assessed by a psychologist using the Kaufman Assessment Battery for Children (K-ABC).[17] Cognitive dysfunction was defined by an MPC score of <85 (ie, −1 SD). We also studied cognitive deficiency, defined by an MPC score of <70 (ie, −2 SDs).

When the child was 8 years old, a postal questionnaire was sent to the parents with questions about schooling. Low academic achievement was defined as being in a specialized school or class, having repeated 1 grade, and/or receiving additional assistance provided at school.

Statistical Analysis

First, we compared children who were lost to follow-up at age 5 or who had missing data on the K-ABC with children included in the study. Then AGA and SGA children were described according to the different definitions. For both