Intrauterine Growth Restriction, Head Size at Birth, and Outcome in Very Preterm Infants

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Objectives To determine whether small head circumference (HC) or birth weight (BW) or both are associated with neonatal and long-term neurologic outcome in very preterm infants.

Study design All 2442 live births from the 1997 Epipage study between 26 and 32 weeks of gestational age in 9 regions of France were analyzed. A total of 1395 were tested at age 5 years for cognitive performance and 1315 with school performance reports at age 8 years. Symmetric growth restriction (SGR) was defined by HC and BW <20th percentile and in the same percentile range, and asymmetric growth restriction by at least 1 of HC and BW <20th percentile and the other in a higher decile range. There were 2 forms of asymmetric growth restriction: head growth restriction (HGR) and weight growth restriction (WGR). Appropriate for gestational age was defined by both BW and HC >20th percentile.

Results Compared with appropriate for gestational age, SGR was significantly associated with neonatal mortality (aOR 2.99, 95% CI 1.78-5.03), moderate and severe cognitive deficiency (aOR 1.65, 95% CI 1.01-2.71 and aOR 2.61, 95% CI 1.46-4.68, respectively), and poor school performance (aOR 1.79; 95% CI 1.13-2.83). HGR was significantly associated with severe cognitive deficiency (aOR 2.07, 95% CI 1.15-3.74). WGR was not significantly associated with cognitive or school performance despite higher rates of neonatal morbidity.

Conclusions SGR in preterm infants was associated with neonatal mortality and impaired cognitive and school performance. The outcome of asymmetric growth restriction differed according to HC. HGR was associated with impaired cognitive function; WGR was not. *(J Pediatr 2015;167:975-81)*.

Changes in perinatal management have been associated with a substantial increase in the survival of infants at very low gestational ages, an increase that raises questions about their long-term neurologic outcomes.[1] Preterm growth-restricted infants are a population of particular interest because they combine immaturity secondary to low gestational age with the consequences of growth restriction.

Growth restriction remains a concept difficult to study especially in preterm infants. It intermixes mechanisms including placental insufficiency, with or without brain sparing,[2] congenital abnormalities, toxic, environmental,[3] and maternal diseases.[4,5] It is difficult to distinguish their consequences from the separate consequences of immaturity. Because these mechanisms might affect various anthropometric measurements, such as head circumference (HC) and birth weight (BW) differently, these measurements might also be associated differently with specific outcomes.

Previous studies have demonstrated that small for gestational age birth is associated with a high mortality rate and impaired cognitive development.[6-9] Although growth restriction is a dynamic process, it is commonly defined by a BW <10th percentile. Moreover, preterm growth reference curves underestimate growth restriction.[10] Growth restriction because of placental insufficiency should, thus, be studied as a dynamic process that reduces the fetus's growth capacity secondary to the failure of compensation mechanisms or the severity of the illness.[11] It is thought that growth-restricted fetuses attempt to compensate for the "substrate limitation associated with placental insufficiency by preferentially

AGA	Appropriate for gestational age
BW	Birth weight
HC	Head circumference
HGR	Head growth restriction
SGR	Symmetric growth restriction
WGR	Weight growth restriction

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perfusing the central nervous system."[12,13] If so, development would be limited first by a reduction in BW and only thereafter by smaller head size. If growth restriction occurs early in pregnancy or if no adaptive mechanism protects the fetus, growth restriction might be symmetric. If it occurs later, however, or is accompanied by adaptive phenomena, it might result in asymmetric growth restriction involving BW only. If this hypothesis is correct, head growth restriction (HGR) appears to be due to another mechanism and may be associated with a different outcome.

Accordingly, we analyzed growth restriction in its different clinical forms by examining 2 specific anthropometric measurements (BW and HC) and their relations to 3 different outcomes in very preterm children: short-term mortality and morbidity and long-term neurodevelopmental outcomes.

Methods

Our data come from the 1997 Epipage cohort study, which included all live births between 22 and 32 weeks of gestation in 1997 in 9 regions on France.[14] Because 65% of those born at 22-25 weeks died before discharge, we limited our analysis to children born alive at 26-32 weeks (n = 2694) for whom HC and BW were available (n = 2442, 90.6%). Two regions with large samples included only 1 of every 2 infants for follow-up (70 infants not included). Parent refusal resulted in exclusion of 89 infants from follow-up. At 5 years of age, 1648 (80%) had medical examinations and 1395 (68%) cognitive assessments, all by trained physicians and psychologists. The parents of 1520 children (74%) also completed questionnaires. Around the children's eighth birthdays, parents received a questionnaire about their school performance. In all, 1315 (64%) responses were available for analysis (**Figure 1**; available at www.jpeds.com).

The Commission Nationale de l'Informatique et des Libertés (French Data Protection Authority) approved the study. Parents provided verbal consent. Ethics committee approval was not required because this was an observational study of usual care, with no intervention.

Gestational age was defined by completed weeks of gestation, determined from the date of the last menstrual period and early ultrasound findings. Maternal and obstetric data were recorded on standardized questionnaires at birth in each maternity unit. Maternal data included nationality, age at birth, and parity. Family socioeconomic status was recorded according to the French classification of occupations and social position, defined by the higher-status parental occupation (or the mother's, if she did not live with the father). Obstetric data included type of pregnancy (singleton or higher-order) and antenatal corticoid use.

Infant Characteristics and Neonatal and Long-Term Outcomes

Neonatal data were prospectively collected at each hospital. This study considers sex, BW, and HC, measured by the maximum occipital-frontal HC at birth. Congenital abnormalities were also recorded. In-hospital mortality was defined as death in the delivery room or neonatal unit. Length of hospitalization was defined as the number of days until discharge home. Bronchopulmonary dysplasia was defined as oxygen dependency at 28 days. Duration of central line was defined as the total number of days during which a central line was maintained, regardless of the reason.

Intraventricular hemorrhage and white matter damage were diagnosed from cranial ultrasonography, performed by qualified neonatologists or radiologists. Major brain lesions included intraventricular hemorrhage with ventricular dilatation (grade III) or intraparenchymal hemorrhage (grade IV), according to the Papile classification, cystic periventricular leukomalacia, or hyperechogenicity persisting more than 14 days without cystic formation.[15]

We used the European definition to define cerebral palsy, which requires at least 2 of the following: abnormal posture or movement, increased tone and hyperreflexia (spastic cerebral palsy), involuntary movements (dyskinetic cerebral palsy), or absence of coordination (ataxic cerebral palsy).[16] The French version of the Kauffman assessment battery for children was used to assess cognitive function, expressed as a mental processing composite score (IQ equivalent), standardized with a mean of 100 and a SD of 15 in a French population born in the 1990s.[17] Moderate cognitive deficiency was defined by a score between 70 and 84, and severe cognitive deficiency <70.

Behavioral problems were assessed by the French versions of the strength and difficulties questionnaire,[18] completed by parents. It includes 4 scales (inattention-hyperactivity, conduct, emotional, and peer problems) that were added together for a total behavioral difficulties score. The cut-off was defined by the 90th percentile of the scores observed in the reference group of term infants included in Epipage. School difficulties were assessed at age 8 years based on a parental questionnaire. Special schooling (institution, special school and special class in mainstream school, compared with mainstream class) or low grades were considered school difficulties.[19]

Growth Restriction

Percentiles of BW and HC were determined by gestational age and sex from the data of this cohort of very preterm births (**Figure 2**). Our population was divided into 4 different categories according to the percentile of their HC and BW.

Symmetric growth restriction (SGR) was defined by BW and HC percentiles both <10th percentile or both between 10th and 19th percentile. Two different types of asymmetric growth restriction were defined. HGR was defined by a HC <20th percentile, with BW in at least the next higher decile group, and weight growth restriction (WGR) by a BW <20th percentile, with HC in at least the next higher decile group. The group without growth restriction, that is, appropriate for gestational age (AGA), was defined by BW and HC both above the 20th percentile.