Effect of Intra- and Extrauterine Growth on Long-Term Neurologic Outcomes of Very Preterm Infants

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Objective To determine whether extrauterine growth is associated with neurologic outcomes and if this association varies by prenatal growth profile.

Study design For 1493 preterms from the EPIPAGE (Étude Épidémiologique sur les Petits Âges Gestationnels [Epidemiological Study on Small Gestational Ages]) cohort, appropriate for gestational-age (AGA) was defined by birth weight >−2 SD and small for gestational-age (SGA) by birth weight ≤−2 SD. Extra-uterine growth was defined by weight gain or loss between birth and 6 months by z-score change. Growth following–the-curve (FTC) was defined as weight change −1 to +1 SD, catch-down-growth (CD) as weight loss ≥1 SD, and catch-up-growth (CU) as weight gain ≥1 SD. At 5 years, a complete medical examination (n = 1305) and cognitive evaluation with the Kauffman Assessment Battery for Children (n = 1130) were performed. Behavioral difficulties at 5 years and school performance at 8 years were assessed (n = 1095).

Results Overall, 42.5% of preterms were AGA-FTC, 20.2% AGA-CD, 17.1% AGA-CU, 5.6% SGA-FTC, and 14.5% SGA-CU. Outcomes did not differ between CU and FTC preterm AGA infants. Risk of cerebral palsy was greater for AGA-CD compared with AGA-FTC (aOR 2.26 [95% CI 1.37-3.72]). As compared with children with SGA-CU, SGA-FTC children showed no significant increased risk of cognitive deficiency (aOR 1.41[0.94-2.12]) or school difficulties (aOR 1.60 [0.84-3.03]). Compared with AGA-FTC, SGA showed increased risk of cognitive deficiency (SGA-FTC aOR 2.19 [1.25-3.84]) and inattention-hyperactivity (SGA-CU aOR 1.65 [1.05-2.60]).

Conclusion Deficient postnatal growth was associated with poor neurologic outcome for AGA and SGA preterm infants. CU growth does not add additional benefits. Regardless of type of postnatal growth, SGA infants showed behavioral problems and cognitive deficiency. *(J Pediatr 2016;175:93-9)*.

Preterm infants are known to be at risk of cognitive deficiency, behavioral problems, and motor dysfunction compared with their normal-term peers. Previous studies have demonstrated that small for gestational-age (SGA) birth is associated with a high rate of mortality and impaired cognitive development. Results of studies of postnatal growth and its relation to neurologic outcome in preterms are not uniform.[1] Some studies found that weight gain after birth had no effect on neurologic outcome,[2] whereas some others found a significant association with cognitive performance.[3] The mechanisms of pre- and postnatal growth differ. Accordingly, poor pre- and postnatal growth could lead to different neurologic outcomes.[4]

Prenatal growth deficiency is associated with specific postnatal morbidities and growth deficiency. Optimal postnatal growth in preterm infants generally is associated with good cognitive performance and neurologic outcome[5-8] in preterm and/or in SGA preterm infants[9,10]; however, the extent to which rapid

AGA	Appropriate for gestational age
BW	Birth weight
CD	Catch-down growth
CU	Catch-up growth
EPIPAGE	Étude Épidémiologique sur les Petits Âges Gestationnels (Epidemiological Study on Small Gestational Ages)
FTC	Following the curve
GA	Gestational age
SGA	Small for gestational age

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Supported by INSERM (National Institute of Health and Medical Research, the Directorate General for Health at the Ministry for Social Affairs, Merck-Sharp and Dohme-Chibret, Medical Research Foundation, and the Hospital Program for Clinical Research (2001 nuAOM01117 of the French Department of Health). The 8-year follow up was supported by the Hospital Program for Clinical Research (2004/054/HP) at the French Department of Health and the Wyeth Foundation for Children and Adolescents. The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2016.05.027

postnatal growth improves cognitive outcome remains unresolved.[11,12] Moreover, the relative importance of antenatal growth malnutrition (SGA preterm) and postnatal renutrition on development of the preterm child is still unknown.

We aimed to study whether extrauterine growth in the first 6 months of life was associated with motor, cognitive, and behavioral outcomes and school performance in very preterm infants and whether this association varied by prenatal growth profile.

Methods

The EPIPAGE (Étude Épidémiologique sur les Petits Âges Gestationnels [Epidemiological Study on Small Gestational Ages]) 1 is a population-based cohort study recording all live births in 1997 between 22 and 32 weeks' gestation across all maternity units in 9 regions in France (**Figure**; available at www.jpeds.com). Infants were followed from birth to 8 years of age. Infants with neonatal malformations (n = 426) were excluded. Among the 2242 infants born between 24 and 32 weeks' gestation who were discharged home alive, 2174 were eligible for follow-up. Because of the large number of infants in 2 regions, only 1 of every 2 children was included for follow-up (68 infants not included). Parents were informed and oral consent was collected. In all, 96 parents refused the follow-up, which led to 2078 children followed. Seventeen infants died between discharge and 6 months of age.

Data on postnatal growth were available for 1493 children. At 5 years, 1305 children (88%) had a physical assessment and 1130 (76%) a cognitive evaluation by trained physicians and psychologists. The Strengths and Difficulties Questionnaire was completed by parents for 1235 (83%) children. At 8 years of age, results of a self-administered parental questionnaire assessing school performance were available for 1098 (74%) children. The French Commission nationale de l'informatique et des libertés approved this study.

Gestational age (GA) at birth referred to the date of last menstrual period or to an early ultrasound finding. It is expressed in complete weeks of gestation. Obstetrical data such as type of pregnancy (single or multiple) or antenatal corticosteroid use and maternal data, such as age of the mother, nationality, and parity, and maternal body mass index were recorded in the maternity unit.

The circumstances of preterm birth were divided in 3 mutually exclusive categories according to the pregnancy complication before birth: (1) vascular context (eg, mother with hypertension before pregnancy, preeclampsia, hypertension during pregnancy); (2) premature rupture of membranes-preterm labor (premature rupture of membranes or chorioamniotitis or idiopathic preterm labor); and (3) other complications (eg, hemorrhage). Socioeconomic status of the family was classified by parental occupation according to the French classification of occupations.

Birth weight (BW) was measured in the maternity ward or the neonatology unit. BW z score was defined by use of the obstetrical noncustomized individualized growth curves defined by Hadlock et al.[13] Optimal weight at birth was defined for every GA with the French national perinatal survey data,[14] corresponding to the population of our study at that time. SGA was defined by BW z score ≤ -2 SD and appropriate for GA (AGA) by BW > -2 SD.

Using a questionnaire sent to parents, we collected growth measurements at 6 months of chronologic age. These data are reported routinely by the attending physician in the Child Health Record Booklet. For each preterm infant with a measurement at 6 months, we calculated the corresponding corrected age. Accordingly, the z score of postnatal weight was calculated by the World Health Organization standard curves for sex and age at the corrected age previously calculated.

Postnatal growth was defined for each preterm infant as the z score for postnatal weight minus the z score at birth. Catch-up growth (CU) was growth gain ≥ 1 SD, catch-down growth (CD) ≥ -1 SD, and following the curve (FTC) no changes higher or lower than 1 SD.

Infant Characteristics and Neonatal Outcomes

Cranial ultrasonography scanning was performed routinely in the neonatology unit by experienced physicians or radiologists. Major brain abnormalities were defined as intraventricular or intraprenchymal hemohrrage (type III or IV from the Papile classification) or periventricular white damage (cystic periventricular leukomalacia or hyperechogenicity persisting for 15 days without cyst formation). Bronchopulmonary dysplasia was defined as oxygen requirement at 28 days of life.[15] Necrotizing enterocolitis was defined as stage II or III of the Bell classification.[16] Late-onset sepsis was defined by a postnatally acquired infection treated with antibiotics for at least 7 days.[17] Growth in the first days of life (g/kg/day) was defined by the use of medical records and calculated as the difference between {[(weight at day 15 or 30) − BW]/number of days}/BW.

Long-Term Outcomes

Cerebral palsy at 5 years of age was defined by the cerebral palsy network criteria[18] and was considered with at least 2 of abnormal posture or movement, increased tone and hyperreflexia, (spastic cerebral palsy), involuntary movements (dyskenetic cerebral palsy), or absence of coordination (ataxic cerebral palsy). Cognitive performance at 5 years of age was evaluated by the French version of the Kauffman Assessment Battery for Children.[19,20] For the mental processing composite, an IQ equivalent was standardized with mean 100 and SD 15 in a French population born in the 1990s. Cognitive deficiencies were defined by mental processing composite score <85.

A French version of the Strengths and Difficulties questionnaire[21] was sent to parents to assess behavioral problems. The questionnaire includes 4 scales (inattention-hyperactivity, conduct, emotional, and peer problems) summed in a fifth scale named total behavioral difficulties. The cut-off was defined in a reference term infant group included in EPIPAGE by the 90th percentile. School difficulties were assessed at 8 years of age by a self-administered parental questionnaire. Special schooling (institution, special class in mainstream school) or low grades compared with mainstream-appropriate class grades were considered difficulties in school.