Cognitive Impairment at Age 5 Years in Very Preterm Infants Born Following Premature Rupture of Membranes

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Objective To evaluate the relationship between preterm premature rupture of membranes (PPROM) and cognitive impairment in 5-year-old children born very preterm.

Study design The Etude Epidémiologique sur les Petits Ages Gestationnels Study is a population-based cohort of children followed up from birth to age 5 years recruited in 9 French regions in 1997. We analyzed data from singletons born between 24 and 32 weeks gestation categorized into 4 groups according to etiology of prematurity: infants born after PPROM, after idiopathic preterm labor, in a vascular context (Vasc), and to women with other complications (Other). Cognitive development at age 5 years was assessed using the Mental Processing Composite score of the Kaufman-Assessment Battery for Children.

Results Among the 1051 children followed up to age 5 years, the mean Mental Processing Composite score was 93.6 ± 19.7, and 13.3% of the children (140 of 1051) had cognitive impairment. After adjustment for potential confounders, the risk of cognitive impairment among infants in the PPROM group was not significantly different than that in the idiopathic preterm labor group (OR, 1.09; 95% CI, 0.62-1.92) and the Other group (OR, 1.36; 95% CI, 0.75-2.47), but was lower than that in the Vasc group (OR, 1.86; 95% CI, 1.16-2.97). In the PPROM group, the risk of cognitive impairment was greater when the latency period (ie, time from rupture to delivery) was <3 days (OR, 2.32; 95% CI, 1.07-5.02).

Conclusion Preterm infants born after PPROM are not at increased risk for cognitive impairment in childhood, but the time between PPROM and birth may influence that risk. *(J Pediatr 2013;163:435-40)*.

In Europe, between 1.1% and 1.6% of liveborn infants are born very preterm (ie, before 33 weeks gestational age).[1] The improved survival of very preterm infants has been associated with an increased rate of neuromotor and cognitive development abnormalities in these survivors.[2,3] With a prevalence of >10% in this population, cognitive impairment is one of the most common sequelae associated with very preterm birth.[4] These cognitive sequelae often result from white matter lesions that go unidentified in the perinatal period.[5] These lesions may be attributable to hemodynamic causes, and also may be the result of infectious[6] or inflammatory processes, as is observed in 50% of births that occur after preterm premature rupture of membranes (PPROM).[7] Infants born after PPROM also may be at increased risk for intraventricular hemorrhage and periventricular leukomalacia.[8-10]

Although PPROM accounts for one-third of preterm births,[11] studies on the long-term outcomes of these infants are rare and have reported conflicting results. Of note is a possible increased risk of cerebral palsy[12-14]; however, this link has yet to be systematically verified.[15,16] Only 1 study reported an increased risk of cognitive impairment in very preterm infants born after PPROM[17]; in that study, this risk was higher in neonates with a latency period (ie, time from

EPIPAGE	Etude Epidémiologique sur les Petits Ages Gestationnels
IPL	Idiopathic preterm labor
K-ABC	Kaufman Assessment Battery for Children
MPC	Mental Processing Composite
PPROM	Preterm premature rupture of membranes
SGA	Small for gestational age
Vasc	Vascular

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*A list of EPIPAGE Study Group members is available at www.jpeds.com (**Appendix**).

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rupture to delivery) exceeding 48 hours compared with those with a shorter latency period.

In a cohort of very preterm infants in the Etude Epidémiologique sur les Petits Ages Gestationnels (EPIPAGE) population, we investigated whether those born after PPROM were at greater risk for cognitive impairment at age 5 years. We also investigated whether the latency period between membrane rupture and birth influenced later cognitive outcome.

Methods

All parents of infants born at 24-32 weeks gestational age between January 1, 1997, and December 31, 1997, in 9 French regions (representing more than one-third of the country) were invited to participate in the EPIPAGE study.[18] The children in the study cohort were followed up at age 2 month, at age 9 months, and then every year up to age 5 years. Out of the 2855 liveborn neonates included in the EPIPAGE cohort, 25 had no available information concerning the etiology of prematurity (**Figure**; available at www.jpeds.com) and were excluded from this analysis. We also excluded 885 neonates from multiple pregnancies (to avoid a confounding bias) and 9 with serious malformations. Owing to the number of preterm neonates born at 32 weeks gestational age, all regions were given the option of including only 1 of every 2 infants born at exactly 32 weeks in the follow-up; 2 regions chose this option (52 infants). In these regions, children whose mother was born on an odd-numbered day were selected. Finally, a total of 1884 children met our inclusion criteria and were eligible for analysis. This study was approved by the French data protection agency (Commission Nationale de l'Informatique et des Libertés).

Maternal, obstetric, and neonatal data were collected at birth following a standardized protocol. All children were invited for a checkup at age 5 years. The parents were contacted in writing, and if no response was received, a system of follow-up contacts by phone or mail was established. The checkup involved medical, social, and psychological assessments, including a cognitive evaluation performed by a psychologist using the Kaufman Assessment Battery for Children (K-ABC).[19]

We divided the infants into 4 mutually exclusive groups according to the pregnancy complications that led to preterm delivery.[11] Infants born after PPROM without other pregnancy complications (PPROM group) were compared with infants born after idiopathic preterm labor (IPL group), defined as spontaneous onset of labor before rupture of membranes; infants born in a vascular context (Vasc group) to mothers with hypertension, defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg during pregnancy, and small for gestational age (SGA) infants, defined as a birth weight <10th percentile for gestational age of the liveborn infants in our sample (with these 2 groups aggregated because intrauterine growth restriction in preterm birth frequently has a vascular cause); and infants born to mothers with other complications (Other group) resulting in preterm delivery, including antepartum hemorrhage without SGA status or maternal hypertension.

The K-ABC has been validated in France for use in children aged 2.5-12.5 years.[19] The K-ABC Mental Processing Composite (MPC) score, considered equivalent to IQ score, is a global measure of cognitive ability. This score was standardized to a mean of 100 (SD ±15) using published French standards. In accordance with the World Health Organization's definition, cognitive impairment was defined as an MPC score <70 (difference of >2 SD).[20]

The following data were included in the analysis: sociodemographic data (ie, sex, maternal nationality, maternal educational level, and family socioeconomic status), antepartal and peripartal data (ie, gestational age, expressed as completed weeks of amenorrhea, antenatal corticosteroids, and mode of delivery), and neonatal data (ie, grade 3-4 intraventricular hemorrhage, periventricular leukomalacia, maternal-fetal infection, ulcero-necrotizing enterocolitis, bronchopulmonary dysplasia, and postnatal corticosteroid use).

The χ^2 test was used to analyze sociodemographic, antenatal, peripartal, and neonatal characteristics associated with the pregnancy complications leading to preterm delivery in the 4 study groups. ANOVA was used to compare mean K-ABC MPC scores. Logistic regression was used to evaluate the relationships between each of the pregnancy complication groups and cognitive impairment at age 5 years. We initially examined these relationships after adjustment for gestational age at birth (treated categorically using gestational age groups, as identified in **Table I**) and for the sociodemographic covariates deemed potentially important on univariate analysis ($P < .20$ for the association with pregnancy complication groups). Later, we made adjustments for antenatal, peripartal, and neonatal covariates meeting the same criteria ($P < .20$ for the associations with pregnancy complication groups). We considered these additional factors separately because they might be involved in the causal relationship between pregnancy complications and cognitive impairment, and thus could act as intermediate factors. Adjusting for their effect helped us explain the associations between pregnancy complication groups and cognitive impairment.

We addressed the risk of selection bias potentially induced by missing values by carrying out a sensitivity analysis using data imputation on both outcome variable and covariates. We used the multiple imputation by Markov chain Monte Carlo method[21] with the MI and MIanalyze procedures implemented in SAS version 9 (SAS Institute, Cary, North Carolina).[22] The imputed dataset was generated by performing 50 imputation cycles; 9.6% of the data were imputed.

To examine the influence of the latency period on cognitive outcome, we divided the population of neonates born after PPROM into 2 groups according to the interval between PPROM and birth. The threshold value for classifying neonates as either "short" or "long" latency corresponded to the median value of the latency period in our sample (3 days). The 2 latency groups were compared by following the same statistical procedure as described previously. Statistical analyses were performed at the conventional 2-tailed α level of 0.05 using SAS version 9.1 (SAS Institute).

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