# Impact of Latency Duration on the Prognosis of Preterm Infants after Preterm Premature Rupture of Membranes at 24 to 32 Weeks' Gestation: A National Population-Based Cohort Study

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**Objective** To assess the impact of latency duration on survival, survival without severe morbidity, and early-onset sepsis in infants born after preterm premature rupture of membranes (PPROM) at 24-32 weeks' gestation.

**Study design** This study was based on the prospective national population-based Etude Épidémiologique sur les Petits Âges Gestationnels 2 cohort of preterm births and included 702 singletons delivered in France after PPROM at 24-32 weeks' gestation. Latency duration was defined as the time from spontaneous rupture of membranes to delivery, divided into 4 periods (12 hours to 2 days [reference], 3-7 days, 8-14 days, and >14 days). Multivariable logistic regression was used to assess the relationship between latency duration and survival, survival without severe morbidity at discharge, or early-onset sepsis.

**Results** Latency duration ranged from 12 hours to 2 days (18%), 3-7 days (38%), 8-14 days (24%), and >14 days (20%). Rates of survival, survival without severe morbidity, and early-onset sepsis were 93.5% (95% CI 91.8-94.8), 85.4% (82.4-87.9), and 3.4% (2.0-5.7), respectively. A crude association found between prolonged latency duration and improved survival disappeared on adjusting for gestational age at birth (aOR 1.0 [reference], 1.6 [95% CI 0.8-3.2], 1.2 [0.5-2.9], and 1.0 [0.3-3.2] for latency durations from 12 hours to 2 days, 3-7 days, 8-14 days, and >14 days, respectively). Prolonged latency duration was not associated with survival without severe morbidity or early-onset sepsis.

**Conclusion** For a given gestational age at birth, prolonged latency duration after PPROM does not worsen neonatal prognosis. *(J Pediatr 2017;182:47-52).*

Preterm premature rupture of membranes (PPROM), defined as spontaneous rupture of membranes before 37 weeks' gestation and before labor, accounts for 3% of pregnancies and one-third of preterm births.[1,2] During the latency period (ie, the time between PPROM and birth), PPROM exposes the fetus to maternofetal infection, abruptio placentae, cord prolapse, and intrauterine death.[1] The main neonatal consequence of PPROM remains prematurity, a leading cause of neonatal mortality and morbidity.[1,2] In cases of PPROM, antenatal exposure to clinical or subclinical infection appears to be an additional specific risk factor of neonatal mortality and respiratory or neurologic complications.[3,4]

Expectant management in the setting of PPROM, and in the absence of obstetric complications, is considered beneficial to the fetus by increasing gestational age at birth[5-8]; however, the consequences of prolonged fetal exposure to PPROM and potential deleterious inflammation remain unclear. Indeed, only a

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| EPIPAGE 2 | Etude Épidémiologique sur les Petits Âges Gestationnels 2 |
| NICU | Neonatal intensive care unit |
| PPROM | Preterm premature rupture of membranes |

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few studies investigated latency duration as an independent risk factor for adverse outcomes in infants born preterm, with conflicting findings.[9-12]

EPIPAGE 2 is a nationwide, population-based prospective cohort of infants born preterm recruited in France in 2011.[13] Within this cohort, we identified all cases of preterm births after PPROM to determine whether for a given gestational age at birth, a prolonged latency period was associated with worse neonatal outcomes.

## Methods

The full details of the EPIPAGE 2 cohort recruitment and data collection have been reported previously.[13] In brief, all infants live born or stillborn and all terminations of pregnancy from $22^{0/7}$ to $34^{6/7}$ weeks' gestation in 25 French regions involving 546 maternity units were eligible. Infants were included in 2011 at 3 different periods by gestational age at birth: 8-month recruitment for births at 22-26 completed weeks' gestation, 6-month recruitment for 27-31 weeks, and 5-week recruitment for 32-34 weeks. Maternal, obstetric, and neonatal data were collected prospectively by following a standardized protocol.

As required by French law and regulations, Etude Épidémiologique sur les Petits Âges Gestationnels 2 (EPIPAGE 2) was approved by the national data protection authority (Commission Nationale de l'Informatique et des Libertés 911009), the appropriate ethics committees (ie, the advisory committee for the treatment of personal health data for research purposes [Comité Consultatif sur le Traitement de l'Information en matière de Recherche, 10.626]), and the committee for the protection of people participating in biomedical research (Comité de Protection des Personnes, CPP SC-2873).

Recommended obstetric management of women with PPROM includes a short course of antibiotics, corticosteroids between 24/25 and 34 weeks' gestation, and, if necessary, tocolysis and in utero transfer.[5] Usually, a single course of antenatal steroids was administered, and tocolytics, if provided, were atosiban, nifedipine, or nicardipine. Magnesium sulfate for fetal neuroprotection was not used routinely in 2011. As recommended, expectant management commonly was practiced before 34 weeks' gestation.[14]

The study population included all singleton fetuses alive at PPROM, with rupture at 24-32 weeks and birth at 24 to 34 weeks. PPROM was defined as spontaneous rupture of membranes occurring at least 12 hours before birth. As recommended, the diagnosis was based on maternal history (including the exact time of amniotic fluid loss) and sterile speculum examination completed by a paraclinical test of diagnosis if necessary.[5-7] From the 7804 births included in the EPIPAGE 2 cohort, exclusion criteria were multiple pregnancies (n = 2020), terminations of pregnancies (n = 1292), severe congenital defects (n = 154), homebirths (n = 49), and births before 24 weeks (n = 546).

The exposure of interest was latency period, defined as the time from rupture to delivery. The primary outcome was perinatal survival, defined as the number of children discharged alive from hospital relative to the number of fetuses alive at PPROM. The secondary outcome was survival to discharge without severe neonatal morbidity.[15] Severe neonatal morbidity was defined as any of the following outcomes: grade III or IV intraventricular hemorrhage (intraventricular hemorrhage)[16]; cystic periventricular leukomalacia (ie, periventricular white-matter echolucencies on ultrasonography)[17]; stage II or III necrotizing enterocolitis[18]; stage 3 or greater retinopathy of prematurity[19] and/or laser treatment; and severe bronchopulmonary dysplasia, defined as requiring oxygen for at least 28 days plus the need for 30% or more oxygen and/or mechanical ventilatory support or continuous positive airway pressure at 36 weeks' postmenstrual age.[20] Because survival of infants born preterm may improve at the cost of increased severe morbidity, we studied the association of latency period duration with these complementary outcomes. As the result of potential intra-amniotic inflammation related to prolonged latency, we considered early-onset neonatal sepsis as a secondary outcome, which was defined, for infants transferred to a neonatal intensive care unit (NICU), by positive bacteriology findings in blood or cerebrospinal fluid during the first 3 days of life.[21]

Gestational age was determined as the best obstetrical estimate combining the last menstrual period and ultrasonography assessment. The following variables also were included in the analysis: maternal characteristics (age, country of birth, health insurance coverage, parity), individual clinical characteristics (presentation, fetal sex, birth weight < third percentile), and antenatal management (antenatal steroids, antenatal antibiotics, tocolysis, delivery route). Universal medical insurance was set as a generalization of the medical insurance for those who have no access to the social security system based mainly on contributions from labor income. Complete steroids treatment was considered with 2 injections of betamethasone administered to the mother at a 24-hour interval.

### Statistical Analyses

Categorical variables were compared by $\chi^2$ or Fisher exact test as appropriate. Medians of quantitative variables were compared by Mann-Whitney *U* or Kruskal-Wallis test. All percentages, medians, and crude ORs were weighted by recruitment period. Logistic regression models were used to estimate the relationship between latency duration and outcomes. Latency duration was treated as a qualitative variable divided into 4 clinically relevant periods (12 hours to 2 days [reference], 3-7 days, 8-14 days, and >14 days). Gestational age at birth was treated as a continuous variable, after we checked the linearity of its association with outcomes by the fractional polynomials method. Multivariate models were adjusted for gestational age at birth and additionally for relevant risk factors of death, severe morbidity, or early-onset sepsis stated in the literature and for covariates that were potential confounders on bivariate analysis ($P < .20$). Results are reported as ORs with 95% CIs. Statistical significance was set at 2-tailed $P < .05$. We investigated interactions between latency duration and use of antenatal antibiotics, corticosteroids, or tocolysis and found no