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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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Title:

Impact of latency duration on preterm infant prognosis after preterm premature rupture of membranes at 24 to 32 weeks' gestation: a national population-based cohort study.

Authors:

Elsa LORTHE^{a,b}, RM, MSc, Pierre-Yves ANCEL^{a,c}, MD, PhD, Héloïse TORCHIN^a, MD, MSc, Monique KAMINSKI^a, MSc, Bruno LANGER^d, MD, Damien SUBTIL^e, MD, PhD, Loïc SENTILHES^f, MD, PhD, Laurence FOIX L'HELIAS^{a,g}, MD, PhD, François GOFFINET^{a,h}, MD, PhD, Gilles KAYEM^{a,b,i}, MD, PhD

For the EPIPAGE 2 Obstetric Writing Group.

EPIPAGE 2 Obstetric Writing Group: Catherine ARNAUD^j, MD, PhD, Bruno CARBONNE^k, MD, Thierry DEBILLON^l, MD, PhD, Pierre DELORME^{a,h}, MD, MSc, Claude D'ERCOLE^m, MD, Michel DREYFUSⁿ, MD, Cécile LEBEAUX^a, MD, MSc, Jacques-Emmanuel GALIMARD^o, MSc, Christophe VAYSSIERE^{j,p}, MD, PhD, Norbert WINER^q, MD, PhD.

Affiliations:

^a Inserm UMR 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team (Epopé), Center for Epidemiology and Statistics Sorbonne Paris Cité, DHU Risks in pregnancy, Paris Descartes University

^b Sorbonne Universités, UPMC Univ Paris 06, IFD, 4 Place Jussieu, 75252 PARIS cedex 05, Paris, France

^c URC - CIC P1419, Cochin Hotel-Dieu Hospital, APHP, Paris F-75014, France

^d Department of Obstetrics and Gynecology, Hautepierre Hospital, Strasbourg, France

^e Department of Obstetrics and Gynecology, Jeanne de Flandre Hospital, Lille, France

^f Department of Obstetrics and Gynecology, Bordeaux University Hospital, Bordeaux, France

^g Department of Neonatal Pediatrics, Trousseau Hospital, AP-HP, Paris, France

^h Department of Obstetrics and Gynecology, Cochin, Broca, Hôtel Dieu Hospital, AP-HP, Paris, France

ⁱ Department of Obstetrics and Gynecology, Trousseau Hospital, APHP, Paris, France

^j Research Unit on Perinatal Epidemiology, Childhood Disabilities and Adolescent Health, INSERM UMR 1027, Paul Sabatier University, Toulouse, France

^k Department of Obstetrics and Gynecology, Princess Grace Hospital, Monaco

^l Department of Neonatal Pediatrics, University Hospital, Grenoble, France

^m Department of Obstetrics and Gynecology, Nord Hospital, Assistance Publique des Hôpitaux de Marseille (AP-HM), Aix Marseille Université, AMU, Marseille, France

ⁿ Department of Gynecology and Obstetrics, University Hospital, Caen, France

^o Inserm UMR 1153, ECSTRA team, CRESS, Université Paris Diderot, Paris 7, SPC, Paris, France

^p Department of Obstetrics and Gynecology, University Hospital, Toulouse, France

^q Department of Obstetrics and Gynecology, University Hospital, INRA, UMR 1280 Physiologie des adaptations nutritionnelles, Nantes, France

Corresponding author: Elsa Lorthe, INSERM U1153, Bâtiment Recherche, Hôpital Tenon, 4 rue de la Chine, 75020 Paris, France. Phone +33 1 56 01 83 67, fax +33 1 56 01 71 88. Email: elsa.lorthe@gmail.com

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Abstract

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

Study design: This study was based on the prospective national population-based EPIPAGE2 cohort of preterm births and included 702 singletons delivered in France after PPRM at 24 to 32 weeks' gestation. Latency duration was defined as the time from spontaneous rupture of membranes to delivery, divided into 4 periods (12hr to 2 days [reference], 3 to 7 days, 8 to 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 EOS.

Results: Latency duration ranged from 12hr to 2 days (18%), 3 to 7 days (38%), 8 to 14 days (24%) and >14 days (20%). Rates of survival, survival without severe morbidity and EOS 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 (adjusted odds ratio 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 hr to 2 days, 3 to 7 days, 8 to 14 days and >14 days, respectively). Prolonged latency duration was not associated with survival without severe morbidity or EOS.

Conclusion: For a given gestational age at birth, prolonged latency duration after PPRM does not worsen neonatal prognosis.

Abbreviations and Acronyms:

aOR: adjusted odds ratio

EPIPAGE 2: Etude épidémiologique sur les petits âges gestationnels 2

GA: gestational age

IVH: intraventricular hemorrhage

IQR: interquartile range

NICU: neonatal intensive care unit

OR: odds ratio

PPROM: preterm premature rupture of membranes

95% CI: 95% confidence interval

INTRODUCTION

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 (i.e., the time between PPRM and birth), PPRM exposes the fetus to materno-fetal infection, abruptio placentae, cord prolapse and intrauterine death.(1) The main neonatal consequence of PPRM remains prematurity, a leading cause of neonatal mortality and morbidity.(1,2) In cases of PPRM, antenatal exposure to clinical or sub-clinical infection appears to be an additional specific risk factor of neonatal mortality and respiratory or neurological complications.(3,4)

Expectant management in the setting of PPRM, 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 PPRM and potential deleterious inflammation remain unclear. Indeed, only a few studies investigated latency duration as an independent risk factor for adverse outcomes in preterm infants, with conflicting findings.(9–12)

The *Etude épidémiologique sur les petits âges gestationnels 2* (EPIPAGE 2) is a nationwide population-based prospective cohort of preterm infants recruited in France in 2011.(13) Within this cohort, we identified all cases of preterm births after PPRM to determine whether for a given gestational age at birth, a prolonged latency period was associated with worse neonatal outcomes.

METHODS

Setting and data collection

Full details of the EPIPAGE 2 cohort recruitment and data collection were previously reported.(13) In brief, all infants live born or stillborn and all terminations of pregnancy from 22^{0/7} to 34^{6/7} weeks of 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 of 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.

PPROM management

Recommended obstetric management of women with PPRM includes a short course of antibiotics, corticosteroids between 24/25 and 34 weeks of 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 routinely used in 2011. As recommended, expectant management was commonly practiced before 34 weeks of gestation.(14)

Participants

The study population included all singleton fetuses alive at PPRM, with rupture at 24 to 32 weeks and birth at 24 to 34 weeks. PPRM was defined as spontaneous rupture of membranes occurring at least 12 hr 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 para-clinical test of diagnosis if necessary.(5–7) From the 7804 births included in the EPIPAGE 2 cohort, exclusion criteria were multiple pregnancies (n=2,020), terminations of pregnancies (n=1,292), severe congenital defects (n=154), homebirths (n=49) and births before 24 weeks (n=546).

Main outcomes and exposure measures

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 PPRM. 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 (IVH);(16) cystic periventricular leukomalacia (i.e., 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 preterm infants may improve at the cost of increased severe morbidity, we studied the association of latency period duration with these complementary outcomes. Owing to potential intraamniotic 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)

Other studied factors

Gestational age was determined as the best obstetrical estimate combining the last menstrual period and ultrasonography assessment. The following variables were also included in the analysis: maternal characteristics (age, country of birth, health insurance coverage, parity), individual clinical characteristics (presentation, fetal gender, birth weight < 3rd 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-hr interval.

Statistical analysis

Categorical variables were compared by chi-square test or Fisher's exact test as appropriate. Medians of quantitative variables were compared by Mann Whitney or Kruskal-Wallis test. All percentages, medians and crude odds ratios (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 hr to 2 days [reference], 3 to 7 days, 8 to 14 days and > 14 days). Gestational age at birth was treated as a continuous variable, after checking 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% confidence intervals (95% CIs). Statistical significance was set at two-tailed $p < .05$. We investigated interactions between latency duration and use of antenatal antibiotics, corticosteroids or tocolysis and found no significant interaction. Variances were estimated by a robust method to account for the intra-class correlation in maternity wards (cluster effect). Data were missing for 0% to 3.7% patients for each covariate and were considered missing at random.⁽²²⁾ Multiple imputations with chained equations with a logistic regression imputation model was used for missing binary data and a multinomial imputation model for missing categorical data. At the conventional two-tailed significance level of 0.05, and based on the fixed sample size, our study had 80% statistical power to show an OR of 2.5 associated with decreased survival for a latency period > 2 days compared with ≤ 2 days. Data were analyzed by use of Stata/SE 13.0 (StataCorp LP, College Station, TX, USA).

RESULTS

Among the 3743 singletons live born or stillborn at 24 to 34 completed weeks of gestation and included in the EPIPAGE 2 cohort, 939 had documented PPRM; 99 and 138 were excluded because PPRM occurred before 24 or after 33 weeks, respectively (Figure 1). Among the 702 neonates included in this analysis, 622 survived until discharge (weighted percentage 93.5% [95% CI 91.8-94.8]) and 538 survived without severe morbidity (weighted percentage 85.4% [82.4-87.9]) (Table 1). Median gestational age at delivery was 31 weeks (interquartile range [IQR] 28-33) and median latency duration 6.1 days (IQR 3-12.1). Latency duration ranged from 12 hr to 2 days for 143 cases (18%), 3 to 7 days for 292 (38%), 8 to 14 days for 145 (24%) and > 14 days for 122 (20%). Fetal deaths accounted for 13 cases (weighted percentage 1.0%) and neonatal deaths for 67 cases (weighted percentage 5.5%); their distribution by latency duration did not differ ($p=.31$). Obstetrics management (use of antibiotics, tocolysis and corticosteroids) was similar by time from PPRM diagnosis to delivery, except for the shortest delays with reduced use of these medications (Table 4, online). Bivariate analysis showed that survival and survival without severe morbidity significantly increased with increasing latency duration (Tables 1, 2). Both rates of survival and survival without severe morbidity significantly increased with advanced gestational age at birth (Table 2). The rate of survival without major morbidity was > 90% for infants delivered after 29 weeks. However, after multivariate adjustment for gestational age at birth, known risk factors and potential confounding factors, latency duration was no longer associated with survival and survival without major morbidity (Table 3). Increased gestational age at birth was associated with improved survival and survival without severe morbidity. Results were similar with latency duration treated as a continuous variable: adjusted OR per day (aOR) 0.99 [95% CI 0.94-1.05] and 1.02 [0.99-1.06] for survival and survival without major morbidity.

Early-onset sepsis was diagnosed in 26 of 665 children transferred to an NICU (weighted percentage 3.4% [2.0-5.7]) (Table 1). No bivariate association was found between latency duration or gestational age and early-onset sepsis (Tables 1, 2). On multivariate analysis, latency duration was not associated with early-onset sepsis (Table 3).

We compared the results from analyses restricted to complete cases and with multiple imputations and concluded the robustness of our models (Table 5, online).

DISCUSSION

Main findings

Our study showed that in cases of preterm birth after PPRM at 24 to 32 weeks, a prolonged latency period did not worsen neonatal prognosis. Survival and survival without severe morbidity were improved with increased gestational age at birth. These data support current obstetric practices and guidelines for PPRM up to 32 weeks of gestation. This result is also relevant for medical teams counseling patients with preterm premature ruptured membranes and for whom it is a frequent source of anxiety.

Strengths and limitations

To our knowledge, these findings are for the first time from a nationwide population-based study with a large number of subjects and with practices consistent with current worldwide recommendations (i.e., antenatal corticosteroids and antibiotics for PPRM).^(5–7) Another major strength is the clinically relevant population, which includes complicated cases of PPRM (with abruptio placentae, chorioamnionitis or intra-uterine fetal death). Such cases, which can be linked to adverse neonatal outcomes, were often excluded from previous studies or trials,^(9,23) which led to underestimation of serious maternal and fetal consequences. We assume that our results better reflect daily practice and clinicians' concerns.

Our study has some limitations. EPIPAGE 2 is an observational study, and unmeasured confounders might have biased our findings. However, this situation seems unlikely because data on main risk factors were collected with standardized procedures and neonatal outcomes were defined by international classifications. The main limitation is inherent to all studies of PPRM. As the EPIPAGE 2 cohort was not designed to consider late-preterm births, the population was truncated for cases of PPRM occurring before 35 weeks but delivery afterwards. Therefore, we chose to include women with PPRM at 24 to 32 weeks, who delivered at 24 to 34 completed weeks. Thus, there is no truncation for the lower boundary and we were able to analyze all women giving birth within 2 weeks after late PPRM. We likely only missed the very few births with the longest latency durations and the best prognosis.(24,25) Overall, we can consider that the risks are slightly overestimated, particularly for long latency durations.

Interpretation

According to our finding of no impact of latency duration on neonatal prognosis for a given gestational age at birth, we can assume no deleterious effect of prolonged latency that could outweigh the benefits of the fetal maturation gain.(9) This result is consistent with those reported by Manuck et al., who studied preterm infants with PPRM at 22 to 33 completed weeks (n=306) identified retrospectively from a bicentric database, and management for their mothers followed current recommendations.(11) The authors used similar definitions of exposure and outcomes as in our study and found no association between latency duration and perinatal morbidity after controlling for gestational age at birth.(11)

In contrast, the analysis of a retrospective database including cases of PPRM from 1997 to 2012, from a network of 330 NICUs in the United States, showed increased risk of death and morbidity for latency duration > 28 days as compared with duration 1 to 7 days after controlling for gestational age at birth.(12) Despite a large number of subjects (n=37,233), this

finding is questionable for several reasons. First, latencies > 28 days occur mostly for children born after the earliest ruptures (especially PPROM < 24 weeks), who often have the poorest outcomes, which can explain the reported result.(26) Second, the study design did not allow for considering stillbirths or deaths in the delivery room, which are competing events with subsequent complications. Finally, the variability of clinical practices across centers and changes over years as well as data collection did not ensure optimal reliability of the results.

The specific association of prolonged latency and neonatal sepsis has been rarely investigated. Recently, a secondary analysis of a randomized controlled trial of magnesium sulfate for preventing cerebral palsy highlighted that prolonged latency after PPROM did not increase the risk of neonatal sepsis, except for latencies > 4 weeks, associated with reduced risk of sepsis.(23) This result agrees with ours and makes sense, because prenatal acute infection is associated with a shortened latency to delivery and with early-onset sepsis.(27)

CONCLUSION

PPROM is a complication of pregnancy that implies high risks of neonatal mortality and morbidity. However, this work suggests that, for a given gestational age at birth, prolonged latency duration does not worsen neonatal prognosis. The main prognostic factor is gestational age at birth. Analysis of long-term development of these infants is warranted to study the neurological consequences of potential intrauterine exposure to inflammation with PPROM.

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Contribution to authorship:

Study concept and design of the EPIPAGE 2 study: PYA, FG, MK.

Study concept and design of the present study: EL, GK.

Acquisition, analysis and interpretation of data: EL, PYA, HT, MK, BL, DS, LS, LFLH, FG, GK, CA, BC, TD, PD, CDE, MD, CL, JEG, CV, NW

Statistical analysis: EL, GK

Drafting of the manuscript: EL, GK

Critical revision of the manuscript for important intellectual content: EL, PYA, HT, MK, BL, DS, LS, LFLH, FG, GK, CA, BC, TD, PD, CDE, MD, CL, JEG, CV, NW

Final approval of the version to be published: EL, PYA, HT, MK, BL, DS, LS, LFLH, FG, GK, CA, BC, TD, PD, CDE, MD, CL, JEG, CV, NW

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TABLE LEGENDS

Table 1: Association of latency duration after preterm premature rupture of membranes and neonatal outcomes before and after adjustment for gestational age (GA) at birth

Table 2: Association of maternal and clinical characteristics and antenatal management with survival, survival without severe morbidity and early-onset sepsis

Table 3: Multivariate analysis of latency period duration associated with survival, survival without severe morbidity or early-onset sepsis after adjusting for GA at birth

Online Table 4: Frequency of antibiotics, tocolysis and corticosteroids use by time from PPROM diagnosis to delivery

Online Table 5: Multivariate analysis of complete-case models of latency period duration associated with survival, survival without severe morbidity and early-onset sepsis

FIGURE LEGEND

Figure 1: Flow chart of infants included in the study

Legend: WG, weeks' gestation; SPL, spontaneous preterm labor; SGA; small-for-gestational age

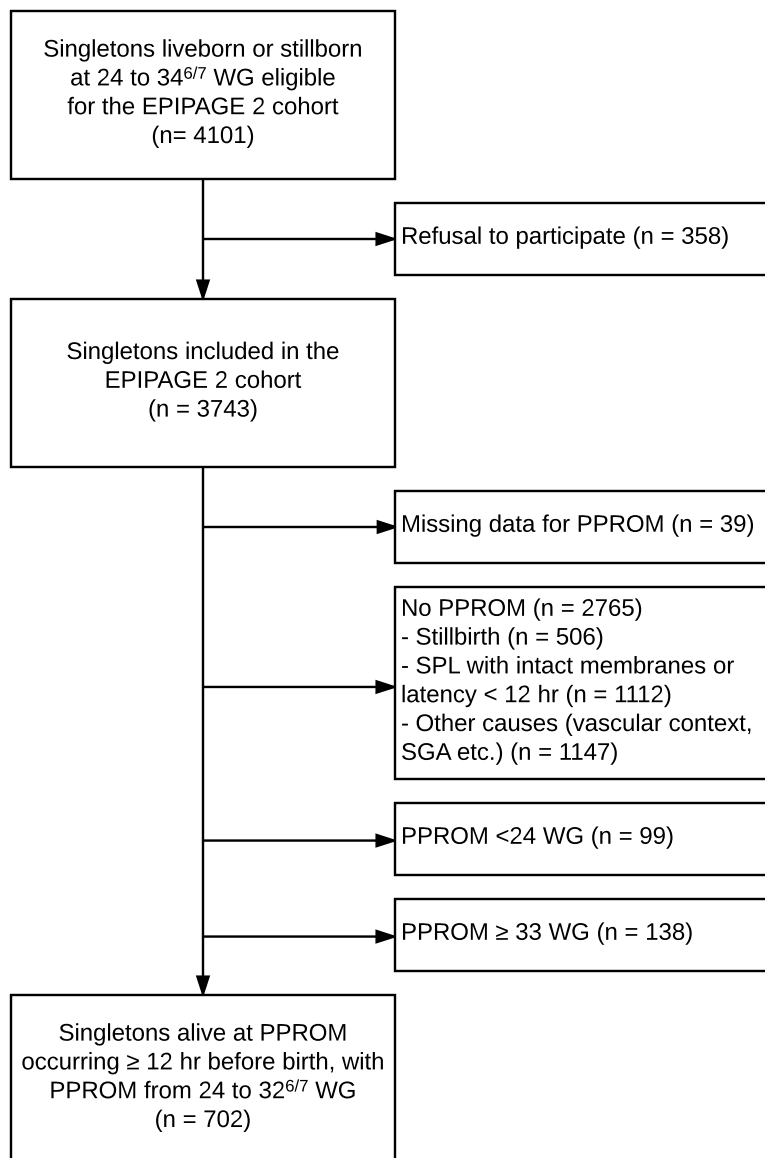


Table 1: Association of latency duration after preterm premature rupture of membranes and neonatal outcomes before and after adjustment for gestational age (GA) at birth

Outcome / latency period duration (days)	n/N (%)^a	Crude OR (95% CI)^a	P value	aOR (95% CI)^b	P value
Survival	622/702 (93.5)				
0.5-2	116/143 (87.8)	1	.004	1	.84
3-7	259/292 (93.0)	1.9 (1.0-3.4)		1.3 (0.7-2.6)	
8-14	131/145 (95.3)	2.8 (1.3-5.9)		1.2 (0.5-2.7)	
> 14	116/122 (97.1)	4.6 (1.8-12.1)		1.1 (0.4-3.1)	
Survival without severe morbidity	538/693 (85.4)				
0.5-2	95/142 (77.6)	1	.04	1	.28
3-7	219/287 (84.9)	1.6 (1.0-2.7)		1.4 (0.8-2.4)	
8-14	117/144 (87.0)	1.9 (0.9-3.9)		1.6 (0.9-3.1)	
> 14	107/120 (91.3)	3.0 (1.3-7.2)		1.9 (0.9-4.1)	
Early-onset sepsis ^c	26/665 (3.4)		.10		.22
0.5-2	4/128 (2.2)	1		1	
3-7	16/279 (5.2)	2.5 (0.7-8.4)		1.9 (0.6-5.8)	
8-14	2/136 (0.9)	0.4 (0.1-2.3)		0.5 (0.1-2.6)	
> 14	4/122 (4.2)	2.0 (0.4-10.6)		1.1 (0.3-4.5)	
Survival without ^d :					
Severe bronchopulmonary dysplasia ^e	579/608 (97.3)				
0.5-2	107/114 (96.0)	1	.23	1	.51
3-7	236/252 (96.3)	1.0 (0.4-2.4)		0.8 (0.3-2.2)	
8-14	126/129 (98.8)	2.7 (0.7-10.9)		2.3 (0.5-9.4)	
> 14	110/113 (98.4)	2.4 (0.6-9.5)		1.1 (0.2-4.7)	
Grade III intra-ventricular or intraparenchymal hemorrhage	605/622 (98.4)				
0.5-2	112/116 (97.7)	1	.40	1	.46
3-7	248/259 (97.2)	0.8 (0.3-2.6)		0.8 (0.2-2.5)	
8-14	129/131 (99.4)	2.3 (0.4-12.8)		2.0 (0.4-11.5)	
> 14	116/116 (100.0)	-		-	
Cystic periventricular leukomalacia	609/622 (97.8)				
0.5-2	113/116 (98.4)	1	.55	1	.47
3-7	254/259 (98.7)	1.3 (0.3-5.7)		1.3 (0.3-5.7)	
8-14	130/131 (97.7)	3.5 (0.4-33.6)		3.3 (0.3-31.8)	
> 14	112/116 (95.7)	0.7 (0.2-3.4)		0.6 (0.1-3.0)	
Stage 2-3 necrotizing enterocolitis	607/622 (98.0)				
0.5-2	111/116 (97.0)	1	.23	1	.23
3-7	255/259 (98.9)	2.9 (0.8-10.9)		2.9 (0.8-10.9)	
8-14	126/131 (96.1)	1.1 (0.3-4.0)		1.1 (0.3-4.0)	
> 14	115/116 (99.5)	5.2 (0.6-45.0)		5.0 (0.6-43.6)	
Stage 3 or more retinopathy of prematurity and/or laser treatment	616/622 (99.5)				
0.5-2	114/116 (98.9)	1	.84	1	.81
3-7	257/259 (99.6)	2.3 (0.3-16.2)		1.9 (0.3-14.5)	
8-14	130/131 (99.7)	2.3 (0.2-25.5)		1.6 (0.1-18.7)	
> 14	115/116 (99.5)	2.0 (0.2-22.6)		0.6 (0.0-9.1)	

Because of missing data, the number of cases may vary slightly among characteristics.

^a Percentages and ORs are weighted according to GA.

^b Adjusted for GA at birth

^c Among children transferred to an NICU

^d Related to survivors to discharge

^e Missing data for 14 children

Table 2: Association of maternal and clinical characteristics and antenatal management with survival, survival without severe morbidity and early-onset sepsis

Characteristics	Death (n=80)	Survival (n=622)	Crude OR	Death or severe morbidity ^a (n=155)	Survival without severe morbidity ^a (n=538)	Crude OR	No early- onset sepsis ^b (n=639)	Early-onset sepsis (n=26) ^b	Crude OR	
	n (%) ^c	n (%) ^c	OR ^c (95% CI)	n (%) ^c	n (%) ^c	OR ^c (95% CI)	n (%) ^c	n (%) ^c	OR ^c (95% CI)	
Maternal characteristics										
Age (years)	< 20	5 (7.0)	31 (3.6)	0.5 (0.2-1.3)	12 (7.5)	23 (3.1)	0.4 (0.2-0.8)	35 (4.0)	1 (2.3)	0.8 (0.1-6.2)
	20-35	17 (72.7)	489 (80.4)	1	113 (72.2)	427 (81.2)	1	498 (80.2)	17 (60.3)	1
	> 35	58 (20.3)	102 (16.0)	0.7 (0.4-1.3)	30 (20.3)	88 (15.7)	0.7 (0.4-1.3)	106 (15.8)	8 (37.4)	3.2 (0.9-10.2)
	Not born in France or Europe	12 (17.0)	139 (21.8)	1.4 (0.7-2.7)	35 (25.7)	116 (21.0)	0.8 (0.4-1.3)	138 (20.8)	9 (53.4)	4.4 (1.5-12.6)
	Universal medical insurance or no insurance	10 (14.3)	99 (15.8)	1.1 (0.5-2.4)	30 (25.5)	78 (14.2)	0.5 (0.3-0.9)	99 (15.9)	6 (16.9)	1.1 (0.4-3.2)
	Multiparous	39 (49.4)	339 (51.5)	1.1 (0.7-1.8)	73 (46.6)	302 (52.3)	1.3 (0.8-2.0)	340 (50.9)	18 (66.5)	1.9 (0.6-6.3)
Clinical characteristics										
	GA at PPROM (w), median (IQR)	25 (24-26)	30 (27-31)	2.0 (1.7-2.4) ^d	26 (25-28)	30 (28-32)	1.6 (1.4-1.7) ^d	30 (27-31)	29 (27-31)	1.0 (0.8-1.1) ^d
	GA at birth (w), median (IQR)	26 (25-27)	31 (29-33)	2.2 (1.8-2.5) ^d	27 (25-30)	31 (29-33)	1.6 (1.4-1.9) ^d	31 (29-33)	31 (28-32)	1.0 (0.8-1.1) ^d
	Latency (d), median (IQR)	3.2 (2-7.4)	6.2 (3-13.0)	1.08 (1.03-1.13) ^e	4.5 (2-9)	6.5 (3-13)	1.08 (1.04-1.11) ^e	6.2 (3-12.9)	4.2 (3.0-15)	0.98 (0.93-1.03) ^e
	Clinical chorioamnionitis	41 (52.8)	303 (44.0)	0.7 (0.4-1.2)	79 (53.5)	260 (42.9)	0.7 (0.4-1.0)	302 (42.8)	20 (83.2)	6.6 (2.3-18.5)
	Abruptio placentae	5 (5.8)	31 (4.0)	0.7 (0.2-1.9)	12 (6.6)	23 (3.6)	0.5 (0.2-1.2)	34 (4.2)	1 (3.1)	0.7 (0.1-5.9)
	Non-cephalic presentation	31 (40.8)	183 (27.6)	0.6 (0.3-0.9)	56 (33.6)	156 (27.6)	0.8 (0.5-1.2)	195 (28.3)	6 (31.2)	1.1 (0.3-4.1)
	Female gender	37 (47.4)	286 (46.1)	0.9 (0.6-1.6)	69 (46.9)	251 (46.2)	1.0 (0.6-1.5)	291 (46.1)	11 (32.2)	0.6 (0.2-1.4)
	Birth weight < 3 rd percentile	9 (11.2)	44 (6.5)	0.6 (0.2-1.2)	12 (9.7)	41 (6.4)	0.6 (0.2-1.6)	52 (7.2)	0 (0)	-
Antenatal management										
	Antibiotics	77 (95.8)	607 (98.1)	2.3 (0.6-9.0)	150 (97.1)	526 (98.1)	1.6 (0.5-5.1)	623 (98.0)	26 (100.0)	-
	Tocolysis	54 (66.5)	468 (73.1)	1.4 (0.8-2.3)	109 (69.4)	406 (73.2)	1.2 (0.7-2.0)	482 (73.3)	18 (64.2)	0.7 (0.2-2.1)
	Antenatal steroids									
	Complete treatment	55 (71.7)	523 (83.1)	1	116 (76.0)	454 (83.4)	1	534 (82.8)	23 (91.6)	1
	Incomplete treatment	9 (11.0)	41 (5.1)	0.4 (0.2-0.9)	18 (10.6)	31 (4.5)	0.8 (0.4-1.8)	45 (5.4)	1 (2.3)	0.5 (0.1-2.2)
	None	14 (17.3)	50 (11.8)	0.6 (0.3-1.2)	18 (13.4)	46 (12.1)	0.4 (0.2-0.8)	50 (11.8)	2 (6.1)	0.4 (0.1-3.0)
	Delivery route									
	Vaginal delivery	46 (56.8)	277 (49.6)	1	79 (48.2)	239 (50.3)	1	285 (49.4)	9 (36.5)	1
	Cesarean section before labour	24 (31.1)	246 (36.1)	1.3 (0.8-2.3)	58 (39.0)	209 (35.3)	0.9 (0.5-1.4)	253 (36.1)	13 (52.0)	1.9 (0.6-6.5)
	Cesarean section during labour	9 (12.1)	97 (14.3)	1.4 (0.6-3.0)	16 (12.8)	89 (14.4)	1.1 (0.5-2.4)	99 (14.5)	4 (11.5)	1.1 (0.3-4.4)

w, weeks' gestation; d, days;

^a Score undefined for 9/702 children (1.3%) because of missing data for at least 1 of the 6 criteria; ^b Among children transferred to an NICU; ^c Percentages and odds ratios (ORs) are weighted according to GA; ^d Association between GA and survival, survival without severe morbidity or early-onset sepsis: crude OR per weeks' gestation; ^e Association between latency duration and survival, survival without severe morbidity or early-onset sepsis: crude OR per day

Missing data <4% for all covariates.

Table 3: Multivariate analysis of latency period duration associated with survival, survival without severe morbidity or early-onset sepsis after adjusting for GA at birth

Factors	Survival ^a	Survival without severe morbidity ^a	Early-onset sepsis ^b
	n ^c =702	n ^c =702	n ^{c,d} =669
Latency period duration (days)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
0.5-2	1	1	1
3-7	1.6 (0.8-3.2)	1.2 (0.7-2.1)	1.5 (0.4-5.2)
8-14	1.2 (0.5-2.9)	1.5 (0.8-2.3)	0.3 (0.1-1.9)
>14	1.0 (0.3-3.2)	1.5 (0.7-3.3)	0.9 (0.2-4.7)
GA at birth (days)	1.12 (1.09-1.15)	1.08 (1.06-1.10)	1.00 (0.98-1.03)

^a Models adjusted for latency duration, GA at birth, maternal characteristics (age, country of birth, health insurance coverage), clinical characteristics (presentation, fetal gender, birth weight < 3rd percentile) and antenatal management (antibiotics, tocolysis, antenatal steroids).

^b Model adjusted for latency duration, GA at birth, maternal characteristics (age, country of birth, health insurance coverage, parity), clinical characteristics (clinical chorioamnionitis, fetal gender) and antenatal management (tocolysis, antenatal steroids).

^c aOR obtained after multiple imputation

^d Among infants transferred to an NICU

Online Table 4: Frequency of antibiotics, tocolysis and corticosteroids use by time from PPRM diagnosis to delivery

	Time from PPRM diagnosis to delivery (days)						Global p-value	p-value
	< 1 n (%)	[1-2[n (%)	[2-3[n (%)	[3-7[n (%)	[7-14[n (%)	≥14 n (%)		
Antibiotics	110 (94.5)	66 (98.1)	88 (100.0)	206 (99.4)	121 (99.0)	93 (95.7)	0.07*	0.18**
Tocolysis	74 (59.0)	47 (73.5)	69 (73.8)	167 (80.6)	97 (75.1)	68 (67.2)	0.09*	0.49**
Corticosteroids								
None	16 (12.6)	12 (29.9)	8 (14.0)	18 (12.1)	7 (9.9)	3 (2.1)	<0.0001*	0.26***
Incomplete course	34 (23.5)	8 (11.9)	1 (0.6)	4 (1.3)	1 (0.4)	2 (1.2)		
Complete course	65 (63.9)	49 (58.2)	78 (85.4)	183 (86.6)	113 (89.7)	90 (96.7)		

Percentages are weighted according to gestational age.

* Comparing the frequency of treatment use during the entire time from PPRM diagnosis to delivery

** Comparing the frequency of treatment use from 1 to ≥14 days

*** Comparing the frequency of treatment use from 2 to ≥14 days

Online Table 5: Multivariate analysis of complete-case models of latency period duration associated with survival, survival without severe morbidity and early-onset sepsis

Factors	Survival^a	Survival without severe morbidity^a	Early-onset sepsis^{b,c}
	n=641	n=633	n=609
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Latency period duration (days)			
0.5-2	1	1	1
3-7	1.3 (0.6-2.9)	1.1 (0.6-2.0)	1.3 (0.3-5.0)
8-14	1.1 (0.4-3.5)	1.4 (0.6-3.2)	0.3 (0.1-2.0)
>14	1.4 (0.3-6.5)	2.2 (0.9-5.8)	0.9 (0.2-4.9)
GA at birth (days)	1.13 (1.09-1.16)	1.08 (1.06-1.10)	1.00 (0.98-1.03)
Hosmer-Lemeshow test	0.41	0.78	0.94
Area under ROC curve	0.91	0.83	0.74

ROC, receiver operating characteristic

aOR obtained by complete-case models.

^a Models adjusted for latency duration, GA at birth, maternal characteristics (age, country of birth, health insurance coverage), clinical characteristics (presentation, fetal gender, birth weight < 3rd percentile) and antenatal management (antibiotics, tocolysis, antenatal steroids).

^b Model adjusted for latency duration, GA at birth, maternal characteristics (age, country of birth, health insurance coverage, parity), clinical characteristics (clinical chorioamnionitis, fetal gender) and antenatal management (tocolysis, antenatal steroids).

^c Among infants transferred to an NICU