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Preterm premature rupture of membranes at 22-25 weeks' gestation: perinatal and 2-year outcomes within a national population-based study (EPIPAGE-2)

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Condensation:

PPROM at 22-25 weeks is associated with high incidence of mortality and morbidity, with wide variations by GA at PPROM.

Implications and contributions:

A. To provide reliable and relevant data related to the prognosis of PPROM at 22-25 weeks to adequately counsel parents during pregnancy and to reflect on our policies of care.

B. Nearly half of the fetuses are delivered within the first week. PPROM at 22-25 weeks is associated with high incidence of perinatal mortality and morbidity, with wide variations by gestational age at PPROM. However, a non-negligible proportion of children survive without severe morbidity both at discharge and at 2 years.

C. This study is the first to describe and quantify perinatal and 2-years outcomes of singletons and twins born after periviable PPROM, using data from a national prospective population-based cohort. The use of different inception points to report rates of survival is helpful in adapting information provided to parents when the GA of birth is not yet known.

Short title: Outcomes of pregnancies with periviable PROM

Abstract

Background: Most clinical guidelines state that with early preterm premature rupture of membranes, obstetric and pediatric teams must share a realistic and individualized appraisal of neonatal outcomes with parents and consider their wishes for all decisions. However, we currently lack reliable and relevant data, according to gestational age at rupture of membranes, to adequately counsel parents during pregnancy and to reflect on our policies of care at these extreme gestational ages.

Objective: To describe both perinatal and 2-year outcomes of preterm infants born after preterm premature rupture of membranes at 22-25 weeks' gestation.

Study design: EPIPAGE-2 is a French national prospective population-based cohort of preterm infants born in 546 maternity units in 2011. Inclusion criteria in this analysis were women diagnosed with preterm premature rupture of membranes at 22-25 weeks' gestation and singleton or twin gestations with fetus(es) alive at rupture of membranes. Latency duration, antenatal management, and outcomes (survival at discharge, survival at discharge without severe morbidity, and survival at 2 years' corrected age without cerebral palsy) were described and compared by gestational age at preterm premature rupture of membranes.

Results: Among the 1435 women with a diagnosis of preterm premature rupture of membranes, 379 were at 22-25 weeks' gestation, with 427 fetuses (331 singletons and 96 twins). Median GA at preterm premature rupture of membranes and at birth were 24 (interquartile range 23-25) and 25 (24-27) weeks, respectively. For each gestational age at preterm premature rupture of membranes, nearly half of the fetuses were born within the week after the rupture of membranes. Among the 427 fetuses, 51.7% were survivors at discharge (14.1%, 39.5%, 66.8% and 75.8% with preterm premature rupture of membranes at 22, 23, 24 and 25 weeks, respectively), 38.8% were survivors at discharge without severe morbidity and

46.4% were survivors at 2 years without cerebral palsy, with wide variations by gestational age at preterm premature rupture of membranes. Survival at 2 years without cerebral palsy was low with preterm premature rupture of membranes at 22 and 23 weeks but reached approximately 60% and 70% with preterm premature rupture of membranes at 24 and 25 weeks.

Conclusion: Preterm premature rupture of membranes at 22-25 weeks is associated with high incidence of mortality and morbidity, with wide variations by gestational age at preterm premature rupture of membranes. However, a non-negligible proportion of children survive without severe morbidity both at discharge and at 2-years' corrected age.

Key words: cerebral palsy, EPIPAGE-2, preterm premature rupture of membranes, perinatal outcome, periviable rupture of membranes, prematurity

Introduction

Early preterm premature rupture of membranes (PPROM), defined as PPROM at 22-25 weeks' gestation, occurs in less than 1% of pregnancies and is associated with a high rate of perinatal morbidity and mortality.[1–4] Fetuses exposed to early PPROM face increased risks of obstetric (placental abruption, cord prolapse, infection) and fetal complications (pulmonary hypoplasia, limb deformities, prematurity and in utero demise)[1,3,4] with short- and long-term potential adverse consequences.

With these high risks of extreme prematurity and severe disability, antenatal care requires considering the uncertainty about neonatal prognosis and the risks of severe maternal complications, particularly sepsis. Management options are induction of labor, either immediately[3] or in cases of severe oligohydramnios or chorioamnionitis,[5] or expectant management with antibiotics and with steroids once viability is reached.[3] Most clinical guidelines state that with early PPROM, obstetric and pediatric teams must share a realistic and individualized appraisal of neonatal outcomes with parents and consider their wishes for all decisions.[2,3,5] However, we currently lack reliable and relevant data, according to gestational age (GA) at PPROM, to adequately counsel parents during pregnancy and to reflect on our policies of care at these extreme GAs. Indeed, evidence-based data concerning periviable complications of pregnancy are scarce: available data are mostly from small-sized retrospective studies, often restricted to women eligible for expectant management, which thus leads to overestimating neonatal survival.[2,3,6]

We aimed to describe and quantify both perinatal and 2-year outcomes of preterm infants born after PPROM at 22 to 25 weeks' gestation, within a prospective population-based cohort at a national level.

Materials and methods

Setting and data collection of the EPIPAGE-2 cohort study

This a secondary analysis of EPIPAGE-2 (Etude épidémiologique sur les petits âges gestationnels 2), a prospective, national, population-based cohort study of preterm infants born in France in 2011.[7] All live births, stillbirths and terminations of pregnancy at $22^{0/7}$ to $34^{6/7}$ weeks' gestation (n=7804), whose parents had not declined to participate, were included in 25 French regions involving 546 maternity units. Only one region, accounting for 2% of all births in France, did not participate. The overall participation rate was 93%. The recruitment periods differed by GA at birth: 22 to 26 weeks (8 months), 27 to 31 weeks (6 months) and 32 to 34 weeks (5 weeks). Extremely preterm births (22-26 weeks) were recruited during a longer period because of their very low incidence and only a sample of moderate preterm births (32-34 weeks) was recruited. Maternal, obstetric, and neonatal data were collected from medical records following a standardized protocol. Full details of the cohort recruitment and data collection are reported elsewhere.[7] The EPIPAGE-2 cohort study was implemented to describe short- and long-term outcomes among preterm infants. For that purpose, in children included in follow-up, a detailed neurological and sensory examination was performed by the referring physician at 2 years' corrected age.[8]

Ethics

As required by French law and regulations, EPIPAGE-2 was approved by the National Data Protection Authority (CNIL n°911009), the appropriate ethics committees (Consultative Committee on the Treatment of Data on Personal Health for Research Purposes, reference n°10.626) and the Committee for the Protection of People Participating in Biomedical Research (reference CPP SC-2873).

Participants

Our study population included all women diagnosed with PPROM at 22 to 25 completed weeks' gestation and fetuses alive at the time of PPROM. PPROM was defined as spontaneous rupture of membranes occurring at least 12 hr before birth. As recommended, the diagnosis was made by the attending obstetric staff based on maternal history and sterile speculum examination visualizing amniotic fluid leakage from the cervical os, with a diagnostic test if necessary.[3,5] Exclusion criteria were lethal malformations, triplets and quadruplets (to obtain a more homogeneous population), as well as multiple pregnancies with twin-to-twin transfusion syndrome (that can be responsible for both iatrogenic PPROM related to fetoscopic selective laser photocoagulation and poorer neonatal outcomes). Differed births or with one of the babies ineligible for analysis were also excluded.

French guidelines and practices

Overall, recommended antenatal care of women with PPROM include expectant management, with antibiotics, corticosteroids from viability to 34 weeks' gestation and, if necessary, tocolysis and *in utero* transfer.[5] Magnesium sulfate was not routinely used for tocolysis or neuroprotection in 2011. According to French legislation, termination of pregnancy (TOP) on parental request can be provided at any time if the fetus is affected by a severe and incurable pathology or if maternal life is seriously jeopardized. With PPROM before 24 weeks' gestation, guidelines from the National College of French Gynecologists and Obstetricians state that medical TOP should not be considered in the absence of oligohydramnios or chorioamnionitis and that all decisions should take into account parental wishes after adequate counseling.[5]

Assessment of the natural history of PPROM

The natural history of periviable PPROM was investigated by the latency period (the time elapsed from rupture to delivery), GA at birth, determined as the best obstetrical estimate

combining last menstrual period and first-trimester ultrasonography assessment, and the specific complications of early PPROM. We focused on the following complications: severe oligohydramnios in the last measurement before delivery (i.e., largest vertical pocket < 2 cm or amniotic fluid index < 5, with anhydramnios defined as amniotic fluid index = 0), placental abruption, cord prolapse, fetal consequences of prolonged oligohydramnios (i.e., pulmonary hypoplasia and/or limb deformities) and clinical chorioamnionitis. The diagnosis of clinical chorioamnionitis was not standardized in this observational cohort, but all relevant data were collected and allowed us to define clinical chorioamnionitis as maternal temperature ≥ 37.8°C (100°F) associated with any two of the following criteria: uterine tenderness, purulent or foul-smelling amniotic fluid, maternal tachycardia, fetal tachycardia, and maternal leukocytosis ≥ 15,000 cells/mm^3. Data to assess maternal outcomes, including infectious complications, were not exhaustive in the EPIPAGE 2 questionnaires and were thus not analyzed.

Antenatal management

We described antenatal care provided to women in terms of in utero transfer, treatments and mode of delivery. Maternity wards were classified as type 3 when associated with a neonatal intensive care unit (NICU). Steroids treatment was considered when the mother received at least 1 injection of betamethasone.

Perinatal and 2-year outcomes

Perinatal outcomes included vital status, classified as TOP, antepartum stillbirth, death during labor or in the delivery room (after spontaneous preterm labor or induction of labor), death in the NICU[9] and survival at discharge. We also investigated survival at discharge without severe morbidity (i.e., without grade 3-4 intraventricular haemorrhage,[10] cystic periventricular leukomalacia,[11] stage II or III necrotizing enterocolitis,[12] stage 3 or greater retinopathy of prematurity[13] and/or laser treatment and severe bronchopulmonary dysplasia defined as

213 requiring oxygen for at least 28 days in addition to the requirement of 30% or more oxygen
214 and/or mechanical ventilator support or continuous positive airway pressure at 36 weeks'
215 postmenstrual age[14]). Z-score birth weights were calculated from EPOPé intrauterine growth
216 curves corrected for sex and gestational age.[15] The third outcome was survival at 2 years'
217 corrected age without cerebral palsy whatever the stage. Cerebral palsy was defined according
218 to the diagnostic criteria of the Surveillance of Cerebral Palsy in Europe (SCPE) network.[16]
219 We thought to report deafness and blindness as well but there were no cases in our
220 population.[8]

221 *Statistical analysis*

222 We first compared characteristics and outcomes by type of pregnancy (single or multiple) and
223 found no significant difference, especially concerning median GA at PPROM, latency and
224 GA at birth, except for tocolysis and spontaneous onset of labor, which were significantly
225 more frequent in twins (Tables A.1 and A.2). Thereafter we analyzed singletons and twins
226 together. We described natural history of PPROM, antenatal management and perinatal
227 outcomes overall, then compared them by week of gestational age at PPROM. Data are
228 reported as percentages with 95% confidence intervals (95% CI) or medians with interquartile
229 range (IQR). Medians of quantitative variables were compared by a nonparametric equality-
230 of-medians test. When comparing by week of gestational age, to account for the non-
231 independence of twins, we used generalized estimating equations (GEE) to obtain p-values,
232 assuming an exchangeable correlation structure.[17] To account for the duration of the
233 recruitment periods by gestational age at birth, a weighted coefficient was allocated to each
234 individual (1 for births at 22-26 weeks, 1.346 for births at 27-31 weeks and 7 for births at 32-
235 34 weeks). Attrition is a key issue in longitudinal cohort studies.[8] In this analysis, the
236 proportion of infants eligible but lost to follow-up was 17.7% of infants alive at 2 years'
237 corrected age (8.2% of all fetuses included). We compared characteristics of eligible infants

with and without follow-up and found no difference, except for low maternal age and low socio-economic status that were associated with loss to follow-up (Table A.3). In addition to complete-cases analysis, we performed multiple imputations with chained equations with a logistic regression imputation model for missing binary data and a multinomial imputation model for missing categorical data. Imputation model variables included both those potentially predicting non-response and/or outcomes (type of maternity unit, maternal age and country of birth, socioeconomic status, parity, gestational ages at PPROM and at birth, latency duration, multiple pregnancy, in utero transfer, antenatal steroids and antibiotics, magnesium sulfate, tocolysis, clinical chorioamnionitis, cord prolapse, placental abruption, small for gestational age, cesarean section, sex, severe neonatal morbidities) and outcomes (survival, cerebral palsy). Outcomes were estimated within each of the 30 imputed datasets generated with 20 iterations, and results were pooled for a final analysis according to Rubin's rules. Statistical significance was set at two-tailed $p < .05$. Data were analyzed by use of Stata/SE 13.0 (StataCorp LP, College Station, TX, USA).

Results

Among the 1435 women with a diagnosis of PPROM, 379 were at 22 to 25 weeks' gestation, with 427 fetuses alive (331 singletons and 96 twins) (Figure 1). Pregnancy was complicated by PPROM at 22, 23, 24 and 25 weeks' gestation in 101 (21.4%), 95 (24.1%), 99 (24.0%) and 132 fetuses (30.5%), respectively.

The overall population was 78% French or European, with a median age of 29 years (interquartile range [IQR] 26-34), 91% lived with a partner and 51% were nulliparous, with no significant difference by GA at PPROM (Table A.4).

Median GA at PPROM was 24 (IQR 23-25) weeks. Latency duration ranged from 0.5 to 145 days. Latency duration did not differ by week of GA at PPROM, nor did latency exceeding 2 days, 7 days or 14 days (Table 1). Whatever the GA at PPROM, nearly half of the fetuses were born within the first week of latency. Consequently, GA at birth significantly increased with GA at PPROM (Table 1). Only 5 infants (weighted percentage 7.1%) were born at 32-34 weeks. The overall weighted rates of placental abruption, cord prolapse and clinical chorioamnionitis were 4.3% (95% CI 2.8-6.8), 2.9% (1.7-4.9) and 9.5% (7.0-12.8), respectively. Eight fetuses (1.7% [0.9-3.4]) presented pulmonary hypoplasia and/or limb deformities. The frequency of these complications did not differ by week of GA at PPROM. Severe oligohydramnios was diagnosed in 217 fetuses (61.1% [55.3-66.7]), with increased frequency for the earliest PPROM (61%, 76%, 57%, 53% at 22, 23, 24 and 25 weeks, respectively, p=.05).

We found major differences in the obstetric management by GA at PPROM (Table 1). More than 95% of infants were born in a type 3 maternity unit with PPROM at 24 or 25 weeks versus 58% and 78% with PPROM at 22 and 23 weeks. Accordingly, rates of *in utero* transfer were two- to threefold higher after 24 weeks. Most fetuses were exposed to antenatal steroids and caesarean section when PPROM occurred after the threshold considered for neonatal resuscitation in France in 2011 (24 weeks). The use of antenatal antibiotics, mainly amoxicillin and 3rd generation cephalosporins, was lower at 22 weeks (81% vs > 92% afterwards). Causes and indications for delivery were mainly spontaneous onset of labor (62.2%) and induction of labor or cesarean section for clinical chorioamnionitis (18.5%).

With PPROM at 22-25 weeks, pregnancy outcomes were TOP (10 fetuses, 2.0%), antepartum stillbirth (21 fetuses, 5.6%), death during labor (81 fetuses, 16.6%), death in the delivery room (58 fetuses, 12.0%), death in the NICU (56 infants, 12.1%) or discharge alive (201 infants, 51.7%), with significant differences by GA at PPROM (Figure 1, Table 2). TOPs

were mostly performed for the earliest cases of PPROM (7, 1, 2 and 0 TOPs with PPROM at 22, 23, 24 and 25 weeks, respectively) complicated by anhydramnios and/or chorioamnionitis. Stillbirths and deaths in the delivery room were mainly related to specific complications of PPROM (clinical chorioamnionitis, oligohydramnios, placental abruption or cord prolapse) or spontaneous delivery before 24 weeks. Deaths in the NICU occurred within the first week for 41% and within the first month for 84% of deceased children. These deaths were mostly related to respiratory failure (38%), central nervous system injury (23%) or infection (14%).

Among the 315 liveborn infants, 68.2% survived until discharge, 51.6% survived until discharge without severe morbidity (38.8% of all fetuses) and 58.9% were survivors at 2 years' corrected age without cerebral palsy (43.4% of all fetuses). Overall, 13 infants had cerebral palsy (1, 1, 7 and 4 with PPROM at 22, 23, 24 and 25 weeks, respectively) but none had visual or auditory impairment. When considering all fetuses or liveborn infants, rates of survival, survival at discharge without severe morbidity and survival at 2 years' corrected age without cerebral palsy significantly improved with increased GA at PPROM (Tables 2 and 3). For example, among all fetuses, rates of survival at discharge were 14.1%, 39.5%, 66.8% and 75.8% with PPROM at 22, 23, 24 and 25 weeks, respectively. However, when focusing on survivors at discharge or survivors at 2 years CA, survival at discharge without severe morbidity or survival at 2 years' corrected age without cerebral palsy did not differ by GA at PPROM (Tables 2 and 3).

Comment

Main findings

This descriptive study shows that with PPROM at 22-25 weeks' gestation, overall and for each GA at PPROM, nearly half of the fetuses were delivered within the first week. Obstetric management appears to be strongly influenced by GA at PPROM and by the threshold of

viability considered in France in 2011 (24 weeks' gestation). Overall, PPROM at 22-25 weeks was associated with high frequencies of perinatal mortality and morbidity. Both perinatal and childhood prognosis, related to all fetuses or to liveborn infants, significantly improved with advancing GA at PPROM: survival without cerebral palsy was low with PPROM at 22 and 23 weeks, but not zero, and reached approximately 60% and 70% with PPROM at 24 and 25 weeks. Nevertheless, incidences of severe morbidity and subsequent cerebral palsy by GA at PPROM were similar among survivors, and potentially related to GA at birth and to postnatal management taking GA at birth into consideration.

Strengths and limitations

The strengths of our study include a large sample of singletons and twins born preterm after PPROM at 22-25 weeks, which allowed for reporting characteristics and outcomes stratified by week of GA at PPROM, and follow-up at 2 years' corrected age. Because singletons and twins have similar latency durations and outcomes, our findings are relevant for both types of pregnancies, even though the prognosis could slightly differ between twins with intact or ruptured membranes. Unlike all published studies,[2,4,18–20] our sample stems from a prospective population-based cohort at a national level, thereby reflecting the diversity of antenatal management and outcomes in "real-life" practices. Moreover, accounting for all pregnancy outcomes when estimating neonatal prognosis allows for providing realistic figures that do not overestimate the chances of survival. The use of different inception points and thus denominators to report rates of survival is helpful in adapting information provided to parents during pregnancy when the GA of birth is not yet known.[21] Finally, the use of standardized definitions for outcomes allows for comparison with other international studies or cohorts.[21]

The main limitation of this study is the proportion of missing data related to loss to follow-up at 2 years' corrected age, although attrition was moderate in relation to the cohort size and its

geographical extent.[8] Appropriate statistical methods, with multiple imputations, allowed for accounting for missing data and obtaining non-biased estimators. Another limitation, due to the design of the EPIPAGE 2 cohort, involves left truncation and right-censoring of the sample at $34^{6/7}$ weeks.[22] We avoided left truncation by including women with both PPROM and delivery from 22 weeks. Concerning right-censoring, we likely missed the cases of PPROM at 22-25 weeks for fetuses delivered at 35 weeks and afterwards. We assume that such cases are exceptional and have a favorable neonatal prognosis. Their non-inclusion leads to a very slight underestimation of the chances of survival or disease-free survival. A disadvantage of these population-based data is that we are limited in investigating precisely the medical teams' willingness to provide antenatal active care (such as antenatal steroids or performing a cesarean section), which can change as the pregnancy progresses. Moreover, some specific complications, namely pulmonary hypoplasia, are likely underdiagnosed as autopsies were not systematically performed to determine the cause of fetal or neonatal death.

Interpretation

Because of the high risks of extreme prematurity and severe disability, a key point in antenatal care is to adequately inform parents facing PPROM at 22-25 weeks and to consider their wishes in all decisions.[1,3,5,23,24] However, in this context, the information given to parents and the resulting management decisions depend very little on individual socioeconomic and clinical characteristics (except for GA) but are largely influenced by the institution and the practitioner who gives the information.[24–28] There is indeed great variability in how caregivers understand the prognosis of early PPROM, including neurodevelopmental impairment, and their willingness to propose active management.[26] This variability can be explained by significant variations in published rates of survival with early PPROM, leaving practitioners with a great uncertainty.

Indeed, reported survival after early PPROM ranges from 20% to 85%, survival without severe morbidity from 20% to 70% and cerebral palsy from 0% to 10%.[2,4,6,18–20] Many reasons account for these variations. Selection bias, related to exclusion of women electing TOP or immediate induction of labor as well as women not eligible for expectant management or related to preadmission bias in tertiary-care referral centers, leads to overestimating latency durations and survival rates.[2,4,6,18–20] Ranges of GA at PPROM are wide and differ widely across studies; hence, overall non-stratified results do not allow for appropriate comparisons. Small sample sizes do not provide precise estimations.[2,6,20] Finally, published studies feature a retrospective design over 5 to 15 years,[6,18,20] but medical practices may have evolved and mortality rates may decrease.[29] Therefore, comparing our findings with previous publications is challenging.[21]

We report high rates of mortality and morbidity when preterm births occur following early PPROM. Most children will be delivered extremely preterm, and their immaturity and fragility are major risk factors of adverse outcomes. The frequency of the other obstetric complications (placental abruption, cord prolapsed and chorioamnionitis) is lower than or similar to that previously described.[2,6,19,20] With PPROM at 22-25 weeks' gestation, perinatal outcomes appear to be influenced by medical practices, which are themselves affected by the resuscitation threshold considered in France in 2011 (24 weeks).[24,28,30,31] This hypothesis requires further investigation.

Because French guidelines about management of women with PPROM are broadly similar to those of other countries, our results may be generalizable to most developed countries with similar practices and are relevant to question the strategies of management of early pregnancy complications.[32] Improving the prognosis of these pregnancies probably requires a rethinking of care policies in a multidisciplinary way, involving obstetricians, neonatologists, care networks, parent associations and policy makers.

Conclusion

Following PPROM, both parents and professionals are left with a great deal of uncertainty regarding the evolution of pregnancy, complications and fetal and neonatal prognosis. Our findings on the prognosis of PPROM at 22-25 weeks, based on prospective, population-based data at a national level, provide new insights that can be used as a support for counseling parents, especially during pregnancy when the GA of birth is not yet known. The impact of the practitioner's decisions on the prognosis should lead to homogenize and optimize the antenatal management practices.

404 **Contribution to authorship:**

405 Study concept: EL, GK

406 Study supervision: GK

407 Design of the present study: EL, GK

408 Acquisition, analysis and interpretation of data: All authors

409 Statistical analysis: EL, GK

410 Drafting of the manuscript: EL, GK

411 Critical revision of the manuscript for important intellectual content: All authors

412 Final approval of the version to be published: All authors

413 Agreement to be accountable for all aspects of the work: All authors

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634 Table 1: Obstetric and neonatal characteristics by gestational age (GA) at PPROM

		GA at PPROM				
	Total	22 w	23 w	24 w	25 w	p-value
	n (%)	n (%)	n (%)	n (%)	n (%)	
Characteristics	N=427	N=101	N=95	N=99	N=132	
Obstetric characteristics						
GA at birth (w) median (IQR) (n=427)	25 (24-27)	23 (22-24)	24 (24-28)	25 (24-27)	26 (26-28)	<.001
GA at birth among survivors at discharge (w) median (IQR) (n=201)	27 (26-29)	28 (26-29)	28 (26-32)	27 (25-29)	26 (26-28)	.17
GA at birth (w) (n=427)						
22-23	95 (19.4)	67 (64.1)	28 (23.8)	-	-	<.001
24-26	235 (48.1)	24 (23.0)	50 (42.4)	78 (66.4)	83 (55.7)	
27-29	74 (20.4)	8 (10.3)	11 (12.6)	16 (18.3)	39 (35.2)	
30-34	23 (12.1)	2 (2.6)	6 (21.2)	5 (15.3)	10 (9.1)	
Latency (d) median (IQR) (n=427)	8.0 (2.9-20.9)	6.1 (2.4-16.0)	9.0 (2.4-31.0)	8.0 (3.2-21.0)	8.3 (2.9-19.0)	.82
Latency > 2d (n=427)	332 (80.6)	77 (77.0)	69 (77.9)	78 (82.1)	108 (83.9)	.57
Latency > 7d (n=427)	197 (53.0)	45 (46.4)	43 (55.9)	44 (53.2)	65 (55.0)	.62
Latency > 14d (n=427)	121 (36.7)	26 (28.2)	30 (44.8)	26 (37.9)	39 (35.2)	.31
Obstetric management						
Born in type 3 maternity unit (n=427)	348 (83.8)	57 (57.9)	69 (77.9)	94 (95.8)	128 (97.3)	<.001
Antenatal discussion of care limitation (n=422)	97 (21.6)	38 (37.1)	23 (25.4)	22 (18.9)	14 (9.8)	<.001
In utero transfer (n=425)	207 (49.8)	21 (21.3)	33 (34.6)	67 (71.0)	86 (64.9)	<.001
Antibiotics (n=424)	394 (93.5)	81 (81.3)	86 (92.3)	98 (100.0)	129 (98.0)	-
Tocolysis (n=424)	246 (57.7)	27 (26.8)	46 (41.8)	71 (75.7)	102 (77.5)	<.001
Corticosteroids (n=424)	274 (68.7)	26 (28.2)	44 (56.3)	84 (88.8)	120 (91.3)	<.001
Magnesium Sulfate (n=418)	13 (3.1)	2 (2.6)	1 (0.9)	3 (2.9)	7 (5.2)	.34
Spontaneous labor (n=426)	277 (62.6)	69 (68.0)	70 (71.9)	65 (57.6)	73 (55.5)	.13
Caesarean delivery (n=423)	154 (39.2)	11 (12.5)	21 (22.3)	41 (49.6)	81 (62.7)	<.001
Cephalic presentation (n=395)	218 (56.0)	43 (51.9)	45 (53.1)	54 (58.2)	76 (58.9)	.74
Neonatal characteristics						
Male (n=424)	238 (56.9)	60 (61.6)	45 (45.7)	56 (60.8)	77 (59.4)	.24
Birth weight (g) median (IQR) (n=409)	799 (630-1043)	560 (500-730)	730 (630-1120)	795 (680-1060)	900 (780-1090)	<.001
Birth weight < 10^{th} percentile (n=408)	72 (19.3)	14 (15.0)	10 (10.3)	17 (25.9)	31 (23.6)	.049

635 GA: gestational age, PPROM: preterm premature rupture of membranes, w: weeks' gestation, IQR: interquartile range, SD: standard deviation, d: days

636 Data are n (%) unless indicated. Percentages are weighted by recruitment period.

637

638 Table 2: Outcomes by GA at PPROM

		GA at PPROM				
	Total	22 w	23 w	24 w	25 w	p-value
Outcomes	n/N (%) [95%CI]	n/N (%) [95%CI]	n/N (%) [95%CI]	n/N (%) [95%CI]	n/N (%) [95%CI]	
Perinatal death among all fetuses						
Termination of pregnancy	10/427 (2.0) [1.1-3.8]	7/101 (6.7) [3.2-13.4]	1/95 (0.9) [0.1-5.9]	2/99 (1.7) [0.4-6.6]	0/132	<.001
Antepartum stillbirth	21/427 (5.6) [3.1-9.8]	9/101 (8.6) [4.5-15.8]	4/95 (8.5) [2.2-28.2]	4/99 (3.4) [1.3-8.9]	4/132 (2.9) [1.1-7.6]	
Death during labor or in delivery room	139/427 (28.6) [24.4-33.2]	65/101 (62.6) [52.5-71.6]	49/95 (41.6) [30.3-53.8]	16/99 (13.6) [8.3-21.6]	9/132 (6.3) [3.3-11.7]	
Death in NICU	56/427 (12.1) [9.3-15.5]	8/101 (8.0) [4.0-15.3]	11/95 (9.6) [5.2-17.1]	17/99 (14.5) [8.9-22.7]	20/132 (15.1) [9.9-22.3]	
Survival at discharge						
Among all fetuses	201/427 (51.7) [46.3-57.1]	12/101 (14.1) [8.2-23.3]	30/95 (39.5) [26.8-53.7]	60/99 (66.8) [56.1-76.1]	99/132 (75.8) [67.7-82.3]	<.001
Among liveborn infants	201/315 (68.2) [62.6-73.4]	12/44 (31.1) [18.8-46.9]	30/58 (62.1) [46.9-75.3]	60/88 (73.7) [63.1-82.2]	99/125 (79.7) [71.7-85.9]	<.001
Survival at discharge without severe morbidity*						
Among all fetuses	140/418 (38.8) [33.3-44.7]	9/101 (10.6) [5.6-19.2]	19/94 (29.5) [17.4-45.4]	36/95 (46.8) [34.5-59.6]	76/128 (60.6) [51.8-68.8]	<.001
Among liveborn infants	140/306 (51.6) [45.2-58.0]	9/44 (23.3) [12.7-39.0]	19/57 (46.7) [30.1-64.1]	36/84 (51.9) [38.8-64.7]	76/121 (63.9) [54.8-72.0]	<.001
Among survivors at discharge	140/192 (76.7) [69.9-82.3]	9/12 (75.0) [44.2-91.9]	19/29 (75.7) [56.0-88.5]	36/56 (71.5) [57.2-82.5]	76/95 (80.8) [71.6-87.6]	.68

639 GA: gestational age, NICU: neonatal intensive care unit, PPROM: preterm premature rupture of membranes, w: weeks' gestation

640 All percentages obtained with complete-cases analysis, denominators can vary slightly accordingly to missing data, namely for survival at discharge without
641 severe morbidity (9 missing data).

642 * Survival at discharge without severe morbidity is defined as survival at discharge without grades 3-4 intraventricular haemorrhage, cystic periventricular
643 leukomalacia, stages II or III necrotizing enterocolitis, stage 3 or greater retinopathy of prematurity and/or laser treatment and severe bronchopulmonary
644 dysplasia.

645

Table 3: Outcomes at 2-years' corrected age by GA at PPROM

Outcomes	Total % (95% CI)	GA at PPROM 22 w % (95% CI)	 23 w % (95% CI)	 24 w % (95% CI)	 25 w % (95% CI)	p-value
Death after discharge (n=201)	1.2 (0.4-3.7)	0	0	1.3 (0.2-8.7)	1.8 (0.4-6.9)	-
Cerebral palsy among survivors at 2-years' corrected age						
CC (n=163)	7.2 (4.1-12.3)	11.2 (1.5-50.4)	3.2 (0.4-20.5)	11.8 (5.4-24.1)	5.0 (1.8-12.7)	.41
MI (n=198)	9.1 (4.5-13.7)	13.1 (0.0-35.4)	5.8 (0.0-14.7)	13.1 (4.0-22.3)	7.1 (0.9-13.2)	.62
Survival at 2-years' corrected age without cerebral palsy						
Among all fetuses						
CC (n=392)	43.4 (37.6-49.4)	10.5 (5.6-19.1)	36.0 (23.2-51.1)	55.5 (43.2-67.2)	66.3 (57.0-74.5)	<.001
MI (n=427)	46.4 (40.8-52.1)	12.3 (5.2-19.4)	37.2 (23.2-51.1)	57.3 (45.8-68.8)	69.1 (60.8-77.5)	<.001
Among liveborn infants						
CC (n=280)	58.9 (52.4-65.1)	24.0 (13.0-40.0)	57.9 (41.5-72.7)	61.8 (49.0-73.1)	70.4 (60.9-78.4)	<.001
MI (n=315)	61.3 (55.2-67.3)	27.1 (12.9-41.2)	58.5 (43.0-74.0)	63.2 (51.7-74.8)	72.7 (64.4-81.0)	<.001
Among survivors at 2 years' corrected age						
CC (n=163)	92.8 (87.7-95.9)	88.9 (49.6-98.5)	96.8 (79.5-99.6)	88.2 (75.9-94.6)	95.1 (87.3-98.2)	.41
MI (n=198)	90.9 (86.3-95.5)	86.9 (64.6-100.0)	94.2 (85.3-100.0)	86.9 (77.7-96.0)	92.9 (86.8-99.1)	.62

GA: gestational age, PPROM: preterm premature rupture of membranes, w: weeks' gestation, CC: complete cases analysis, MI: multiple imputation

Missing data for cerebral palsy at 2-years' corrected age are related to 3/201 deaths after discharge, and 35/198 children lost to follow-up. Percentages of cerebral palsy and survival without cerebral palsy were obtained using multiple imputations for missing data.

Table A.1: Comparison of characteristics between singleton and twin pregnancies

	Singletons N=331	Twins N=96	p-value
Maternal characteristics			
Maternal age (y) median (IQR) (n=426)	29 (26-34)	29 (26-32)	.99
Born in France/Europe (n=406)	243 (78.3)	70 (78.6)	.97
Marital life (n=413)	287 (90.3)	88 (95.4)	.29
Tobacco use (n=412)	89 (27.5)	16 (17.4)	.16
Nulliparous (n=426)	150 (47.6)	60 (62.7)	.06
Obstetric characteristics			
GA at PPROM (w) median (IQR) (n=427)	24 (23-25)	24 (23-25)	.77
GA at birth (w) median (IQR) (n=427)	25 (24-28)	25 (24-27)	.80
GA at birth among survivors at discharge (w) median (IQR) (n=201)	27 (26-30)	27 (25-28)	.66
Latency (d) median (IQR) (n=427)	8.0 (2.8-23.0)	8.0 (2.9-18.0)	.91
Latency > 2d (n=427)	256 (80.4)	76 (81.1)	.88
Latency > 7d (n=427)	153 (53.5)	44 (50.8)	.65
Latency > 14d (n=427)	89 (36.6)	32 (38.1)	.82
Obstetric management			
Born in type 3 maternity (n=427)	266 (83.0)	82 (86.8)	.50
Antenatal discussion of care limitation (n=422)	81 (23.4)	16 (15.1)	.20
In utero transfer (n=425)	155 (48.7)	52 (53.8)	.52
Antibiotics (n=424)	302 (92.8)	92 (96.2)	.37
Tocolysis (n=424)	174 (52.6)	72 (76.0)	.004
Corticosteroids (n=424)	210 (68.6)	64 (69.1)	.95
Magnesium Sulfate (n=418)	13 (3.9)	0 (0)	-
Spontaneous labor (n=426)	197 (57.2)	80 (82.2)	.003
Cesarean delivery (n=423)	111 (36.6)	43 (48.5)	.13
Cephalic presentation (n=395)	168 (56.1)	50 (55.5)	.92

GA: gestational age, PPROM: preterm premature rupture of membranes, w: weeks' gestation, IQR: interquartile range, SD: standard deviation, d: days, y: years

Data are n (%) unless indicated. Percentages are weighted by recruitment period.

Table A.2: Comparison of neonatal characteristics and outcomes between singleton and twin pregnancies

	Singletons N=331	First twin N=48	Second twin N=48	p-value
Neonatal characteristics				
Male (n=424)	187 (57.2)	23 (51.7)	28 (60.0)	.56
Birth weight (g) Median (IQR) (n=409)	800 (635-1060)	730 (580-1000)	800 (620-1030)	.76
Birth weight < 10^{th} percentile (n=408)	51 (18.1)	11 (24.9)	10 (22.6)	.59
Perinatal death among all fetuses				
Termination of pregnancy	8 (2.1)	1 (1.9)	1 (1.9)	.74
Antepartum stillbirth	17 (6.0)	3 (6.3)	1 (1.9)	
Death during labor or in delivery room	116 (30.4)	12 (22.7)	11 (20.8)	
Death in NICU	42 (11.5)	6 (12.0)	8 (16.5)	
Survival at discharge				
Among all fetuses (n=427)	148 (50.0)	26 (57.1)	27 (58.9)	.51
Among liveborn infants (n=315)	148 (66.9)	26 (74.5)	27 (71.1)	.65
Survival at discharge without severe morbidity				
Among all fetuses (n=418)	112 (40.7)	14 (31.9)	14 (32.6)	.46
Among liveborn infants (n=306)	112 (54.8)	14 (41.9)	14 (39.5)	.17
Among survivors at discharge (n=192)	112 (83.1)	14 (57.0)	14 (56.3)	.002
Survival at 2-years' corrected age without cerebral palsy				
Among all fetuses (n=392)	104 (40.3)	22 (53.2)	24 (55.4)	.17
Among liveborn infants (n=280)	104 (55.7)	22 (71.4)	24 (67.3)	.21
Among survivors at 2 years old (n=163)	104 (89.2)	22 (100.0)	24 (96.6)	-

GA: gestational age, NICU: neonatal intensive care unit, PPROM: preterm premature rupture of membranes, w: weeks' gestation

All percentages obtained with complete-cases analysis, denominators can vary slightly accordingly to missing data, namely for survival at discharge without severe morbidity (9 missing data) and survival at 2-years' corrected age without cerebral palsy (35 missing data).

* Survival at discharge without severe morbidity is defined as survival at discharge without grades 3-4 intraventricular haemorrhage, cystic periventricular leukomalacia, stages II or III necrotizing enterocolitis, stage 3 or greater retinopathy of prematurity and/or laser treatment and severe bronchopulmonary dysplasia.

672 Table A.3: Comparison of infants with and without follow-up at 2 years' corrected age

	Cerebral palsy data available among survivors at 2-years CA eligible for the study		
Characteristics	Yes (n=163) n (%)	No (n=35) n (%)	p-value
Maternal characteristics			
Maternal age (n=198) median (IQR)	29 (26-33)	27 (22-30)	.006
Born in France/Europe (n=194)	120 (76.7)	22 (70.7)	.53
Parents' socio-economic status (n=189)*			<.001
Professional	36 (25.7)	1 (2.9)	
Intermediate	27 (15.3)	0 (0)	
Administrative, public service, self-employed, students	51 (31.4)	10 (34.4)	
Shop assistants, service workers	25 (13.5)	3 (9.8)	
Manual workers	17 (12.5)	16 (52.9)	
No known occupation	3 (1.6)	0 (0)	
Nulliparous (n=197)	84 (54.0)	13 (37.0)	.10
Obstetric characteristics			
GA at PPROM (w) (n=198)			
22	10 (5.8)	2 (6.8)	.33
23	26 (20.1)	4 (10.9)	
24	50 (32.3)	9 (24.3)	
25	77 (41.8)	20 (58.0)	
GA at birth (w) (n=198)			
22-23	0 (0)	0 (0)	.81
24-26	93 (44.3)	21 (52.7)	
27-29	55 (35.3)	8 (27.0)	
30-34	15 (20.4)	6 (20.3)	
Latency (d) median (IQR) (n=198)	17.5 (6.0-31.2)	17.2 (4.0-23.0)	.79
Twin pregnancy (n=198)	47 (26.2)	6 (15.9)	.39
Placental abruption (n=198)	11 (5.9)	2 (6.8)	.91
Cord prolapse (n=198)	5 (2.6)	1 (2.5)	.90
Obstetric management			
Born in type 3 maternity unit (n=198)	161 (99.1)	35 (100.0)	.54
In utero transfer (n=198)	105 (64.4)	22 (60.4)	.52
Clinical chorioamnionitis (n=192)	14 (7.9)	6 (17.7)	.052

Antibiotics (n=198)	157 (96.7)	34 (96.6)	.97
Tocolysis (n=198)	116 (68.9)	24 (67.2)	.97
Corticosteroids (n=198)	151 (93.5)	32 (92.5)	.72
Magnesium Sulfate (n=196)	7 (3.9)	2 (6.9)	.49
Caesarean delivery (n=196)	99 (62.3)	18 (51.3)	.36
Neonatal characteristics			
Male (n=198)	93 (59.5)	20 (58.0)	.95
Birth weight < 10^{th} percentile (n=198)	29 (21.5)	8 (23.6)	.83
Severe bronchopulmonary dysplasia (n=182)	23 (13.1)	6 (18.8)	.30
Severe necrotizing enterocolitis (n=195)	5 (2.9)	1 (2.6)	.71
Severe retinopathy of prematurity (n=198)	6 (2.9)	2 (5.9)	.55
Severe cerebral lesion (IVH and/or cPVL) (n=198)	14 (7.0)	2 (5.0)	.71

* Defined as the highest occupational status of the mother and father, or mother only if living alone.

CA: corrected age, cPVL: cystic periventricular leucomalacia, GA: gestational age, IVH: intraventricular hemorrhage, PPROM: preterm premature rupture of membranes, w: weeks' gestation, d: days, IQR: interquartile range

Data are n (%) unless indicated. Percentages are weighted by recruitment period.

Table A.4: Maternal characteristics by gestational age at PPROM

		GA at PPROM				
	Total	22 w	23 w	24 w	25 w	p-value
	n (%)	n (%)	n (%)	n (%)	n (%)	
Characteristics	N=427	N=101	N=95	N=99	N=132	
Maternal age (y) median (IQR) (n=426)	29 (26-34)	29.5 (26-33)	29 (26-34)	29 (26-34)	29 (25-33)	.26
Born in France/Europe (n=406)	313 (78.3)	79 (83.5)	63 (74.5)	69 (76.2)	102 (79.4)	.56
Marital life (n=413)	375 (91.4)	83 (88.9)	84 (92.7)	89 (93.5)	119 (90.3)	.68
Nulliparous (n=426)	210 (50.9)	46 (45.0)	49 (59.2)	55 (55.0)	60 (45.2)	.23
Tobacco use (n=412)	105 (25.3)	25 (26.1)	23 (26.5)	21 (19.5)	36 (28.3)	.58

GA: gestational age, PPROM: preterm premature rupture of membranes, w: weeks' gestation, y: years, IQR: interquartile range, SD: standard deviation

Data are n (%) unless indicated. Percentages are weighted by recruitment period.

List of figures:

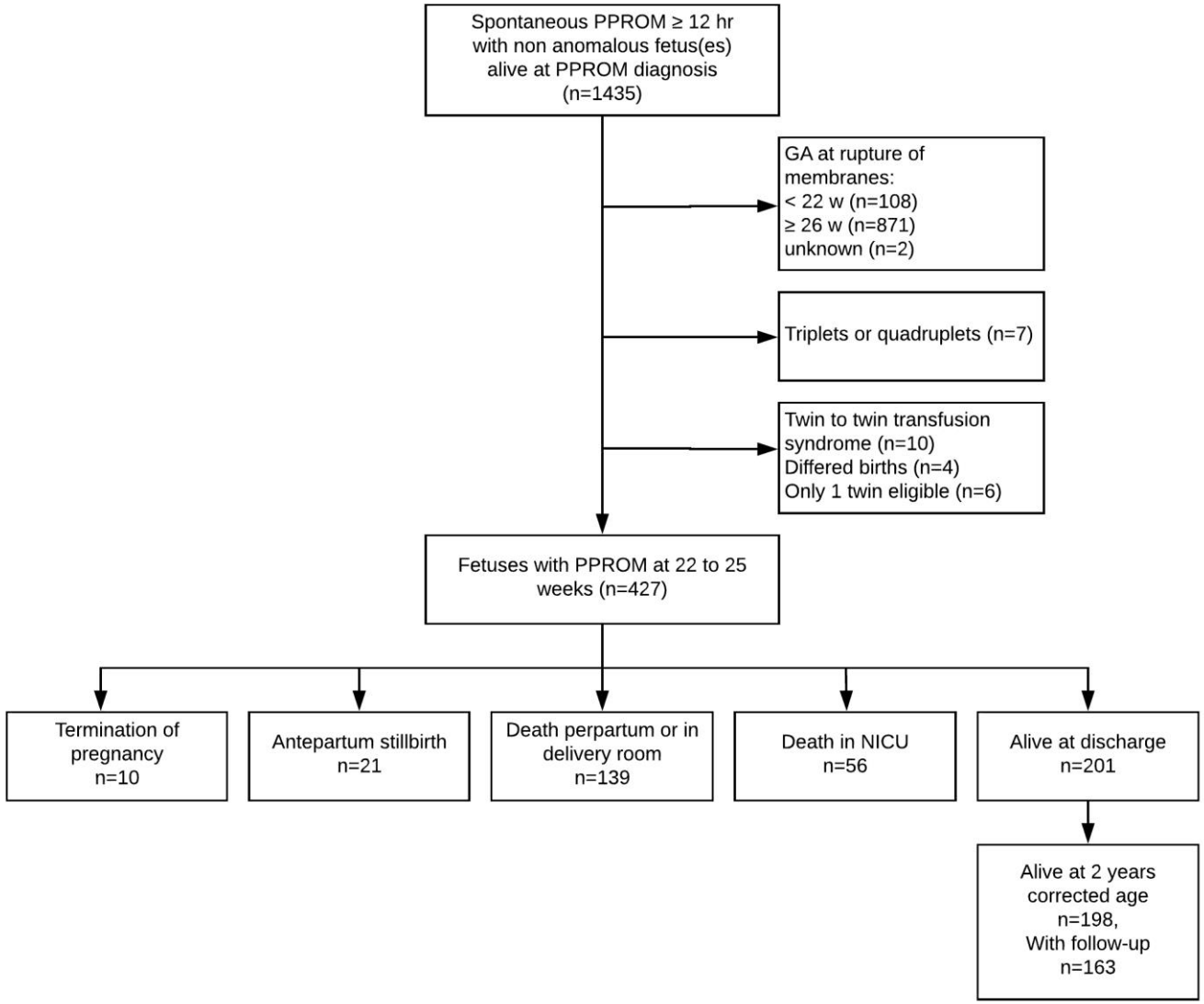
Figure 1: Flow chart

Description of figure 1:

The flow chart summarizes how the sample size of the analysis was reached.

Legends of figure 1:

GA: gestational age, NICU: neonatal intensive care unit, PPROM: preterm premature rupture of membranes, w: weeks


Spontaneous PPROM ≥ 12 hr with non anomalous fetus(es) alive at PPROM diagnosis (n=1435)
GA at rupture of membranes:
< 22 w (n=108)
≥ 26 w (n=871)
unknown (n=2)
Triplets or quadruplets (n=7)
Twin to twin transfusion syndrome (n=10)
Differed births (n=4)
Only 1 twin eligible (n=6)
Fetuses with PPROM at 22 to 25 weeks (n=427)
Termination of pregnancy n=10
Antepartum stillbirth n=21
Death perpartum or in delivery room n=139
Death in NICU n=56
Alive at discharge n=201
Alive at 2 years corrected age n=198, With follow-up n=163

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