OBSTETRICS

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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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: We sought 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 gestational age 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 nonnegligible proportion of children survive without severe morbidity both at discharge and at 2 years' corrected age.

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

Introduction

Early preterm premature rupture of membranes (PPROM), defined as PPROM at 22–25 weeks' gestation, occurs in <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, and infection) and fetal (pulmonary hypoplasia, limb deformities, prematurity, and in utero demise)[1,3,4] complications 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 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 22–25 weeks' gestation, within a prospective population-based cohort at a national level.

Cite this article as: Lorthe E, Torchin H, Delorme P, et al. Preterm premature rupture of membranes at 22–25 weeks' gestation: perinatal and 2-year outcomes within a national population-based study (EPIPAGE-2). Am J Obstet Gynecol 2018;219:298.e1-14.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2018.05.029

AJOG at a Glance

Why was this study conducted?

To provide reliable and relevant data related to the prognosis of preterm premature rupture of membranes (PPROM) at 22−25 weeks to adequately counsel parents during pregnancy and to reflect on our policies of care.

Key findings

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 nonnegligible proportion of children survive without severe morbidity both at discharge and at 2 years.

What does this add to what is known?

This study is the first to describe and quantify perinatal and 2-year 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 gestational age of birth is not yet known.

Materials and Methods

Setting and data collection of the EPIPAGE-2 cohort study

This was 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 (TOPs) at $22^{0/7}$−$34^{6/7}$ weeks' gestation (n = 7804), whose parents had not declined to participate, were included in 25 French regions involving 546 maternity units. Only 1 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: 22−26 weeks (8 months), 27−31 weeks (6 months), and 32−34 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 (National Commission on Informatics and Liberty no. 911009), the appropriate ethics committees (Consultative Committee on the Treatment of Data on Personal Health for Research Purposes, reference no. 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 22−25 completed weeks' gestation and fetuses alive at the time of PPROM. PPROM was defined as spontaneous rupture of membranes occurring at least 12 hours 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, 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 <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 (ie, 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 (ie, 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 2 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.

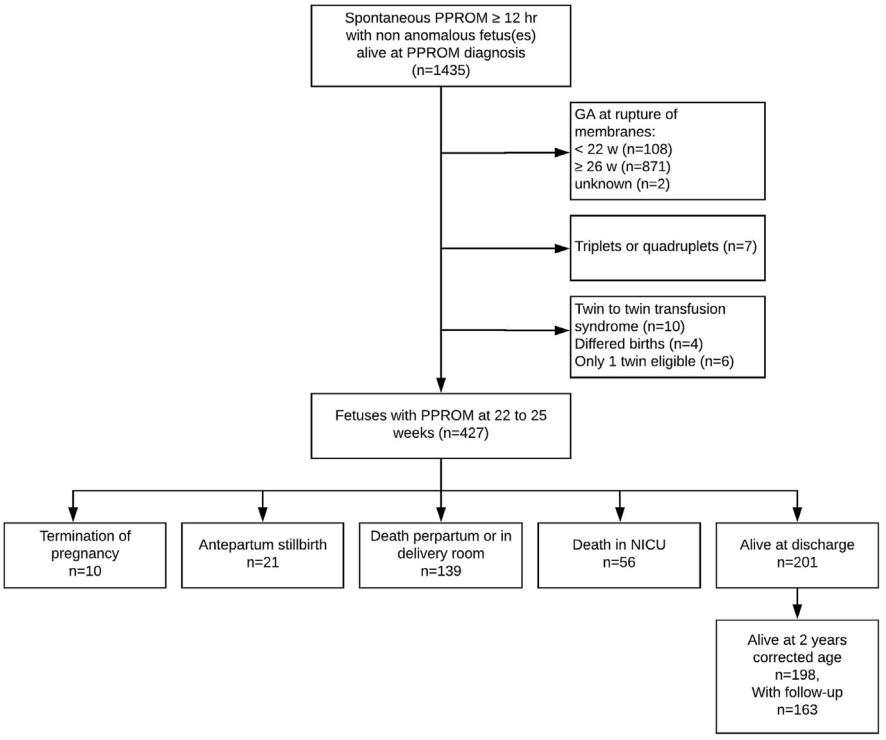
Antenatal management

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). Steroid 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 (ie, without grade 3–4 intraventricular hemorrhage,[10] cystic periventricular leukomalacia,[11] stage II or III necrotizing enterocolitis,[12] stage ≥3 retinopathy of prematurity,[13] and/or laser treatment and severe bronchopulmonary dysplasia defined as requiring oxygen for at least 28 days in addition to the requirement of ≥30% oxygen and/or mechanical ventilator support or continuous positive airway pressure at 36 weeks' postmenstrual age[14]). Z-score birthweights were calculated from EPOPé intrauterine growth curves corrected for sex and GA.[15] The third outcome was survival at 2 years' corrected age without cerebral palsy whatever the stage. Cerebral palsy was defined according to the diagnostic criteria of the Surveillance of Cerebral Palsy in Europe network.[16] We thought to report deafness and blindness as well but there were no cases in our population.[8]

FIGURE
Flowchart of patients included in the study



Flow chart summarizes how sample size of analysis was reached.

GA, gestational age; *NICU*, neonatal intensive care unit; *PPROM*, preterm premature rupture of membranes.

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Statistical analysis

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

TABLE 1
Obstetric and neonatal characteristics by gestational age at preterm premature rupture of membranes

Characteristics	Total N = 427	GA at PPROM 22 wk N = 101	23 wk N = 95	24 wk N = 99	25 wk N = 132	*P* value
Obstetric characteristics						
GA at birth, wk, 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, wk, median (IQR) n = 201	27 (26–29)	28 (26–29)	28 (26–32)	27 (25–29)	26 (26–28)	.17
GA at birth, wk, 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 >2 d, n = 427	332 (80.6)	77 (77.0)	69 (77.9)	78 (82.1)	108 (83.9)	.57
Latency >7 d, n = 427	197 (53.0)	45 (46.4)	43 (55.9)	44 (53.2)	65 (55.0)	.62
Latency >14 d, 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
Cesarean 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
Birthweight, g, median (IQR) n = 409	799 (630–1043)	560 (500–730)	730 (630–1120)	795 (680–1060)	900 (780–1090)	<.001
Birthweight <10th percentile, n = 408	72 (19.3)	14 (15.0)	10 (10.3)	17 (25.9)	31 (23.6)	.049

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

GA, gestational age; *IQR*, interquartile range; *PPROM*, preterm premature rupture of membranes.

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binary data and a multinomial imputation model for missing categorical data. Imputation model variables included both those potentially predicting nonresponse and/or outcomes (type of maternity unit, maternal age and country of birth, socioeconomic status, parity, GAs at PPROM and at birth, latency duration, multiple pregnancy, in utero transfer, antenatal steroids and antibiotics, magnesium sulfate, tocolysis, clinical chorioamnionitis, cord prolapse,

TABLE 2
Outcomes by gestational age at preterm premature rupture of membranes

Outcomes	Total n/N (%) [95% CI]	GA at PPROM				*P* value
		22 wk	23 wk	24 wk	25 wk	
		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[a]						
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

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

CI, confidence interval; *GA*, gestational age; *NICU*, neonatal intensive care unit; *PPROM*, preterm premature rupture of membranes.

[a] Survival at discharge without grades 3–4 intraventricular hemorrhage, cystic periventricular leukomalacia, stages II or III necrotizing enterocolitis, stage ≥3 retinopathy of prematurity, and/or laser treatment and severe bronchopulmonary dysplasia.

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placental abruption, small for GA, cesarean delivery, sex, severe neonatal morbidities) and outcomes (survival, cerebral palsy). Outcomes were estimated within each of the 30 imputed data sets generated with 20 iterations, and results were pooled for a final analysis according to Rubin rules. Statistical significance was set at 2-tailed $P < .05$. Data were analyzed by use of software (Stata/SE 13.0; StataCorp LP, College Station, TX).

Results

Among the 1435 women with a diagnosis of PPROM, 379 were at 22–25 weeks' gestation, with 427 fetuses alive (331 singletons and 96 twins) (Figure). 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 (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 0.5–145 days. Latency duration did not differ by week of GA at PPROM, nor did latency >2, 7, 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% (95% CI, 1.7–4.9), and 9.5% (95% CI, 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%, and 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

TABLE 3
Outcomes at 2 years' corrected age by gestational age at preterm premature rupture of membranes

Outcomes	Total % (95% CI)	GA at PPROM 22 wk % (95% CI)	23 wk % (95% CI)	24 wk % (95% CI)	25 wk % (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 y 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 y 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 y 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

Missing data for cerebral palsy at 2 y 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 MI for missing data.

CC, complete-cases analysis; *CI*, confidence interval; *GA*, gestational age; *MI*, multiple imputation; *PPROM*, preterm premature rupture of membranes.

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born in a type 3 maternity unit with PPROM at 24 or 25 weeks vs 58% and 78% with PPROM at 22 and 23 weeks. Accordingly, rates of in utero transfer were 2- to 3-fold higher >24 weeks. Most fetuses were exposed to antenatal steroids and cesarean delivery when PPROM occurred after the threshold considered for neonatal resuscitation in France in 2011 (24 weeks). The use of antenatal antibiotics, mainly amoxicillin and third-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 delivery 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 and 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 <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 0, 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 nonbiased 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. We assume that such cases are exceptional and have a favorable neonatal prognosis. Their noninclusion 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 (eg, antenatal steroids or performing a cesarean delivery), 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 20−85%, survival without severe morbidity from 20−70%, and cerebral palsy from 0−10%.[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 nonstratified 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 5−15 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 prolapse, 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. ■

Acknowledgment

We are grateful to the participating children and their families and to all maternity and neonatal units in France. The authors thank Laura Smales for editorial assistance and acknowledge the collaborators of the EPIPAGE-2 obstetric writing group: Pierre-Yves Ancel, MD, PhD (Inserm Unité Mixte de Recherche [UMR] 1153, Obstetrical, Perinatal, and Pediatric Epidemiology Research Team [EPOPé], Center for Epidemiology and Statistics Sorbonne Paris Cité, Département Hospitalo-Universitaire Risks in Pregnancy, Paris Descartes University, Unité de Recherche Clinique−Centre d'Investigations Cliniques P1419, Département Hospitalo-Universitaire Risks in Pregnancy, Cochin Hotel-Dieu Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France); Catherine Arnaud, MD, PhD (Research Unit on Perinatal Epidemiology, Childhood Disabilities, and Adolescent Health, INSERM UMR 1027, Paul Sabatier University, Toulouse, France); Julie Blanc, MD (Department of Obstetrics and Gynecology, Aix Marseille University, Marseille, France); Pascal Boileau, MD, PhD (Department of Neonatal Pediatrics, Poissy Saint Germain Hospital, Poissy, France, Equipe d'Accueil 7285 Versailles Saint Quentin en Yvelines University, Versailles, France); 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All the collaborators of the EPIPAGE-2 obstetric writing group have no conflict of interest or compensation in relation with this article to disclose. All of them consented to such acknowledgment.

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Received Jan. 29, 2018; revised April 26, 2018; accepted May 22, 2018.

EPIPAGE-2 was funded by the French Institute of Public Health Research/Institute of Public Health and its partners: the French Health Ministry, the National Institute of Health and Medical Research (Inserm), the National Institute of Cancer, and the National Solidarity Fund for Autonomy (CNSA); the National Research Agency through the French EQUIPEX program of investments for the future (reference ANR-11-EQPX-0038); and the PREMUP Foundation. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure: Dr d'Ercole is a consultant for the Ferring Laboratory; this laboratory was not involved in this work in any way. The remaining authors report no conflict of interest.

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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, wk, median (IQR) n = 427	24 (23–25)	24 (23–25)	.77
GA at birth, wk, median (IQR) n = 427	25 (24–28)	25 (24–27)	.80
GA at birth among survivors at discharge, wk, 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 >2 d, n = 427	256 (80.4)	76 (81.1)	.88
Latency >7 d, n = 427	153 (53.5)	44 (50.8)	.65
Latency >14 d, 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

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

GA, gestational age; *IQR*, interquartile range; *PPROM*, preterm premature rupture of membranes.

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

	Singletons	First twin	Second twin	
	N = 331	N = 48	N = 48	*P* value
Neonatal characteristics				
Male, n = 424	187 (57.2)	23 (51.7)	28 (60.0)	.56
Birthweight, g, median (IQR) n = 409	800 (635–1060)	730 (580–1000)	800 (620–1030)	.76
Birthweight <10th 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[a]				
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 y 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 y, n = 163	104 (89.2)	22 (100.0)	24 (96.6)	—

Data are n (%) unless indicated. All percentages obtained with complete-cases analysis, denominators can vary slightly according to missing data, namely for survival at discharge without severe morbidity (9 missing data) and survival at 2 y corrected age without cerebral palsy (35 missing data).

IQR, interquartile range; *NICU*, neonatal intensive care unit.

[a] Survival at discharge without grades 3–4 intraventricular hemorrhage, cystic periventricular leukomalacia, stages II or III necrotizing enterocolitis, stage ≥3 retinopathy of prematurity, and/or laser treatment and severe bronchopulmonary dysplasia.

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

Characteristics	Cerebral palsy data available among survivors at 2 y corrected age eligible for study		*P* value
	Yes, n = 163	No, n = 35	
Maternal characteristics			
Maternal age, y, median (IQR) n = 198	29 (26–33)	27 (22–30)	.006
Born in France/Europe, n = 194	120 (76.7)	22 (70.7)	.53
Parents' socioeconomic status, n = 189[a]			<.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, wk, 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, wk, 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
Cesarean delivery, n = 196	99 (62.3)	18 (51.3)	.36
Neonatal characteristics			
Male, n = 198	93 (59.5)	20 (58.0)	.95
Birthweight <10th percentile, n = 198	29 (21.5)	8 (23.6)	.83

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(continued)

TABLE A.3
Comparison of infants with and without follow-up at 2 years' corrected age *(continued)*

Characteristics	Cerebral palsy data available among survivors at 2 y corrected age eligible for study		*P* value
	Yes, n = 163	No, n = 35	
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

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

cPVL, cystic periventricular leukomalacia; *GA*, gestational age; *IQR*, interquartile range; *IVH*, intraventricular hemorrhage; *PPROM*, preterm premature rupture of membranes.

[a] Highest occupational status of mother and father, or mother only if living alone.

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TABLE A.4
Maternal characteristics by gestational age at preterm premature rupture of membranes

Characteristics	Total N = 427	GA at PPROM				*P* value
		22 wk N = 101	23 wk N = 95	24 wk N = 99	25 wk 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

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

GA, gestational age; *IQR*, interquartile range; *PPROM*, preterm premature rupture of membranes.

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