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.

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## 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