Original Research

Cause of Preterm Birth as a Prognostic Factor for Mortality

Pierre Delorme, MD, François Goffinet, MD, PhD, Pierre-Yves Ancel, MD, PhD, Laurence Foix-L'Hélias, MD, PhD, Bruno Langer, MD, PhD, Cécile Lebeaux, MD, Laetitia Martin Marchand, MSc, Jennifer Zeitlin, PhD, Anne Ego, MD, PhD, Catherine Arnaud, MD, PhD, Christophe Vayssiere, MD, PhD, Elsa Lorthe, MSc, Xavier Durrmeyer, MD, Loïc Sentilhes, MD, PhD, Damien Subtil, MD, PhD, Thierry Debillon, MD, PhD, Norbert Winer, MD, PhD, Monique Kaminski, MSc, Claude D'Ercole, MD, PhD, Michel Dreyfus, MD, PhD, Bruno Carbonne, MD, PhD, and Gilles Kayem, MD, PhD

OBJECTIVE: To investigate the association of the cause of preterm birth on in-hospital mortality of preterm neonates born from 24 to 34 weeks of gestation.

METHODS: L'Etude épidémiologique sur les petits âges gestationnels (EPIPAGE)-2 is a prospective, nationwide, population-based cohort of very preterm births. After dividing causes of preterm birth into six mutually exclusive groups, we analyzed the association of each cause with in-hospital deaths of preterm neonates born alive with adjustment for organizational, maternal, and obstetric factors.

RESULTS: The analysis included 3,138 singleton live births from 24 to 34 weeks of gestation with a newborn in-hospital mortality rate of 5.0% (95% confidence interval 4.5–5.7). Preterm labor was the most frequent cause of preterm birth (n=1,293 [43.5%]) followed by preterm premature rupture of membranes (n=765 [23.9%]), hypertensive disorders without suspected fetal growth restriction (n=397 [12.7%]), hypertensive disorders with suspected fetal growth restriction (n=408 [10.9%]), placental abruption after an uncomplicated pregnancy (n=92 [3.0%]), and suspected fetal growth restriction without hypertensive disorders (n=183 [5.9%]). Neonates born because of suspected fetal growth restriction with or without hypertensive disorders (adjusted odds ratio [OR] 3.0 [1.9–4.7] and adjusted OR 2.3 [1.1–4.6], respectively) had higher adjusted risks of in-hospital death than those born after preterm labor. Risks of in-hospital mortality for preterm births caused by preterm premature rupture of membranes (adjusted OR 1.3 [0.9–1.9]), hypertensive disorders without fetal growth restriction (adjusted OR 0.7 [0.4–1.4]), or placental abruption (adjusted OR 1.6 [0.7–3.7]) were similar to those born after preterm labor.

CONCLUSION: Among neonates born alive before 34 weeks of gestation, only those born because of suspected fetal growth restriction have a higher mortality risk than those born after preterm labor.

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From Inserm UMR 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team (Epopé), Center for Epidemiology and Statistics Sorbonne Paris Cité, DHU Risks in pregnancy, Paris Descartes University, the Department of Gynecology and Obstetrics, St. Joseph Hospital, the Department of Obstetrics and Gynecology, Hôtel Dieu Hospital, CIC P1419 Cochin Hotel-Dieu Hospital, Assistance Publique–Hôpitaux de Paris, the Department of Neonatal Pediatrics, Trousseau Hospital, Sorbonne Universités, and the Department of Obstetrics and Gynecology, Trousseau Hospital, Paris, the Department of Obstetrics and Gynecology, Hautepierre Hospital, Strasbourg, University Hospital and the Department of Neonatal Pediatrics, University Hospital, Grenoble, the Research Unit on Perinatal Epidemiology, Childhood Disabilities and Adolescent Health, Paul Sabatier University, and the Department of Obstetrics and Gynecology, University Hospital, Toulouse, the Department of Neonatal Pediatrics and Intensive Care, CHI, CRC, Créteil, the Department of Obstetrics and Gynecology, Angers University Hospital, Angers, the Department of Obstetrics and Gynecology, Jeanne de Flandre Hospital, Lille, the Department of Obstetrics and Gynecology, University Hospital, UMR 1280 Physiologie des adaptations nutritionnelles, Nantes, the Department of Obstetrics and Gynecology, Nord Hospital, Assistance Publique des Hôpitaux de Marseille (AP-HM), Aix Marseille Université, AMU, Marseille, and the Department of Gynecology and Obstetrics, University Hospital, Caen, France; and the Department of Obstetrics and Gynecology, Princess Grace Hospital, Monaco.

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Corresponding author: Pierre Delorme, MD, INSERM UMR 1153, 123 Boulevard de Port Royal, Paris, France; e-mail: pitdelorme@gmail.com.

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In Europe prematurity accounts for 5.5–11.1% of births and is the leading cause of in-hospital newborn mortality.[1] In women at risk of very preterm birth, it is crucial to give the parents the most accurate information regarding the neonatal prognosis. The prognostic assessment is currently based primarily on gestational age, although neonatal mortality may be associated with other factors, including birth weight, fetal sex, socioeconomic factors, and geographic origin.[2,3]

Knowledge about the relations between the circumstances leading to the preterm delivery and neonatal outcome is sparse, although these may affect the prognosis. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development has proposed an algorithm to predict the neonatal prognosis, which takes into account information available only after birth (birth weight) and does not include the cause of the preterm delivery.[4] This cause, however, may be associated with biological phenomena affecting prognosis such as inflammation and cerebral hypoxemia.[5,6] Moreover, the frequency of beneficial practices (antenatal corticosteroid therapy, cesarean delivery, and inborn status) may vary according to the cause of preterm birth. The potential improvement in our understanding of the prognostic factors of mortality appears to justify consideration of the cause of preterm birth. Using the cause of preterm birth to improve prognostic models and antenatal care requires that only antenatal factors be considered.

Our study used data from L'Etude épidémiologique sur les petits âges gestationnels (EPIPAGE)-2 national population-based cohort of preterm births seeking to identify the main cause of each birth and to analyze the associations between these causes and neonatal mortality.

MATERIALS AND METHODS

The study population comes from EPIPAGE-2, a national population-based cohort that included all stillbirths, terminations of pregnancy, and live births between 22 and 31 completed weeks of gestation in all maternity units in 25 French regions (21 of the 22 metropolitan regions and four overseas regions) during the inclusion period.

Inclusions took place during an 8-month period in 2011 in 25 regions in France for all extremely preterm births (22–26 weeks of gestation) and a 6-month period for all very preterm births (27–31 weeks of gestation). The study also included a sample of moderately preterm births (stillbirths, late terminations, and live births at 32–34 weeks of gestation) in the same regions, including all birth during a 5-week set period.

A coordinating committee was set up in each region specifically for the implementation of the study. Staff members were selected in each maternity ward and each neonatal unit to supervise inclusions and data collection. During recruitment, members of the regional coordinating committee visited all maternity units to ensure that all eligible children were identified.

At birth and during the neonatal period, data were collected in the maternity and neonatal units, extracted from the medical records, and completed by questions to obstetric and neonatal teams. Data extracted from maternity and neonatal records were entered directly online with a secure interface to maintain the confidentiality and privacy of data and personal information. The EPIPAGE coordination team used a centralized system to monitor and validate inclusions and data collection at the national level.

The recruitment durations were calculated to obtain a sample size that would provide a number of children at each week of gestation sufficient to demonstrate, among other things, differences in prognosis between preterm groups. Details about the design and methods of the national EPIPAGE-2 cohort have been published elsewhere.[7] The committee for the protection of people participating in biomedical research (CPP: March 18, 2011, ref SC-2873) approved this study.

The study population included singleton liveborn neonates from 24 weeks of gestation to 34 weeks 6 days of gestation. Neonates with one or more severe malformations that might affect mortality, regardless of any association with chromosomal abnormalities, were excluded. Three perinatal specialists (G.K., F.G., and L.F.-L.), blinded to outcome, consensually determined the severity of the malformations. Multiple-order pregnancies were excluded because the prenatal decision-making process might well differs because of the cotwin and the frequency of twin–twin transfusion syndrome.

In 1998, it became mandatory in France to transfer women likely to deliver preterm to a level 3 facility before 33 weeks of gestation and to a level 2 facility between 33 and 36 weeks of gestation. Perinatal care has been organized by region, in perinatal networks, with direct relations between maternity units and the reference centers.[8] The overall results for EPIPAGE-2 show that in 2011 active care for extremely preterm births usually took place for neonates born at and after 24 weeks of gestation.[9] In-hospital mortality was defined as death before discharge home.

The EPIPAGE-2 questionnaire was constructed to provide precise prospective information about the

circumstances of the preterm delivery. Its principal cause was determined from the following information: medical indications for hospitalization; diseases identified during prenatal surveillance, including during hospitalization, especially suspected fetal growth restriction; mode of labor onset; and indications for cesarean delivery or induction of labor. Antenatal suspicion of fetal growth restriction was defined by an estimated fetal weight below the 10th percentile (according to the reference curve used at the hospital), growth arrest, and relevant fetal Doppler abnormalities.

Cases were excluded from the study if they had rare causes of preterm delivery (eg, acute fatty liver of pregnancy, severe fetal anemia, sickle cell anemia, psychiatric) that were very specific and difficult to group with other causes of preterm birth (n=107 for 15 different disorders [Appendix 1, available online at http://links.lww.com/AOG/A724]).

We defined six groups corresponding to the principal causes of preterm delivery:

1. Preterm labor group: preterm labor with intact membranes;
2. Preterm premature rupture of membranes (PROM) group: preterm PROM, defined by rupture of the membranes more than 24 hours before delivery;
3. Hypertensive disorders without fetal growth restriction group: hypertensive disorders (pregnancy-related hypertension, preeclampsia, hemolysis, elevated liver enzymes and low platelet count syndrome, and eclampsia) without prenatally suspected fetal growth restriction;
4. Hypertensive disorders with fetal growth restriction group: hypertensive disorders with suspected fetal growth restriction;
5. Placental abruption group: placental abruption after normal uncomplicated pregnancy (without hypertensive disorders, preterm labor, or preterm PROM); and
6. Fetal growth restriction without hypertensive disorders group: suspected fetal growth restriction without hypertensive disorders.

The following decision rules were applied when there were several potential causes: Women with preterm labor with intact membranes or preterm PROM were classified in their respective groups, even if a cesarean delivery was performed for maternal–fetal infection or fetal heart rate abnormalities. Placental abruption was classified in the preterm labor group if regular contractions had been developing longer than 24 hours, in the preterm PROM group when it had occurred, and as hypertensive disorders when they were present. When fetal growth restriction or hypertensive disorders or both were associated with preterm labor or preterm PROM, they were classified as preterm labor or preterm PROM if labor began spontaneously or if a cesarean delivery was performed for maternal–fetal infection and as hypertensive disorders or fetal growth restriction without hypertensive disorders if labor was induced or a cesarean delivery performed for these reasons.

Two principal causes were identified in 8.2% of cases and three in 0.6%. In the preterm labor group, 3% of the women had hypertensive disorders and 3.4% suspected fetal growth restriction. In the preterm PROM group, 2% had hypertensive disorders and 5% suspected fetal growth restriction. Among the women in both hypertensive disorder groups, 4% had preterm labor and 3% preterm PROM. Of the women with fetal growth restriction without hypertensive disorders, 4% had preterm labor and 7% preterm PROM.

Gestational age refers to completed weeks of gestation and was the best estimate based on the date of the last menstrual period and an early prenatal ultrasonogram. Births before 24 weeks of gestation were not included because causes associated with preterm delivery before 24 weeks of gestation differ from those in the 24- to 34-week period, because there are usually no cesarean deliveries for suspected fetal growth restriction before 24 weeks of gestation in France.

The following factors were studied: social and demographic characteristics (maternal age, parity, country of birth, mother's health insurance coverage, marital status, and smoking), fetal sex, antenatal corticosteroid therapy, and being inborn, defined by birth in a level 3 establishment at a gestational age less than 32 weeks of gestation and in a level 2 or 3 facility at 32–34 weeks of gestation.

Categorical variables were compared with the χ^2 test or Fisher exact test, as appropriate. For continuous outcomes, data were analyzed with *t* tests for normally distributed variables and Wilcoxon or Kruskal-Wallis tests for nonnormally distributed variables, as appropriate. Descriptive statistics and bivariate tests were weighted according to the duration of the inclusion period because it varied with gestational age at birth to enable inclusion of sufficient numbers of births in each gestational age category (Fig. 1; Table 1).[7] This weighting was not necessary for the multivariable analysis, which included gestational age.[10] Weighted data are designated with an asterisk.

The independent effect of the cause of preterm birth on the risk of in-hospital mortality was tested and quantified with a two-level multivariable logistic

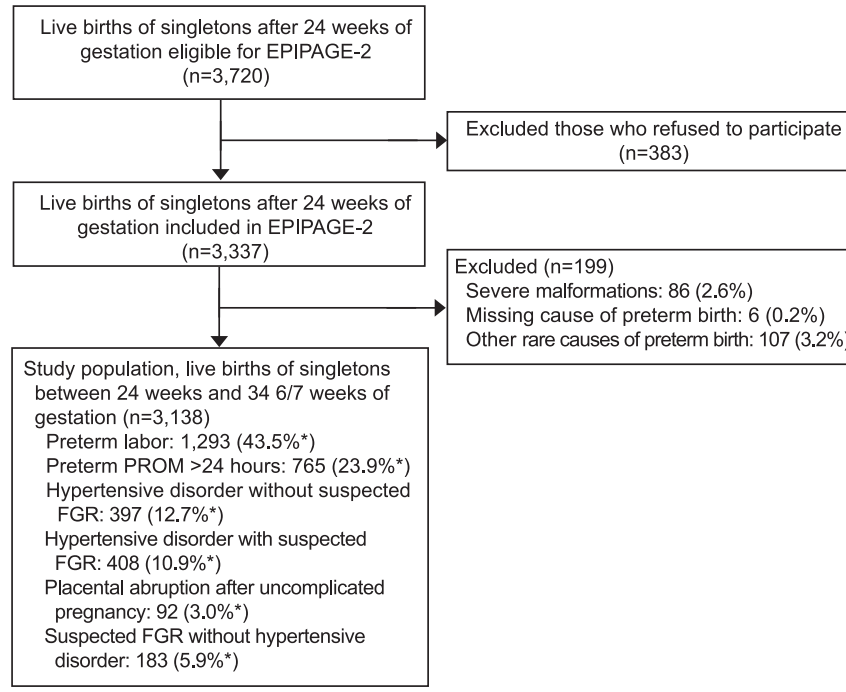

Fig. 1. Flowchart. *Weighted according to the recruitment period. PROM, premature rupture of membranes; FGR, fetal growth restriction. *Delorme. Cause of Preterm Birth and Newborn Mortality. Obstet Gynecol 2016.*

regression and a random intercept to take into account the hierarchical structure of the data with women clustered in maternity units. We tested for possible interactions among the causes of preterm birth and gestational age.

A first model including gestational age only was used to analyze the effect of the cause of preterm birth (model 1). We then built a model (model 2) by including all potential prognostic factors of newborn death identified from the literature (mother's age and place of birth, parity, health insurance, living with a partner, smoking, fetal sex, antenatal steroids, inborn status, and gestational age).

There were no missing values for gestational age, birth weight, inborn status, newborn vital status, or maternal age. All participants were included, regardless of missing data for social, demographic, or obstetric characteristics; multivariate analysis included a categorical variable for missing responses (missing data indicator). The missing value rate was 1% for previous deliveries, 5% for geographic origin, 8.9% for health insurance, 4% for living with partner, 3% for smoking status, 0.1% for fetal sex, and 1.8% for antenatal steroids.

We used Stata 12 for all analyses.

RESULTS

Figure 1 presents the flowchart culminating in the 3,138 births included in the analysis. The data for these births come from 328 maternity units, each contributing from 1 to 82 deliveries with a mean of 9.5 births per facility.

Preterm labor was the principal cause of delivery in 43.5%* (*the percentages weighted according to duration of recruitment period) of the cases (95% confidence interval [CI] 41.1–45.9%) and preterm PROM in 23.9%* (95% CI 21.9–26.0%). The cause of delivery was a hypertensive disorder without antenatally suspected fetal growth restriction in 12.7%* (95% CI 11.2–14.4%) and with it in 10.9%* (95% CI 9.6–12.4%), placental abruption after uncomplicated pregnancy in 3.0%* (95% CI 2.3–3.9%), and suspected fetal growth restriction without hypertensive disorders in 5.9%* (95% CI 4.9–7.2%) (Fig. 1). Among the 591 preterm births resulting from suspected fetal growth restriction with or without any hypertensive disorders, the main reasons for delivery were fetal heart rate abnormalities (21%), abnormal Doppler (15%), arrested growth diagnosed from the growth curve (7%), mother's health (18%) (in the hypertensive disorder group only), and most often (38%) a combination of factors related to fetal heart rate, Doppler flow, and arrested growth.

Gestational age was not normally distributed among the groups of causes. Median gestational age differed significantly for the different causes of preterm birth ($P \leq .001$) as did the gestational age distribution ($P < .001$): groups with hypertensive disorders

Table 1. Characteristics of Preterm Births by Main Cause of Preterm Birth

Characteristics	Preterm Labor (n=1,293)	Preterm PROM Greater Than 24 h (n=765)	Hypertensive Disorder Without Suspected FGR (n=397)	Hypertensive Disorder With Suspected FGR (n=408)	Placental Abruption After Uncomplicated Pregnancy (n=92)	Suspected FGR Without Hypertensive Disorder (n=183)	*P*
Social and epidemiologic*							
Mother's age (y)							.06
Younger than 20	4 (3–6)	3 (2–5)	4 (2–8)	3 (2–7)	2 (1–6)	5 (2–13)	
20–35	78 (75–81)	74 (69–78)	75 (69–80)	68 (61–73)	85 (73–91)	74 (65–82)	
Older than 35	18 (15–21)	23 (19–27)	21 (16–27)	29 (23–36)	13 (7–24)	21 (14–29)	
Parity							**<.01**
0	52 (49–56)	46 (41–51)	57 (51–64)	58 (52–65)	35 (23–49)	52 (43–62)	
1	26 (22–29)	30 (25–34)	19 (14–25)	17 (12–22)	25 (16–38)	28 (19–37)	
2 or more	22 (19–25)	24 (20–28)	24 (18–30)	25 (20–32)	40 (27–55)	20 (13–29)	
Mother's place of birth							.15
Europe	83 (80–85)	79 (74–83)	76 (69–81)	82 (76–86)	96 (91–98)	83 (74–89)	
Northern Africa	7 (5–9)	7 (5–10)	8 (5–13)	6 (4–10)	1.5 (0.5–5)	5 (2–10)	
Other Africa	6 (5–8)	9 (6–12)	9 (6–14)	8 (5–11)	0.5 (0–4)	6 (3–13)	
Other	4 (3–6)	5 (4–8)	7 (4–11)	4 (3–7)	2 (1–6)	6 (3–14)	
National health insurance							.52
Yes	87 (84–89)	84.5 (80–88)	86 (81–90)	86.2 (80–91)	88 (74–95)	92.7 (86–96)	
Complementary universal health insurance	12 (10–15)	15 (12–19)	13 (9–18)	13.5 (9–19)	12 (5–26)	7 (3–14)	
No	1 (0.3–1)	0.5 (0.2–1)	1 (0.4–4)	0.3 (0–1.4)	0	0.3 (0–2)	
Lives with a partner							.32
Yes	89 (86–91)	88 (84–91)	91 (86–95)	89 (83–92)	94 (83–98)	83 (74–90)	
No	11 (9–13)	12 (9–16)	9 (5–14)	11 (7–17)	6 (2–17)	17 (10–26)	
Smoking during pregnancy							**<.001**
Yes	22 (19–25)	28 (24–32)	11 (8–16)	23 (17–29)	51 (37–64)	40 (30–49)	
No	78 (75–81)	72 (68–76)	89 (84–92)	77 (70–83)	49 (36–63)	60 (51–70)	
Obstetric*							
Birth weight (g)	1,865±577	1,772±546	1,604±485	1,210±377	1,754±470	1,254±367	**<.01**
Gestational age (wk)*							**<.001**
24–28	18 (16–19)	18 (16–21)	11 (9–14)	19 (16–23)	17 (11–24)	14 (10–19)	
29–32	28 (25–31)	30 (26–34)	45 (38–51)	44 (38–50)	36 (23–46)	41 (31–50)	
33–34	54 (51–58)	52 (47–56)	44 (37–51)	37 (30–44)	47 (36–63)	45 (36–56)	
Fetal sex							**<.01**
Male	58 (55–62)	58 (53–62)	51 (44–58)	45 (38–52)	67 (53–78)	48 (39–58)	
Female	42 (38–45)	42 (38–48)	49 (42–56)	55 (48–62)	33 (21–47)	52 (42–61)	
Antenatal steroids							**<.001**
Yes	63 (59–67)	83 (78–87)	77 (70–82)	85 (79–90)	23 (14–34)	91 (83–95)	
No	37 (33–40)	17 (14–22)	23 (18–30)	15 (10–21)	77 (66–86)	9 (5–17)	
Inborn							**<.001**
Yes	78 (75–81)	86 (83–89)	83 (78–87)	85 (80–88)	63 (50–75)	88 (82–92)	
No	22 (19–24)	14 (11–17)	17 (13–22)	15 (12–19)	37 (25–50)	12 (8–17)	

PROM, premature rupture of membranes; FGR, fetal growth restriction.
Data are % (95% confidence interval) or mean±standard deviation unless otherwise specified.
Bold indicates significance ($P<.005$).
There were missing data for previous deliveries: 1%, geographic origin: 5%, medical insurance: 8.9%, living with partner: 4%, smoking status: 3%, fetal sex: 0.1%, antenatal steroids: 1.8%.
* Weighted according to differential recruitment.

had higher rates of births between 29 and 32 weeks of gestation as did the preterm labor and preterm PROM groups between 33 and 34 weeks of gestation (Table 1).

In-hospital mortality was 5.0% (95% CI 4.5–5.7%) and was strongly associated with gestational age at birth (Fig. 2): 71.5% at 24 weeks of gestation, 39.0% at 25 weeks of gestation, 25.5% at 26 weeks of

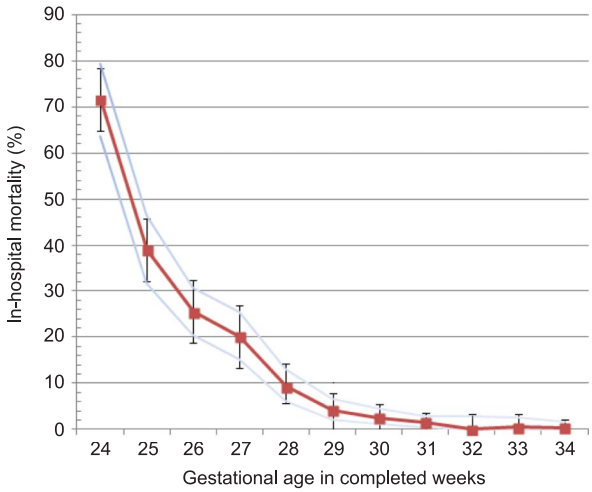

Fig. 2. In-hospital mortality for overall population by gestational age with 95% confidence intervals.

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gestation, and less than 5% from 29 weeks of gestation. Twenty-four (6.4%) neonates died in the first 24 hours after birth, 92 (27.6%) from day 1 to day 7 after birth, 90 (27.7%) from day 8 to day 28, and 143 (38.3%) after day 28. The median date of death overall was day 9 (interquartile range 4–20); for preterm labor it was day 9 (interquartile range 4–18), for preterm PROM day 14 (interquartile range 4–27), for hypertensive disorders without fetal growth restriction day 7 (interquartile range 3–12), with fetal growth restriction day 8 (interquartile range 4–19), for placental abruption day 5 (interquartile range 3–7), and for isolated fetal growth restriction day 9 (interquartile range 4–31).

Cause of preterm birth was associated with in-hospital mortality (P=.01) in the bivariate analysis. The highest crude mortality rate (7.3%) was observed for the group with both hypertensive disorders and fetal growth restriction and the lowest for the group with hypertensive disorders without fetal growth restriction (2.4%, crude odds ratio [OR] 0.4, 95% CI 0.2–0.9).

After adjustment for gestational age and individual characteristics (model 2), the odds of in-hospital mortality tripled in the group with fetal growth restriction and hypertensive disorders (7.3%, adjusted OR 3.0, 95% CI 1.9–4.7) and doubled in the isolated fetal growth restriction group (3.3%, adjusted OR 2.3, 95% CI 1.1–4.6) compared with the preterm labor group.

A sensitivity analysis excluding births between 32 and 34 weeks of gestation because of their low mortality rate (0.3%) showed the same results (mortality 12.4%, adjusted OR 2.9, 95% CI 1.8–4.6 for fetal growth restriction with hypertensive disorders and 8.3%, adjusted OR 2.3, 95% CI 1.1–4.7 for isolated fetal growth restriction). To investigate the effect of suspected fetal growth restriction across gestational age, we performed 2-level logistic regressions with all the adjustment factors used in model 2 for neonates born between 24 and 28 weeks of gestation and neonates born between 29 and 32 weeks of gestation. The order of magnitude of the odds ratios did not change.

The fetal growth restriction groups had the highest rate of the following prenatal factors: antenatal corticosteroids (85% with and 91% without hypertensive disorder), inborn births (85% and 88%), and female fetal sex (55% and 52%). The fetal growth restriction groups were associated with high mortality rates despite their association with these prenatal factors favorably linked to reduced in-hospital mortality (Table 2, models 1 and 2). In-hospital mortality among neonates born because of suspected fetal growth restriction was 5.9% (95% CI 4.2–7.7%) (Fig. 3): 100% at 24 weeks of gestation (one case), 37.5% at 25 weeks of gestation, 38% at 26 weeks of gestation, 32.7% at 27 weeks of gestation, and less than 5% after 29 weeks of gestation.

In-hospital mortality for the preterm PROM and preterm labor groups was 5.3% (95% CI 4.6–6.0%), 72% at 24 weeks of gestation (one case), 38% at 25 weeks of gestation, 23.6% at 26 weeks of gestation, 14.6% at 27 weeks of gestation, and less than 5% after 29 weeks of gestation.

Finally, mortality associated with deliveries resulting from preterm PROM (5.3%, adjusted OR 1.3, 95% CI 0.9–1.9), hypertensive disorders without fetal growth restriction (2.4%, adjusted OR 0.7 [0.4–1.4]), or placental abruption (6%, adjusted OR 1.6, 95% CI 0.7–3.7) was not significantly different from in-hospital mortality after preterm labor (5.2%) after adjustment.

DISCUSSION

After known patient and care prognostic factors were taken into account, suspected fetal growth restriction with or without hypertensive disorders was the only cause of preterm delivery associated with an excess risk of neonatal death. Preterm births caused by preterm PROM, preeclampsia, or isolated placental abruption were associated with a risk of in-hospital death similar to that for preterm labor. These results should improve information provided to parents and decision-making in both prenatal and postnatal management.

Table 2. Associations Between the Main Cause of Preterm Birth and In-Hospital Mortality

Main Cause Leading to Preterm Birth	n	In-Hospital Mortality*	*P*	Bivariate Analysis*		Model 1†		Model 2‡	
				OR	95% CI	aOR	95% CI	aOR	95% CI
Preterm labor	1,293	168 (5.2)	**.01**	1	Referent	1	Referent	1	Referent
Preterm PROM greater than 24 h	765	93 (5.4)		1	0.8–1.4	1.1	0.8–1.6	1.3	0.9–1.9
Hypertensive disorder without suspected FGR	397	16 (2.4)		**0.4**	**0.2–0.9**	0.7	0.4–1.2	0.7	0.4–1.4
Hypertensive disorder with suspected FGR	408	47 (7.3)		1.4	0.9–2.1	**2.2**	**1.4–3.4**	**3.0**	**1.9–4.7**
Placental abruption after uncomplicated pregnancy	92	12 (6.0)		1.1	0.6–2.2	**2.2**	**1.0–4.9**	1.6	0.7–3.7
Suspected FGR without hypertensive disorder	183	13 (3.3)		0.6	0.3–1.1	1.7	0.9–3.3	**2.3**	**1.1–4.6**
Social and epidemiologic characteristics									
Mother's age (y)			**.01**						
20/35	2,324	246 (4.7)		1	Referent	1	Referent	1	Referent
Younger than 20	146	24 (9.2)		**2.1**	**1.3–3.4**	1.6	0.9–2.9	1.5	0.8–2.9
Older than 35	668	79 (5.7)		1.2	0.9–1.7	1.3	0.9–1.8	1.2	0.9–1.7
Parity			.65						
0	1,610	178 (5.1)		1	Referent	1	Referent	1	Referent
1	766	92 (5.3)		1.0	0.8–1.4	1.3	0.9–1.7	1.3	0.9–1.9
2 or more	728	75 (4.6)		0.9	0.6–1.2	1.1	0.8–1.6	1.1	0.7–1.6
Mother's place of birth			.2						
Europe	2,348	244 (4.6)		1	Referent	1	Referent	1	Referent
Northern Africa	206	21 (4.8)		1.0	0.6–1.7	0.9	0.5–1.7	0.8	0.5–1.5
Other Africa	241	35 (7.0)		1.5	1.0–2.3	1.0	0.6–1.6	0.9	0.5–1.5
Other	158	17 (4.9)		1.1	0.6–1.8	0.9	0.5–1.7	0.6	0.3–1.3
National health insurance			**.04**						
Yes	2,432	251 (4.6)		1	Referent	1	Referent	1	Referent
Complementary universal health insurance	366	42 (5.0)		1.1	0.7–1.6	0.9	0.6–1.4	0.9	0.6–1.5
No	27	6 (14.3)		**3.4**	**1.2–9.3**	1.6	0.5–5.0	1.7	0.5–5.8
Lives with a partner									
No	2,629	284 (4.9)	.6	1	Referent	1	Referent	1	Referent
Yes	338	41 (5.4)		1.1	0.8–1.6	0.9	0.6–1.4	0.8	0.5–1.3
Smoking during pregnancy									
No	2,278	256 (5.1)	.73	1	Referent	1	Referent	1	Referent
Yes	757	80 (4.8)		0.9	0.7–1.3	1	0.7–1.3	0.9	0.6–1.2
Obstetric characteristics									
Fetal sex									
Female	1,437	145 (4.4)	.34	1	Referent	1	Referent	1	Referent
Male	1,699	203 (5.5)		1.1	0.9–1.4	**1.4**	**1.1–1.8**	**1.6**	**1.2–2.1**
Antenatal steroids									
No	700	125 (6.6)	**.001**	1	Referent	1	Referent	1	Referent
Yes	2,374	211 (4.3)		**0.6**	**0.5–0.8**	**0.4**	**0.3–0.6**	**0.4**	**0.3–0.5**
Inborn									
No	1,059	153 (9.2)	**<.001**	1	Referent	1	Referent	1	Referent
Yes	2,079	196 (3.7)		**0.4**	**0.3–0.5**	0.9	0.6–1.2	0.9	0.7–1.4

PROM, premature rupture of membranes; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; FGR, fetal growth restriction.
Data are n (%) unless otherwise specified.
Bold indicates significance ($P<.005$).
* Weighted according to differential recruitment.
† Adjusted for gestational age, mixed effects logistic regression.
‡ Adjusted for gestational age, maternal and obstetric characteristics, mixed effects logistic regression.

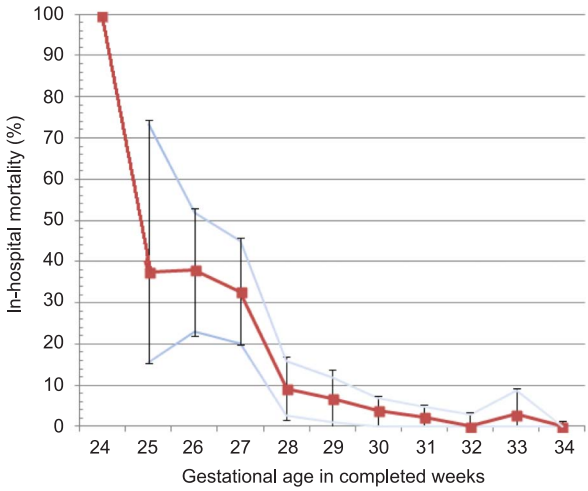

Fig. 3. In-hospital mortality for suspected fetal growth restriction population by gestational age with 95% confidence intervals.

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EPIPAGE-2 is a prospective nationwide cohort study with a 93% participation rate and low rates of missing data.[7,9] The prenatal questionnaire was designed to allow us to study the principal causes of these births. The multilevel analysis enabled us to take into account the nonindependence of data for women treated at the same hospital. Moreover, sample size provided statistical power of 98% and 92% to detect an OR of 2 for the effect of preterm PROM and hypertensive disorders, respectively. Few prospective studies in the general population have analyzed the prenatal factors associated with the death of preterm neonates.[11–13] Only one population-based study including 2,085 singletons studied the cause of the preterm deliveries and found a higher rate of newborn mortality, after adjustment for gestational age, in the "placentation disorders group" including fetal growth restriction, maternal hypertension, and preeclampsia (adjusted OR 1.4, 95% CI 1.0–2.0).[14] This finding does not contradict ours that suspected fetal growth restriction is the main causal factor associated with higher mortality because their placentation disorders group included fetal growth restriction cases. Moreover, our results show that hypertensive disorder do not increase newborn mortality as long as there is no fetal growth restriction.

A standard approach for taking the cause of preterm birth into account in assessing the child's prognosis distinguishes spontaneous from induced deliveries.[15–18] Reviewing the papers using these categories, however, shows clearly that these terms are neither well defined nor consistently used and that the studies mostly fail to take confounding factors into account completely or even at all.[17,19,20] However, the most important flaw is that this classification is not based on the diseases responsible for the preterm birth; depending on the clinical circumstances, the same cause is found in both groups. Thus, preterm PROM can cause preterm delivery either after spontaneous labor or after a cesarean delivery before labor for chorioamnionitis.

Most studies show an excess risk of mortality associated with fetal growth restriction,[21–26] defined postnatally by birth weight below the 10th percentile. Comparison groups for small-for-gestational-age births often bring together all other preterm neonates, regardless of cause. Two authors have reported an association between antenatally suspected fetal growth restriction and excess mortality[27,28] but without examining the cause of preterm birth.

Because the EPIPAGE-2 study was observational and nationwide, its external validity is high. Practices may nonetheless vary between hospitals, especially the criteria used to decide on an intervention to deliver because of fetal growth restriction.

Unlike other studies, mostly retrospective,[17,29] we did not find a higher risk of in-hospital mortality in cases of preterm PROM compared with preterm labor or indeed with all other causes of preterm birth. The comparison with the preterm labor group thus does not explain this absence of excess risk. Distinguishing preterm labor from preterm PROM can be difficult in retrospective studies. The diagnosis of preterm PROM can be questionable given the lack of certainty that membrane rupture preceded the onset of labor. We chose a minimum cutoff of 24 hours between rupture and delivery to define preterm PROM, as in the Extremely premature infants Cure (EPICure; please see http://www.epicure.ac.uk) cohort.[11]

The absence of an association between mortality and placental abruption may appear surprising. One explanation might be that only neonates born alive were included in this study and that most fetal deaths from this cause occur in utero or per partum. In a large series of similar cases, Salihu et al[30] found that in utero mortality (8.3%) was twice as high as neonatal mortality (4.2%). The small number of patients in the placental abruption group might also explain this lack of significance: our power to detect an OR of 2 for placental abruption compared with the preterm labor group was only 50%.

The odds of in-hospital death after preterm delivery for suspected fetal growth restriction with or without hypertensive disorders are triple those of

born because of preterm labor, whereas odds for preterm births caused by preterm PROM, hypertensive disorder without suspected fetal growth restriction, or isolated placental abruption were similar to that for preterm labor. This information should be used before birth for advising parents and in the decision-making process. A similar analysis of these children's short- and long-term morbidity might provide a better evaluation of their prognosis.

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