Placental Complications and Bronchopulmonary Dysplasia: EPIPAGE-2 Cohort Study

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abstract

OBJECTIVE: To investigate the relationship between placenta-mediated pregnancy complications and bronchopulmonary dysplasia (BPD) in very preterm infants.

METHODS: National prospective population-based cohort study including 2697 singletons born before 32 weeks' gestation. The main outcome measure was moderate to severe BPD. Three groups of placenta-mediated pregnancy complications were compared with no placenta-mediated complications: maternal disorders only (gestational hypertension or preeclampsia), fetal disorders only (antenatal growth restriction), and both maternal and fetal disorders.

RESULTS: Moderate to severe BPD rates were 8% in infants from pregnancies with maternal disorders, 15% from both maternal and fetal disorders, 23% from fetal disorders only, and 9% in the control group ($P < .001$). When we adjusted for gestational age, the risk of moderate to severe BPD was greater in the groups with fetal disorders only (odds ratio [OR] = 6.6; 95% confidence interval [CI], 4.1–10.7), with maternal and fetal disorders (OR = 3.7; 95% CI, 2.5–5.5), and with maternal disorders only (OR = 1.7; 95% CI, 1.0–2.7) than in the control group. When we also controlled for birth weight, the relationship remained in groups with fetal disorders only (OR = 4.2; 95% CI, 2.1–8.6) and with maternal and fetal disorders (OR = 2.1; 95% CI, 1.1–3.9).

CONCLUSIONS: Placenta-mediated pregnancy complications with fetal consequences are associated with moderate to severe BPD in very preterm infants independently of gestational age and birth weight, but isolated maternal hypertensive disorders are not. Fetal growth restriction, more than birth weight, could predispose to impaired lung development.

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Dr Torchin carried out the analyses and drafted the initial manuscript; Dr Ancel designed the EPIPAGE-2 study, coordinated and supervised data collection, supervised the analyses, and reviewed and revised the manuscript; Dr Goffinet designed the data collection instruments, participated in analysis interpretation, and reviewed and revised the manuscript; Drs Hascoët and Truffert designed the data collection instruments and critically reviewed the manuscript; Ms Tran supervised the database as data manager of the EPIPAGE-2 study and critically reviewed the manuscript; Dr Lebeaux coordinated data collection and critically reviewed the manuscript; Dr Jarreau conceptualized this study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

WHAT'S KNOWN ON THIS SUBJECT: Low gestational age and low birth weight for gestational age are known risk factors for bronchopulmonary dysplasia. Whether placenta-mediated pregnancy complications are related to bronchopulmonary dysplasia in preterm infants is debated.

WHAT THIS STUDY ADDS: Placenta-mediated complications with fetal consequences are associated with bronchopulmonary dysplasia in very preterm infants, but isolated maternal hypertensive disorders are not. Fetal growth restriction could play a role in impaired lung development independently of birth weight.

To cite: Torchin H, Ancel P, Goffinet F, et al. Placental Complications and Bronchopulmonary Dysplasia: EPIPAGE-2 Cohort Study. *Pediatrics*. 2016;137(3):e20152163

Bronchopulmonary dysplasia (BPD), which seems to result from a disrupted alveolar and vascular development in lungs,^{1,2} remains a common complication of very premature birth with short- and long-term morbidity. Children with BPD experience more respiratory disorders during childhood³ and have poorer lung function as adults⁴ compared with those without BPD; BPD is also associated with poor neurodevelopmental outcome.⁵

BPD is strongly associated with low gestational age at birth^{6–8} and low birth weight for gestational age.^{9–12} Mechanical ventilation, oxygen therapy, patent ductus arteriosus, neonatal infection, male gender, and genetic factors are other risk factors.^{10,13,14} Moreover, placenta-mediated pregnancy complications were recently suggested to be associated with BPD. These include maternal disorders resulting from placental dysfunction such as gestational hypertension and preeclampsia and fetal disorders such as fetal growth restriction (FGR), which can occur without maternal hypertension.¹⁵ Maternal blood levels of antiangiogenic factors arising from the placenta are increased in these disorders.^{16–18} The current paradigm suggests that imbalanced circulating proangiogenic and antiangiogenic factors could impair vasculogenesis in fetal lungs, which may lead to general disorders in lung development.^{2,19,20} However, results are conflicting regarding the relationship between placenta-mediated pregnancy complications and BPD. Some studies found an association with BPD,^{21–23} but others did not.^{10,24,25} Most studies focused on maternal disorders but did not look at fetal consequences of placenta-mediated pregnancy complications.

This study aimed to determine whether placenta-mediated pregnancy complications are associated with BPD in a cohort

FIGURE 1
Study participant flowchart.

of very preterm infants. We characterized pregnancies according to maternal and fetal clinical features of placental dysfunction. We speculated that placenta-mediated pregnancy complications would increase the risk of BPD and that it would be highest when mothers and fetuses both had clinical repercussions of placental dysfunction.

METHODS

Study Population

This study included the 2697 singletons born alive between 22 and 31 completed weeks of gestation from the EPIPAGE-2 cohort, a prospective population-based study conducted in 25 regions in France in 2011 that included all deliveries from 22 to 31 completed weeks of gestation and a sample of births from 32 to 34 weeks. The EPIPAGE-2 study was approved by the National Data Protection Authority and ethics committees (Comité Consultatif sur le traitement de l'information en matière de recherche, Comité de

Protection des Personnes Ile-de-France); details about the design and methods have been described elsewhere.²⁶

Multiple pregnancies were excluded, as were birth defects that can lead to respiratory disorders (severe congenital heart diseases, tracheal and lung defects, esophageal atresia, congenital diaphragmatic hernia, congenital myopathies, $n = 25$) and chromosomal aberrations, congenital toxoplasmosis, and congenital cytomegalovirus infections ($n = 15$), which can alter fetal growth regardless of placental function. BPD status was unavailable for 68 of the 2193 infants alive at 36 weeks' postmenstrual age (PMA); placenta-mediated pregnancy complications could not be affirmed for 14 of the remaining children. As a result, we had data on placenta-mediated pregnancy complications and BPD for 2111 infants (Fig 1).

Bronchopulmonary Dysplasia

Moderate to severe BPD was defined as oxygen requirement for a minimum of 28 days and persistent need for oxygen or

ventilatory support at 36 weeks' PMA (mechanical ventilation or positive pressure).²⁷

Placenta-Mediated Pregnancy Complications

Pregnancy complications were prospectively collected in the EPIPAGE-2 study. Gestational hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg occurring after gestational week 20, preeclampsia was defined as gestational hypertension with proteinuria ≥ 0.3 g for 24 hours; and eclampsia was defined as preeclampsia with seizures during pregnancy or shortly after delivery. Chronic hypertension without preeclampsia was not considered as a placenta-mediated complication. Antenatal-suspected FGR was defined as an estimated fetal weight < 10 th percentile (according to the care provider reference curve) with ≥ 1 of the following: abnormal fetal Doppler findings (reduced, absent, or reversed umbilical artery end-diastolic flow; increased middle cerebral artery end-diastolic flow or cerebral redistribution process; reduced, absent, or reversed atrial flow in the ductus venosus), growth arrest, gestational hypertension, or preeclampsia. Growth arrest with abnormal fetal Doppler findings was considered suspected FGR regardless of the estimated fetal weight.

Four mutually exclusive groups of placenta-mediated pregnancy complications were identified: maternal disorders only (gestational hypertension, preeclampsia, HELLP syndrome [hemolysis, elevated liver enzymes, and low platelet count], or eclampsia without antenatal-suspected FGR); fetal disorders only (antenatal-suspected FGR without maternal disorders); maternal and fetal disorders (maternal disorders with antenatal-suspected FGR); and control group (none of these vascular disorders). This group included

mainly women who delivered after idiopathic preterm labor, preterm premature rupture of membranes, chorioamnionitis, and hemorrhage.

Maternal and Newborn Characteristics

Data on maternal characteristics (age, BMI, parity, smoking status, chronic conditions) and pregnancy events (gestational diabetes, placental abruption, cesarean delivery) were extracted from medical records. Antenatal corticosteroids were considered administered if the mother received ≥ 1 injection before delivery.

Gestational age in completed weeks was assigned by the best available obstetric estimate combining the first trimester ultrasonography and the date of the last menstrual period. Birth weight was expressed as percentiles and z scores from Gardosi's intrauterine growth curves corrected for gender and gestational age.²⁸ Patent ductus arteriosus was diagnosed by clinical signs and echocardiographic findings. Neonatal infections were defined by ≥ 1 positive blood culture for common pathogens or ≥ 2 positive blood cultures for coagulase-negative staphylococci. Necrotizing enterocolitis was diagnosed as Bell's stage ≥ 2 .²⁹ Severe cerebral lesions consisted of intraventricular hemorrhage with ventricular dilatation, parenchymal hemorrhage, and periventricular leukomalacia.

Statistical Analysis

Categorical variables were compared by χ^2 tests. Continuous variables are summarized as medians and interquartile ranges (IQRs) and were compared by rank-sum tests. Recruitment lasted 8 months for infants born at 22 to 26 weeks' gestation and 6 months for those born at 27 to 31 weeks; percentages, medians, and crude odds ratios (ORs) were weighted accordingly.²⁶

Analyzed and nonanalyzed infants were compared for the main variables.

Associations between placenta-mediated pregnancy complications and moderate to severe BPD were first analyzed by bivariate analyses. Potential confounding factors were identified as characteristics associated with moderate to severe BPD in our sample (*P* value adjusted on gestational age $\leq .20$) or as relevant factors from the literature. Associations between placenta-mediated pregnancy complications and moderate to severe BPD were then analyzed by multivariate logistic regression: model A, adjusted for gestational age because it is the main predictor of BPD; model B, additionally adjusted for antenatal potential confounders; model C, birth weight z score introduced into the logistic model as a continuous variable to better understand its role in these associations; and model D, postnatal events included in the final model. Because most of neonatal respiratory variables are strongly associated with BPD, they were not introduced in multivariate analyses to avoid overadjustment. Results are reported as ORs with 95% confidence intervals (CIs). Significance was set at *P* $\leq .05$.

Because the effect of other causes of preterm birth on BPD risk is still controversial, we tested the final model with a smaller control group restricted to the 398 neonates born after spontaneous preterm labor without preterm premature rupture of membranes, chorioamnionitis, or maternal hemorrhage.

Statistical analyses involved use of SAS version 9.3 software (SAS Institute, Inc, Cary, NC).

RESULTS

Among infants born alive at 22 and 23 weeks' gestation, all except 1 died before 36 weeks' PMA.

Overall, 445 out of 2638 (14.7%) liveborn infants without congenital defects or congenital infections died before 36 weeks' PMA (Table 1). The in-hospital mortality rates ranged from 6.3% to 17.8% according to pregnancy complication groups. Mortality rates adjusted on gestational age did not differ significantly between the 4 groups.

Table 2 summarizes maternal and neonatal characteristics by placenta-mediated pregnancy complications. Median gestational age was lowest in the control group (29.6 weeks' gestation) as compared with the groups with maternal or fetal disorders (30.1 weeks' gestation, $P < .001$). As expected, birth weight for gestational age was lower in both groups of placenta-mediated complications with antenatal-suspected FGR as compared with the group with maternal disorders only and the control group ($P < .001$). Fetal gender, maternal BMI, parity, smoking during pregnancy, diabetes, administration of antenatal steroids, cesarean

TABLE 1 Mortality Before 36 wk PMA by Placenta-Mediated Pregnancy Complications Among Liveborn Singletons Without Congenital Defects or Infections

	Mortality Before 36 wk PMA					<i>P</i>
	<i>n/N</i>	%	<i>P</i>	OR ^a	95% CI	
Total	445/2638	14.7				
Placenta-mediated complications			<.001			.07
None	356/1738	17.8		1		
Maternal disorders only	23/319	6.3		0.7	0.4–1.2	
Fetal disorders only	20/187	10.0		1.5	0.9–2.6	
Maternal and fetal disorders	42/376	10.4		1.4	1.0–2.1	
Not classified	4/18					

Percentages are weighted by recruitment period.

^a ORs adjusted for gestational age.

deliveries, and place of birth also differed between the 4 groups.

In total, 259 out of 2111 infants (11.1%) showed moderate to severe BPD (Table 3). The rates of moderate to severe BPD decreased from 64.7% at 23 to 24 weeks' gestation to 3.2% at 31 weeks' gestation ($P < .001$). These rates depended on birth weight for gestational age: 14.7% for infants with a birth weight <10th percentile, 11.5% for those in the 10th to 25th percentile, and 9.0% for those in the 25th to 75th percentile ($P = .002$). The proportion of infants with moderate

to severe BPD differed according to placenta-mediated pregnancy complication groups: 8.3% in the group with maternal disorders only, 22.5% in the group with fetal disorders only, 15.4% in the group with maternal and fetal disorders, and 9.2% in the control group ($P < .001$).

Perinatal characteristics of infants with and without moderate to severe BPD are compared in Table 4. The proportion of cesarean deliveries, patent ductus arteriosus, and neonatal infections (adjusted for gestational age) was higher among

TABLE 2 Maternal and Neonatal Characteristics by Placenta-Mediated Complications

	None (Control Group) (<i>N</i> = 1343)		Maternal Disorders Only (<i>N</i> = 287)		Fetal Disorders Only (<i>N</i> = 163)		Maternal and Fetal Disorders (<i>N</i> = 318)		<i>P</i>
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	
Gestational age, wk	29.6	27.7; 30.9	30.1	28.9; 31.1	30.1	28.6; 31.0	30.1	28.6; 31.1	<.001
Birth wt, g	1330	1060; 1595	1200	1000; 1390	920	750; 1125	999	815; 1150	<.001
Birth wt for gestational age, z score	0.2	−0.4; 1.0	−1.2	−1.9; −0.4	−3.0	−3.6; −2.2	−2.6	−3.3; −1.9	<.001
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>P</i>
Male gender	759	56.6	132	46.1	82	50.7	142	44.9	<.001
Maternal age, y									.07
<25	305	22.5	52	18.3	31	19.3	68	21.2	
25–30	440	32.7	86	29.4	58	35.5	88	27.9	
30–35	338	25.5	77	26.9	38	23.3	76	23.8	
≥35	260	19.3	72	25.4	36	21.9	86	27.1	
Maternal BMI									<.001
<18.5	131	10.2	9	3.3	21	12.9	9	3.0	
18.5–25	760	59.1	135	49.6	96	60.9	142	46.5	
25–30	232	18.1	60	22.1	27	16.9	80	26.4	
≥30	163	12.6	67	25.0	15	9.3	74	24.1	
Nulliparity	666	49.2	161	55.8	90	55.7	205	64.4	<.001
Smoking during pregnancy	402	30.5	45	16.3	77	47.7	56	18.0	<.001
Preexisting diabetes	19	1.5	10	3.6	6	3.8	7	2.3	.05
Antenatal steroids (≥1 dose)	1045	79.2	236	83.9	149	92.4	284	90.7	<.001
Cesarean delivery	627	47.7	276	96.5	152	93.3	312	99.3	<.001
Level 3 maternity unit	1094	81.3	253	88.1	151	92.7	292	91.6	<.001

Percentages are weighted by recruitment period. Missing data <5% for each variable.

TABLE 3 Associations Between Gestational Age, Birth wt for Gestational Age, Placenta-Mediated Pregnancy Complications, and Moderate to Severe BPD

	Moderate to Severe BPD at 36 wk PMA		<i>P</i>
	<i>n/N</i>	%	
Total	259/2111	11.1	
Gestational age, wk			<.001
23–24	22/34	64.7	
25	42/106	39.6	
26	70/208	33.7	
27	38/197	19.3	
28	32/271	11.8	
29	18/326	5.5	
30	20/440	4.5	
31	17/529	3.2	
Birth wt for gestational age (percentiles) ^a			.002
<10	105/673	14.7	
10–25	29/235	11.5	
25–75	73/707	9.0	
75–90	19/219	7.5	
≥90	33/277	10.2	
Placenta-mediated complications			<.001
None	142/1343	9.2	
Maternal disorders only	27/287	8.3	
Fetal disorders only	38/163	22.5	
Maternal and fetal disorders	52/318	15.4	

Percentages are weighted by recruitment period.

^a Birth wt is expressed as percentiles from Gardosi's intrauterine growth curves corrected for gender and gestational age.

children with moderate to severe BPD than those with no or mild BPD. Concerning respiratory variables, children with moderate to severe BPD more often received surfactant and, as expected, postnatal steroids.

Table 5 presents the results of multivariate analyses. The association with moderate to severe BPD was significant for all 3 placenta-mediated complication groups when we controlled for gestational age (model A). ORs were only slightly modified after adjustment for maternal characteristics, pregnancy events, and pregnancy management variables (model B). By contrast, controlling for birth weight *z* score decreased the ORs (model C). Additional adjustment on postnatal events (ie, patent ductus arteriosus and neonatal infections) did not change the ORs further (model D). The risk of moderate to severe BPD no longer differed between the infants with maternal disorders only and the control group but remained significantly higher for those with fetal disorders only (OR = 4.2; 95%

CI, 2.1–8.6) and both maternal and fetal disorders (OR = 2.1; 95% CI, 1.1–3.9).

Restriction of the control group to neonates born after idiopathic preterm labor produced the same results (data not shown).

Comparison of Analyzed and Nonanalyzed Infants

Among 2193 surviving infants (Fig 1), 82 were not analyzed because of missing respiratory status (*n* = 68), or we could not determine whether there were placenta-mediated pregnancy complications (*n* = 14). Compared with analyzed infants, nonanalyzed infants had lower gestational age (median 28.3 weeks, IQR [26.9–30.0] vs 29.9 weeks, IQR [28.1–31.0]; *P* < .001), had higher rates of placental abruption (15.0% vs 7.6%, *P* = .02), were less likely to be born in level 3 maternity units (77.4% vs 84.7%, *P* = .08), were more likely to be transferred after birth (26.0% vs 12.7%, *P* < .001), and received slightly fewer antenatal steroids (73.7% vs 82.7%, *P* = .05).

However, the 2 infant types did not differ in birth weight for gestational age (median *z* score: −0.4, IQR [−1.9–0.5] vs −0.4, IQR [−1.8–0.6], *P* = .83), cesarean delivery rates, and maternal characteristics (age, BMI, parity).

DISCUSSION

We found an association between placenta-mediated pregnancy complications and moderate to severe BPD if these complications had fetal consequences during pregnancy. Indeed, infants from both groups of placenta-mediated complications with antenatal-suspected FGR had increased risk of moderate to severe BPD, whereas BPD rates in the group with maternal disorders only did not differ from that in the control group.

The strengths of the EPIPAGE-2 study include the prospective and population-based cohort design. Definitions of BPD²⁷ and other neonatal outcomes²⁶ followed international classifications. Detailed recording of pregnancy events with standardized definitions allowed us to identify placenta-mediated pregnancy complications, such as new-onset hypertension and preeclampsia syndrome. Placental histology results would have been useful to accurately identify vascular lesions, but they were available for only a limited number of pregnancies and therefore were not used. Epidemiologic studies have used numerous definitions for FGR. The most widely used is weight below the 10th percentile at birth. However, this definition raises some difficulties. First, it groups FGR fetuses that do not reach their growth potential and present Doppler abnormalities or signs of fetal degradation,^{30,31} and constitutional small for gestational age (SGA) fetuses. Studies have shown that neonatal outcomes are better for constitutional SGA than FGR infants.³¹ Moreover, some infants with a birth weight above the

TABLE 4 Maternal and Neonatal Characteristics by BPD Status at 36 wk PMA

	Moderate to Severe BPD (N = 259)			No or Mild BPD (N = 1852)			P	OR ^a	95% CI	P
	Median	IQR		Median	IQR					
Gestational age, wk	27.1	26.1; 28.9		30.0	28.4; 31.0		<.001			
Birth wt, g ^b	840	710; 1040		1240	1010; 1500		<.001	0.7	0.7–0.8	<.001
Birth wt for gestational age, z score	−1.0	−2.5; 0.3		−0.4	−1.7; 0.6		<.001	0.7	0.6–0.8	<.001
	n	%		n	%		P	OR ^a	95% CI	P
Male gender	130	50.3		985	53.2		.39	0.9	0.7–1.2	.54
Maternal age, y							.16			.18
<25	57	21.5		399	21.4			0.9	0.6–1.3	
25–30	92	35.9		580	31.2			1		
30–35	67	26.2		462	25.2			1.1	0.7–1.6	
≥35	43	16.4		411	22.2			0.7	0.5–1.0	
Maternal BMI							.17			.08
<18.5	23	9.1		147	8.3			1.3	0.8–2.3	
18.5–25	124	49.4		1009	56.8			1		
25–30	55	22.6		344	19.5			1.4	1.0–2.0	
≥30	48	18.9		271	15.4			1.6	1.1–2.3	
Nulliparity	157	60.1		965	52.1		.02	1.3	1.0–1.7	.07
Smoking during pregnancy	64	27.2		516	28.3		.30	0.9	0.6–1.2	.49
Preexisting diabetes	7	2.8		35	2.0		.40	2.0	0.8–5.1	.13
Gestational diabetes	14	6.1		135	8.0		.31	1.0	0.6–1.9	.88
Antenatal steroids (≥1 dose)	206	80.8		1508	82.9		.42	0.9	0.6–1.3	.62
Cesarean delivery	174	70.5		1193	65.5		.11	2.2	1.6–3.0	<.001
Level 3 maternity unit	232	89.3		1558	84.1		.03	1.5	1.0–2.3	.08
Patent ductus arteriosus	196	75.4		522	27.3		<.001	3.7	2.7–5.3	<.001
Postnatal bacteremia	122	46.8		374	20.8		<.001	1.8	1.3–2.4	<.001
Necrotizing enterocolitis	15	5.8		55	3.0		.02	1.4	0.7–2.7	.29
Severe cerebral lesion	33	12.4		118	6.2		<.001	1.3	0.8–2.0	.30
Surfactant							<.001			<.001
None	10	4.3		771	43.7			1		
1 dose	129	49.7		857	46.5			5.0	2.5–9.8	
≥2 doses	115	46.0		182	9.8			20.3	10.2–40.5	
Postnatal steroids	108	40.9		76	3.8		<.001	7.3	5.0–10.6	<.001

Missing data <5% for each variable except for gestational diabetes (7.6%) and postnatal bacteremia (5.6%). Percentages are weighted by recruitment period.

^a Adjusted on gestational age.^b OR for a birth wt increase of 100 g.

TABLE 5 Multivariate Analyses of Association Between Placenta-Mediated Pregnancy Complications and Moderate to Severe BPD

	Moderate to Severe BPD at 36 wk PMA											
	Model A			Model B			Model C			Model D		
	(adjusted on gestational age)			(adjusted on gestational age + antenatal variables)			(adjusted on gestational age, antenatal variables and birth wt)			(adjusted on gestational age, birth wt, antenatal + postnatal variables)		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Placenta-mediated complications			<.001			<.001			<.001			.001
None	1			1			1			1		
Maternal disorders only	1.7	1.0–2.7		1.7	1.0–2.8		1.2	0.7–2.2		1.4	0.8–2.4	
Fetal disorders only	6.6	4.1–10.7		7.4	4.5–12.2		3.8	2.0–7.3		4.2	2.1–8.6	
Maternal and fetal disorders	3.7	2.5–5.5		3.9	2.5–6.1		2.1	1.2–3.8		2.1	1.1–3.9	
Gestational age, wk	0.5	0.4–0.6	<.001	0.5	0.4–0.6	<.001	0.5	0.4–0.5	<.001	0.6	0.5–0.7	<.001
Birth wt, z score	—			—			0.8	0.7–0.9	.002	0.8	0.7–1.0	.01

Model A: Adjusted on gestational age.

Model B: Adjusted on maternal age, BMI, parity, preexisting diabetes, smoking during pregnancy, fetal gender, care level of the maternity units, antenatal steroids, and gestational age.

Model C: Adjusted on maternal age, BMI, parity, preexisting diabetes, smoking during pregnancy, fetal gender, care level of the maternity unit, antenatal steroids, gestational age, and birth wt for gestational age (continuous variable).

Model D: Adjusted on maternal age, BMI, parity, preexisting diabetes, smoking during pregnancy, fetal gender, care level of the maternity unit, antenatal steroids, gestational age, birth wt for gestational age (continuous variable), patent ductus arteriosus, and postnatal bacteremia.

—, Models A and B are not adjusted on birth weight; ORs for birth weight are therefore not applicable.

10th percentile are actually growth restricted. Detailed ultrasound information allowed us to distinguish between FGR and constitutional SGA fetuses by using antenatal criteria (ie, estimated fetal weight, growth arrest, and abnormal Doppler findings). As a result, in our cohort, birth weight was below the 10th percentile by Gardosi's weight charts for 92% of the infants in both groups with antenatal suspected FGR, whereas it was above the 10th percentile for 93% of the infants in the control group. We constructed our groups on the basis of antenatal data only; 48% of the infants with maternal disorders only showed birth weight below the 10th percentile, whereas FGR was not diagnosed during pregnancy. We took this situation into account by adjusting our analyses on the actual birth weight.

About 7% of the eligible infants did not participate in the EPIPAGE-2 study because of parental refusals. However, their gestational age, birth weight, and vital status were available and did not differ significantly from those of participating infants.³² In addition, data for 82 infants (3.7%) whose parents had agreed to participate were not analyzed because of missing

data. The proportion of infants with BPD may have been higher than in the analyzed group because of lower gestational age. However, this selection concerned few infants and probably did not introduce any bias in the associations between placenta-mediated pregnancy complications and BPD.

Respiratory management characteristics, such as surfactant administration, duration of mechanical and noninvasive ventilation, and postnatal use of corticosteroids, were not considered in the analyses. These variables are strongly correlated with BPD because they reflect an early adverse clinical respiratory course or are markers of BPD. Therefore, including them in the logistic regression analysis might have led to overadjustment.

Early deaths (in the delivery room or neonatal ward) occur frequently in very preterm infants and could affect the associations observed between pregnancy events and BPD. However, in our study, mortality rates did not differ between the groups.

As far as we know, this is the first study evaluating the effects of placenta-mediated pregnancy complications on moderate to severe

BPD by separately analyzing their maternal or fetal consequences. One important result is that the risk of moderate to severe BPD is high in pregnancies with fetal disorders but not in those with only maternal disorders. These were not the expected results and could help explain the contradictory findings in the literature. Indeed, previous studies found a positive association^{21,23,33} or no association^{10,25,34} between placenta-mediated complications and BPD. However, a few studies distinguished between preeclamptic women with and without FGR. Bose et al¹¹ described a positive association between maternal preeclampsia with FGR and BPD and no association between maternal preeclampsia without FGR and BPD. In contrast to our analysis, FGR fetuses were classified in the control group if their mothers did not develop preeclampsia. Moreover, we tried to clarify the part of growth restriction in the relationship between placenta-mediated complications with fetal disorders and BPD by controlling for the actual birth weight for gestational age. As expected, birth weight for gestational age was associated with moderate to severe BPD, and

it explained in part the association between placenta-mediated complications and moderate to severe BPD. However, a statistically significant association remained, which suggests an independent impact of placenta-mediated complications with fetal disorders on moderate to severe BPD risk.

Our initial hypothesis was that all placenta-mediated pregnancy complications would increase the risk of moderate to severe BPD, but this hypothesis was not confirmed. Pregnancies with placenta-mediated complications share an imbalance between angiogenic and antiangiogenic factors,^{16,17} which may be responsible for impaired lung development in children.¹⁹ Whether the angiogenic pattern is similar in the different clinical presentations of placenta-mediated complications is unclear; however, some studies found few differences in maternal serum levels of antiangiogenic factors between preeclamptic women with and without FGR.¹⁸ In our results, these 2 groups had differing risks for moderate to severe BPD. Therefore, the antiangiogenic hypothesis is not supported by our results. By contrast, the risk for moderate to severe BPD was higher in both groups with fetal disorders (isolated or associated with maternal disorders), even if the magnitude of ORs differed. Additional investigations are needed to elucidate the mechanisms linking pregnancy events with fetal disorders and BPD. One of them could be the so-called fetal programming phenomenon, that is, the epigenetic alterations induced by the environment in which fetuses develop during pregnancy. This phenomenon is one of the key mechanisms leading to the development of metabolic

disorders during adulthood in FGR infants^{35,36} and could have many other consequences.

CONCLUSIONS

Placenta-mediated pregnancy complications with fetal consequences are associated with moderate to severe BPD, regardless of gestational age and birth weight. In contrast, maternal disorders without fetal consequences are not associated with moderate to severe BPD. These results raise new questions about the mechanisms linking placental vascular disorders and BPD, suggesting fetal programming of impaired lung development.

ACKNOWLEDGMENTS

We acknowledge the collaborators of the EPIPAGE-2 Study Group:

Alsace: D. Astruc, P. Kuhn, B. Langer, J. Matis (Strasbourg), C. Ramousset; Aquitaine: X. Hernandez (Bayonne), P. Chabanier, L. Joly-Pedespan (Bordeaux), M. J. Costedoat; Auvergne: B. Lecomte, D. Lemery, F. Vendittelli (Clermont-Ferrand); Basse-Normandie: G. Beucher, M. Dreyfus, B. Guillois (Caen); Bourgogne: A. Burguet, J. B. Gouyon, P. Sagot (Dijon), N. Colas; Bretagne: J. Sizun (Brest), A. Beuchée, P. Pladys, F. Rouget (Rennes), R. P. Dupuy (St-Brieuc), F. Charlot, S. Roudaut; Centre: A. Favreau, E. Saliba (Tours); Champagne-Ardenne: N. Bednarek, P. Morville (Reims), M. Palot; Franche-Comté: G. Thiriez (Besançon), C. Balamou; Haute-Normandie: L. Marpeau, S. Marret (Rouen); Ile-de-France: G. Kayem (Colombes), X. Durrmeyer (Créteil), M. Granier (Evry), M. Ayoubi, A. Baud, B. Carbonne, L. Foix L'Hélias, F. Goffinet,

P. H. Jarreau, D. Mitanchez (Paris), P. Boileau (Poissy), C. Duffaut, E. Lorthé; Languedoc-Roussillon: P. Boulot, G. Cambonie, H. Daudé (Montpellier), A. Badessi, N. Tsaoussis; Limousin: A. Bédu, F. Mons (Limoges), C. Bahans; Lorraine: J. Fresson, J. M. Hascoët, A. Miton, O. Morel, R. Vieux (Nancy); Midi-Pyrénées: C. Alberge, C. Arnaud, C. Vayssière (Toulouse), M. Baron; Nord-Pas-de-Calais: M. L. Charkaluk, V. Pierrat, D. Subtil, P. Truffert (Lille), C. Delaeter; PACA et Corse: C. D'Ercole, C. Gire, U. Simeoni (Marseille), A. Bongain (Nice), M. Deschamps, C. Grangier; Pays de Loire: J. C. Rozé, N. Winer (Nantes), V. Rouger, C. Dupont; Picardie: J. Gondry (Amiens), B. Baby; Rhône-Alpes: M. Debeir (Chambéry), O. Claris, J. C. Picaud, S. Rubio-Gurung (Lyon), A. Ego, T. Debillon (Grenoble), H. Patural (Saint-Etienne), A. Rannaud; Guadeloupe: A. Poulichet, J. M. Rosenthal (Point à Pitre); Guyane: A. Favre (Cayenne); Martinique: V. Lochelongue; La Réunion: P. Y. Robillard (Saint-Pierre), S. Samperiz, D. Ramful (Saint-Denis); Inserm UMR 1153: P. Y. Ancel, V. Benhammou, B. Blondel, M. Bonet, A. Brinis, M. L. Charkaluk, M. Durox, L. Foix L'Hélias, F. Goffinet, M. Kaminski, G. Kayem, B. Khoshnood, C. Lebeaux, L. Marchand-Martin, V. Pierrat, M. J. Saurel-Cubizolles, D. Tran, L. Vasante-Annamale, J. Zeitlin.

ABBREVIATIONS

BPD: bronchopulmonary dysplasia
CI: confidence interval
FGR: fetal growth restriction
IQR: interquartile range
OR: odds ratio
PMA: postmenstrual age
SGA: small for gestational age

This trial has been registered with (identifier CNIL no. 911009, CCTIRS 10.626, CPP SC-2873).

DOI: 10.1542/peds.2015-2163

Accepted for publication Dec 18, 2015

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: The EPIPAGE-2 Study was supported by the French Institute of Public Health Research/Institute of Public Health and its partners the French Health Ministry, the National Institutes of Health and Medical Research, the National Institute of Cancer, and the National Solidarity Fund for Autonomy; grant ANR-11-EQPX-0038 from the National Research Agency through the French Equipex Program of Investments in the Future; and the PremUp Foundation.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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