Association of Chorioamnionitis with Cerebral Palsy at Two Years after Spontaneous Very Preterm Birth: The EPIPAGE-2 Cohort Study

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Objective To assess whether chorioamnionitis is associated with cerebral palsy (CP) or death at 2 years' corrected age in infants born before 32 weeks of gestation after spontaneous birth.

Study design EPIPAGE-2 is a national, prospective, population-based cohort study of children born preterm in France in 2011; recruitment periods varied by gestational age. This analysis includes infants born alive after preterm labor or preterm premature rupture of membranes from $24^{0/7}$ to $31^{6/7}$ weeks of gestation. We compared the outcomes of CP, death at 2 years' corrected age, and "CP or death at age 2" according to the presence of either clinical chorioamnionitis or histologic chorioamnionitis. All percentages were weighted by the duration of the recruitment period.

Results Among 2252 infants born alive spontaneously before 32 weeks of gestation, 116 (5.2%) were exposed to clinical chorioamnionitis. Among 1470 with placental examination data available, 639 (43.5%) had histologic chorioamnionitis. In total, 346 infants died before 2 years and 1586 (83.2% of the survivors) were evaluated for CP at age 2 years. CP rates were 11.1% with and 5.0% without clinical chorioamnionitis (P = .03) and 6.1% with and 5.3% without histologic chorioamnionitis (P = .49). After adjustment for confounding factors, CP risk rose with clinical chorioamnionitis (aOR 2.13, 95% CI 1.12-4.05) but not histologic chorioamnionitis (aOR 1.21, 95% 0.75-1.93). Neither form was associated with the composite outcome "CP or death at age 2."

Conclusions Among infants very preterm born spontaneously, the risk of CP at a corrected age of 2 years was associated with exposure to clinical chorioamnionitis but not histologic chorioamnionitis. *(J Pediatr 2020;222:71-8)*.

Cerebral palsy (CP), the most common cause of motor deficiency in young children, occurs in about 5% of very premature births.[1-3] It has been suggested that chorioamnionitis, either clinical or histologic, is associated with CP.[4,5] Definitions of prenatal inflammation/infection vary widely, and its impact on the fetal brain remains controversial.[6] Three meta-analyses have shown conflicting results about an association between chorioamnionitis and CP in infants born premature.[5,7-9] Most previous studies have included children born prematurely without distinguishing the causes of these preterm deliveries, primarily, placental vascular disease, preterm premature rupture of membranes (PPROM), or preterm labor.[10,11] However, the clinical path leading to preterm birth, including fetal and obstetric complications and mode of delivery, differs in women with vascular disorders and those with preterm labor and PPROM.[12] Inflammation may be involved in cases of preterm labor or PPROM and lead to spontaneous preterm birth, whereas vascular disease is associated with placental insufficiency, medically induced prematurity, and greater in-hospital mortality.[12,13] Including all subtypes of preterm births may thus be inappropriate, first, because chorioamnionitis is nearly absent in the

CP	Cerebral palsy
IVH	Intraventricular hemorrhage
PPROM	Preterm premature rupture of the membranes

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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 Institute of Health and Medical Research, the National Institute of Cancer, and the National Science Foundation for Autonomy; the National Research Agency through the French Equipex Program of Investments in the Future (ANR-11-EQPX-0038); and the PremUp Foundation. The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.03.021

subgroup of infants with vascular disease,[14] and second, because adverse outcomes are induced by different physiopathologic pathways that depend on the preterm birth subtype.[12,13,15,16] Intrauterine inflammation with elevated fetal cytokines may be independently harmful for the developing brain of the infant born preterm and provoke neonatal cerebral white matter damage that may subsequently be diagnosed as CP.

Thus, we studied the impact of chorioamnionitis on CP and/or death in a homogeneous population of infants born after preterm labor or PPROM in the EPIPAGE-2 cohort, a French prospective population-based study.[17] The main objective was to assess the association between clinical chorioamnionitis and/or histologic chorioamnionitis and CP at a corrected age of 2 years in children born before 32 weeks of gestation.

Methods

EPIPAGE-2 is a nationwide, prospective, population-based study scheduled to follow up children born preterm to the age of 12 years.[18] Neonates born from 22 to 34 completed weeks of gestation in France were eligible for inclusion. Recruitment took place in 2011 in all maternity units in 25 participating regions accounting for 98% of all births in France. Inclusions lasted 8 months for preterm births from $22^{0/7}$ to $26^{6/7}$ weeks of gestation, 6 months for those from $27^{0/7}$ to $31^{6/7}$ weeks of gestation, and 5 weeks for those from $32^{0/7}$ to $34^{6/7}$ weeks of gestation.[17] Referring physicians assessed the presence of CP or other neurosensory deficiencies at 2 years' corrected age.

Ethics

The National Data Protection Authority (CNIL no. 911009) and the appropriate ethics committees (Consultative Committee on the Treatment of Data on Personal Health for Research Purposes, no. 10.626; Committee for the Protection of People Participating in Biomedical Research, CPP SC-2873) approved the study. Recruitment occurred only after families had received information and data collection only after they consented to participate in the study.

Participants

Singletons and twins born alive from $24^{0/7}$ to $31^{6/7}$ weeks of gestation after a spontaneous birth involving PPROM (rupture of the membranes more than 24 hours before delivery) or preterm labor (defined as regular contractions accompanied by cervical change, including intact membranes and membranes ruptured for less than 24 hours before delivery) were included in this study. The method of classifying the cause of preterm birth has previously been described.[13]

Exclusion criteria were other causes of preterm birth; births before 24 weeks of gestation because such infants did not routinely receive intensive care in France in 2011[18]; births after 32 weeks because CP occurs in 1% of infants born later[2]; and severe congenital malformations, prenatal cytomegalovirus and toxoplasmosis infections, fetal alcohol syndrome, and congenital hypothyroidism, all repeatedly associated with CP.[4] Four authors independently reviewed cases of congenital anomalies. We also excluded all triplets and quadruplets, as well as twin pregnancies with complications, such as twin–twin transfusion syndrome or intrauterine fetal death of one co-twin, because of the intermediate factors of morbidity in multiple pregnancies.[4]

Main Outcomes and Exposure Measures

Clinical Chorioamnionitis and Histologic Chorioamnionitis. Clinical chorioamnionitis was diagnosed by maternal temperature >37.8°C (100°F) associated with at least 2 of the following 5 criteria: maternal tachycardia >100 beats/min, fetal baseline tachycardia >160 beats/min, uterine tenderness, maternal leukocytosis >15 000 cells/mm^3, and foul-smelling vaginal discharge or amniotic fluid.[19]

Within the EPIPAGE-2 study, the CHORHIST project was specifically designed to study the impact of histologic chorioamnionitis on neurologic outcomes, from data collected by pathologists with a standardized form to assess the extent of histologic chorioamnionitis and funisitis.[17] According to this standardized classification, histologic placental findings were divided into 3 stages: no histologic chorioamnionitis; histologic chorioamnionitis defined by the presence of neutrophils in the membranous amniochorion and/or membranes; and histologic chorioamnionitis with histologic funisitis, defined by neutrophil infiltration into the fetal vessels in the chorionic plate and umbilical cord.[20]

Outcomes: CP and Death. The primary outcome was CP, a disease due to permanent movement and posture disturbances resulting from a nonprogressive lesion of the developing brain. It was defined according to the diagnostic criteria of the Surveillance of Cerebral Palsy in Europe network.[3] Data for children at 2 years of corrected age were collected with a standardized questionnaire completed by the referring physician. The secondary outcome was a composite outcome, "CP or death," which included infants who died before the age of 2 years and those who presented CP at that age, to take the potential competitive risk between these outcomes into account.

Other Factors Studied. Maternal characteristics examined were age, region of birth, personal health insurance coverage, obesity (body mass index ≥30 kg/m^2), and addictions (smoking, alcohol, or drugs). Obstetric characteristics were parity, number of fetuses, cervical cerclage, PPROM, antenatal corticosteroids, antenatal magnesium sulfate, "inborn" status, antenatal antibiotics, mode of delivery, and gestational age. Antenatal steroid treatment was defined by administration to the mother of at least one betamethasone injection.

The neonatal variables examined were sex, birth weight, death in the delivery room or neonatal intensive care unit, early-onset sepsis, necrotizing enterocolitis (Bell stage ≥2), severe bronchopulmonary dysplasia, severe intraventricular hemorrhage (IVH), and cystic periventricular leukomalacia. Early-onset sepsis was defined as proven neonatal bacterial

infection with positive cultures of cerebrospinal fluid or blood before 72 hours of life. Severe bronchopulmonary dysplasia was defined as oxygen supplementation for at least 28 days and persistent need for oxygen (fraction of inspired oxygen ≥30%) and/or ventilatory support (mechanical ventilation or positive pressure) at 36 weeks' postmenstrual age.[21] The criteria for IVH required its association with ventricular dilatation (grade III IVH) or intraparenchymal hemorrhage (grade IV IVH), based on the Papile grading system.[22] Cystic periventricular leukomalacia was defined by periventricular white-matter echolucencies associated with cavitation on ultrasonography.[23]

Statistical Analyses

Categorical variables were compared by a χ^2 test or Fisher exact test, as appropriate. Continuous variables were described by their medians and IQRs and were compared by rank-sum tests. All percentages, medians, and crude ORs were weighted to account for the different durations of recruitment for different gestational-age categories of preterm birth, based on their frequencies. Percentages are expressed as weighted percentages (wtd %).

Because the associations of histologic chorioamnionitis alone and histologic chorioamnionitis + funisitis with CP, death, and "CP or death" were similar, the following analyses treat histologic chorioamnionitis and histologic chorioamnionitis + funisitis as the same exposure variable. Preterm labor and PPROM were considered together for the same reason (**Table I**; available at www.jpeds.com).

The associations between clinical chorioamnionitis and histologic chorioamnionitis with CP, death, and "CP or death" at age 2 were studied by bivariate analyses and multivariate logistic regression models that used generalized estimated equations to take the non-independence of observations for twins into account. These analyses were performed for cases with available data for either clinical chorioamnionitis or histologic chorioamnionitis and were adjusted for maternal age, obesity, number of fetuses, gestational age at birth, sex, and antenatal steroid use, because these potential confounding factors have previously been associated with CP in the literature.[1,4,24] Adjusting for gestational age is customary in observational studies comparing groups with different gestational age compositions, even if this factor is probably more an intermediate than a confounding variable.[25]

Missing data rates ranged from 0% to 1.7% for the covariates included in the multivariate analyses, 16.8% for the primary outcome (CP), and 0% for death. Missing data for the covariates were considered missing at random. We performed a complete-case analysis (logistic regression restricted to infants with complete data for the diagnosis of clinical chorioamnionitis or histologic chorioamnionitis, the outcome, and all covariates). We also conducted an analysis after multiple imputations for missing data for all covariates and the main outcome, with a logistic regression imputation model for binary variables. The imputation model included variables predicting nonresponse and/or correlated with outcomes (maternal, obstetric, and neonatal characteristics, severe IVH, cystic periventricular leukomalacia, bronchopulmonary dysplasia, necrotizing enterocolitis, early- and late-onset sepsis, postnatal corticotherapy, physiotherapy, blindness, and deafness at 2 years). Finally, we conducted an analysis after multiple imputations for missing data for all covariates but not for CP, with a logistic regression imputation model for binary variables. Missing data were imputed by chained equations with the R package "mice" v2.25. Conversely, placental examination was missing for 34.7% of cases. These data were not imputed because they were not missing at random (**Table II**; available at www.jpeds.com). P values <.05 were considered statistically significant. Statistical analyses used R v3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Among the 3816 live births eligible from the EPIPAGE-2 study, 329 were excluded because of congenital malformations or diseases, or as triplets or quadruplets or as twins with twin–twin transfusion syndrome, and 85 more for missing clinical chorioamnionitis data. Then, 1150 cases were excluded because the cause of preterm birth was neither preterm labor nor PPROM. **Table III** (available at www.jpeds.com) describes the distribution of clinical chorioamnionitis and histologic chorioamnionitis by cause of preterm birth. Finally, the analysis of the association between clinical chorioamnionitis and outcomes at 2 years included 2252 children, of whom 1470 had a placental examination available to enable analysis of the association of histologic chorioamnionitis with outcomes at age 2 years (**Figure**). The remaining 782 (34.7%) women had no placental examination. Factors associated with this lack of examination were maternal birth in sub-Saharan Africa, gestational age >28 weeks, absence of clinical chorioamnionitis, and vaginal delivery, but not CP (**Table II**).

Of these 2252 infants, 116 (5.2%) were exposed to clinical chorioamnionitis and 639 of 1470 (43.5%) to histologic chorioamnionitis (with all percentages weighted according to the length of the recruitment period). Among these 1470 children, 82 (5.5%) were exposed to both clinical chorioamnionitis and histologic chorioamnionitis and 557 (39.1%) to histologic chorioamnionitis but not clinical chorioamnionitis.

On bivariate analysis, clinical chorioamnionitis was associated with maternal age >35 years, nulliparity, obesity, singleton pregnancy, PPROM, antenatal antibiotics, gestational age <28 weeks, cesarean delivery, early-onset sepsis, and CP. Histologic chorioamnionitis was associated with maternal birth in sub-Saharan Africa, no medical insurance, obesity, singleton pregnancy, cervical cerclage, PPROM, antenatal antibiotics, gestational age <28 weeks, early-onset sepsis, neonatal death, and death at age 2 years (**Table IV**).

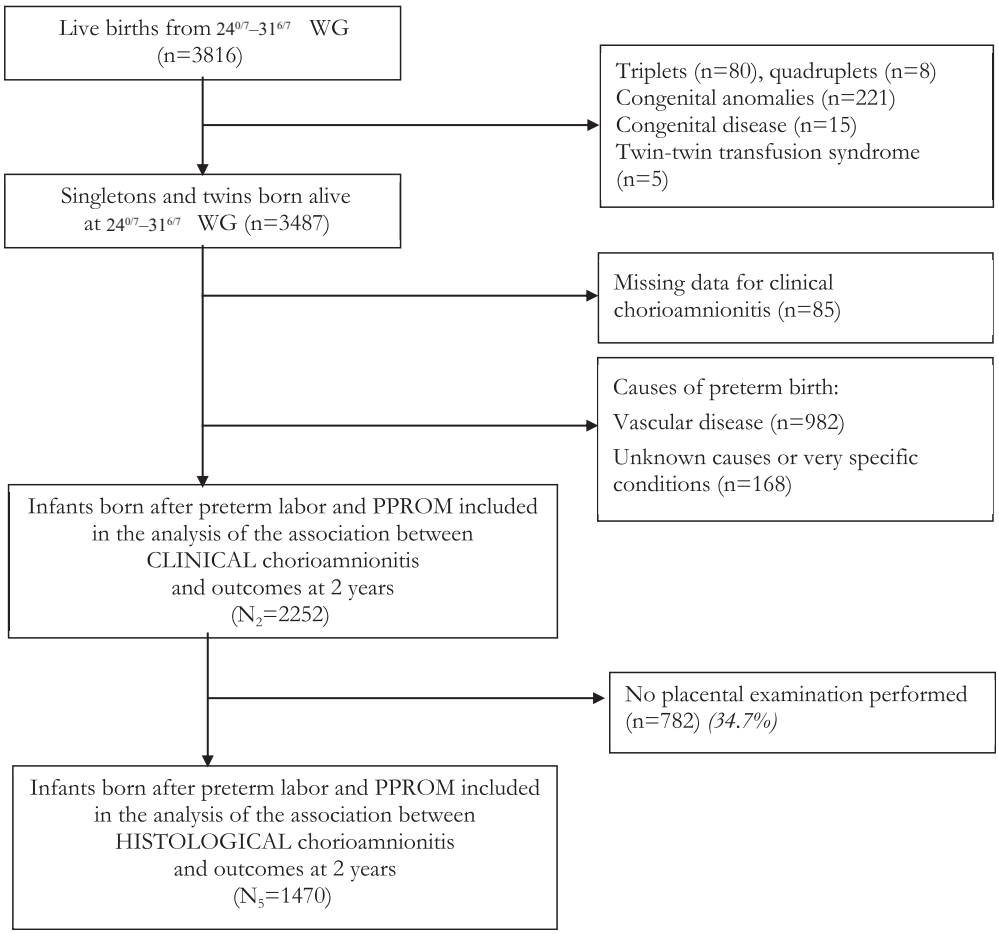

Figure. Study flow chart. Among 2252 live births (N2), a placental examination was available for 1470 cases (N5). Among 1586 infants evaluated for CP at 2 years (N1), a placental examination was available for 1018 cases (N4). *WG*, weeks of gestation.

In all, 346 infants (267 born at 24-26 weeks of gestation and 79 at 27-31 weeks of gestation) died before age 2 years. Among the 1906 children alive at 2 years, 1586 were evaluated for CP and 320 (16.8%) lost to follow-up. Among the latter, 16 (5.0%) were exposed to clinical chorioamnionitis and 83 (40.5%) to histologic chorioamnionitis, that is, they did not differ for this exposure (**Table IV**).

Overall, 85 (5.3%) children were diagnosed with CP. More specifically, at 2 years' corrected age, the CP rate was 11.1% in chorioamnionitis-exposed and 5.0% in nonexposed children (P = .03). Associations of maternal, obstetric, and neonatal characteristics with CP are reported in **Table V** (available at www.jpeds.com). After multivariate analysis and multiple imputation, clinical chorioamnionitis exposure was associated with CP (aOR 2.13, 95% CI 1.12-4.05) but not with death (aOR 1.10, 95% CI 0.60-1.92) or with the composite "CP or death" outcome (aOR 1.42, 95% CI 0.87-2.26) (**Table VI**). Histologic chorioamnionitis was not associated with CP (6.1% vs 5.3% with and without histologic chorioamnionitis; aOR 1.21, 95% CI 0.75-1.93), death (aOR 0.87, 95% CI 0.62-1.23), or "CP or death" (aOR 0.89, 95% CI 0.66-1.19). Results were similar for clinical chorioamnionitis + histologic chorioamnionitis and clinical chorioamnionitis alone. Likewise, associations with CP, death, or "CP or death" were similar with histologic chorioamnionitis without clinical chorioamnionitis and with histologic chorioamnionitis alone (**Table VI**). Similar associations were observed without imputation for CP (**Table VII**; available at www.jpeds.com).

Discussion

The primary finding of this study is that among infants very preterm who were born after preterm labor or PPROM, those with clinical chorioamnionitis were at increased CP risk; those with histologic chorioamnionitis were not. The main strength of the study is its large prospective population-based design, with detailed data for pregnancy and neonatal outcomes. The second strength is the analysis of the association between chorioamnionitis and CP in a large homogeneous population of infants very preterm who were born after preterm labor or PPROM.[16,17] To that end, we excluded children who were born preterm after pregnancies complicated by fetal growth restriction or placental dysfunction

Table IV. Demographic and baseline characteristics and outcomes for infants born after preterm labor and PPROM with or without either clinical or histologic chorioamnionitis

Characteristics and outcomes	No clinical chorioamnionitis (N = 2136) n (wtd %)	Clinical chorioamnionitis (N = 116) n (wtd %)	No histologic chorioamnionitis (N = 831) n (wtd %)	Histologic chorioamnionitis (N = 639) n (wtd %)
Maternal and obstetric characteristics				
Maternal age, y				
<20	97 (4.6)	7 (5.6)	42 (5.0)	29 (4.7)
20-35	1627 (76.2)	79 (68.4)	626 (75.2)	474 (74.3)
>35	410 (19.2)	30 (25.9)*	163 (19.8)	134 (21.0)
Region of birth				
Europe	1726 (80.8)	93 (80.2)	709 (85.3)	502 (78.6)
North African	76 (3.6)	4 (3.4)	26 (3.1)	21 (3.3)
Sub-Saharan African	90 (4.2)	3 (2.6)	17 (2.0)	38 (5.9)†
Other	52 (2.4)	6 (5.2)	12 (1.4)	14 (2.2)
Missing data	192 (9.0)	10 (8.6)	67 (8.1)	64 (10.0)
No medical insurance	224 (10.5)	11 (9.5)	72 (8.7)	77 (12.1)*
Missing data	216 (10.1)	17 (14.7)	64 (7.7)	81 (12.7)
Smoker	474 (22.9)	28 (24.4)	178 (22.0)	157 (25.3)
Obesity	250 (12.9)	27 (26.5)†	92 (12.2)	104 (18.1)*
Missing data	201 (9.4)	11 (9.5)	70 (8.4)	49 (7.7)
Nulliparity	1155 (54.2)	49 (43.5)*	465 (55.7)	334 (52.3)
Type of pregnancy				
Singleton	1373 (64.0)	91 (78.3)*	485 (57.8)	462 (72.1)†
Twin	763 (36.0)	25 (21.7)	346 (42.2)	177 (27.9)
Cerclage	158 (7.4)	11 (9.5)	40 (4.8)	65 (10.2)†
Missing data	143 (6.7)	7 (6.0)	57 (6.9)	32 (5.0)
Preterm labor	1053 (49.4)	28 (23.6)†	469 (56.4)	230 (35.8)†
PPROM	1073 (50.6)	88 (76.4)†	355 (43.6)	409 (64.2)†
Antenatal corticosteroids	1713 (81.9)	91 (81.1)	667 (82.5)	534 (84.9)
Antenatal antibiotics	1374 (64.6)	102 (87.7)†	478 (57.9)	499 (78.2)†
Cesarean delivery	962 (46.5)	63 (56.7)*	414 (51.4)	286 (46.2)
Clinical chorioamnionitis	–	–	13 (1.6)	82 (13.0)†
Histologic chorioamnionitis (among available placentas)	557 (39.2)	82 (85.5)†	–	–
Gestational age, weeks of gestation				
$24^{0/7}$-$27^{6/7}$	823 (33.5)	59 (46.1)*	262 (26.9)	367 (48.0)†
$28^{0/7}$-$31^{6/7}$	1313 (66.5)	57 (53.9)	569 (73.1)	272 (52.0)
Neonatal characteristics and outcomes				
Birth weight, median (IQR)	1200 (590)	1065 (573)	1242 ± 361	1084 ± 347†
Male	1168 (54.6)	62 (53.5)	481 (57.6)	310 (48.3)†
Neonatal death	314 (12.7)	23 (18.1)	117 (12.0)	125 (17.5)*
Early-onset sepsis	53 (2.6)	8 (7.9)*	10 (1.3)	26 (4.6)†
IVH grade III or IV	180 (7.9)	10 (9.8)	63 (6.8)	59 (9.2)
Cystic periventricular leukomalacia	54 (2.6)	1 (0.8)	20 (2.5)	18 (2.8)
Infants' outcomes at 2 y				
Death	323 (13.1)	23 (18.1)	119 (12.3)	128 (17.9)*
Cerebral palsy	76 (5.0)	9 (11.1)*	31 (5.3)	27 (6.1)
Lost to follow-up	304 (16.8)	16 (17.2)	122 (17.1)	83 (16.2)

wtd%: Percentages are weighted by recruitment period.
χ^2 and Fisher tests were performed with weighting by recruitment period.
For each variable in rows, if missing data >5%, the numbers and percentages of missing data are added to a supplementary row.
*$P < .05$.
†$P < .001$.

because of the different physiologic mechanisms leading to preterm birth and their poor outcomes for neonatal mortality, CP at 2 years, and cognitive function at age 5 years.[1,13,26] Another strength is the homogeneous data collection for the placentas examined, based on a form designed for the EPIPAGE-2 study and used prospectively for the histologic analyses.

The rate of missing data for histologic examination, although a limitation of our study, does not bias our findings. It is normal to send placentas for this examination in the most severe cases, such as those with clinical chorioamnionitis or delivery at an early gestational age. This weakness may thus artificially increase the prevalence of histologic chorioamnionitis in our population but it does not modify the potential association between histologic chorioamnionitis and CP.

Another potential limitation of our study is the 16.8% rate of missing data about CP at 2 years. This rate is nonetheless similar to that in other large studies of infants' outcome at 2 years.[10,11] To provide the best estimate of the association of CP with clinical chorioamnionitis and histologic chorioamnionitis and to address this limit on the primary outcome, we used a model with multiple imputations to

Table VI. Association of chorioamnionitis with CP and/or death at 2 years in very preterm births

Outcomes	No chorioamnionitis n/N (wtd %)	Chorioamnionitis n/N (wtd %)	Crude OR (95% CI) *P* value	aOR* (95% CI) *P* value	aOR† (95% CI) *P* value
Clinical chorioamnionitis (regardless of histologic status)					
CP	76/1509 (5.0)	9/77 (11.1)	2.43 (1.11-5.33)	2.25 (0.99-4.61)	2.13 (1.12-4.05)
N_1 = 1586			*P* = .03	*P* = .04	*P* = .02
Death before age 2 y	323/2136 (13.1)	23/116 (18.1)	1.38 (0.86-2.22)	1.10 (0.57-2.01)	1.10 (0.60-1.92)
N_2 = 2252			*P* = .18	*P* = .76	*P* = .15
CP or death	399/1832 (19.5)	32/100 (29.8)	1.64 (1.06-2.55)	1.53 (0.88-2.60)	1.42 (0.87-2.26)
N_3 = 1932			*P* = .03	*P* = .12	*P* = .15
Histologic chorioamnionitis (regardless of clinical status)					
CP	31/590 (5.3)	27/428 (6.1)	1.21 (0.70-2.07)	0.84 (0.46-1.53)	1.21 (0.75-1.93)
N_4 = 1018			*P* = .49	*P* = .57	*P* = .43
Death before 2 y	119/831 (12.3)	128/639 (17.9)	1.47 (1.11-1.94)	0.88 (0.61-1.27)	0.87 (0.62-1.23)
N_5 = 1470			*P* = .008	*P* = .51	*P* = .43
CP or death	150/709 (18.9)	155/556 (25.5)	1.42 (1.09-1.85)	0.90 (0.65-1.23)	0.89 (0.66-1.19)
N_6 = 1265			*P* = .03	*P* = .49	*P* = .45
Histologic chorioamnionitis and clinical chorioamnionitis					
CP	51/962 (5.1)	7/56 (11.5)	2.55 (1.01-5.59)	2.28 (0.90-5.08)	3.21 (1.73-5.94)
N_4 = 1018			*P* = .03	*P* = .06	*P* = .0002
Death before 2 y	231/1388 (14.4)	16/82 (17.6)	1.21 (0.67-2.08)	0.88 (0.41-1.77)	0.87 (0.44-1.68)
N_5 = 1470			*P* = .54	*P* = .73	*P* = .69
CP or death	282/1193 (21.3)	23/72 (29.1)	1.46 (0.87-2.45)	1.38 (0.72-2.54)	1.31 (0.74-2.28)
N_6 = 1265			*P* = .15	*P* = .32	*P* = .35
Histologic chorioamnionitis without clinical chorioamnionitis					
CP	31/585 (5.3)	20/372 (5.3)	0.99 (0.56-1.74)	0.72 (0.36-1.38)	0.91 (0.58-1.43)
N_7 = 957			*P* = .99	*P* = .33	*P* = .69
Death before 2 y	116/818 (12.1)	112/557 (17.9)	1.49 (1.14-2.00)	0.92 (0.63-1.35)	0.89 (0.63-1.27)
N_8 = 1375			*P* = .007	*P* = .68	*P* = .53
CP or death	147/701 (18.7)	132/484 (24.9)	1.40 (1.06-1.84)	0.82 (0.58-1.16)	0.85 (0.62-1.16)
N_9 = 1185			*P* = .02	*P* = .27	*P* = .30

The study subpopulations are classified as follows.
N_1: children evaluated for CP at 2 years of corrected age.
N_2: children with available outcome for survival at 2 years of corrected age.
N_3: children with available outcomes for CP or death at 2 years of corrected age.
N_4, N_5, and N_6 correspond to the same populations as N_1, N_2, and N_3, respectively, restricted to the cases with available placental examinations.
N_7, N_8, and N_9 correspond to the same populations as N_4, N_5, and N_6, respectively, restricted to the cases without clinical chorioamnionitis, to study the impact of histologic chorioamnionitis only.
See the flow chart of the study (**Figure**) for the different subpopulations.
Crude and aORs were calculated with generalized estimated equation models.
*aOR: Complete-case analysis, adjusted for gestational age, maternal age, obesity, antenatal corticosteroids, twinning, and infant sex.
†aOR: Multiple imputations for covariates and outcome, restricted to cases with available diagnosis of clinical chorioamnionitis or placental histology, adjusted for gestational age, maternal age, obesity, antenatal corticosteroids, twinning, and infant sex.

deal with missing data and including neonatal neurologic data strongly associated with CP.[27]

The lack of use of magnesium sulfate for neuroprotection in 2011 in France also raises concern about the study's external validity. Nonetheless, magnesium sulfate administration should not modify the association between chorioamnionitis and CP, and its rate of administration was similar among the groups.[28]

The association between clinical chorioamnionitis or histologic chorioamnionitis and CP is controversial. Among the 3 meta-analyses that have studied it,[5,7,9] 2 found an increased risk of CP in cases of clinical chorioamnionitis. Interestingly, the strength of this association increased with the accuracy of the clinical criteria used to define clinical chorioamnionitis.[5,7] The association between histologic chorioamnionitis and CP is even more controversial, and the most recent meta-analysis yielded discordant results, with aORs ranging from 0.35 to 2.48.[9,29,30]

Our findings come from the largest nationwide population-based prospective study we are aware of; its data about clinical chorioamnionitis and histologic chorioamnionitis are accurate and its practices consistent with current worldwide recommendations (ie, antenatal corticosteroids for preterm labor or PPROM and antibiotics for PPROM). Two multicenter studies with large sample sizes did not find any association between histologic chorioamnionitis and CP, but they also included children born after placental disease.[10,11] In one of these studies, Pappas et al studied 1194 children born before 27 weeks of gestation and found CP rates of 4.9% in the cases with and 4.5% in those without histologic chorioamnionitis (P = .50).[10] In 2016, in a retrospective study in Japan, Miyazaki et al reported similar rates of CP among 2201 infants evaluated at 3 years (9.7% with and 6.3% without histologic chorioamnionitis; aOR 0.91, 95% CI 0.67-1.59).[11] These 2 studies, however, were not population-based and also included preterm births from all causes. They were therefore subject to potential biases, eg, overrepresentation of growth-restricted infants not exposed to inflammation.

CP occurrence is now considered to be a complex primary motor developmental disorder secondary to the additional effects of multiple ante-, intra- or postpartum risk factors.[31] Our results suggest that when preterm birth is due to preterm labor or PPROM, clinical chorioamnionitis—but not histologic chorioamnionitis—is a risk factor for CP. Two potential hypotheses may explain this result. First, local inflammation

may be stronger in clinical chorioamnionitis and produce greater effects on the fetus. Another hypothesis, however, is that many cases of histologic chorioamnionitis are not caused by infection. Although inflammation has generally been considered to result from microbial presence in amniotic fluid, a host inflammatory response may instead, by its effect on cervical dilation or rupture of the membranes, promote microbial colonization and invasion. Some data support this hypothesis: studies of amniotic fluid that used both cultures and broad-range polymerase chain reaction combined with mass spectrometry have found that sterile intra-amniotic inflammation is more common than low virulence (eg, *Ureaplasma* or *Mycoplasma* spp) microbial-associated intra-amniotic inflammation in women with preterm labor and as common in women with PPROM. These findings suggest that sterile inflammation is more common and more closely associated with spontaneous preterm birth than is low virulence microbial-associated inflammation.[32,33] Histologic chorioamnionitis may therefore be sterile or associated with organisms of low virulence that have a milder impact, if any, on the neonatal brain.[34] Conversely, clinical chorioamnionitis is caused by highly pathogenic bacteria that are mostly group B Streptococcus and *Escherichia coli*,[19,35] which can cause neonatal sepsis with greater neonatal morbidity and mortality.[36] Clinical chorioamnionitis certainly represents a more recent set of events leading to premature delivery, and histologic chorioamnionitis reflects a broader list of etiologies over a longer period of time during pregnancy.

Our findings support current obstetric practices, especially for the management of PPROM before 32 weeks of gestation, in the absence of obstetric complications. Expectant management benefits the fetus by increasing gestational age at birth.[37-39] In cases of clinical chorioamnionitis, however, immediate delivery must be discussed. The possible risks caused by clinical chorioamnionitis have to be weighted against, for example, the risks of extreme prematurity.[38,40]

In this large prospective national population-based cohort study, among infants born very preterm after preterm labor or PPROM, we found that clinical chorioamnionitis was associated with an increased risk of CP, whereas histologic chorioamnionitis was not. However, analyses of long-term development with detailed data on cognitive and behavioral functions to confirm these findings are warranted to study the neurologic consequences of intrauterine exposure to subclinical inflammation. ■

Submitted for publication Dec 9, 2019; last revision received Feb 18, 2020; accepted Mar 11, 2020.

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Appendix

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All the collaborators of the EPIPAGE2 Obstetric writing group have no conflict of interest or compensation in relation with this article to disclose. All of them consented to such acknowledgment.

Table I. Association between PPROM, histologic chorioamnionitis, alone or associated with funisitis, and CP, death, and the composite outcome CP or death among infants born after preterm labor or PPROM

	CP at 2 years			Death at 2 years			CP or death		
Characteristics	**n/N (wtd %)**	**OR (95% CI)***	**aOR (95% CI)†**	**n/N (wtd %)**	**OR (95% CI)***	**aOR (95% CI)†**	**n/N (wtd %)**	**OR (95% CI)***	**aOR (95% CI)†**
Preterm labor	55/992 (5.5)	ref	ref	216/1400 (13.3)	ref	ref	271/1208 (20.1)	ref	ref
PPROM	30/594 (5.0)	0.92 (0.58-1.45)	0.89 (0.56-1.40)	130/852 (13.3)	1.00 (0.78-1.29)	0.99 (0.76-1.31)	160/724 (20.0)	0.99 (0.79-1.25)	0.98 (0.76-1.25)
No histologic chorioamnionitis	31/590 (5.3)	ref	ref	119/831 (12.3)	ref	ref	150/709 (18.9)	ref	ref
Histologic chorioamnionitis alone	12/211 (5.3)	1.05 (0.62-1.76)	0.87 (0.50-1.48)	61/315 (17.4)	1.43 (1.02-2.02)	0.80 (0.54-1.19)	73/272 (24.5)	1.37 (0.99-1.89)	0.81 (0.56-1.17)
Histologic chorioamnionitis + funisitis	15/217 (6.9)	1.17 (0.70-1.97)	0.95 (0.55-1.60)	67/324 (18.4)	1.56 (1.12-2.17)	0.81 (0.55-1.19)	82/284 (26.5)	1.51 (1.11-2.07)	0.85 (0.59-1.22)

*Percentages and unadjusted ORs are weighted (wtd%) by length of recruitment period.
†Adjusted for gestational age.

Table II. Demographic and baseline characteristics and outcomes of cases with missing and available placental examination for determination of histologic chorioamnionitis among infants born after preterm labor or PPROM

Characteristics	Missing placentas N = 782 N (%)	Available placentas N = 1470 N (%)	*P* value
Maternal and obstetric characteristics			
Maternal age, y			
<20	33 (4.2)	71 (4.8)	
20-35	606 (77.5)	1100 (74.9)	.40
>35	143 (18.3)	297 (20.2)	
Region of birth			
European	608 (85.3)	1211 (90.4)	
North African	33 (4.9)	47 (3.5)	.002
Sub-Saharan African	38 (5.5)	55 (4.1)	
Others	32 (4.3)	26 (1.9)	
Missing data	71 (9.1)	131 (8.9)	
No medical insurance	86 (12.4)	149 (11.2)	.49
Missing data	88 (11.2)	145 (9.9)	
Smoking	167 (22.0)	335 (23.5)	.45
Nulliparity	405 (52.6)	799 (54.7)	.36
Number of fetuses			
Singletons	517 (66.1)	947 (64.4)	.45
Twins	265 (33.9)	523 (35.6)	
PPROM	397 (51.1)	764 (52.2)	.60
Antenatal corticosteroids	603 (78.7)	1201 (82.9)	.02
Cesarean delivery	325 (41.6)	700 (47.9)	.01
Clinical chorioamnionitis	21 (2.7)	95 (6.5)	.0002
Gestational age, weeks of gestation			
$24^{0/7}$-$27^{6/7}$	253 (32.4)	629 (42.8)	<.0001
$28^{0/7}$-$31^{6/7}$	529 (67.6)	841 (57.2)	
Neonatal characteristics			
Birth weight, mean ± SD	1273 ± 374	1173 ± 363	<.0001
Male sex	439 (56.1)	791 (53.8)	.31
Neonatal outcomes			
Neonatal death	95 (12.1)	242 (16.5)	.008
EOS	25 (3.5)	36 (2.7)	.40
Outcomes at 2 y			
CP	27 (4.8)	58 (5.7)	.49

For each variable in rows, in case of missing data over 5%, the numbers and percentages of missing data were added on a supplementary row.

Table III. Distribution of clinical and histologic chorioamnionitis/funisitis by cause of preterm birth in live births occurring between $24^{0/7}$ and $31^{6/7}$ weeks of gestation

	Cause of preterm birth (N = 3402)				
	Spontaneous preterm birth (N = 2252)		Vascular disease (N = 982)		
Types of chorioamnionitis	Preterm labor (N = 1400) n (%)	PPROM (N = 52) n (%)	Hypertensive disorders and abruptio placenta (N = 457) n (%)	Suspected FGR (N = 525) n (%)	Unknown or rare causes (N = 168) n (%)
Clinical chorioamnionitis	41/1400 (2.9)	75/852 (8.8)	1/457 (0.2)*	2/525 (0.4)*	3/168 (1.8)
Histologic chorioamnionitis alone	306/896 (34.2)	333/574 (58.0)	7/336 (1.5)†	9/418 (1.7)†	19/124 (15.3)
Histologic chorioamnionitis + funisitis	121/896 (13.5)	130/574 (22.6)	3/336 (0.7)	3/418 (0.6)	8/124 (6.4)
No placental examination	504/1400 (36.0)	278/852 (32.6)	121/457 (26.5)	107/525 (20.4)	44/168 (26.2)

FGR, fetal growth restriction; *HELLP*, hemolysis, elevated liver enzymes, low platelet count.
Suspected FGR indicates <10th percentile suspected prenatally based on estimated fetal weight.
Hypertensive disorder and abruptio placentae are cases not accompanied by suspected FGR.
Data on clinical chorioamnionitis were available for all cases. Data for histologic chorioamnionitis were available for 2348 of 3402 cases.
*Three patients had mixed causes of prematurity: they presented criteria for clinical chorioamnionitis, but the main conditions leading to preterm birth were severe preeclampsia and HELLP syndrome, both with suspected FGR, and 1 case of abruptio placenta without suspected FGR.
†Among the 16 cases of histologic chorioamnionitis associated with placental vascular disease, medical records revealed 8 had mixed causes of prematurity. The main cause of preterm birth was a history of placental dysfunction and the associated causes were clinical chorioamnionitis for 1, PPROM for 3, and preterm labor for 4.

Table V. Maternal, obstetric, and neonatal characteristics associated with CP and/or death at 2 years: bivariate analysis

Characteristics	No CP or death n = 1501	CP n = 85	CP or death n = 431	CP Crude OR* (95% CI)	CP or death Crude OR* (95% CI)
Maternal and obstetric characteristics					
Maternal age, y					
<20	42 (2.8)	6 (7.1)	29 (6.8)	2.64 (0.98-5.95)	2.51 (1.54-4.08)
20-35	1145 (76.3)	63 (74.1)	321 (74.8)	ref	ref
>35	314 (20.9)	16 (18.8)	79 (18.4)	0.88 (0.45-1.58)	0.90 (0.66-1.21)
Ethnicity					
White	1229 (89.4)	72 (93.5)	336 (87.5)	ref	ref
North African	52 (3.8)	1 (1.3)	12 (3.1)	0.33 (0.18-1.53)	0.84 (0.42-1.55)
Sub-Saharan African	59 (4.3)	4 (5.2)	25 (6.5)	1.16 (0.34-2.91)	1.55 (0.94-2.48)
Other	34 (2.5)	0 (0)	11 (2.9)	–	1.18 (0.57-2.29)
Missing data	127	8	47		
No medical insurance	116 (8.4)	11 (11.9)	56 (15.1)	1.93 (0.99-3.76)	1.97 (1.38-2.80)
Missing data	122	10	60		
Nulliparity	834 (56.0)	45 (52.3)	233 (54.4)	0.87 (0.56-1.36)	0.93 (0.74-1.16)
Obesity	181 (13.0)	17 (22.1)	59 (16.0)	1.97 (1.13-3.43)	1.27 (0.91-1.77)
Missing data	112	8	60		
History of psychiatric disease	34 (2.4)	3 (3.8)	14 (3.5)	1.63 (0.50-5.24)	1.49 (0.78-2.82)
History of addiction to alcohol	3 (0.2)	0 (0)	2 (0.005)	–	2.58 (0.42-15.99)
Drug use	26 (1.8)	1 (1.3)	4 (0.01)	0.72 (0.10-5.12)	0.56 (0.19-1.67)
Medically assisted reproduction	293 (19.7)	16 (19.9)	70 (16.8)	1.01 (0.58-1.77)	0.82 (0.61-1.11)
Medication in the first trimester	240 (16.7)	11 (13.9)	63 (15.3)	0.81 (0.42-1.56)	0.90 (0.66-1.24)
Gestational age					
$24^{0/7}$-$27^{6/7}$	454 (30.2)	37 (43.5)	331 (76.8)	1.78 (1.14-2.76)	7.63 (5.97-9.83)
$28^{0/7}$-$31^{6/7}$	1047 (69.8)	48 (56.5)	100 (23.2)	ref	ref
Number of fetuses					
Singletons	917 (61.1)	63 (72.9)	310 (71.9)	ref	ref
Twins	584 (38.9)	22 (27.1)	121 (28.1)	0.58 (0.35-0.95)	0.61 (0.48-0.77)
Antenatal corticosteroids	980 (67.1)	47 (56.0)	134 (45.4)	0.64 (0.41-1.01)	0.42 (0.34-0.53)
PPROM	768 (51.4)	44 (52.4)	220 (51.4)	1.02 (0.66-1.59)	1.00 (0.80-1.25)
Clinical chorioamnionitis	68 (4.5)	9 (10.6)	32 (7.4)	2.43 (1.11-5.34)	1.75 (1.12-2.73)
Histologic chorioamnionitis	401 (41.8)	27 (46.6)	155 (50.8)	1.21 (0.70-2.07)	1.42 (1.09-1.85)
Histologic chorioamnionitis without clinical chorioamnionitis	352 (38.9)	20 (39.2)	132 (47.3)	1.21 (0.71-2.08)	1.44 (1.09-1.91)
Missing data	541	27	126		
Cesarean delivery	751 (50.4)	33 (39.3)	133 (31.3)	0.65 (0.56-1.80)	0.47 (0.37-0.60)
Neonatal characteristics					
Birth weight, g					
<1500	1061 (70.7)	67 (78.8)	404 (94.4)	1.54 (0.93-2.70)	6.98 (4.65-10.97)
1500-2500	439 (29.2)	18 (21.2)	24 (5.6)	ref	ref
>2500	1 (0.01)	0 (0)	0 (0)	–	–
Male sex	813 (54.2)	47 (55.3)	249 (57.8)	1.02 (0.66-1.59)	1.15 (0.92-1.44)
Severe IVH	53 (3.6)	10 (11.8)	126 (41.1)	3.90 (1.89-8.06)	19.4 (13.4-28.1)
cPVL	17 (1.1)	11 (12.9)	28 (9.6)	12.97 (5.78-29.1)	9.30 (5.0-17.4)
BPD	89 (6.1)	6 (13.9)	18 (9.0)	2.53 (1.24-5.14)	1.64 (0.93-2.89)
NEC	47 (3.2)	2 (2.4)	19 (6.1)	0.71 (0.16-3.16)	2.07 (1.18-3.65)
EOS	32 (2.2)	1 (1.2)	20 (6.5)	0.57 (0.08-4.01)	2.89 (1.59-5.24)

BPD, bronchopulmonary dysplasia; *cPVL*, cystic periventricular leukomalacia; *EOS*, early-onset sepsis; *NEC*, necrotizing enterocolitis.
Severe IVH is defined as grade III or IV IVH.
EOS is defined as proven neonatal bacterial infection with positive cultures of the cerebrospinal fluid or blood before 72 hours.
For each variable in rows, if missing data >5%, the numbers and percentages of missing data are added to a supplementary row. There are no missing data for the following variables: maternal age, gestational age, number of fetuses, clinical chorioamnionitis, birth weight, and male sex.
*Unadjusted ORs are weighted by recruitment period.

Table VII. Association of chorioamnionitis and CP and/or death at 2 years in very preterm births with no imputation for outcome

Outcomes	No chorioamnionitis n/N (wtd %)	Chorioamnionitis n/N (wtd %)	Crude OR (95% CI) *P* value	aOR* (95% CI) *P* value	aOR† (95% CI) *P* value
Clinical chorioamnionitis (regardless of histologic status)					
CP	76/1509 (5.0)	9/77 (11.1)	2.43 (1.11-5.33) *P* = .03	2.25 (0.99-4.61) *P* = .04	2.21 (1.00-4.87) *P* = .05
Death before 2 y	323/2136 (13.1)	23/116 (18.1)	1.38 (0.86-2.22) *P* = .18	1.10 (0.57-2.01) *P* = .76	1.10 (0.61-1.92) *P* = .74
CP or death	399/1832 (19.5)	32/100 (29.8)	1.64 (1.06-2.55) *P* = .03	1.53 (0.88-2.60) *P* = .12	1.48 (0.88-2.43) *P* = .13
Histologic chorioamnionitis (regardless of clinical status)					
CP	31/590 (5.3)	27/428 (6.1)	1.21 (0.70-2.07) *P* = .49	0.84 (0.46-1.53) *P* = .57	1.03 (0.56-1.89) *P* = .92
Death before 2 y	119/831 (12.3)	128/639 (17.9)	1.47 (1.11-1.94) *P* = .008	0.88 (0.61-1.27) *P* = .51	0.84 (0.60-1.19) *P* = .33
CP or death	150/709 (18.9)	155/556 (25.5)	1.42 (1.09-1.85) *P* = .03	0.90 (0.65-1.23) *P* = .49	0.84 (0.62-1.16) *P* = .31

wtd%: percentages are weighted by recruitment period.
Crude and aORs were calculated with generalized estimated equation models.
*aOR: Complete-case analysis, adjusted for gestational age, maternal age, obesity, antenatal corticosteroids, twinning, and infant sex.
†aOR: Multiple imputations for covariates, restricted to cases with available diagnosis of clinical chorioamnionitis or placental histology, adjusted for gestational age, maternal age, obesity, antenatal corticosteroids, twinning, and infant sex.