Association of chorioamnionitis with cerebral palsy at two years after spontaneous very preterm birth: the epipage-2 cohort study

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TITLE PAGE

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SHORT TITLE (6 words/max 8 words)

Association of chorioamnionitis with cerebral palsy

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STRUCTURED ABSTRACT (248 words)

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 (WG) after spontaneous birth.

Study design: EPIPAGE-2 is a national, prospective, population-based cohort study of preterm children born 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} to 31^{+6}WG. We compared the outcomes of CP, death at 2 years' corrected age,and "CP or deathat age 2"according tothe presence of either clinical chorioamnionitis (CCA) or histological chorioamnionitis (HCA).All percentages were weighted by the duration of the recruitment period.

Results: Among 2,252 infants born alive spontaneously before 32 WG, 116 (5.2%) were exposed to CCA. Among 1,470 with placental examination data available, 639 (43.5%) had HCA. In total, 346 infants died before 2 years and 1,586 (83.2% of the survivors) were evaluated for CP at age 2. CP rates were 11.1% with and 5.0%without CCA (*P*=.03) and 6.1% with and 5.3% without HCA (*P*=.49). After adjustment for confounding factors, CP risk rose with CCA (adjusted OR [aOR]2.13, 95% CI 1.12-4.05) but not HCA(aOR1.21,95% 0.75-1.93). Neither form was associated with the composite outcome "CP or death at age 2".

Conclusions: Among very preterm infants born spontaneously, the risk of CP at a corrected age of two years was associated with exposure to CCA but not HCA.

Keywords: cerebral palsy;chorioamnionitis;intrauterine infection;cohort study;preterm birth

Abbreviations:

aOR	**adjusted odds ratio**
CCA	**clinical chorioamnionitis**
CI	**confidence interval**
CP	**cerebral palsy**
GA	**gestational age**
HCA	**histological chorioamnionitis**
IVH	**intraventricular hemorrhage**
PPROM	**preterm premature rupture of the membranes**
PTL	**preterm labor**
WG	**weeks of gestation**

MAIN TEXT

Introduction

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 (CCA) or histological (HCA),is associated with CP.[4,5]Definitions of prenatal inflammation/infectionvary widely, and its impact on the fetal brain remains controversial.[6]Three meta-analyses have shownconflicting results aboutan association between chorioamnionitis and CP in premature infants.[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 (PTL).[10, 11] However, the clinical path leading to preterm birth, including fetal and obstetric complications and mode of delivery, differs in women with vascular disordersandthose with PTL and PPROM.[12]Inflammation may be involved in cases of PTL or PPROM andlead to spontaneous preterm birth, whereas vascular disease is associated with placental insufficiency,

medically induced prematurity,and higher in-hospital mortality.[12, 13]Including all subtypes of preterm births may thus be inappropriate, first, because chorioamnionitis is nearly absent in the subgroup of infants with vascular disease,[14]and second, because adverse outcomesare induced by different physiopathological pathwaysthat depend on the preterm birth subtype.[12, 13, 15, 16]Intrauterine inflammation with elevated fetal cytokines may be independently harmful for the preterm infant's developing brain andprovokeneonatal cerebral white matter damage that may subsequentlybe diagnosed as CP.

Thus, we studied the impact of chorioamnionitis on CP and/or death in a homogeneous population of infants born afterPTL or PPROM in the EPIPAGE-2 cohort, a French prospective population-based study.[17]The main objective was to assess the association between CCA and/or HCA and CP at a corrected ageof two years in children born before 32 WG.

Methods

EPIPAGE-2is a nationwide, prospective, population-based study scheduled to follow up preterm children to the age of 12 years.[18]Neonates born from 22 to 34 completed WG 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 8months for preterm births from 22^{+0} to 26^{+6}WG, 6months for thosefrom27^{+0} to 31^{+6}WG,and 5weeks for those from 32^{+0} to 34^{+6}WG.[17]Referring physicians assessed the presence of CP or other neurosensory deficiencies at two 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} to 31^{+6}WGafter a spontaneous birth involving PPROM (rupture of the membranes more than 24 hoursbefore delivery) or PTL (defined as regular contractions accompanied by cervical change, including intact membranes and membranes ruptured for less than 24 hoursbefore delivery) were included in this study. The method of classifyingthe cause of preterm birth has previously been described.[13]

Exclusion criteria were: other causes of preterm birth; births before 24 WG becausesuch infants did not routinely receive intensive care in France in 2011;[18]births after32 weeksbecause CPoccurs 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(EM, LFH, GK, and FG) independently reviewed cases of congenital anomalies.We also excluded all triplets and quadruplets,as well as twin pregnancieswith complications,such as twin-twin transfusion syndromeor intrauterine fetal deathof one co-twin, because of the intermediate factors of morbidity in multiple pregnancies.[4]

Main outcomes and exposure measures

CCA and HCA

CCA was diagnosed by maternal temperature >37.8°C (100°F) associated with at least two of the following five 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 HCA on neurological outcomes, from data collected by pathologists with a standardizedform to assess the extent of HCA and funisitis.[17]According to this standardized classification, histological placental findings were divided intothree stages: noHCA; HCA defined by the presence of neutrophils in the membranous amniochorion and/or membranes; and HCA

with histological funisitis, defined by neutrophil infiltration into the fetal vessels in the chorionic plate and umbilical cord.[20]

Outcomes: cerebral palsy and death

The primary outcome was CP, a disease due to permanent movement and posture disturbances resultingfrom a nonprogressive lesion of the developing brain.Itwas 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 ageof two yearsand those who presented CP at that age, to take the potential competitive risk between these outcomes into account.

Otherfactors studied

Maternal characteristics examined wereage, 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 (GA).Antenatal steroid treatment was defined by administration to the mother of at least one betamethasone injection.

The neonatal variables examined were gender, birth weight, death in the delivery room or neonatal intensive care unit, early-onset sepsis, necrotizing enterocolitis (Bell's 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 hoursof life.Severe bronchopulmonary dysplasia was defined as oxygen supplementation for at least 28 days and persistent need for oxygen (FiO_2 ≥ 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 analysis

Categorical variables were compared by a Chi-square test or Fisher's exact test, as appropriate. Continuous variables were described by theirmediansand interquartile ranges(IQR) 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 HCA alone and HCA + funisitis with CP, death, and "CP or death"were similar, the following analyses treat HCA and HCA + funisitis as the same exposure variable. PTL and PPROM were considered together for the same reason (Table I; online only).

The associations between CCA and HCA with CP, death, and"CP or death" atage 2 were studied by bivariate analyses and multivariate logistic regression models that usedgeneralized estimated equations to take the non-independence of observations for twins into account. These analyses were performed for cases with available data for either CCAor HCAand were adjusted for maternal age, obesity, number of fetuses, GAat birth, gender, and antenatal steroid use, because these potential confounding factors have previously been associated with CP inthe literature.[1, 4, 24]Adjusting for GA is customary in observational studies comparinggroups with different GA 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 two analyses: 1) a complete-case analysis(logistic regression restricted to infants with complete data for the diagnosis of CCA or HCA, the outcome, and all covariates); 2) 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/orcorrelated 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 two years); 3) 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 equationswith 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; online only).*P*-values<.05were considered statistically significant. Statistical analyses used R v3.5.1.

Results

Among the3,816 livebirthseligible from the EPIPAGE-2 study, 329 were excluded because of congenital malformations or diseases, or as triplets or quadruplets oras twins with twin-twin transfusion syndrome, and 85 more for missing CCA data. Then 1,150cases were excluded because the cause of preterm birth was neitherPTL nor PPROM.Table III (online only) describes the distribution of CCA and HCA by cause of preterm birth. Finally, the analysis of the association between CCA and outcomes at 2 years included 2,252 children,of whom 1,470 had a placental examination available to enable analysis of the association of HCA with outcomes at age 2(FigureI). The remaining 782 (34.7%) women had no placental examination. Factors associated with this lack of examinationwere maternal birth in sub-Saharan Africa, GA > 28 weeks, absence of CCA, and vaginal delivery, but not CP. (Table II; online only).

Of these 2,252infants, 116(5.2%) were exposed to CCA and 639/1,470(43.5%) toHCA (with all percentages weighted according to the length of the recruitment period).Among these 1,470 children, 82 (5.5%) were exposed to both CCA and HCA and 557 (39.1%) to HCA but not CCA.

On bivariate analysis, CCA was associated with maternal age >35, nulliparity, obesity, singleton pregnancy, PPROM, antenatal antibiotics, GA <28 weeks, cesarean delivery, early-onset sepsis, and CP. HCA was associated with maternal birth in sub-Saharan Africa, no medical insurance, obesity, singleton pregnancy, cervical cerclage, PPROM, antenatal antibiotics, GA <28 weeks, early-onset sepsis,neonatal death,and death at age2 (Table IV).

In all, 346 infants (267 born at 24–26 WG and 79 at 27–31 WG) died before age 2. Among the 1,906 children alive at two years, 1,586 were evaluated for CP and 320 (16.8%) lost to follow up. Among the latter, 16 (5.0%) were exposed to CCA and 83 (40.5%) to HCA, that is, they did not differ for this exposure (Table IV).

Overall, 85 (5.3%) children were diagnosed with CP. More specifically, at two years' corrected age, the CP rate was 11.1% in chorioamnionitis-exposed and 5.0%in non-exposed children (*P*=.03).Associations of maternal, obstetric and neonatal characteristics with CP are reported in table V (online only). After multivariate analysis and multiple imputation, CCA exposure was associated with CP (aOR2.13,95% CI 1.12-4.05] but not with death (aOR1.10,95% CI 0.60-1.92)or with the composite "CP or death"outcome (aOR1.42, 95% CI 0.87-2.26)(TableVI). HCA was not associated with CP (6.1%versus 5.3% withand without HCA;aOR=1.21, 95% CI0.75-1.93),death (aOR0.87, 95% CI 0.62-1.23), or"CP or death"(aOR0.89, 95% CI 0.66-1.19).Results were similar for CCA + HCA and CCA alone. Likewise,associations with CP, death, or "CP or death" were similar with HCA without CCA and with HCA alone(Table VI).Similar associations were observed without imputation for CP (Table VII; online only).

Discussion

The primary finding of this study is that among very preterm infants born after PTLor PPROM, those with CCA were at increased CP risk; those withHCA were not.

The main strength of the study is its large prospective population-based design, with detailed data forpregnancy and neonatal outcomes. The second strength is the analysis of the association

between chorioamnionitis and CP in a large homogeneous population of very preterm infants born after PTL or PPROM.[16, 17]To that end, we excluded preterm children born after pregnancies complicated by fetal growth restrictionor placental dysfunction because of the different physiological mechanisms leading to preterm birth and theirpoor outcomes for neonatal mortality, CP at two years, and cognitive function at age 5.[1, 13, 26]Another strength is the homogeneous data collection forthe placentas examined, based on a formdesigned for the EPIPAGE-2 study and used prospectively for the histological analyses.

The rate of missing data for histological 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 CCA or delivery at an early GA. This weakness may thus artificially increase the prevalence of HCA in our population but it doesnot modifythe potential association between HCA and CP.

Another potential limitation of our study is the 16.8% rate of missing data about CP at two years. This rate is nonetheless similar tothat in other large studiesof infants' outcome at two years.[10, 11] To provide the best estimate of the association of CP with CCA and HCA and to address this limit on the primary outcome, we used a model with multiple imputations to deal with missing data and includingneonatal neurological 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 CCA or HCA and CP is controversial. Among the three meta-analyses that have studied it,[5, 7, 9]two found an increased risk of CP in cases of CCA. Interestingly,the strength of this association increased with the accuracy of the clinical criteria used to define CCA.[5, 7]The association between HCAand CP is even more controversial, and the most recent meta-analysis yielded discordant results, with aORsranging from 0.35 to 2.48.[9, 29, 30]

Our findingscome from the largest nationwide population-based prospective study we are aware of; its data about CCA and HCA are accurate and its practices consistent with current worldwide recommendations (i.e., antenatal corticosteroids for PTL or PPROM and antibiotics for PPROM). Moreover, no other study with a similar design has limited inclusion to women with PPROM andPTL. Two recent multicenter studies with large sample sizesdid not find any association between HCA and CP, but they also included children born after placental disease.[10, 11]In one of these studies, Pappas et al.)studied 1,194 children born before 27 WG and found CP rates of 4.9% in the cases with and 4.5% in those without HCA (*P*=.50).[10] In 2016, in a retrospective study in Japan, Miyazaki et al reported similar rates of CP among 2,201 infants evaluated at 3 years (9.7% with and 6.3% without HCA; aOR0.91, 95% CI 0.67-1.59).[11] These two studies, however, were not population-based and alsoincluded preterm births from all causes.They were therefore subject to potential biases, e.g., 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 post-partum risk factors.[31]Our results suggest that when preterm birth is due toPTL or PPROM,CCA — but not HCA — is a risk factor forCP. Two potential hypotheses may explain this result. First, local inflammation may be stronger in CCA and producegreater effects on the fetus. Another hypothesis, however, is that many cases of histological 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 recent data support this hypothesis:recent studies of amniotic fluid that usedboth cultures and broad-range polymerase chain reaction combined with mass spectrometry have found that sterile intra-amniotic inflammation is more common than low virulence (e.g.,*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]HCA may therefore be sterile or associated with organisms of low virulence that have a milder impact, if any, on the neonatal brain.[34] Conversely, CCA is caused by highly pathogenic bacteria that are mostly group B Streptococcus and *Escherichia coli,*[19, 35]which can cause neonatal sepsis with higherneonatal morbidity and mortality.[36]CCA certainly represents a more recent set of events leading to premature delivery, whileHCA 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 32WG, in the absence of obstetric complications. Expectant management benefits the fetus by increasing GA at birth.[37-39]In cases of CCA, however, immediate delivery must be discussed.The possible risks caused by CCA have to be weighted against, for example, the risks of extreme prematurity.[38, 40]

Conclusion

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

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DISCLOSURE OF INTEREST:

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FIGURE LEGEND

FigureI: Study flow chart

Among 2,252 live births (N_2), a placental examination was available for 1470 cases (N_5).
Among 1,586 infants evaluated for CP at 2 years (N_1), a placental examination was available for 1018 cases (N_4).

Table IV: Demographic and baseline characteristics and outcomes for infants born after preterm

		No CCA (N=2136) n (wtd %)	CCA (N=116) n (wtd %)	No HCA (N=831) n (wtd %)	HCA (N=639) n (wtd %)
MATERNAL AND OBSTETRIC CHARACTERISTICS					
Maternal age, years	<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)*
PTL		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 section		962 (46.5)	63 (56.7)*	414 (51.4)	286 (46.2)
CCA		-	-	13 (1.6)	82 (13.0)**
HCA (among available placentas)		557 (39.2)	82 (85.5)**	-	-
Gestational age	24^{+0}–27^{+6}	823 (33.5)	59 (46.1)*	262 (26.9)	367 (48.0)**
WG	28^{+0}–31^{+6}	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 YEARS					
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.
* P <.05, ** P< .001
Chi-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.

Table VI: Association of chorioamnionitis with cerebral palsy and/or death at 2 years in very preterm births

	No chorioamnionitis n/N (wtd %)	Chorioamnionitis n/N (wtd %)	Crude OR (95% CI) *P*-value	aOR[1] (95% CI) *P*-value	aOR[2] (95%CI) *P*-value
CCA (regardless of histological 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	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
HCA (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 years	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
HCA and CCA					
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 years	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
HCA without CCA					
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 years	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

Legend:

The study subpopulations are classified as:
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 CCA, to study the impact of HCA only.
See the flow chart of the study (Figure 1) for the different subpopulations.

aOR[1]: Complete-case analysis, adjusted for GA, maternal age, obesity, antenatal corticosteroids, twinning and infant gender.
aOR[2]: Multiple imputations for covariates and outcome, restricted to cases with available diagnosis of CCA or placental histology, adjusted for GA, maternal age, obesity, antenatal corticosteroids, twinning, and infant gender.
Crude and adjusted ORs were calculated with generalized estimated equation models.

Figure I: Study flow chart

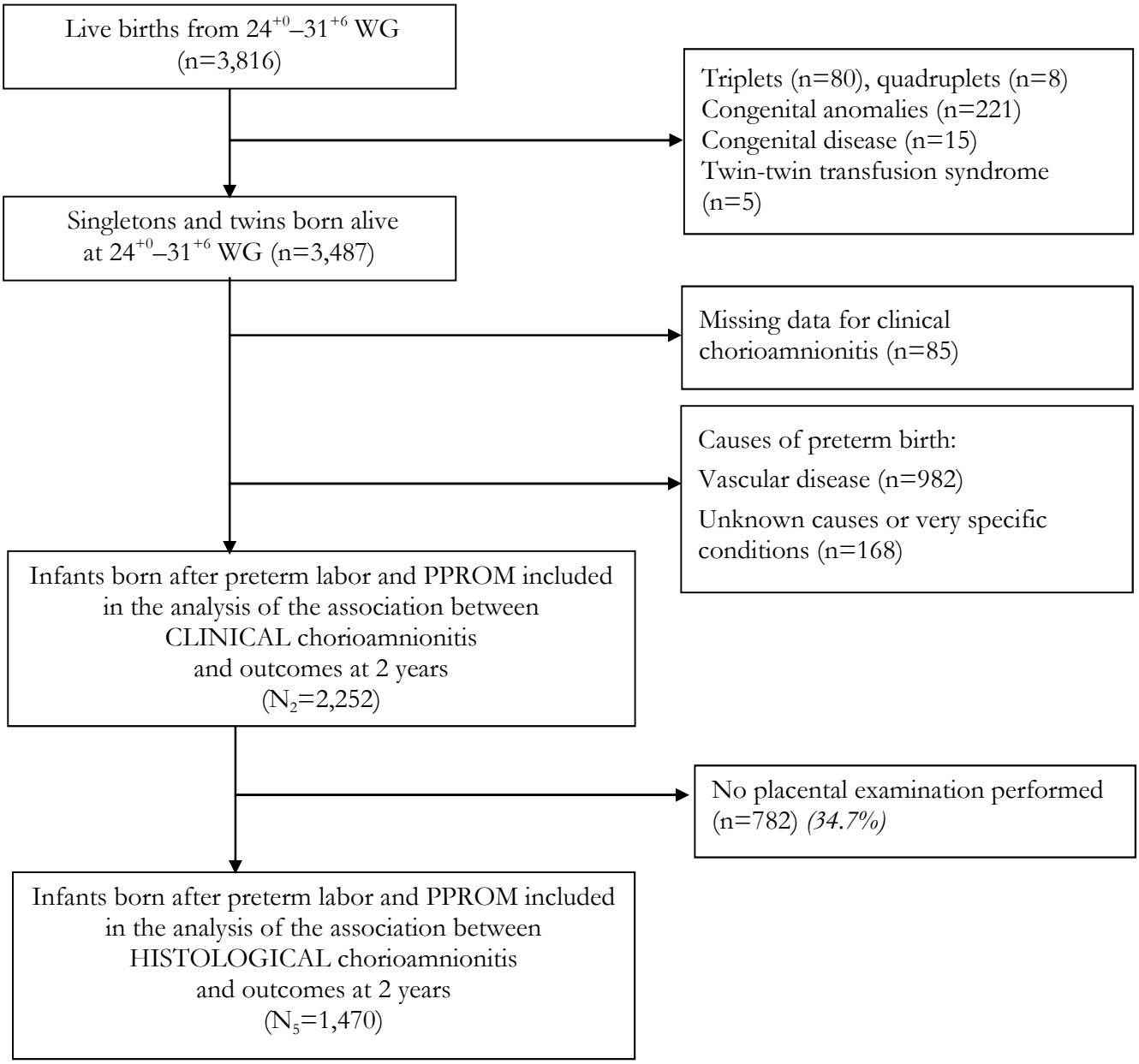

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Table III; online: Distribution of clinical and histological chorioamnionitis/funisitis by cause of preterm birth in live births occurring between 24^{+0} and 31^{+6} weeks of gestation

	Cause of preterm birth (N=3,402)				
	Spontaneous preterm birth (N=2,252)		**Vascular disease (N=982)**		**Unknown or rare causes (N=168)**
Type of chorioamnionitis	**PTL (N=1,400)**	**PPROM (N=852)**	**Hypertensive disorders and abruptio placenta (N=457)**	**Suspected FGR (N=525)**	
	n (%)	n (%)	n (%)	n (%)	n (%)
CCA	41/1,400 (2.9)	75/852 (8.8)	1/457 (0.2) *	2/525 (0.4) *	3/168 (1.8)
HCA alone	306/896 (34.2)	333/574 (58.0)	7/336 (1.5) **	9/418 (1.7) **	19/124 (15.3)
HCA + funisitis	121/896 (13.5)	130/574 (22.6)	3/336 (0.7)	3/418 (0.6)	8/124 (6.4)
No placental examination	504/1,400 (36.0)	278/852 (32.6)	121/457 (26.5)	107/525 (20.4)	44/168 (26.2)

PTL: preterm labor, PPROM: preterm premature rupture of membranes, suspected FGR: fetal growth restriction < 10th percentile suspected prenatally based on estimated fetal weight, CCA: clinical chorioamnionitis, HCA: histological chorioamnionitis
Hypertensive disorder and abruptio placentae are cases not accompanied by suspected FGR.
Data on CCA were available for all cases. Data for HCA were available for 2,348/3,402 cases.

* Three patients had mixed causes of prematurity: they presented criteria for CCA, but the main conditions leading to preterm birth were severe preeclampsia and HELLP syndrome, both with suspected FGR, and one case of abruptio placenta without suspected FGR.
** Among the 16 cases of HCA 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 CCA for 1, PPROM for 3 and PTL for 4.

Table II; online: Demographic and baseline characteristics and outcomes of cases with missing and available placental examination for determination of histological chorioamnionitis among infants born after preterm labor (PTL) or preterm premature rupture of membranes (PPROM)

		Missing placentas N=782 n (%)	**Available placentas N=1470** N (%)	***P* value**
MATERNAL AND OBSTETRIC CHARACTERISTICS				
Maternal age, years	<20	33 (4.2)	71 (4.8)	.40
	20-35	606 (77.5)	1100 (74.9)	
	>35	143 (18.3)	297 (20.2)	
Region of birth	European	608 (85.3)	1211 (90.4)	.002
	North African	33 (4.9)	47 (3.5)	
	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 section		325 (41.6)	700 (47.9)	.01
Clinical chorioamnionitis		21 (2.7)	95 (6.5)	.0002
Gestational age, WG	24^{+0}-27^{+6}	253 (32.4)	629 (42.8)	<.0001
	28^{+0}-31^{+6}	529 (67.6)	841 (57.2)	
NEONATAL CHARACTERISTICS				
Birth weight	Mean ± SD	1273 ± 374	1173 ± 363	<.0001
Male gender		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 YEARS				
Cerebral palsy		27 (4.8)	58 (5.7)	.49

WG: weeks' gestation, EOS: early-onset sepsis

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 I; online: Association between preterm premature rupture of membranes (PPROM), histological chorioamnionitis (HCA), alone or associated with funisitis, and cerebral palsy, death, and the composite outcome cerebral palsy or death among infants born after preterm labor (PTL) or PPROM

	Cerebral palsy at 2 years			**Death at 2 years**			**Cerebral palsy or death**		
	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)**
PTL	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 HCA	31/590 (5.3)	ref	ref	119/831 (12.3)	ref	ref	150/709 (18.9)	ref	ref
HCA 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)
HCA + 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 VII; online: Association of chorioamnionitis and cerebral palsy (CP) and/or death at 2 years in very preterm births with no imputation for outcome

	No chorioamnionitis n/N (wtd %)	**Chorioamnionitis** n/N (wtd %)	**Crude OR (95%CI)** ***P*** **value**	**aOR[1] (95%CI)** ***P*** **value**	**aOR[2] (95%CI)** ***P*** **-value**
CCA (regardless of histological 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 years	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
HCA (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 years	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

CCA: clinical chorioamnionitis, HCA: histological chorioamnionitis
wtd%, percentages are weighted by recruitment period
aOR[1]: Complete-case analysis, adjusted for gestational age, maternal age, obesity, antenatal corticosteroids, twinning, and infant gender.
aOR[2]: Multiple imputations for covariates, restricted to cases with available diagnosis of CCA or placental histology, adjusted for gestational age, maternal age, obesity, antenatal corticosteroids, twinning, and infant gender.
Crude and adjusted ORs were calculated with generalized estimated equation models.

Table V; online: Maternal, obstetric, and neonatal characteristics associated with cerebral palsy and/or death at 2 years: bivariate analysis

		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	<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	24^0-27^6	454 (30.2)	37 (43.5)	331 (76.8)	1.78 [1.14-2.76]	7.63 [5.97-9.83]
	28^0-31^6	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]
CCA		68 (4.5)	9 (10.6)	32 (7.4)	2.43 [1.11-5.34]	1.75 [1.12-2.73]
HCA		401 (41.8)	27 (46.6)	155 (50.8)	1.21 [0.70-2.07]	1.42 [1.09-1.85]
HCA without CCA		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 section		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 gender		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]

CP: cerebral palsy, CCA: clinical chorioamnionitis, HCA: histological chorioamnionitis, PPROM: preterm premature rupture of membranes, severe IVH: grade III or IV intraventricular hemorrhage, cPVL: cystic periventricular leukomalacia, BPD: bronchopulmonary dysplasia, NEC: necrotizing enterocolitis,

EOS: early-onset sepsis defined as proven neonatal bacterial infection with positive cultures of the cerebrospinal fluid or blood before 72 hours.

* Unadjusted ORs are weighted 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. There are no missing data for the following variables: maternal age, gestational age, number of fetuses, clinical chorioamnionitis, birth weight and male gender