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Research Article

Placental Histological Features and Neurodevelopmental Outcomes at Two Years in Very-Low-Birth-Weight Infants

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ABSTRACT

Background: We evaluated the rates of placental pathologic lesions and their relationship with two-year neurodevelopmental outcomes in very-low-birth-weight (VLBW) infants.
Methods: This is a cohort observational study comprising 595 VLBW infants during 2007 to 2015. Neurodevelopmental assessment was carried out at 24 months corrected age.
Results: In univariate analysis the rates of survival with normal neurodevelopmental outcomes were lower in pregnancies with severe histologic chorioamnionitis (38 of 43, 88.4% when compared with 305 of 450, 67.8%), severe maternal vascular malperfusion (MVM) (17 of 37, 45.9% when compared with 326/492, 66.3%), and intravillous hemorrhage (37 of 82, 45.1% when compared with 306 of 449, 68.1%). In logistic models, severe MVM (adjusted odds ratio [adj. OR] = 0.45, 95% confidence interval [CI] = 0.22 to 0.92), severe fetal vascular malperfusion (FVM) (adj. OR = 0.46, 95% CI = 0.22 to 0.45), and intravillous hemorrhage (adj. OR = 0.38, 95% CI = 0.22 to 0.62) were associated with lower rates of infant survival with normal neurodevelopmental outcome. FVM (adj. OR = 0.46, 95% CI = 0.21 to 0.97) and intravillous hemorrhage (adj. OR = 0.37, 95% CI = 0.22 to 0.62) were also the only placental lesions that were independent predictors of a lower rate of intact survival in stepwise analysis for prognostic factors of the entire cohort.
Conclusions: Placental pathologic findings such as severe MVM, FVM, and intravillous hemorrhage are significant predictors of neonatal survival and subsequent adverse neurodevelopmental outcomes. Data on the placental pathology could be useful in the neurodevelopmental follow-up of VLBW infants.

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Ethics approval: The present clinical trial was approved by ethical committee of IRCCS Foundation Policlinico San Matteo, Pavia (number: 24043/2012 / URL: trials.sanmatteo.loc).

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Introduction

Very-low-birth-weight infants (VLBW) account for approximately 1% to 1.5% of all births but are responsible for a considerable portion of neurodevelopmental impairments among survivors.[1] Meta-analytic reviews suggest that among VLBW survivors, the pooled prevalence of cerebral palsy and cognitive and motor delays are 6.8%, 16.9%, and 20.6%, respectively.[2] Although lower gestational age and birth weight are by far the most predictive factors of neonatal death and abnormal infant neurodevelopmental outcomes, other antenatal and postnatal variables play a key role in the neonatal prognosis.[3] Among these, etiology of VLBW, antenatal steroid and magnesium sulfate use, pregnancy, and neonatal complications have been associated with adverse infant outcomes.[4-7] Most of the pathophysiologic events leading to VLBW births occur at the placental level; choriodecidual inflammation, maternal and FVM, loss of placental integrity, and villitis are placental pathologic lesions involved in the pathogenesis of preterm delivery and fetal growth restriction (FGR).[8,9] Surprisingly, with the only possible exception of chorioamnionitis, studies on placental lesions of VLBW infants are mostly incomplete, represented by small case series or case-control investigations.[10] The role of chorioamnionitis as an adverse factor in developmental outcomes of VLBW is controversial,[11-13] whereas FVM and abruptio placentae have been associated with early markers of infant brain damage.[14,15] The recognition of placental features associated with neurodevelopmental impairment of VLBW could be very useful to identify newborns requiring proper neurodevelopmental follow-up due to an increased risk of developing neurodevelopmental impairments. The purpose of this study was to evaluate the association between placental pathologic lesions, neonatal mortality, and neurodevelopmental outcomes at age two years in a cohort of VLBW infants.

Methods

The study population included all VLBW infants delivered consecutively at our institution between 2007 and 2015. The trial was approved by ethical committee of Foundation IRCCS Policlinico San Matteo. The eligibility criteria included (1) absence of fetal malformations, known chromosomal anomalies, or congenital infections; (2) enrollment for prenatal care during the first trimester of pregnancy with ultrasound-confirmed gestational age; and (3) delivery of a viable fetus $\leq$1500 g and $\geq$24 weeks of pregnancy. Demographic data of participants were collected upon enrollment in the study. Clinical data were collected at discharge and were stored together with the pathology data in a computer database.

Obstetrics and fetal variables

FGR was diagnosed based on longitudinal evaluation of fetal abdominal circumference, estimated fetal weight, and Doppler pulsatility index of umbilical artery according to standard criteria.[16] When feasible, a conservative management plan for FGR was adopted according to a predefined protocol, which included antenatal visits, ultrasonographic surveillance, and cardiotocographic monitoring. Ultrasonographic evaluation included weekly monitoring of amniotic fluid volume and fetal biometry fortnightly. Doppler studies of fetal circulation included weekly or biweekly measurements of blood flow velocity waveforms of the umbilical artery, middle cerebral artery, and ductus venosus depending on the severity of blood flow abnormalities. Amniotic fluid volume was expressed using the amniotic fluid index and measured sonographically as the sum of the deepest vertical pool in each of the four maternal abdominal quadrants. Clinical chorioamnionitis was defined as the presence of maternal fever (>38 C) in addition to two other signs such as maternal (>100/min) or fetal tachycardia (>160/min), uterine tenderness, or foul/purulent amniotic fluid.[17] During the period of the study, preterm labor and preterm premature rupture of membranes (PPROM) were treated according to a definite protocol including the maternal use of atosiban and nifedipine for 48 hours as tocolytic drugs among women with intact membranes, betamethasone up to 36 weeks of pregnancy irrespective of the cause of prematurity, and magnesium sulfate for neonatal neuroprotection up to 34 weeks of pregnancy. For women diagnosed with PPROM without other complications, a standard approach with initial hospitalization, expectant management, and erythromycin or penicillin administration for at least 10 days was used. When feasible, women were followed weekly as outpatients up to 36 weeks of pregnancy. Both outpatient and in-hospital ultrasonographic evaluations were carried out by the same group of obstetricians who were experienced in perinatal medicine. To evaluate the severity of the growth deficit, the birth weight *z* score was computed for each case by comparing the actual birth weight with the standard Italian birth weight for gestational age, adjusted for maternal parity and fetal sex. Preeclampsia was diagnosed according to standard criteria.[18]

Pathologic variables

Pathologists were unaware of FGR or other maternal diseases; only gestational age was known at the time of evaluation/revision of the specimens.

The guidelines used for the release of placentas to the pathology unit were those suggested by Langston et al.[19] Histologic lesions assessed and classified according to the Amsterdam Placental Workshop Group Consensus statement[20,21] were placental inflammatory immune processes including maternal and fetal acute inflammatory responses (chorioamionitis stage and grade); noninfectious chronic villitis (villitis of unknown origin) distinguishing between low grade (more than one focus, each involving < 10 contiguous villi, either focal if seen on only one slide or multifocal if seen on two or more slides) and high grade (patchy in case of multiple foci, at least one affecting >10 contiguous villi; diffuse when more than 30% distal villi were involved); FVM including obstructive lesions of the umbilical cord and proximal (chorionic or stem vessels) villous thrombosis; avascular villi, intramural fibrin deposition, and karyorrhexis reserving the term high-grade FVM for severe cases ($\geq$45 avascular villi in three disk sections, two or more thrombi in the proximal fetal vessels, or multiple nonocclusive thrombi); maternal vascular malperfusion (MVM) lesions including accelerated villous maturation and distal villous hypoplasia and decidual vasculopathy (persistence of arterial smooth muscle, fibrinoid necrosis, atherosis, absence of spiral artery remodeling); and loss of integrity of placenta, which is a subcategory of MVM and includes infarcts; acute and chronic abruptio and marginal abruptio was classified separately by the other causes of MVM. Finally, MVM was defined as severe in the case of multiple lesions involving >30% of placental parenchyma. Given its recently evidenced strong relationship with fetal death,[22] a histologic diagnosis of intravillous hemorrhage whether or not being associated with placental abruption, was evaluated as a single pathologic category. The fixed placental weight was recorded after trimming extraplacental membranes and removing the umbilical cord. Placental volumes were derived from measurements of major and minor diameters and thickness (largest diameter $\times$ smallest diameter $\times$ thickness). Placental area was calculated by assuming an elliptical surface (largest diameter $\times$ smallest diameter $\times$ $\pi/4$). To evaluate placental

efficiency (grams of the fetus produced per gram of placenta) we used fetal/placental weight ratio.

Neonatal data and follow-up

Perinatal and neonatal data were recorded for each infant according to the Vermont Oxford Network database collection criteria.[23] In addition, for each newborn, the clinical risk index for babies score was calculated, designed to quantify the clinical severity based on six variables evaluated during the first 12 hours of life (birth weight, gestational age, minimum and maximum FiO_2 to keep a saturation between 88% and 95%, worst bases excess, and presence of congenital abnormalities).[24]

Each newborn underwent a serial head sonographic examination. Periventricular and intraventricular hemorrhage (IVH) and other neonatal head ultrasound findings were classified and grouped according to Rademaker[25] as normal, when there were no abnormalities or only minor abnormalities, (Group 1); slightly abnormal, in the presence of grade I/II IVH, periventricular leukomalacia grade I, germinal layer necrosis, or a combination of these features, or ventricular dilatation as the sole feature (Group 2); or severely abnormal, when one or more of the following features were present: grade III/IV IVH, cystic periventricular leukomalacia grade II/III, thalamic lesions, focal infarctions, posthemorrhagic ventricular dilatation needing therapeutic intervention (Group 3).

Each newborn was examined by a pediatric neuropsychiatrist, at term corrected age; neonatal neurological examinations were classified as normal, in the absence of any abnormal neurological sign, or abnormal, in the presence of pathologic neurological signs of varying degrees. Every infant was afterward followed up with neurological assessments every three months during the first year of life and every six months in the second year.[26] Ophthalmologic and audiometric examinations were performed periodically to exclude sensorial abnormalities.

At 24 months corrected age every infant underwent a complete neurological examination and Griffiths' Mental Developmental Scales-Extended Revised[27] to obtain the General Quotient (GQ) and five subquotient scores corresponding to five neurodevelopmental areas (locomotor, personal-social, hearing and speech, eye-hand coordination, performance). Neurodevelopmental outcomes were classified according to the neurological examination and the GQ into (1) normal (no pathologic signs on neurological examination and GQ $\geq$ 88); (2) minor sequelae (tone or reflex abnormalities or asymmetry without functional deficits and presence of at least one sign from the triad described by Amiel-Tison and Gosselin[28]: 76$\leq$ GQ $\leq$ 87, squint or refractive errors, mild hypoacusia); and (3) major sequelae (one or more of the following: disabling or nondisabling cerebral palsy, GQ $\leq$ 75, sensorineural hearing loss requiring active intervention, severe visual impairment of peripheral or central origin).

Statistical analysis

Chi-square analysis was used to compare categorical variables. Comparisons of continuous variables between multiple groups were performed by Kruskal-Wallis ANOVA with Bonferroni correction for pairwise comparisons.[29] Partitioning of chi-square statistics with Bonferroni correction was used to compare categories in multiway contingency tables. Penalized logistic regression analysis was used to test the association of placental pathologic variables with survival and two-year neurodevelopmental outcomes correcting for potential confounders. Models included neonatal outcomes as dependent variables and gestational age, birth weight, fetal sex, type of delivery (vaginal versus Caesarean), and type of placental lesion as explanatory variables. To study the relative importance of the placental lesions across the various etiologies of VLBW, we included in the model an interaction term between the type of placental lesion and the type of etiology of VLBW. Finally, to evaluate the best independent pathologic predictors of two-year intact survival in the whole population of VLBW, we used a stepwise logistic regression including two-year infant outcomes as dependent variables, and all pathologic variables studied, gestational age, birth weight, type of delivery, and sex of the newborn, as initial explanatory variables.

Results

During the period of the study, of 595 (518 mothers) VLBW infants delivered at our institution, 21 subjects were excluded due to the lack of maternal or histologic placental data or unexpected severe fetal malformations, leaving 574 (503 mothers) newborns for analysis. The characteristics of the population under study is reported in Table 1. Major determinants of VLBW were FGR (52%), spontaneous prematurity (43.7), twins (28%), preeclampsia (27%), and PPROM (12.5%).

Obstetrics, and neonatal characteristics and placental lesions

The rates of maternal body mass index $\geq$30 or maternal age $\geq$40 years were 8.9% (45 of 503) and 9.5% (48 of 503), respectively. Table 2 reports the main obstetric and neonatal variables according to the main pathologic features. Severe MVM, FVM, and chorioamnionitis (stage$\geq$2 and grade = 2) were recorded in 6.4%, 7.4%, and 15.5% of the cases, respectively. Given the different VLBW etiologies, birth weight *z* scores (*z* score was computed for each case by comparing the actual birth weight with the standard Italian birth weight for gestational age, adjusted for maternal parity and fetal sex) were lower, and the rates of FGR and preeclampsia were higher among pregnancies complicated by severe FVM than those without this lesion. On the other hand, severe histological chorioamnionitis was associated with lower gestational age, birth weight, placental

TABLE 1.
Maternal and Obstetrics Characteristics of Population Enrolled

N = 574	Median (IQR)
Maternal age	33 (29-37)
BMI	23 (21-26)
Gestational age	29.4 (27-31.3)
Birth weight	1100 (854-1354)
Birth weight percentile	6 (1-48)
Maternal ethnic origin	
Europe	441 (76.8)
Africa	49 (8.5)
Asia	15 (2.6)
North America	16 (2.8)
South America	53 (9.2)
Maternal education $\leq$8 years	181 (31.5)
Nulliparous	378 (65.9)
First trimester BMI $\geq$30	45 (7.8)
Previous preterm or LBW	47 (8.2)
Smoking during pregnancy	111 (19.3)
Reproductive failures $\geq$3	18 (3.1)
Twins	161 (28)
FGR	298 (52)
Preeclampsia	155 (27)
Spontaneous prematurity	251 (43.7)
PPROM	72 (12.5)

Abbreviations:
BMI = Body mass index
FGR = Fetal growth restriction
IQR = Interquartile range
LBW = Low birth weight
PPROM = Premature preterm rupture of membranes

weight, and higher rates of spontaneous delivery, PPROM, and clinical chorioamnionitis. Overall, the rate of neonatal death was 13.9% (80 of 574), and in univariate analysis, severe MVM, FVM, and chorioamnionitis were associated with increased rates of neonatal death. After adjustment for gestational age and birth weight, severe MVM (adjusted odds ratio [adj. OR] = 3.98, 95% confidence interval [CI] = 1.73 to 9.16) and severe FVM (adj. OR = 3.28, 95% CI = 1.37 to 7.85), but not chorioamnionitis (adj. OR = 0.77, 95% CI = 0.4 to 1.49), were still associated with an increased risk of neonatal death. Loss of placental integrity was associated with lower gestational age and birth weight *z* scores and was more common among FGR pregnancies (Table 3). Intravillous hemorrhage was more common among FGR pregnancy, in spontaneous prematurity, and in pregnancies with a clinical diagnosis of abruptio, whereas villitis of unknown origin was associated with increased rates of FGR and of umbilical artery Doppler abnormalities. After adjustment for gestational age and birth weight, loss of placental integrity (adj. OR = 1.9, 95% CI = 1.02 to 3.66) and intravillous hemorrhage (adj. OR = 2.2, 95% CI = 1.16 to 4.11) were still significantly associated with an increased risk of neonatal death.

Placental lesions and infant neurodevelopmental outcomes

Of the 494 surviving infants, 43 (8.7%) subjects who had been judged neurologically normal at discharge from hospital were lost during follow-up, leaving 451 infants with complete two-year neurodevelopmental outcome measures. Of these, 153 infants (33.9%) were clinically considered as neurologically abnormal at the time of discharge. Overall, 41.7% (20 of 48) with severe and 46.7% (28 of 60) with mild two-year neurodevelopmental impairments had no abnormal neurological findings at discharge from the hospital. Infants delivered after histologically severe chorioamnionitis probably as a result of a lower gestational age had a lower general quotient, eye-hand coordination and performance subscale scores, and higher rates of severe neurodevelopmental sequelae compared with patients without placental lesion (Table 4).

In crude analysis, MVM, FVM, and chorioamnionitis were associated with lower rates of survival without major neurodevelopmental abnormalities, whereas MVM and chorioamnionitis were associated with lower survival rates with intact neurodevelopmental outcomes. Intravillous hemorrhage was associated with a two-year lower general quotient and locomotor, hearing and speech, and performance scores and with an excess rate of infant severe neurodevelopmental sequelae compared with pregnancies without these lesions. As a consequence, this placental lesion was also associated with a lesser likelihood of intact survival or survival without major developmental sequelae.

The odds ratios of intact survival and survival without major neurodevelopmental sequelae associated with placental lesions

TABLE 2.
Obstetrics, Hystologic, and Neonatal Characteristics According to Placental Lesions Indicating FVM, MVM, and Severe Chorioamnionitis

	Severe MVM		Severe FVM		Severe Chorioamnionitis	
	Yes (n = 37)	No (n = 537)	Yes (n = 41)	No (n = 533)	Yes (n = 89)	No (n = 485)
Gestational age	28 (26-31.5)	29 (26-31)	30 (27-34)	29 (26-31)	26 (24-27)*	29 (27-31)
Birth weight	939 (662-1261)	1098 (798-1354)	1031 (759-1398)	1092 (793-1350)	815 (687-1022)*	1130 (859-1376)
z-score birth weight	−1.82 (−3.7-0.05)	−1.57 (−3.3-0.09)	−3.05 (−3.8-1.3)*	−1.4 (−3.1-0.03)	0.22 (−0.6 + 0.88)*	−2 (−3.6-0.41)
Placental weight	240 (204-316)	260 (211-321)	274 (215-329)	260 (210-320)	250 (208-335)*	260 (207-334)
Fetal/placental ratio	4.1 (3.19-4.8)	4.1 (3.1-4.9)	4.1 (2.7-4.8)	4.1 (3.1-4.9)	3.4 (2.9-4.1)*	4.3 (3.1-5)
Twins	7 (18.9)	154 (28.7)	15 (36.6)	146 (27.4)	16 (18)*	145 (29.9)
FGR	21 (56.8)	277 (51.6)	29 (70.7)*	269 (50.5)	13 (14.6)*	285 (58.8)
Preeclampsia	15 (40.5)	140 (26.1)	18 (43.9)*	137 (25.7)	0 (-)*	155 (32)
Spontaneous preterm birth	16 (43.2)	235 (43.8)	7 (17.1)*	244 (45.8)	76 (85.4)*	175 (36.1)
PPROM	2 (5.4)	70 (13)	8 (19.5)	64 (12)	30 (33.7)*	42 (8.7)
ARED	8 (21.6)	82 (15.3)	9 (22)	81 (15.2)	2 (2.2)*	88 (18.1)
Caesarean section	29 (78.4)	392 (73)			47 (52.8)	374 (77.1)
CTG abnormalities	18 (48.6)	229 (42.6)	21 (51.2)	226 (42.4)	20 (22.5)	227 (46.8)
Antenatal diagnosis of abruptio	3 (8.1)	50 (9.3)	6 (14.6)	47 (8.8)	10 (11.2)	43 (8.9)
Clinical chorioamnionitis	3 (8.1)	26 (4.8)	1 (2.4)	28 (5.3)	11 (12.4)*	18 (3.7)
Antenatal steroids	33 (89.2)	473 (88.1)	37 (90.2)	469 (88)	76 (85.4)	430 (88.7)
Magnesium sulfate	7 (18.9)	52 (9.7)	9 (22)	50 (9.4)	11 (12.4)	48 (9.9)
CRIB II score						
<5	25 (67.6)	418 (77.8)	31 (75.6)	412 (77.3)	55 (61.8)	388 (80)
5-10	3 (8.1)	78 (14.5)	7 (17.1)	74 (13.9)	20 (22.5)	61 (12.6)
>10	9 (24.3)*	41 (7.6)	3 (7.3)	47 (8.8)	14 (15.7)	36 (7.4)
BPD	6 (16.2)	118 (22)	7 (17.1)	117 (22)	33 (37.1)	91 (18.8)
NEC	1 (2.7)	31 (5.8)	1 (2.4)	31 (5.8)	7 (7.9)	25 (5.2)
Early sepsis	1 (2.7)	12 (2.2)	0 (-)	13 (2.4)	4 (4.5)	9 (1.9)
Late sepsis	5 (13.5)	84 (15.6)	6 (14.6)	83 (15.6)	27 (30.3)	62 (12.8)
IVH > 2	1 (2.7)	18 (3.4)	2 (4.9)	17 (3.2)	7 (7.9)	12 (2.5)
PVLC > 3	1 (2.7)	10 (1.9)	1 (2.4)	10 (1.9)	7 (7.9)*	4 (0.8)
Neonatal death	13 (35.1)*	67 (12.5)	11 (26.8)*	69 (12.9)	20 (22.5)*	60 (12.4)

Abbreviations:
ARED = Absent or reverse end diastolic flow
BPD = Biparietal diameter
CRIB = Clinical risk index for babies
CTG = Cardiotocography
FGR = Fetal growth restriction
FVM = Fetal vascular malperfusion
IVH = Intraventricular hemorrhage
MVM = Maternal vascular malperfusion
NEC = Necrotizing enterocolitis
PPROM = Premature preterm rupture of membranes
PVCL = Periventricular cystic leukomalacia
* $P < 0.05$ Partitioning of chi-square statistics with Bonferroni correction.

TABLE 3.
Obstetrics, Hystologic, and Neonatal Characteristics According to Placental Lesions

	Loss of Integrity		Intravillous Hemorrhage		Villitis Unknown Origin	
	Yes (n = 83)	No (n = 491)	Yes (n = 85)	No (n = 489)	Yes (n = 83)	No (n = 491)
Gestational age	28 (26-30)*	29 (26-31)	29 (26-30)	29 (26-31)	30 (28-32)*	29 (26-31)
Birth weight	978 (778-1279)	1095 (794-1360)	1037 (783-13079)	1090 (795-1354)	1138 (841-1350)*	1072 (787-1353)
z-score birth weight	−0.61 (−2.7 + 0.46)*	−1.73 (−3.4-0.17)	−0.8 (−2.4 + 0.41)*	−0.16 (−1.7-0.16)	−2.6 (−4-1.1)	−1.3 (−3.1- 0.01)
Placental weight	256 (207-323)	260 (210-321)	262 (208-333)	260 (210-319)	260 (210-315)	260 (210-321)
Fetal/placental ratio	3.9 (3.2-4.6)	4.1 (3-5)	3.9 (3-4.6)	4.1 (3.1-5)	4.3 (3-5.1)	4.1 (3.1-4.9)
Twins	19 (22.9)	142 (28.9)	31 (36.5)	130 (26.6)	22 (26.5)	139 (28.3)
FGR	24 (28.9)*	264 (53.8)	33 (38.8)*	264 (54)	56 (67.5)*	241 (49.1)
Preeclampsia	17 (20.5)	138 (28.1)	11 (12.9)*	143 (29.2)	28 (33.7)	126 (25.7)
Spontaneous preterm birth	44 (53)	207 (42.2)	49 (57.6)*	201 (41.1)	23 (27.7)*	227 (46.2)
PPROM	9 (10.8)	63 (12.8)	9 (10.6)	63 (12.9)	7 (8.4)	65 (13.2)
ARED	14 (16.9)	76 (15.5)	13 (15.3)	77 (15.7)	20 (24.1)*	70 (14.3)
Caesarean	64 (77.1)	357 (72.7)	62 (72.9)	359 (73.4)	62 (74.7)	359 (73.1)
CTG abnormalities	32 (38.6)	215 (43.8)	33 (38.8)	214 (43.8)	39 (47)	208 (42.4)
Antenatal diagnosis of abruptio	15 (18.1)*	38 (7.7)	18 (21.2)*	35 (7.2)	2 (2.4)*	51 (10.4)
Clinical chorioamnio-nitis	6 (7.2)	23 (4.7)	11 (12.9)*	18 (3.7)	4 (4.8)	25 (5.1)
Antenatal steroids	69 (83.1)	437 (89)	79 (92.9)	427 (87.3)	75 (90.4)	431 (87.8)
Magnesium sulfate	9 (10.8)	50 (10.2)	7 (8.2)	52 (10.6)	11 (13.3)	48 (9.8)
CRIB II score						
<5	58 (69.9)	387 (78.8)	63 (74.1)	380 (77.7)	71 (85.5)	372 (75.8)
5-10	14 (16.9)	67 (13.6)	13 (15.3)	68 (13.9)	9 (10.8)	72 (14.7)
>10	11 (13.3)	39 (7.9)	9 (10.6)	41 (8.4)	3 (3.6)	47 (9.6)
BPD	16 (19.3)	108 (22)	19 (22.4)	105 (21.5)	15 (18.1)	109 (22.2)
NEC	3 (3.6)	29 (5.9)	4 (4.7)	27 (5.5)	5 (6)	26 (5.3)
Early sepsis	3 (3.6)	10 (2)	2 (2.4)	11 (2.2)	1 (1.2)	12 (2.4)
Late sepsis	18 (21.7)	71 (14.5)	20 (23.5)	69 (14.1)	18 (21.7)	71 (14.5)
IVH > 2	3 (3.6)	16 (3.3)	2 (2.4)	17 (3.5)	3 (3.6)	16 (3.3)
PVLC > 3	2 (2.4)	9 (1.8)	2 (2.4)	9 (1.8)	1 (1.2)	10 (2)
Neonatal death	19 (22.9)*	61 (12.4)	20 (23.5)*	60 (12.3)	8 (9.6)	72 (14.7)

Abbreviations:
ARED = Absent or reverse end diastolic flow
BPD = Biparietal diameter
CRIB = Clinical risk index for babies
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PVCL = Periventricular cystic leukomalacia
* $P < 0.05$ Partitioning of chi-square statistics with Bonferroni correction.

adjusted for the confounding effect of gestational age, birth weight, fetal sex, and type of delivery are reported in Table 5. Severe MVM and FVM and intravillous hemorrhage were associated with an overall reduced intact survival and survival without major sequelae. There were several interactions between placental lesions and etiology of VLBW suggesting that some lesions were strongly associated with some causes and less in others. Severe chorioamnionitis was absent among pregnancies delivered as a result of preeclampsia. The effect of intravillous hemorrhage on two-year survival with intact neurodevelopmental outcomes was significant among twins (nine of 31 when compared with 87 of 123, adj. OR = 0.12, 95% CI = 0.05 to 0.32) but not in singleton pregnancies (28 of 51 when compared with 217 of 326, adj. OR = 0.66, 95% CI = 0.35 to 1.25, *P* for interaction = 0.005) and more marked among preeclamptic (three of 11 when compared with 105 of 132, adj. OR = 0.04, 95% CI = 0.006 to 0.25) than normotensive pregnancies (34 of 71 when compared with 199 of 317, adj. OR = 0.52, 95% CI = 0.3 to 0.9, *P* for interaction = 0.015).

Finally, in the whole population of VLBW, and after correction for gestational age, birth weight, sex of the newborns, and type of delivery, the best independent predictors of two-year infant intact neurodevelopmental outcomes corresponded to severe FVM (adj. OR = 0.46, 95% CI = 0.21 to 0.97) and intravillous hemorrhage (adj. OR = 0.37, 95% CI = 0.22 to 0.62).

Discussion

The results of this study suggest that placental pathologic lesions in VLBW deliveries are rather heterogeneous and that their frequencies follow the etiologic causes of prematurity or fetal growth defects. Inflammatory lesions were more common among spontaneous prematurity and PPROM, whereas severe FVM, loss of placental integrity, intravillous hemorrhage, and villitis of unknown origin were more common among FGR and pregnancies with preeclampsia. After correction for the confounding effect of gestational age and birth weight, which are the most powerful predictors of adverse neonatal outcomes, severe MVM, FVM, and intravillous hemorrhage were significantly associated with lower rates of two-year intact infant neurodevelopmental outcomes. The relative size of the risk of adverse neonatal outcomes associated with intravillous hemorrhage was modulated by other etiologic VLBW factors. In the whole population, only severe FVM and intravillous hemorrhage were independent predictors of a lower rate of intact neurodevelopmental outcomes. Literature data on the relationship between placental pathologic features and subsequent infant neurodevelopmental outcomes among VLBW are limited and mostly confined to the relationship between clinical and histological chorioamnionitis, early infant brain damage, and subsequent infant neurodevelopmental outcomes.[8,10] Although in our data prematurity-associated placental inflammation correlated strongly

TABLE 4.
Placental Characteristics According to Neurodevelopmental Outcomes

	Severe MVM		Severe FVM		Severe Chorioamionitis	
	Yes (n = 24)	No (n = 427)	Yes (n = 28)	No (n = 423)	Yes (n = 61)	No (n = 390)
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
GQ	102 (95-109)	102.5 (83.5-110.5)	103 (89.2-106.5)	102 (95-109)	100 (82.5-106)*	102 (95-110)
Locomotor	105 (96-111)	102 (91.6-110.5)	100 (89.4-1069)	105 (96-112)	100 (88-106.5)*	105 (96-112)
Personal-social	100 (69.5-1049)	107 (94.4-112)	105 (95.4-112)	107 (93-112)	105 (88-110)	107 (95-112)
Hearing-speech	100.5 (69.5-104)	96 (81-104)	98 (76.5-101.89)	96 (80-104)	95 (75.5-100)	96 (83-104.5)
Eye-hand coordination	102 (94.2-112)	103 (94-109)	103 (94.7-111.5)	103 (94-109)	99 (89.5-104)*	104 (96-110.5)
Performance	100 (86.5-103)	105 (93.5-110)	101 (83.3-107)	105 (94-110)	101.5 (86-105.3)*	105 (94-111)
	N. (%)	N (%)	N. (%)	N (%)	N. (%)	N. (%)
Neurologically suspected or abnormal at discharge	6 (25)	147 (34.4)	4 (14.3)*	149 (35.2)	29 (47.5)*	124 (31.8)
Sequelae:						
Intact	17 (70.8)	326 (76.3)	20 (71.4)	323 (76.4)	38 (62.3)	305 (78.2)
Mild abnormal	4 (16.7)	56 (13.1)	3 (10.7)	57 (13.5)	14 (23)	46 (11.8)
Severe	3 (12.5)	45 (10.5)	5 (17.9)	43 (10.2)	9 (14.8)*	39 (10)
GQ < 75	3 (12.5)	38 (8.9)	5 (17.9)	36 (8.5)	8 (13.1)	33 (8.5)
Survival without major sequelae	21/37 (56.7)*	382/494 (77.3)	23/39 (59)*	380/492 (77.23)	52/81 (64.2)*	351/450 (78)
Intact survival	17/37 (45.9)*	326/494 (66)	20/39 (51.2)	323/492 (65.6)	38/43 (88.37)*	305/450 (67.8)
	Loss of Integrity		Intravillous Hemorrhage		Villitis Unknown Origin	
	Yes (n = 61)	No (n = 390)	Yes (N = 62)	No (N = 389)	Yes (N = 71)	No (N = 380)
GQ	104.5 (91.4-111)	102 (95-108)	98 (76-110)*	102 (96-109)	102 (97-107)	102 (92-109)
Locomotor	105 (96-110.5)	105 (95.2-111)	100 (87.5-107.5)*	105 (96-111.5)	105 (98-111)	105 (93-111)
Personal-social	107 (95-116)	107 (94-112)	107 (96-112)	100 (87.5-107.5)	107 (100-112)	106 (93-112)
Hearing-speech	99.5 (78.5-105)	95 (80-104)	94 (63.5-105)*	96 (84-104)	95.5 (88-104)	96 (78-104)
Eye-hand coordination	103 (98-112)	103 (94-109)	100 (86-111.5)	104 (96-109)	104 (96-107)	103 (94-110)
Performance	103 (98.5-111)	105 (93-110)	100 (84-110)*	105 (94-110)	105 (93-110)	104 (93-110)
	N. (%)	N. (%)	N. (%)	N. (%)	N. (%)	N. (%)
Neurologically suspected or abnormal at discharge	16 (26.2)	137 (35.1)	17 (27.4)	136 (35)	21 (29.6)	132 (34.7)
Sequelae:						
Intact	45 (73.8)	298 (76.4)	37 (59.7)	306 (78.7)	59 (83.1)	290 (76.3)
Mild abnormal	10 (16.4)	50 (12.8)	11 (17.7)	49 (12.6)	7 (9.9)	53 (13.9)
Severe	6 (9.8)	42 (10.8)	14 (22.6)*	34 (8.7)	5 (7)	43 (11.3)
GQ < 75	4 (6.6)	37 (9.5)	13 (21)	28 (7.2)	5 (7)	36 (9.5)
Survival without major sequelae	55/80 (68.7)	348/451 (77.2)	48/82 (58.5)*	305/449 (67.9)	66/79 (83.5)	337/452 (74.5)
Intact survival	45/80 (56.2)	298/451 (66)	37/82 (45.1)*	306/449 (67.9)	59/79 (74.7)*	284/452 (62.8)

Abbreviations:
GQ = General quotient, Griffiths' Mental Developmental Scales
IQR = Interquartile range
* $P < 0.05$ Partitioning of chi-squared statistics with Bonferroni correction.

with reduced survival and increased rates of neurodevelopmental sequelae in crude analysis, this association disappeared after correction for gestational age and birth weight. Our data largely confirm data from previous population studies obtained in very preterm infants suggesting that the adverse effects of histological chorioamnionitis on infant neurodevelopmental outcomes are mainly related to the complications of prematurity rather than to a direct effect of histologically diagnosed placental inflammation on the brain of preterm fetuses.[11,12] According to these suggestions, Bierstone et al.[13] in a cohort multicenter study of neonates ≤32 weeks' gestational age confirmed that gestational age-related neonatal complications attenuate the apparent adverse effect of chorioamnionitis on infant neurodevelopmental outcome.

MVM is characterized by placental vascular lesions such as infarcts and retroplacental hemorrhage, by villous lesions such as villous hypoplasia or accelerated villous maturation, or by lesions

TABLE 5.
Odds Ratios of Intact Survival and Survival Without Major Neurodevelopmental Sequelae Associated With Placental Lesions Adjusted for the Confounding Effect of Gestational Age, Birth Weight, Fetal Sex, and Type of Delivery

	Survival Without Major Neurodevelopmental Impairments	Survival with Normal Neurodevelopmental Outcome
	OR (95% CI)	OR (95% CI)
Maternal vascular underperfusion	0.38 (0.18-0.82)	0.45 (0.22-0.92)
Fetal vascular underperfusion	0.32 (0.15-0.69)	0.46 (0.22-0.45)
Chorioamnionitis	1.1 (0.6-2)	0.75 (0.43-1.29)
Loss of placental integrity	0.72 (0.41-1.27)	0.73 (0.44-1.21)
Intravillous hemorrhage	0.35 (0.2-0.6)	0.38 (0.22-0.62)
Villitis unknown origin	1.48 (0.75-2.91)	1.54 (0.86-2.75)

Abbreviations:
CI = Confidence interval
OR = Odds ratio as obtained by penalized logistic regression

suggesting a defective spiral artery modeling. All these lesions could lead to a malperfusion of the placental bed and subsequent placenta and fetal hypoxia.[30] This type of lesion has been associated with an increased risk of abnormal developmental outcomes in a cohort, uncontrolled study suggesting that a hypoxic placental pattern could interfere with fetal growth and infant brain development.[8] On the other hand, animal studies have found that both acute and mild intrauterine hypoperfusion similar to MVM of the human placenta are able to produce neurodevelopmental disorders typical of FGR and prematurity.[31]

FVM is a placental pathologic lesion involving the thrombosis of the chorionic plate or umbilical cord vessels, which is uncommon in term but diagnosed in up to 25% of premature deliveries.[32] This lesion is more frequently found in FGR and preeclamptic pregnancies or in pregnancies complicated by a maternal hypercoagulable state but has also been observed in cases of ascending uterine infection.[20,21,32] In several retrospective or case-control studies, FVM has been associated with fetal demise, neonatal encephalopathy, or cerebral palsy.[8-10,14] Stepwise logistic regression in our study confirms that FVM is an independent predictor of a low two-year intact survival in the whole population of VLBW infants.

Intravillous hemorrhage from a placental lesion is often seen in immature villi characterized by the extravasation of intact red blood cells in villous stroma leading to villous coagulative necrosis.[33] The rupture of the villous vascular integrity with subsequent infarct is considered to be a lesion suggestive for hypoxic-ischemic placental injury.[33] The lesion is most commonly, but not exclusively, associated with placental abruption, preceding clinical manifestations of placental detachment by a median of eight hours.[33] Other significant placental features and perinatal complications associated with intravillous hemorrhage are chorioamnionitis, intervillous thrombosis, FGR, and fetal death.[34] In a recent case-control study of fetal death[22] intravillous hemorrahge was present in 7% of the cases and 0.1% of the controls confirming old data associating intravillous hemorrhage with fetal death.[34] In our study intravillous hemorrhage was an independent predictor of a lower rate of two-year intact infant survival in the whole population of VLBW. The extent of the adverse effect was modulated by other clinical factors being higher in twins than in singleton and in preeclamptic compared with normotensive pregnancies.

Villitis of unknown origin was more common among FGR pregnancies and was associated with better two-year intact survival in univariate analysis, but its effect disappeared after correction for potential confounders, suggesting that the role of this lesion on neurodevelopmental outcomes of VLBW infants is limited.

From a biological viewpoint placental lesions suggestive for FVM have been associated with reduced blood movement in the intervillous space in diffusion-weighted magnetic resonance imaging studies of dysfunctional placentas, suggesting that this type of lesion correlates to the severity of growth failure.[35] Intravillous hemorrhage leads to coagulation necrosis of villi and to the formation of intervillous thrombi, both lesions impairing fetomaternal exchanges in FGR pregnancies.[30,33]

The main strengths of the study involve the type of the study and the methods used. Data on neurodevelopmental outcomes of VLBW infants including placental pathology are lacking. Most data derive from single series without controls or are mainly aimed at the evaluation of the effect of chorioamnionitis on subsequent neurodevelopmental outcomes in preterm deliveries.[10,12] To avoid the so-called survival bias,[36] which most studies of subsequent infant outcomes have not taken into account, we have included among the outcomes both neonatal death and infant neurodevelopmental outcomes. Intravillous hemorrhage, when basal oriented, could be the result of mechanical placental separation after surgical procedures such as dilatation and curettage or Caesarean section.[30,33] Although pathologists involved in the study were well aware of this possibility, to avoid the potential confounding effects of Caesarean sections we included the type of delivery (vaginal versus Caesarean) in the study of the relationship between placental intravillous hemorrhage and neonatal outcomes. As this was a single-center study, the results should be interpreted cautiously and cannot be readily generalized for other institutions. Although unlikely, given the cohort approach and the method used, potential biases could have been introduced in the type of maternal population (e.g., prevalence of obesity, maternal age, racial differences) enrolled, the treatments used (protocols of maternal and neonatal care), and placental histological interpretations. Finally, another possible bias is the proportion (8.7%) of infants without brain lesions and who had been judged neurologically normal at hospital discharge who were lost to follow-up. Although a subsequent severe motor handicap seems unlikely in these infants, we cannot exclude subsequent minor disabilities.

Conclusions

In conclusion, the results of this study have demonstrated that among VLBW infants, placental pathologic findings such as severe MVM, FVM, and intravillous hemorrhage are significantly associated with neonatal survival and subsequent neurodevelopmental outcomes. Etiologic factors of VLBW can modulate the effect of placental pathologic findings on infants' neurodevelopmental outcomes. Data on placental pathology results should be taken into consideration in the follow-up of VLBW infants at risk for neurodevelopmental impairment.

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