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ORIGINAL ARTICLE

Associations between the aetiology of preterm birth and mortality and neurodevelopment up to 11 years

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Abstract

Aim: To investigate how the aetiology of very preterm birth/very low birth weight is associated with mortality and later neurodevelopmental outcomes.

Methods: Very preterm/very low-birth weight singletons were categorised based on the aetiology of preterm birth: spontaneous preterm birth ($n=47$, 28.1%), preterm premature rupture of membranes ($n=56$, 33.5%) or placental vascular pathology ($n=64$, 38.3%). Mortality, cerebral palsy, severe cognitive impairment by 11 years of age (<2SD) and mean full-scale intelligence quotient at 11 years were studied in association with birth aetiology.

Results: There was no difference in mortality or rate of cerebral palsy according to birth aetiologies. The rate of severe cognitive impairment was lower (4.9% vs. 15.3%) in the preterm premature rupture of the membrane group in comparison to the placental vascular pathology group (OR 0.2, 95% CI 0.03–0.9, adjusted for gestational age). At 11 years, there was no statistically significant difference in the mean full-scale intelligence quotient.

Conclusion: Placental vascular pathology, as the aetiology of very preterm birth/very low birth weight, is associated with a higher rate of severe cognitive impairments in comparison to preterm premature rupture of membranes, although there was no difference in the mean full-scale intelligence quotient at 11 years. The aetiology of very preterm birth/very low birth weight was not associated with mortality or the rate of cerebral palsy.

KEYWORDS
cognitive outcome, neurodevelopment, PPROM, pre-eclampsia, very preterm birth

Abbreviations: CP, Cerebral Palsy; IQ, Intelligence Quotient; PPROM, Preterm Premature Rupture of Membranes; SD, Standard Deviation.

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1 | INTRODUCTION

Preterm birth is a risk factor for cognitive[1,2] and motor[3–5] impairments such as cerebral palsy (CP), while some preterm infants survive without these neurodevelopmental impairments. Preterm birth has several aetiologies with different growth environments for the foetus. Different intrauterine environments preceding very preterm birth might explain part of the variation in long-term neurodevelopmental outcomes.

The common causes of preterm birth include spontaneous onset of preterm labour with intact membranes, preterm premature rupture of membranes (PPROM) and iatrogenic preterm birth due to a maternal or foetal indication.[3,4] An iatrogenic preterm birth is often a consequence of pre-eclampsia and/or intrauterine growth restriction.[3,4] In addition, multiple pregnancy is a common aetiology for preterm birth. Multiple pregnancy is a heterogeneous group including monochorionic and dichorionic twin pregnancies, and higher order pregnancies. Multiple pregnancy may also overlap with other aetiologies.

Previous reports on associations between the aetiology of preterm birth and mortality and neurodevelopmental outcomes are conflicting. Some studies have suggested that spontaneous preterm birth and PPROM increase the risk for CP[5–8] whereas pre-eclampsia and placental insufficiency have been indicated to be risk factors for poorer cognitive development in children born preterm.[9–11] In our PIPARI study cohort, abnormal foetal blood flow patterns decreased the brain volumes by about 10% at term equivalent age[12] and decreased the Bayley Mental Developmental Index by over 10 points at 2 years of corrected age[13] in very preterm infants. An iatrogenic preterm birth has also been suggested to be associated with an increased risk of mortality[14] but not all studies support this finding.[15,16] It is important to provide more data on long-term effects of the aetiology of preterm birth.

Our aim was to study the association between the aetiology of very preterm birth/very low birth weight and mortality and neurodevelopmental outcomes up to early adolescence. The hypothesis was that the neurodevelopmental outcomes differ according to aetiologies of preterm birth.

> **Key notes**
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> - Placental vascular pathology, as the aetiology of very preterm birth/very low birth weight, associated with higher rate of severe cognitive impairments in comparison to preterm premature rupture of membranes.
> - There was no difference in the mean full-scale intelligence quotient at 11 years according to birth aetiologies.
> - The aetiology of very preterm birth/very low birth weight was not associated with mortality or the rate of cerebral palsy.

2 | PATIENTS AND METHODS

2.1 | Subjects

This study is part of the multidisciplinary follow-up study PIPARI (Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age). The regional cohort consisted of very preterm/very low-birth weight infants born in Turku University Hospital, Finland, between 2001 and 2006, and living in the hospital's catchment area. The inclusion criterion was birth weight ≤1500 g and was expanded in 2004 to include all infants born <32 weeks of gestation regardless of birth weight. At least one of the parents had to speak and understand written Finnish or Swedish. Infants with major congenital anomalies or diagnosed genetic syndromes were excluded. The flowchart of the participants is shown in Figure 1.

The medical records were scrutinised to verify the aetiology of preterm birth. Infants were categorised based on the aetiology of preterm birth: (1) spontaneous preterm birth group, that is, spontaneous labour with intact membranes, (2) PPROM group, that is, spontaneous preterm premature rupture of membranes before the onset of labour, (3) placental vascular pathology group, that is, iatrogenic delivery because of pre-eclampsia, intrauterine growth restriction and/or abnormal placental/foetal blood flow. We excluded infants from multiple pregnancies ($n=78$) and infants ($n=9$) who could not be classified into any of the predetermined birth aetiology groups. These infants were born for the following reasons: suspicion of placental abruption ($n=5$), mother's infection ($n=1$), mother's chronic disease ($n=1$), foetal arrhythmia ($n=1$) and pathological cardiotocography ($n=1$). One infant was excluded because of missing data.

Perinatal data (Table 1) were collected prospectively. Neonatal diagnoses (Table 2) were established according to Vermont Oxford Network definitions.[17] Small for gestational age was defined as a birth weight more than 2 standard deviations (SD) below the mean. The brain magnetic resonance imaging was carried out at term and the findings were classified as described previously by Setänen et al.[18] Major pathologies consisted of consequences from intraventricular haemorrhages of grade 3 and 4, any injury in the cortex, basal ganglia, thalamus, internal capsule, corpus callosum, cerebellum or white matter, an increased width of the extracerebral space >5 mm, a ventricular/brain ratio of >0.35, ventriculitis, or other major brain pathologies (infarctions).

2.2 | Outcome measures

2.2.1 | Mortality

The data on mortality were collected prospectively along with the other perinatal data. In the present study, we studied mortality by 2 years of corrected age.

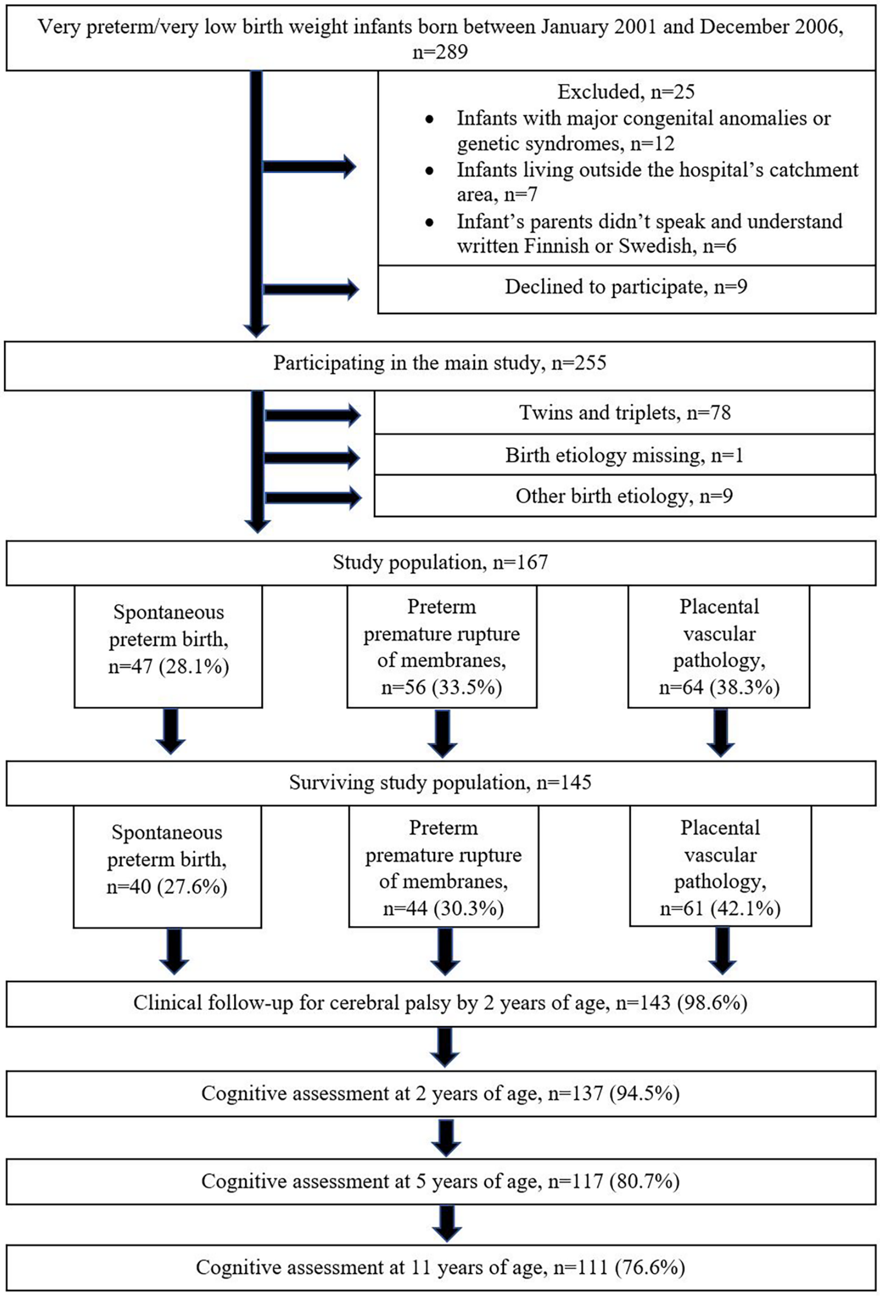

FIGURE 1 Flow chart of the participants.

2.2.2 | Cerebral palsy

The diagnosis of CP was confirmed by one experienced child neurologist by 2 years of corrected age after a systematic clinical follow-up as described previously by Uusitalo et al.[19] The follow-up included Hammersmith Infant Neurological Examination[20] by a trained physician and a physiotherapist. If a child already had a diagnosis of CP before 2 years of corrected age, the diagnosis was also confirmed at 2 years of corrected age in all cases. Gross Motor Function Classification System[21] was used for grading the severity of CP. All children with CP were included in the study.

2.2.3 | Cognitive development

Cognitive development was assessed at 2, 5 and 11 years by experienced psychologists who were blinded to the aetiology of preterm birth. At 2 years of corrected age, the Bayley Scales of Infant Development, Second Edition,[22] was used. The Mental Development Index was calculated based on the test norms. Severely impaired children whose scores could not be determined, were assigned scores 50, which is the minimum score of the test. Severe cognitive impairment at 2 years was defined as a mental development index of <70 (<−2SD). At 5 years of chronological age, the short

TABLE 1 Perinatal characteristics of very preterm/very low-birth weight infants according to birth aetiology groups. A variable is marked with an asterisk if there was a statistically significant difference between the groups.

	All preterm infants, $n=167$	Spontaneous preterm birth, $n=47$ (28.1%)	Preterm premature rupture of membranes, $n=56$ (33.5%)	Placental vascular pathology, $n=64$ (38.3%)
Gestational age*, mean, median [min, max], weeks	28.5, 28.6 [22.7, 35.8]	27.5, 27.1 [23.4, 34.4]	27.5, 26.6 [22.7, 34.9]	30.1, 29.9 [24.1, 35.9]
Male, *n* (%)	96 (57.5)	26 (55.3)	38 (67.9)	32 (50.0)
Caesarean delivery*,**, *n* (%)	98 (58.7)	11 (23.4)	26 (46.4)	61 (95.3)
Birth weight, mean, median [min, max], grams	1072.0, 1080.0 [384, 2025]	1075.8, 1040.0 [570, 1970]	1044.7, 970.0 [485, 1735]	1093.1, 1145.0 [384, 2025]
Birth weight z-score*, mean, median, [min, max] missing $n=1$	−1.4, −1.3 [−4.9,3.4]	−0.4, −0.6, [−3.5,3.4]	−0.8, −0.7 [−3.5,1.0]	−2.5, −2.5 [−4.9,0.5]
Small for gestational age*, *n* (%)	49/166 (29.5)	3 (6.4)	3/55 (5.5)	43 (67.2)
Antenatal steroids, *n* (%)	149 (89.2)	41 (87.2)	51 (91.1)	57 (89.1)
Mother's age***, mean, median, [min, max], years	31.0, 31.0, [16,43]	29.7, 29.0, [16,42]	32.7, 33.0 [19,43]	30.5, 30.5, [19,41]
Smoking during pregnancy, *n* (%)	26/160 (16.3)	10/45 (22.2)	11/54 (20.4)	5/61 (8.2)
Father's education, tertiary levels[a], *n* (%)	30/135 (22.2)	7/35 (20)	9/42 (21.4)	14/58 (24.1)
MRI at term, major pathologies[a], *n* (%)	35/139 (25.2)	10/37 (27.0)	9/42 (21.4)	16/60 (26.7)

*$p<0.001$ between the placental vascular pathology group and the other aetiological groups, **$p=0.045$ between the preterm premature rupture of membranes group and the spontaneous preterm labour group. ***$p=0.02$ between the preterm premature rupture of membranes group and the spontaneous preterm labour group.

Abbreviation: MRI, magnetic resonance imaging.

[a]Data were obtained only for the surviving study infants.

TABLE 2 Neonatal diagnoses of the surviving very preterm/very low-birth weight infants according to birth aetiology groups. A variable is marked with an asterisk if there was a statistically significant difference between the groups.

	Surviving preterm infants, n = 145	Spontaneous preterm birth, n = 40	Preterm premature rupture of membranes, n = 44	Placental vascular pathology, n = 61
Bronchopulmonary dysplasia, n (%)	20/144 (13.9)	6/39 (15.4)	8 (18.2)	6 (9.8)
Necrotising enterocolitis (stage 2 or 3), n (%)	8/139 (5.8)	2 (5.0)	3/42 (7.1)	3/57 (5.3)
Surgical necrotising enterocolitis, n (%)	5/141 (3.5)	2 (5.0)	1/42 (2.4)	2/59 (3.4)
Early sepsis (≤3 vrk), n (%)	2/143 (1.4)	2 (5.0)	0/43 (0)	0/60 (0)
Late sepsis (>3 vrk), n (%)	26/145 (17.9)	7 (17.5)	8 (18.2)	11 (18.0)
Patent ductus arteriosus, n (%)	56/143 (39.2)	22 (55.0)	13/43 (30.2)	21/60 (35.0)
Operated patent ductus arteriosus, n (%)	16/142 (11.3)	6 (15.0)	6/42 (14.3)	4/60 (6.7)

version of the Wechsler Preschool and Primary Scale of Intelligence – Revised, Finnish translation,[23] was used. The short version of the test included three subtests from the verbal scale (Information, Sentences and Arithmetic) and three subtests from the performance scale (Block Design, Geometric Design and Picture Completion). The full-scale intelligence quotient (IQ) was estimated according to the test manual based on the Verbal Intelligence Quotient and the Performance Intelligence Quotient. Severe cognitive impairment at 5 years was defined as a full-scale IQ of <70 (<−2SD). At 5 years, we only have the data of those study children who were successfully assessed. At 11 years, cognitive development was assessed with the Wechsler Intelligence Scale for Children, Fourth Edition, Finnish translation.[24,25] The full-scale IQ was estimated according to the test manual based on Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index and Processing Speed Index. Severely impaired children whose scores could not be determined were assigned scores 40, which is the minimum score of the test. Severe cognitive impairment at 11 years was defined as a full-scale IQ of <70 (<−2SD). In addition, full-scale IQ was also studied as continuous variable at 11 years.

Finally, severe cognitive impairment was defined according to the most recent cognitive assessment. There were two children who had severe cognitive impairment according to an earlier cognitive assessment but had full-scale IQ of >69 at 11 years, and therefore not defined as having severe cognitive impairment.

2.3 | Ethics statement

The Ethics Review Committee of the Hospital District of South-West Finland approved the PIPARI study protocol in December 2000 and in January 2012. Parents have given their written consent after receiving verbal and written information about the study. The children also gave their written consent at 11 years.

2.4 | Data analysis

Continuous variables were described by means (SD) and medians [min, max]. Differences in continuous perinatal characteristics between the three birth aetiology groups (spontaneous preterm birth group, PPROM group, placental vascular pathology group) were studied using ANOVA. The homogeneity of variances was tested using Levene Statistic without any statistical significance. As for the categorical perinatal characteristics and neonatal diagnoses, a Chi-squared test was used. *p*-values were corrected with Bonferroni or with post hoc Tukey HSD correction for multiple comparisons, when the three aetiological groups were compared.

Regarding the surviving and the deceased infants, differences in continuous perinatal characteristics were studied using an independent sample *t*-test. The Levene's test was used to assess the equality of variances. As for the categorical perinatal characteristics, a Chi-squared test or Fisher's exact test was used.

Associations between birth aetiologies and categorical outcome variables (mortality, CP, severe cognitive impairment, severe cognitive impairment and CP, severe cognitive impairment without CP) were studied using binomial logistic regression analysis adjusted for gestational age (based on statistically significant univariate association). Association between birth aetiologies and a continuous outcome variable (full-scale IQ at 11 years) was studied using ANOVA adjusted for gestational age and paternal education that has been previously found to be associated with cognition in this cohort. Small sample sizes in the outcome groups (mortality, CP, severe cognitive impairment, severe cognitive impairment and CP, severe cognitive impairment without CP) did not enable more extensive adjustments. Residuals were checked to justify the analyses. Possible multicollinearity was checked; a correlation coefficient equal to or greater than 0.8 and/or a tolerance value less than 0.1 and/or a Phi and Cramer's V equal to or greater than 0.8 was considered a sign of multicollinearity. Statistical analyses were performed using SPSS v28.0 (IBM Corp.). A two-tailed $p < 0.05$ was considered statistically significant.

3 | RESULTS

Of a total of 167 very preterm/very low-birth weight infants, 47 (28.1%) were allocated into spontaneous preterm birth group, 56 (33.5%) into PPROM group and 64 (38.3%) into placental vascular pathology group. Perinatal characteristics according to birth aetiology are shown in Table 1. Infants in the placental vascular pathology group had higher gestational age ($p<0.001$), were more often born small for gestational age ($p<0.001$) and delivered by a Caesarean section ($p<0.001$) compared to infants in other birth aetiology groups. Infants in the PPROM group were more likely to be born by Caesarean delivery ($p=0.045$) and to older mothers ($p=0.02$) than infants in the spontaneous preterm birth group.

The neonatal diagnoses of the surviving infants ($n=145$) are shown in Table 2. There were no statistically significant differences between the aetiological groups in neonatal diagnoses.

3.1 | Mortality

A total of 22 (13.2%) infants died; 7/47 (14.9%) infants in the spontaneous preterm birth group, 12/56 (21.4%) infants in the PPROM group and 3/64 (4.7%) infants in the placental vascular pathology group. Eleven infants died before 12h of age, an additional 10 infants died before discharge and one infant after discharge. The non-survivors had lower ($p<0.001$) gestational age (mean 25.1 (SD 1.6), median 25.1 [min 22.7, max 29.4] weeks versus mean 29.0 (SD 2.9), median 28.9 [min 23.4, max 35.9] weeks) and birth weight (mean 737.6 (SD 235.3), median 672.5 [min 384, max 1400] grams versus mean 1122.8 (SD 326.1), median 1150 [min 400, max 2025] grams), and they were less often born small for gestational age (9.5% vs. 32.4%, $p=0.04$). The mothers of the survivors had more often received at least one dose of antenatal corticosteroids (91.7% vs. 72.7%, $p=0.007$). The other perinatal characteristics did not differ between non-survivors and survivors.

In crude comparisons the mortality was higher (OR = 5.5, 95% CI 1.5–20.8) in the PPROM group than in the placental vascular pathology group, but the difference was not statistically significant after adjusting for gestational age. There were no statistically significant differences between the other aetiological groups in mortality.

3.2 | Cerebral palsy

Of the surviving study children, 143/145 (98.6%) participated in the clinical follow-up and 10 (7.0%) had diagnosis of CP by 2 years of corrected age. There were 3/39 (7.7%) children with CP in the spontaneous preterm birth group, 4/43 (9.3%) in the PPROM group and 3/61 (4.9%) in the placental vascular pathology group (Table 3). These differences did not reach statistical significance.

3.3 | Cognitive outcome

Cognitive assessment was performed in 137/145 (94.5%) of the surviving study children by the age of 11 years. Of these 137 children, 14 (10.2%) had their latest assessment at 2 years, 12 (8.8%) at 5 years and 111 (81.0%) at 11 years. Severe cognitive impairment was found in 15/137 (10.9%) children by 11 years; in 2 children at 2 years and in 13 children at 11 years. The rate of severe cognitive impairment by 11 years according to the aetiology of preterm birth is shown in Table 3. The rate of severe cognitive impairment was lower (4.9% vs. 15.3%) in the PPROM group in comparison to the placental vascular pathology group (OR 0.2, 95% CI 0.03–0.9, adjusted for gestational age). There were no other statistically significant differences in the rates of severe cognitive impairment between birth aetiology groups.

A post hoc analysis was performed separately for children with severe cognitive impairment and/without CP. Of the 15 children with severe cognitive impairment, five (33.3%) also had CP. There were no statistically significant differences in the rate of children with severe cognitive impairment and CP between the aetiological

TABLE 3 The effect of birth aetiology on cerebral palsy (CP), severe cognitive impairment and severe cognitive impairment and/without CP in surviving very preterm/very low-birth weight study children ($n=145$).

	Spontaneous preterm birth, $n=40$	Preterm premature rupture of membranes, $n=44$	Placental vascular pathology, $n=61$
CP	3/39 (7.7)	4/43 (9.3)	3/61 (4.9) reference group
n (%)	OR 1.6, 95% CI 0.3–8.4	OR 2.0, 95% CI 0.4–9.4	
Missing $n=2$	aOR 0.6, 95% CI 0.1–3.4	aOR 0.5, 95% CI 0.1–2.5	
Severe cognitive impairment	4/37 (10.8)	2/41 (4.9)	9/59 (15.3) reference group
n (%)	OR 0.7, 95% CI 0.2–2.4	OR 0.3, 95% CI 0.1–1.4	
Missing $n=8$	aOR 0.4, 95% CI 0.1–1.6	aOR 0.2, 95% CI 0.03–0.9	
Severe cognitive impairment without CP	1/37 (2.7)	1/41 (2.4)	8/59 (13.6) reference group
n (%)	OR 0.2, 95% CI 0.1–1.5	OR 0.2, 95% CI 0.02–1.3	
Missing $n=8$	aOR 0.1, 95% CI 0.01–0.9	aOR 0.1, 95% CI 0.01–0.8	
Severe cognitive impairment and CP	3/37 (8.1)	1/41 (2.4)	1/59 (1.7) reference group
n (%)	OR 4.8, 95% CI 0.5–47.7	OR 1.4, 95% CI 0.1–23.7	
Missing $n=8$	aOR 3.3, 95% CI 0.3–39.4	aOR 1.0, 95% CI 0.05–19.3	

Note: Diagnosis of CP was confirmed by 2 years of corrected age. The analyses were performed using logistic regression both unadjusted (OR) and adjusted (aOR) for gestational age.

groups. A total of 10/137 (7.3%) children had severe cognitive impairment without CP. In comparison to the placental vascular pathology group, the rate of children with severe cognitive impairment without CP was lower in the spontaneous preterm birth group (13.6% vs. 2.7%) (OR 0.1, 95% CI 0.01–0.9, adjusted for gestational age) and in the PPROM group (13.6% vs. 2.4%) (OR 0.1, 95% CI 0.01–0.8, adjusted for gestational age). The effect of birth aetiology on severe cognitive impairment and/without CP is shown in Table 3.

At 11 years, the mean (SD) and median [min, max] full-scale IQ of children born preterm (*n* = 111/145, 76.6%) was 87.0 (16.2) and 90.0 [40,119]. The mean (SD) and median [min, max] full-scale IQ was 85.3 (16.9) and 90.0 [40,107] in the spontaneous preterm birth group, 89.9 (12.3) and 92.0 [63,112] in the PPROM group and 86.2 (17.9) and 89.0 [47,119] in the placental vascular pathology group (Figure 2). There were no statistically significant differences in the mean values of full-scale IQ between the aetiological groups and these results remained the same after adjusting for gestational age and paternal education (Table 4). A sensitivity analysis without the children with CP did not change the results either.

4 | DISCUSSION

This study classified aetiologies of preterm birth in three categories: spontaneous preterm birth, PPROM and placental vascular pathology. Severe cognitive impairments were more common in the placental vascular pathology group in comparison to the PPROM group. This result is in line with our previous finding on the association between abnormal foetal blood flow pattern and poorer cognitive development[13] and previous studies that have reported poorer cognitive development after very preterm delivery because of pre-eclampsia and/or placental insufficiency.[9–11]

Spontaneous very preterm labour and PPROM, typically related to histologic chorioamnionitis and placental microbe recovery,[26] have been suggested to predict CP.[5–8] The choriodecidual bacterial colonisation leads to a pathway, where multiple pro-inflammatory cytokines are produced, which stimulates contractions and predisposes chorioamniotic membranes to rupture.[27] Increased levels of various cytokines have also been linked to neuronal death that precedes periventricular leucomalacia and intracranial haemorrhage,[27] which are common findings in CP. Since the literature has suggested that the prenatal risk factors for cognitive impairment and CP may be different, we decided to assess severe cognitive impairment and CP as separate outcomes instead of one combined outcome of neurodevelopmental impairment. In children with CP, the severity of cognitive impairment is suggested to be associated with the severity of motor impairment.[28] Thus, we also decided to analyse the risk of severe cognitive impairment separately in children with and without CP. In the present study, placental vascular pathology was associated with an increased risk of severe cognitive impairment especially in children without CP.

Morsing et al.[29] reported the poorest cognitive function in very preterm born children after pregnancies with placental vascular pathologies if the pregnancy was complicated with pre-eclampsia as well as abnormal umbilical artery blood flow and intrauterine growth restriction. Another important issue regarding placental vascular pathologies in relation to child outcome is the timing of delivery. Deciding an optimal timing for delivery is often challenging and requires balancing between possibly compromising maternal health and foetal well-being while trying to alleviate risks of prematurity. In preterm pre-eclampsia between 24 and 34 weeks of gestation, a delayed delivery may be associated with decreased neonatal morbidity while growth retardation is increased,[30] thus, potentially compromising brain growth and thereby later cognitive development. So far the outcomes of the studies on the optimal timing of labour induction in preterm pre-eclampsia have focused mainly on the neonatal period and further research on long-term neurodevelopmental prognosis is needed. Finally, as very preterm born children reach early adolescence, the environmental factors become increasingly significant in regard to cognitive development.[31] In our study, we adjusted the analyses of the association between the aetiology of preterm birth and cognition at 11 years for paternal education since it has been previously found to be associated with cognition in this cohort.[2]

It has been suggested that gestational age at birth is the strongest risk factor predicting mortality in preterm infants whereas the cause

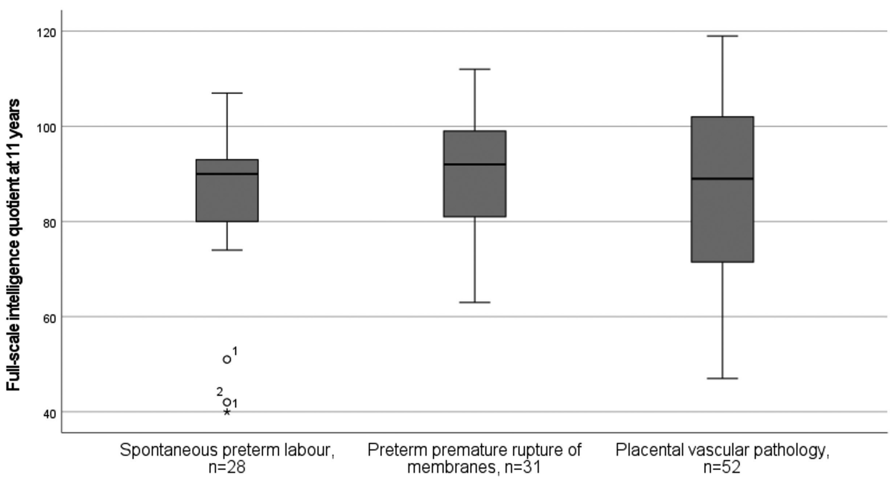

FIGURE 2 Mean full-scale intelligence quotient at 11 years in very preterm/very low-birth weight study children according to the aetiology of preterm birth, *n* = 111.

TABLE 4 The effect of birth aetiology on the mean full-scale IQ of very preterm/very low-birth weight study children at 11 years (*n* = 111).

	Spontaneous preterm birth, *n* = 28	Preterm premature rupture of membranes, *n* = 31	Placental vascular pathology, *n* = 52
Full-scale IQ at 11 years, mean (SD) [minimum, maximum]	85.3 (16.9) [40, 107] b = −0.9, 95% CI −8.3 to 6.5 b_a = 1.0, 95% CI −6.9 to 8.9	89.9 (12.3) [63, 112] b = 3.7, 95% CI −3.4 to 10.8 b_a = 5.0, 95% CI −2.5 to 12.4	86.2 (17.9) [47, 119] reference group

Note: The analyses were performed using ANOVA both unadjusted (b) and adjusted (b_a) for gestational age and paternal education.

of delivery seems to have no impact or a milder impact.[5,16] This is in line with our results. Although we found a higher mortality rate in the PPROM group than in the placental vascular pathology group, the statistically significant differences disappeared after adjusting for gestational age. Roberts et al.[16] did not find differences in mortality when comparing spontaneous preterm labour, PPROM and medically indicated preterm labour. Morken et al.[5] found an increased risk of death in preterm infants born at 34–36 weeks if the birth was iatrogenic compared with spontaneous preterm birth, however, there was no such difference in the lower gestational ages. They speculated that iatrogenic preterm births near term result from more severe pregnancy complications than spontaneous preterm births near term, whereas in lower gestational weeks the lower gestational age itself poses a major risk for mortality. However, Kurkinen-Räty et al.[14] found a higher neonatal mortality rate in the indicated preterm birth group also at 24–33 gestational weeks compared with spontaneous preterm birth. The main cause of death in the indicated preterm birth group was respiratory distress syndrome. In these previous studies, the iatrogenic preterm birth group has also included various other pregnancy complications, in addition to placental vascular pathologies, and therefore they are not directly comparable to the present study. Gray et al.[15] reported that pre-eclampsia as a primary cause of very preterm delivery did not increase neonatal mortality.

The main strength of this study is that it is part of a well-designed longitudinal study with low attrition in the follow-up from pregnancy until early adolescence; the participation rate at 11 years of age was 76.6%. The majority of previous studies have assessed cognition before school age. By assessing the cognition of the children at 11 years of age, we were able to obtain a reliable cognitive outcome at early adolescence. In fact, the majority of severe cognitive impairments in this study became apparent only at the age of 11 years. By including the children with severe cognitive impairment at 2 years or 5 years, we were able to compensate for the potential selection bias of the study cohort at 11 years. All of the assessments were carried out by trained clinicians. A major strength of the present study is that the birth aetiology was categorised precisely and multiple pregnancies were excluded. The study findings can be generalised to level three neonatal intensive care units.

One limitation of this study was a small number of patients in each subgroup. Therefore, the main result about the group differences in the rate of severe cognitive impairments was close to the border of statistical significance. The mean cognitive score at 11 years was not different between the groups. As there was a large variation in cognitive outcome especially in the vascular pathology group, large study groups and meta-analyses are needed to show potential group differences. It is not known whether the variation in the cognitive outcome is related to the duration of placental vascular pathology. In our hospital, the majority of the population is Caucasian origin, which should be noticed in the generalisability of the findings.

In conclusion, placental vascular pathology, as the aetiology of very preterm birth/very low birth weight, associated with higher rate of severe cognitive impairments in comparison to PPROM, although there was no difference in the mean full-scale IQ at 11 years of age. The aetiology of very preterm birth/very low birth weight was not associated with mortality or the rate of CP.

AUTHOR CONTRIBUTIONS

Linda Grönroos: Conceptualization; data curation; investigation; writing – original draft; writing – review and editing. **Päivi Rautava:** Conceptualization; investigation; methodology; project administration; supervision; writing – original draft; writing – review and editing. **Sirkku Setänen:** Conceptualization; data curation; investigation; writing – original draft; writing – review and editing. **Anna Nyman:** Data curation; investigation; writing – review and editing. **Eeva Ekholm:** Conceptualization; investigation; writing – review and editing. **Liisa Lehtonen:** Conceptualization; investigation; methodology; project administration; supervision; writing – review and editing. **Milla Ylijoki:** Conceptualization; data curation; investigation; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest relevant to this article to disclose.

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