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ORIGINAL ARTICLE

Placental histology predicted adverse outcomes in extremely premature neonates in Norway—population-based study

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Abstract

Aim: We evaluated the role of placental pathology in predicting adverse outcomes for neonates born extremely preterm (EPT) before 28 weeks of gestation.

Methods: This was a prospective observational study of 123 extremely preterm singletons born in a hospital in western Norway, and the placentas were classified according to the Amsterdam criteria. The associations between histologic chorioamnionitis (HCA), by the presence or the absence of a foetal inflammatory response (FIR+ or FIR−), maternal vascular malperfusion (MVM) as a whole and adverse neonatal outcomes were evaluated by logistic regression analyses. Adverse outcomes were defined as perinatal death, necrotising enterocolitis (NEC), bronchopulmonary dysplasia (BPD), brain pathology by magnetic resonance imaging at term-equivalent age, retinopathy of prematurity and early-onset neonatal sepsis. The results are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Results: HCA was associated with NEC (OR 12.2, 95% CI 1.1 to 137.1). HCA/FIR+ was associated with BPD (OR 14.9, 95% CI 1.8–122.3) and brain pathology (OR 9.8, 95% CI 1.4–71.6), but HCA/FIR− was not. The only neonatal outcome that MVM was associated with was low birthweight.

Conclusion: Placental histology provided important information when assessing the risk of adverse neonatal outcomes following EPT birth.

KEYWORDS
adverse outcomes, extremely premature birth, neonates, pathology, placenta

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence intervals; EONS, early-onset neonatal sepsis; EPT, extremely preterm; FIR, foetal inflammatory response; GA, gestational age; HCA, histologic chorioamnionitis; MRI, magnetic resonance imaging; MVM, maternal vascular malperfusion; NEC, necrotising enterocolitis; OR, odds ratio; ROP, retinopathy of prematurity; SGA, small for gestational age.

1 | INTRODUCTION

The survival rates after extremely preterm (EPT) birth have increased in high-income countries in recent decades to more than 80% for deliveries at 25 weeks of gestation.[1] However, EPT birth affects the development of most organ systems, and complications are inevitable. Neonates born EPT face a high risk of intracerebral haemorrhage, white matter lesions of the brain, early-onset neonatal sepsis (EONS), necrotising enterocolitis (NEC), retinopathy of prematurity (ROP) and chronic lung disease, namely bronchopulmonary dysplasia (BPD).[1,2] All of these complications may cause life-long morbidity and are related to gestational age (GA), at birth as well as birth weight.[3] Despite GA and birth weight, it is virtually impossible to predict, at birth, which EPT neonates will eventually develop short-term or long-term complications. Environmental, social and genetic determinants and intrauterine conditions are probably important, and neonates are most likely to be born with individual susceptibilities. However, strategies to identify those at risk have failed.[4] This is a clinical challenge and makes it difficult to tailor treatment and clinical follow-ups.

The link between placental dysfunction and diseases later in life is well known.[5] However, studies exploring the associations between placental pathology and outcomes in EPT neonates have shown conflicting results.[6,7] This could have been due to the small study samples and lack of standardised protocols in evaluating the placentas. The Amsterdam Placenta Consensus Group[8] has described a consensus on placental sampling and definitions of placental lesions. The aim of this study was to use the Amsterdam criteria to examine the placental characteristics in a cohort of EPT births in western Norway and to explore whether placental pathology could predict adverse neonatal outcomes.

Key Notes

- This Norwegian prospective observational study evaluated the role of placental pathology in predicting adverse outcomes for 123 neonates born extremely preterm before 28 weeks of gestation.
- Histologic chorioamnionitis was associated with necrotising enterocolitis, and it was also associated with bronchopulmonary dysplasia and brain pathology if there was a positive foetal inflammatory response.
- The only neonatal outcome that maternal vascular malperfusion was associated with was low birthweight.

2 | MATERIALS AND METHODS

2.1 | Participants and study design

This study was part of the large, prospective, population-based Project Extreme Prematurity study, also known as BabyPEP. It was conducted between 7 October 2010 and 24 September 2018 in the only two tertiary referral hospitals in western Norway: Haukeland University Hospital and Stavanger University Hospital. Women with threatened preterm delivery before 28 weeks of gestation were invited to take part, and the babies were included if they born before that gestational age. The placentas were sent for histological examination, and detailed prenatal, perinatal and neonatal histories, examinations and treatments were consecutively recorded in a database during the neonates' hospital stays. Magnetic resonance imaging (MRI) of the brain was performed at term-equivalent age.

The current study comprised singleton neonates born before 28 weeks of gestation at Haukeland University Hospital. We excluded multiple pregnancies and cases without placental examinations (Figure 1).

Written consent was obtained from the parents, and the Regional Committees for Medical and Health Research Ethics (REK ID 2010-00496) approved the study.

2.2 | Definitions

GA was determined by ultrasound biometry at 17–19 weeks of gestation or the first trimester in 88.6% of cases and estimated according *to* in vitro fertilisation in the other 11.4%. Small for gestational age (SGA) was defined as a birthweight below the 10th percentile, according to Norwegian sex-specific birth weight centiles.[9] The birth weight *z*-scores were calculated with reference to the 2013 Fenton growth charts.[10]

Perinatal death was defined as occurring within the first 28 days of life. EONS was clinical symptoms of infection within 72 h of life, as well as a positive blood culture and/or elevated C-reactive protein. NEC comprised cases verified by pre-operative ultrasound or X-ray, during surgery, or by autopsy. BPD was defined as being dependent on oxygen supplementation or non-invasive ventilatory support at 36 weeks of GA.[11] Brain MRI scans were scored by a paediatric neuroradiologist (SMA) and dichotomised into normal or any pathology.

Retinopathy of prematurity was graded, as defined by the Committee for Classification of Retinopathy of Prematurity,[12] and dichotomised into no or mild ROP (grade 1–2) and severe ROP (grade 3–5). The Apgar score was dichotomised using a threshold of 4 at 5 min, and the lowest pH value measured in arterial blood gas during the first 24 h was dichotomised using a threshold of pH 7.0.

2.3 | Classifications of placental histological findings

The delivered placentas had been examined by perinatal pathologists as part of our routine practice following EPT birth. All the slides were later re-examined and classified, according to the Amsterdam Placental Workshop Group Consensus Statement,[8] by two of the perinatal pathologists (EBB and KC). A final diagnosis was achieved in a few challenging cases by discussions between these two pathologists. Clinical information that was available from the pathology requisition form included GA, birth weight, the Apgar scores at 1 and 5 min, umbilical artery pH and major pregnancy complications. Histologic chorioamnionitis (HCA)

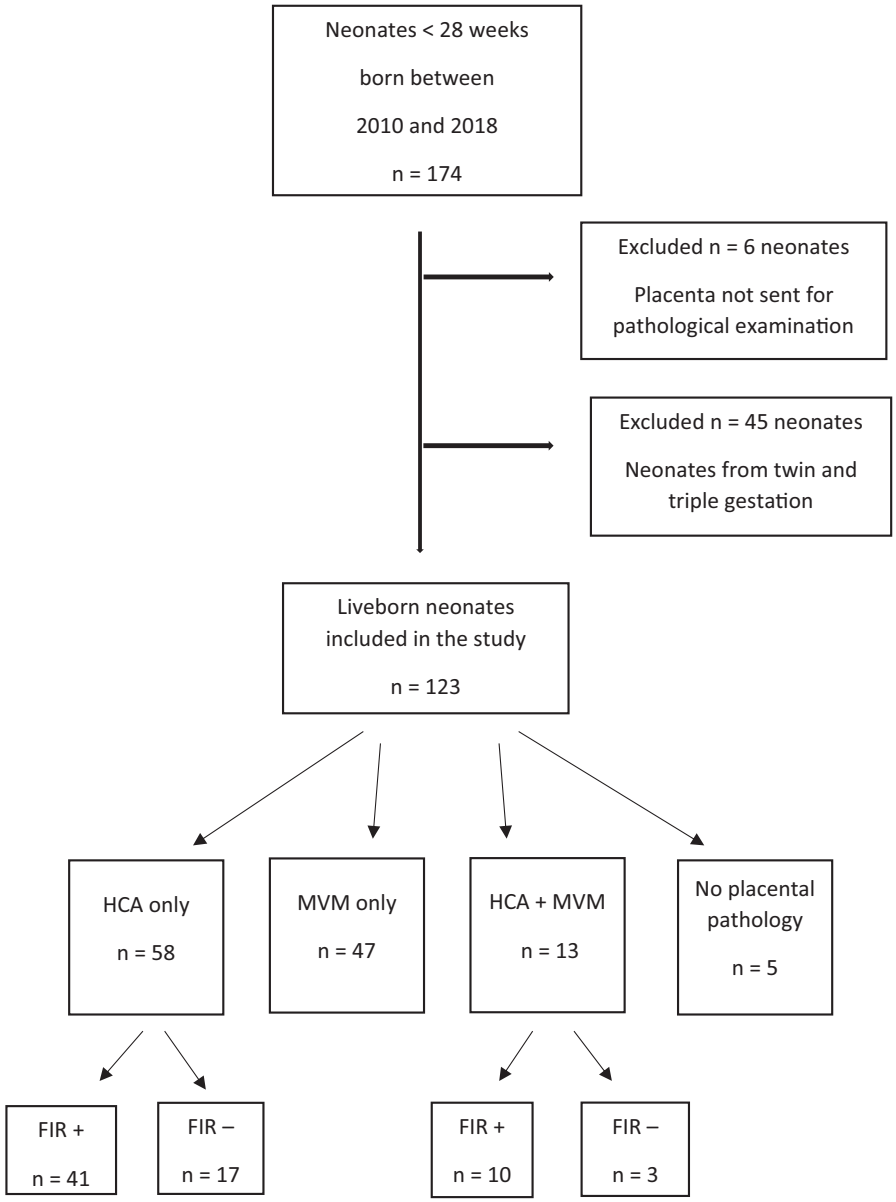

FIGURE 1 Flow chart of the study cohort of children born extremely preterm at <28 weeks of gestation in western Norway from October 2010 to September 2018 and the placental findings. Abbreviations: FIR, foetal inflammatory response; HCA, histologic chorioamnionitis; MVM, maternal vascular malperfusion

was defined as polymorphonuclear leukocytes infiltrating the placenta, the extraplacental membranes and the umbilical cord. HCA was further classified according to the presence or the absence of a foetal inflammatory response (FIR+ and FIR−) in the chorionic vessels, umbilical vein and/or umbilical artery or arteries (Figures 2 and 3).

A diagnosis of maternal vascular malperfusion (MVM) was based on a constellation of findings in the placenta. This included low placental weight (weight <10th centile), villous infarction, retroplacental haemorrhage or histological findings as distal villous hypoplasia, accelerated villous maturation or decidual arteriopathy. MVM was used as a whole and not graded.

2.4 | Statistics

Continuous variables were tested for normal distribution and compared using the independent samples t-test or the Mann–Whitney *U* test, as appropriate. Associations between categorical variables were evaluated using the Pearson's chi-square test or Fisher's exact test. We carried out logistic regression analyses to identify the associations between placental findings and adverse neonatal outcomes, each serving as the dependent variable. Independent variables were the GA at birth and birth weight *z*-score as continuous variables and HCA and MVM as categorical variables. The model was additionally adjusted for the antenatal potential confounders of sex, antenatal steroids and antenatal antibiotics. *p* Values of ≤0.05 were considered significant. Results were expressed as odds ratios (OR) with 95% confidence intervals (CI). Data were analysed using SPSS Statistics for Windows, version 26.0 (IBM Corp, New York, USA).

3 | RESULTS

A total of 174 EPT neonates were identified during the study period, and 129 of these were live-born singletons and met the initial inclusion criteria. However, six placentas were not sent for pathological

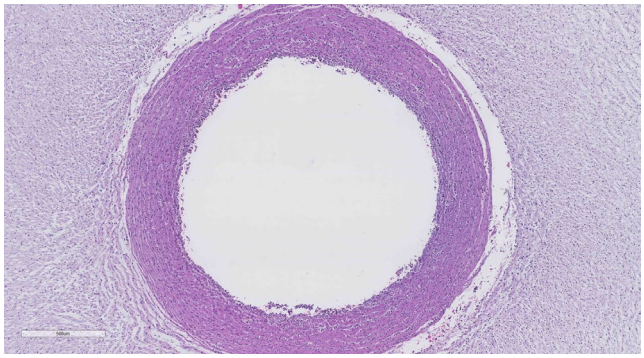

FIGURE 2 Umbilical vein with foetal neutrophils marginating beneath the endothelium, extending into the vascular smooth muscle and out into Wharton jelly

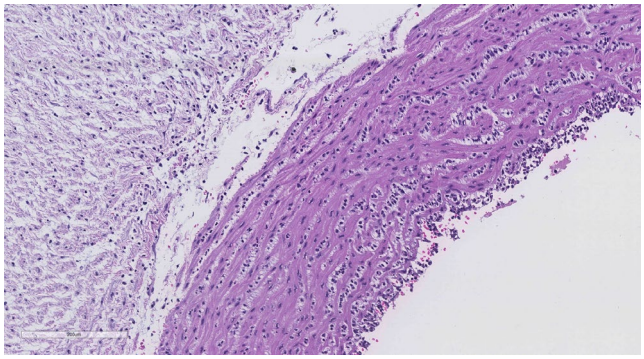

FIGURE 3 Higher magnification

examination, and this meant that 123 cases were included in our analyses. HCA was demonstrated in 58 placentas (47.2%), MVM in 47 (38.2%) and both HCA and MVM in 13 (10.6%). Five placentas (4.1%) had no identified pathology (Figure 1). The placentas were small, with a weight below the 10th percentile, in 12 cases. Table 1 presents the maternal, pregnancy and neonatal characteristics and outcomes of the study group.

During the perinatal period, 15 patients died (12.2%) and these deaths were caused by the following: NEC ($n = 8$), respiratory failure ($n = 2$), severe brain pathology ($n = 2$), EONS ($n = 1$), multi-organ failure ($n = 1$) and complications during delivery ($n = 1$). Autopsies were performed in seven cases, with a partial autopsy in one case.

Five neonates (4.1%) developed EONS, and 21 cases (17.1%) had NEC. BPD was diagnosed in 67 cases (54.5%), severe ROP in 34 cases (27.6%) and brain pathology seen in 43 (35.0%). In general, there were no differences between the placental pathology groups with regard to neonatal outcomes (Table 1). However, GA was lower in the HCA group than the MVM group ($p = 0.010$). The number of SGA neonates was higher, and the mean birth weight was lower in the group with MVM than the group with HCA ($p < 0.001$). Also, there was a higher proportion of neonates with 5-min Apgar scores of less than 4 in the combined HCA and MVM groups than the MVM only group (38.5% vs. 12.8%, $p = 0.049$).

Table 2 shows the association between HCA and MVM and adverse neonatal outcomes in our population using multiple logistic regression. GA was lower in the group with HCA than the group with MVM (25^5 vs. 26^3, $p = 0.003$), and birth weight was lower in the MVM group than the HCA group (694.0 g vs. 861.3 g, $p < 0.001$) and the HCA+ MVM group (694.0 g vs. 893.1 g, $p = 0.003$). This meant that the subsequent analyses were adjusted for GA and the birth weight *z*-score. HCA was associated with NEC (OR 12.16, 95% CI 1.08–137.1). No associations were found between MVM and adverse neonatal outcomes. A sub-analysis of cases with HCA, with and without FIR, revealed an association between FIR and BPD (OR 14.91, 95% CI 1.82–122.3) and any brain pathology at MRI (OR 9.83, 95% CI 1.35–71.60), after adjusting for relevant confounders such as GA, birth weight *z*-score, sex, antenatal steroids and antenatal antibiotics (Table 3).

4 | DISCUSSION

Placental pathology affected 96% of the EPT neonates in this population-based study. Some just had HCA or MVM, and some had both. The placental pathology in this study was in accordance with the findings of previous studies that examined placental histology in preterm births.[13,14] HCA was associated with increased odds of developing NEC and HCA with FIR+ was associated with BPD and brain pathology, assessed by an MRI scan at term-equivalent age. MVM was of no significance in predicting adverse neonatal outcomes.

Previous studies have reported divergent results regarding the contribution of chorioamnionitis in the pathogenesis of NEC. A case–control study by Duci et al.[15] found that both clinical chorioamnionitis and HCA independently predicted the risk of NEC. This was consistent with our findings. However, Lee et al.[16] found that HCA did not predict NEC in a study of 354 very preterm infants. A 2013 meta-analysis by Been et al.[17] reached the same conclusion, but their subgroup analysis demonstrated an association between NEC and HCA with foetal involvement, compared with infants without chorioamnionitis.

Divergent results have also been reported for the association between HCA and BPD.[7,18,19] One 2019 review[19] supported an association between the two, but it did not distinguish between clinical and histologic chorioamnionitis. Kim et al.[20] found that only high-grade HCA was associated with BPD, suggesting that the association between HCA and outcomes in EPT neonates varied according to the extent of inflammation. FIR, which manifests as funisitis or chorionic vasculitis, is considered to be the histological manifestation of the foetal inflammatory response syndrome.[21] One study reported that foetal inflammatory response syndrome was associated with both BPD and intraventricular haemorrhage, which partly agreed with our results.[22]

We found an association between HCA with FIR+ and brain pathology, detected by MRIs performed at term-equivalent age. Reiman et al.[23] found no correlation between histological placental inflammation and brain lesions at term age in a cohort of very

TABLE 1 Maternal and neonatal characteristics, according to the placental pathology findings of 123 extremely preterm singletons born in western Norway from October 2010 to September 2018

		Placental pathology		
	Total	HCA	MVM	HCA and MVM
Variables	N = 123	N = 58	N = 47	N = 13
Maternal and pregnancy characteristics				
Age (years), mean (SD)	30.5 (5.7)	30.3 (5.6)	30.5 (5.7)	30.9 (6.5)
BMI (kg/m^2), mean (SD)	25.3 (5.9)	25.3 (5.7)	25.5 (5.7)	26.0 (7.9)
Smoking, n/N (%)	12/123 (9.8)	7/58 (12.1)	2/47 (4.3)	2/13 (15.4)
Primiparity, n/N (%)	71/123 (57.7)	36/58 (62.1)	26/47 (55.3)	5/13 (38.5)
Preeclampsia, n/N (%)	29/123 (23.6)	0/58 (0.0)	29/47 (61.7)	0/13 (0.0)
HELLP syndrome, n/N (%)	5/123 (4.1)	0/58 (0.0)	5/47 (10.6)	0/13 (0.0)
Eclampsia, n/N (%)	1/123 (0.8)	0/58 (0.0)	1/47 (2.1)	0/13 (0.0)
Clinical chorioamnionitis, n/N (%)	14/123 (11.4)	14/58 (24.1)	0/47 (0.0)	0/13 (0.0)
Antenatal antibiotics, n/N (%)	46/123 (37.4)	36/58 (62.1)	6/47 (12.8)	3/13 (23.1)
Antenatal steroids, n/N (%)	110/123 (89.4)	52/58 (89.7)	43/47 (91.5)	11/13 (84.6)
pPROM, n/N (%)	32/123 (26.0)	24/58 (41.4)	0/47 (0.0)	5/13 (38.5)
Onset of labor, n/N (%)				
Spontaneous	73/123 (59.3)	54/58 (93.1)	5/47 (10.6)	10/13 (76.9)
Induced	1/123 (1.6)	1/58 (1.7)	0/47 (0.0)	0/13 (0.0)
Caesarean section	49/123 (39.8)	3/58 (5.2)	42/47 (89.4)	3/13 (23.1)
Mode of delivery, n/N (%)				
Spontaneous vaginal	58/123 (47.2)	41/58 (70.7)	4/47 (8.5)	10/13 (76.9)
Forceps	2/123 (0.8)	2/58 (3.4)	0/47 (0.0)	0/13 (0.0)
Caesarean section	63/123 (51.2)	15/58 (25.9)	43/47 (91.5)	3/13 (23.1)
Placental weight[a] (g), mean (SD)	223 (77)	241 (59)	183 (55)	286 (135)
Placental weight <10th %-ile, n/N (%)	12/121 (9.8)	1/57 (1.7)	10/46 (21.3)	1/13 (7.7)
Neonatal characteristics				
GA (weeks^{days}), mean (range)	26^5 (23^0–27^6)	25^5 (23^0–27^6)	26^3 (23^2–27^6)	25^5 (23^3–27^6)
Birthweight (g), mean (SD)	802.9 (221)	861.3 (205)	694.0 (187)	893.1 (272)
Birthweight *z*-score, mean (SD)	−0.20 (1.0)	0.27 (0.6)	−1.01 (0.8)	0.49 (1.1)
Small for GA[b], n/N (%)	31/123 (25.2)	1/58 (1.7)	30/47 (63.8)	0/13 (0.0)
Male sex, n/N (%)	64/123 (52.0)	33/58 (56.9)	20/47 (42.6)	8/13 (61.5)
VT first 24 h after birth, n/N (%)	94/118 (76.4)	46/57 (79.3)	36/45 (76.6)	9/11 (69.2)
Perinatal death, n/N (%)	15/123 (12.2)	7/58 (12.1)	7/47 (14.9)	1/13 (7.7)
Bronchopulmonary dysplasia, n/N (%)	67/107 (54.5)	30/57 (51.7)	26/47 (55.3)	8/13 (61.5)
Brain pathology by MRI, n/N (%)	43/89 (35.0)	25/45 (43.1)	13/32 (27.7)	4/9 (30.8)
Retinopathy (≥grade 3), n/N (%)	34/101 (27.6)	17/50 (29.3)	13/37 (27.7)	3/11 (23.1)
Early onset neonatal sepsis, n/N (%)	5/123 (4.1)	3/58 (5.2)	1/47 (2.1)	1/13 (7.7)
Necrotizing enterocolitis, n/N (%)	21/123 (17.1)	9/58 (15.5)	10/47 (21.3)	2/13 (15.4)
Apgar score <4 at 5 min, n/N (%)	27/123 (22.0)	14/58 (24.1)	6/47 (12.8)	5/13 (38.5)
pH < 7.0[c], n/N (%)	7/122 (5.7)	5/58 (8.6)	0/47 (0.0)	2/13 (15.4)

Abbreviations: GA, gestational age; HCA, histological chorioamnionitis; HELLP, haemolysis, elevated liver enzymes, low platelets; MVM, maternal vascular malperfusion; pPROM, preterm pre-labour rupture of membranes; SD, standard deviation; VT, ventilator treatment.

[a]Trimmed weight without cord and membranes.

[b]Birth weight <10 percentile.

[c]Lowest arterial value measured within first 24 h.

TABLE 2 Association between placental pathology and adverse neonatal outcomes in 123 extremely preterm singletons born in western Norway from October 2010 to September 2018

	Perinatal death	EONS	NEC	BPD	Brain pathology[a]	ROP ≥ grade 3
Risk factor	aOR 95% CI	aOR 95% CI	aOR 95% CI	aOR 95% CI	aOR 95% CI	aOR 95% CI
MVM	0.74 (0.09, 6.47)	1.55 (0.14, 17.54)	1.17 (0.20, 6.70)	1.12 (0.35, 3.57)	0.91 (0.24, 3.36)	0.69 (0.14, 3.44)
HCA	8.04 (0.44, 146.0)	n.a.	12.16 (1.08, 137.1)	1.73 (0.47, 6.34)	0.68 (0.15, 3.11)	1.74 (0.31, 9.85)

Abbreviations: aOR, adjusted odds ratio, that is, adjusted for gestational age and birth weight *z*-score (as a continuous variable), and MVM and HCA (dichotomous); BPD, bronchopulmonary dysplasia; CI, confidence interval; EONS, early-onset neonatal sepsis; HCA, histologic chorioamnionitis; MVM, maternal vascular malperfusion; n.a., not applicable due to too few cases; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

[a]Brain pathology assessed by term-equivalent MRI.

TABLE 3 Association between the foetal inflammatory response (FIR) and adverse neonatal outcomes in 71 extremely preterm singletons with histologic chorioamnionitis (HCA) born in western Norway from October 2010 to September 2018

	Perinatal death	EONS	NEC	BPD	Brain pathology[a]	ROP ≥ grade 3
HCA, FIR	aOR 95% CI	aOR 95% CI	aOR 95% CI	aOR 95% CI	aOR 95% CI	aOR 95% CI
Yes	0.24 (0.02, 2.64)	n.a.	0.43 (0.03, 6.18)	14.91 (1.82, 122.3)	9.83 (1.35, 71.60)	0.35 (0.05, 2.70)

Abbreviations: aOR, adjusted odds ratio, namely adjusted for gestational age and birth weight *z*-score (as a continuous variable), maternal vascular malperfusion (no/yes), foetal sex (female/male), antenatal steroids (no/yes) and antenatal antibiotics (no/yes); BPD, bronchopulmonal dysplasia; CI, confidence interval; EONS, early-onset neonatal sepsis; n.a., not applicable due to too few cases; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

[a]Brain pathology assessed by term-equivalent MRI.

low birth weight or very preterm infants born at <32 weeks. We did not have access to follow-up data regarding neurodevelopmental outcomes for our group. However, one study reported that adverse near-term brain MRI and late cerebral ultrasound findings in EPT and very preterm infants were associated with adverse neurodevelopmental outcomes at 18–22 months.[24] MVM was significantly associated with SGA and small placentas weighing less than the 10th percentile, but we did not find any associations between MVM and adverse neonatal outcomes. This may be attributed to our definition of MVM which included either gross and microscopic infarctions, retroplacental haemorrhage and/or distal villous hypoplasia/accelerated villous maturation. MVM was used as a whole and not graded further. Vinnars et al.[25] studied the individual components of MVM and found histologically verified placental infarction to be associated with cerebral palsy in neonates born before 27 weeks of gestation. We explored the impact of severe MVM, which included villous infarction affecting more than 10% of the parenchyma, in our preliminary analyses, and we found a borderline significant association between severe MVM and brain pathology at MRI ($p = 0.054$). A study by Oh et al.[26], which used the Amsterdam criteria, reported an association between MVM and intraventricular haemorrhage in premature infants born at up to 34 weeks and SGA infants with a birth weight of up to 1800 g. The inclusion of very preterm and moderately preterm infants may have influenced the prognostic role of MVM. In addition, other studies have shown that placental vascular pathology or malperfusion were a risk factor for the development of NEC in EPT neonates[27] and BPD,[6] respectively.

Histologic chorioamnionitis and MVM were not associated with severe ROP in our study. This was in accordance with a study by van Vliet et al.[28] of infants born at <32 weeks of gestation or with a birth weight of less 1500 g. The authors reported no difference in the incidence of ROP between infants with HCA and infants with placental underperfusion.

Our results indicate an important difference between an infectious inflammatory disease and a more chronic maternal vascular disease for adverse outcomes of EPT neonates. HCA represents an inflammatory response, usually with the presence of microorganisms in the amniotic fluid and an increase in inflammatory cytokines.[29] Meanwhile, MVM represents a failure to remodel spiral arteries, leading to abnormal maternal perfusion of the placenta with subsequent placental hypoxia and release of anti-angiogenic mediators. The placenta is an adaptive organ and undergoes multiple morphological and aberrant global gene expression changes in response to prolonged hypoxia.[5] Thus, a chronic process such as MVM may trigger compensatory mechanisms in the foetus, mother and placenta,[30] while an acute infection (HCA) may be more harmful, either due to toxic mediators, fewer compensatory mechanisms or both.[14] Long-term effects from these pathologies still need to be established and may be associated with different trajectories. Due to the compensatory and adaptive mechanisms of the placenta, adverse neonatal outcomes may not just depend on the type of placental pathology, but also on the duration and timing of a harmful event in the placenta. Placental pathology has not been a priority for pathologists and clinicians, and there has

been a common perception that examining the placenta is of little clinical significance. There has been no consensus on which placentas should be examined, and this has resulted in arbitrary gross examinations, confusing pathological diagnoses and long response times. These practices, or lack of them, have confirmed the inadequacy of placental examinations. However, we have gradually developed greater knowledge of the placenta. This study underlines that FIR+ increases the risk of BPD and brain pathology in EPT neonates. Further studies are needed to investigate whether it is possible to reduce FIR+ in this vulnerable group of newborn infants.

4.1 | Strengths and limitations

The major strength of our study was that it included a homogenous cohort of EPT neonates and that the placentas were examined following a structured, pre-specified method and reported according to current international guidelines.[8] Our results may have been limited by the relatively low number of study participants, due to the fact that several of the outcome measures only affected a small proportion of the cohort. The other limitation was that this was a single-centre study.

5 | CONCLUSION

Placental pathology affected 96% of EPT neonates in the study, and these fell into two main categories: acute inflammatory and maternal malperfusion. We found that HCA was associated with NEC, while HCA with FIR+ was associated with both BPD and brain pathology, as seen on MRI scans at term-equivalent age. MVM, on the contrary, was only associated with a low birth weight. Information on placental pathology may be useful for clinicians, but further studies are needed to investigate how placental changes in early GA differ to changes later in pregnancy.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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