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# Placental histology for infants with hypoxic ischaemic encephalopathy compared with healthy controls: a case-control study

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## Abstract

**Background** The role of the placenta in the development of hypoxic ischaemic encephalopathy (HIE) remains undefined. There is limited research comparing placental histology for infants with HIE and healthy controls. This is limiting our ability to understand its role in HIE. This study hypothesised that placental pathology is more common in infants with HIE compared with healthy infants and aimed to report the differences in placental histology between infants with HIE and healthy controls.

**Methods** A case-control study of infants with moderate andsevere HIE and healthy controls at a single tertiary Neonatal Intensive Care Unit. Placental histology was reviewed by one perinatal histopathologist using consensus guidelines.

**Results** Seventy-four cases and 98 controls were included. Cases had a higher incidence of pathology, including fetal vascular malperfusion, histological chorioamnionitis and delayed villous maturation.

**Conclusion** This study demonstrates a higher incidence of placental pathology for infants born with HIE suggesting that the placenta is an important factor in the pathogenesis of HIE. Further research is required to delineate this relationship.

## Impact

- Placental pathology is more common in infants with hypoxic ischaemic encephalopathy.
- Fetal vascular malperfusion, histological chorioamnionitis and delayed villous maturation were increased in cases compared with controls.
- These findings have implications for future research and provide a foundation for further studies aiming to provide a better understanding of HIE pathogenesis and treatment.

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## Background

Neonatal encephalopathy (NE) remains a significant cause of neonatal morbidity and mortality and childhood disability across the world [1, 2]. NE has many different aetiologies, including genetic, metabolic, infection, stroke and hypoxia ischaemia. NE due to hypoxia ischaemia, known as hypoxic ischaemia encephalopathy (HIE), is the most common cause of NE. Within the classification of hypoxia ischaemia, it is well understood that hypoxia ischaemia can be acute, subacute, chronic or mixed pattern. Acute hypoxia ischaemia is recognised as an intrapartum sentinel event and accounts for 30–40% of cases of HIE. Subacute, chronic and mixed pattern hypoxia ischaemia is assumed to be the cause for the remaining cases however the mechanisms leading to these patterns of hypoxia ischaemia remain uncertain [3].

There is an increased appreciation for the role that maternal and placental factors have in the development of the fetus, including fetal brain health and development [4]. This complex and dynamic relationship is known as the maternal-placental-fetal (MPF) triad. The health of this triad and how each element interacts affects the growth and development of the fetus [5]. Improving our understanding of the MPF triad provides an opportunity for enhanced antenatal and intrapartum care to positively influence the outcomes of at-risk fetuses.

Placental pathology is known to be associated with the development of HIE. Placental lesions associated with inflammation and fetal malperfusion likely affect the capacity of the fetus to maintain adequate oxygenation and organ perfusion in the hypoxic ischaemic environment of labour. This likely increases a fetus's vulnerability to peripartum hypoxic-ischemic injury and plays a role in the mechanisms and timing of brain injury [6, 7].

There remains controversy over the influence that placental pathology has on outcomes in infants with HIE [8–10]. Some research suggests that placental pathology in HIE does not impact their outcome [8]. To conclude that placental pathology has no impact on outcomes in HIE, one must compare to placental histology of infants without HIE. There is limited research comparing placentae of infants with HIE and healthy infants [3, 9, 10]. Determining the differences between the placentae of infants with healthy brains and those with injured brains may provide insights to the role of the placenta in HIE.

The aim of this study was to determine if placental pathology is more common in newborn infants with HIE compared with healthy controls.

## Methods

This was a retrospective case-control study performed in a single tertiary Neonatal Intensive Care Unit. This case-control study of placental histology was part of a larger study investigating the relationships between placental pathology, cardiotocography (CTG) and neuroimaging for newborn infants with moderate or severe HIE. All participants in this arm of the study were inborn.

## Participants

### Cases

Cases were infants with moderate or severe HIE born between 2006 and 2021 with a gestational age at birth of 36 + 0 weeks or greater. The grade of encephalopathy was determined using the modified Sarnat criteria [11] and continuous aEEG recording over the initial days of life, this classification was extracted from the clinical notes. In all cases, history and investigations including neuroimaging were consistent with a diagnosis of HIE. Cases were included if placental slides were available for analysis. Infants were excluded if (1) gestation < 36 + 0 weeks; (2) abnormal anatomy on brain MRI; (3) an alternative diagnosis was found to explain their encephalopathy other than hypoxia ischaemia (including metabolic/genetic/ infectious causes). Thoresen scoring system was used to analyse brain MRIs to determine the presence of brain injury [12]. A total injury score of more than 2 was used as a cut off for reporting an MRI as abnormal.

An intrapartum sentinel event was defined as: shoulder dystocia, placental abruption, uterine rupture, cord accident amniotic fluid embolus and other (maternal collapse, fetomaternal haemorrhage, postnatal asphyxia, subgaleal haemorrhage, antepartum haemorrhage).

Controls were recruited over a period of 12 months from January 2022 to January 2023. Contemporaneous control data was not possible as healthy infants do not have placental histology performed in this institution. It was felt that infants having placental histology for other reasons did not represent a group of healthy control infants. Inclusion criteria: (1) placenta available for analysis; (2) intrapartum cardiotocography (CTG) available for a minimum duration of 40 min; (3) born at $\geq$ 36 weeks' gestation and considered to be healthy with a normal neurological status and an Apgar score $\geq$ 8 at 5 min; (4) no resuscitation after 5 min from birth; (5) no admission to NICU/ prolonged neonatal stay or need for neonatal follow up following discharge.; and (6) no clinical indication for placental analysis. A normal neurological examination was defined as vigorous on delivery (Apgar score $\geq$ 8) and a normal newborn discharge examination. CTG was a requirement for controls as this study was part of a larger study exploring the associations of placental pathology and CTG. All controls were vigorous on delivery and did not require delivery room interventions apart from initial steps.

Exclusion criteria: (1) maternal history of recurrent miscarriage (≥ 3) or coagulopathy; or (2) clinical indication for placental analysis (including: maternal thromboembolic disease, suspicion for infection, admission

to NICU, severe intrauterine growth restriction). These exclusions were used as these MPF triads were not considered to represent a healthy control MPF triad. Maternal and infant charts were reviewed for clinical details.

### Placental analysis

Cases in this study had HIE at birth and this was the indication for placental analysis. As this was a retrospective study, the decision for placental histology was based on the clinical presentation and at the request of the treating physician. Controls were recruited for this study as they were considered to be healthy MPF triads. Their enrolment in this study was their only reason for placental assessment; they had no other indication for assessment.

Case placentae were archived placental slides and control placental slides were prepared onsite. Placental slides were reviewed by one perinatal histopathologist (ED) using the 2016 Amsterdam consensus guidelines for reporting placental histology [4, 5]. Macroscopic details (including coiling index (CI) and placental weight) were collected. For cases, this information was collected from archived clinical histology report after placental slides were reviewed. Coiling index (CI) is a measure of the number of complete coils per centimetre length of cord (normal reference range 0.1–0.3 coils/cm) [13, 14]. The reviewer was blinded to the clinical details of the cases, however had birth weight and gestation available for interpretation of placental weight centiles and birth weight-to-placenta weight ratio (BW: PW) calculations.

Placental pathology (Fig. 1) was classified into grades and stages of histological chorioamnionitis (HCA) and pattern and/or severity of fetal vascular malperfusion (FVM), maternal vascular malperfusion (MVM), villitis of unknown etiology (VUE) and delayed villous maturation (DVM) as per the Amsterdam criteria. Specifically, for FVM, it was defined as low grade or high grade and into global and segmental. High grade FVM is manifested by the finding of more than one focus of avascular villi (a cumulative assessment of >45 avascular villi over 3 sections examined or an average of >15 villi per section) with or without thrombus, or 2 or >occlusive or non-occlusive thrombi within the chorionic plate or major stem villi or multiple occlusive thrombi [15]. For the purpose of analysis, categories of pathology were classified as present or absent as the sub-category classifications for each pathology were too small for meaningful analysis.

FIRS was considered to be present if the placental histology showed evidence of chorioamnionitis on the fetal side of the placenta. Fetal inflammatory response was defined as per the Amsterdam criteria as inflammation within fetal vessels (stage I; chronic vasculitis or umbilical phlebitis; stage II; Involvement of the umbilical vein and one or more umbilical arteries; stage III; necrotising funisitis and graded as grade I; not severe; grade II; severe) [15].

### Statistical analysis

Statistical analysis was performed using Stata SE Version 17 (StatCorp, College Station, Texas). For summary statistics, continuous normally distributed variables were reported as means and standard deviation (SD) and continuous non-normally distributed variables were reported as medians and interquartile range. T test was used for binary and normally distributed continuous variables. Wilcoxon rank sum test was used for binary and non-normal continuous variable. Chi squared test was used for categorical variable with a cell count greater than 20. Fischer's exact test was used for two binary variables where the cell counts were less than 20. Statistical significance was set at a p-value $<0.05$. Risk ratio (RR) and 95% confidence intervals (95% CI) were calculated also. Univariate analysis was performed for each placental pathology. Due to the small sample size, it was not possible to determine the relationship between multiple placental pathologies and HIE.

## Results

This study included 74 cases of moderate or severe HIE and 98 healthy controls. Demographics for the cases and controls are shown in Table 1. Sixty-three cases had brain MRIs. Thirty-three were abnormal. Placental histology for cases and controls are shown in Table 2.

All controls had a normal newborn examination with growth parameters within the normal limits for gestation.

### Fetal vascular malperfusion

FVM was more common in cases. Eighteen (24%) cases had FVM. Fifteen cases with FVM had CI recorded, of which 5 (33%) had hyper-coiling of the umbilical cord. Five (28%) cases with FVM had an intrapartum sentinel event, a lower proportion than the rate of ISE for all cases (43%). Eight cases with FVM had HCA and 6 cases had DVM, of which 3 cases had both HCA and DVM.

Table 3 outlines the cases and controls who had hyper-coiling (defined by CI>0.3) and whether FVM was present. There was a higher incidence of FVM with hyper-coiling in cases compared with controls (50% v 17%). Of the 5 cases with FVM and hyper-coiling, 2 (40%) had high-grade FVM. In contrast, no controls with FVM and hyper-coiling had high-grade FVM.

### Maternal vascular malperfusion

MVM was more common in controls than cases, but this difference was not statistically significant. Birth weight was significantly lower for cases with MVM compared with controls with MVM. Cases with MVM had higher

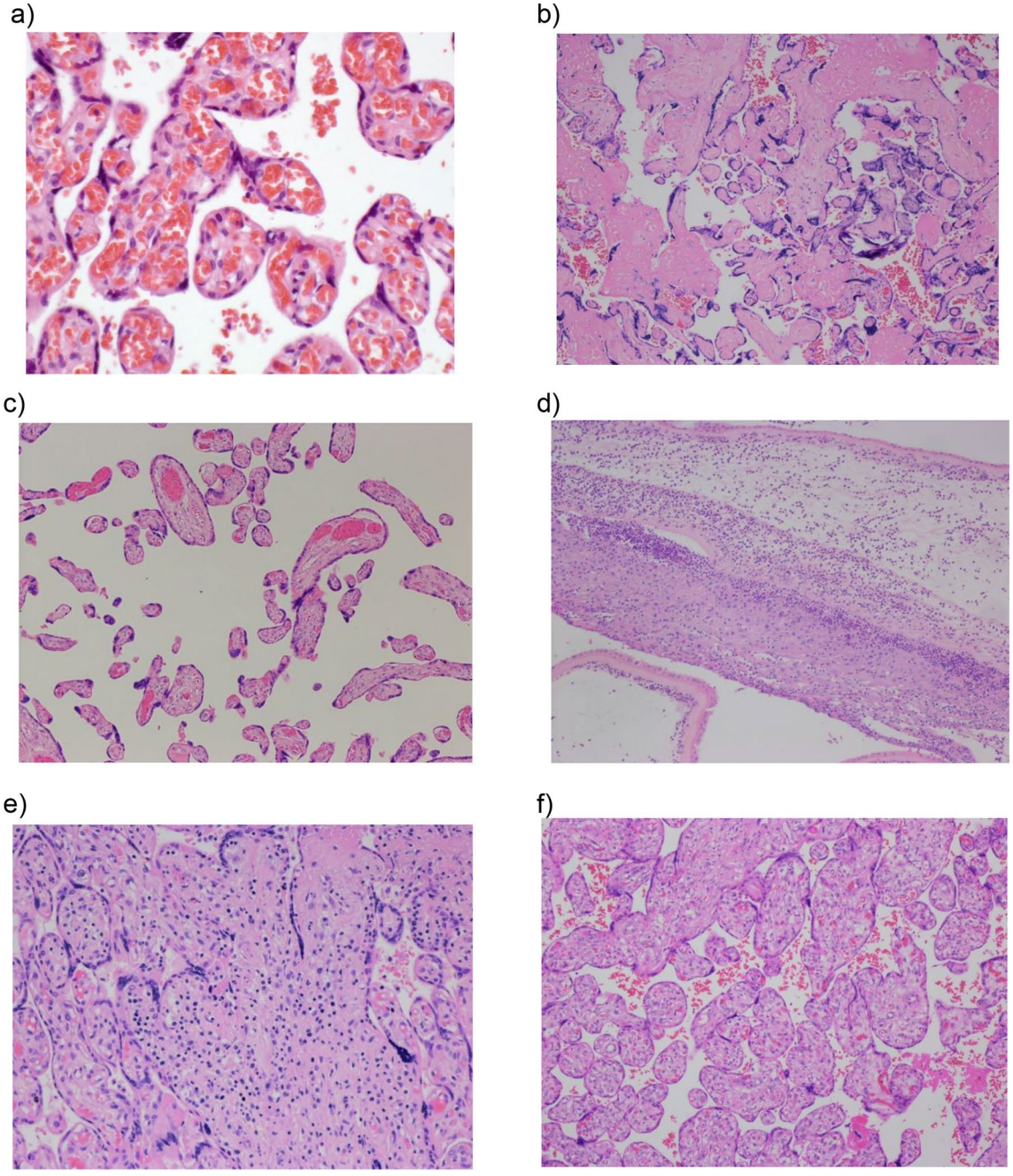


**Fig. 1** Examples of placental pathology. **a**) normal third trimester chorionic villi – 40x, **b**) fetal vascular malperfusion (FVM): high grade – 20x, **c**) maternal vascular malperfusion (MVM): accelerated villous maturation – 20x, **d**) acute suppurative chorioamnionitis (HCA) – 20x, **e**) villitis of unknown etiology (VUE) – 40x, **f**) delayed villous maturation (DVM) – 20x

BW: PW than controls with MVM but this was not statistically significant.

#### Histological chorioamnionitis

Thirty-six (49%) cases had HCA of which 22 (61%) had FIRS. This was significantly different to the control group. Those with FIRS were at greater risk of developing HIE.

#### Vilitis of unknown etiology

VUE was more common in controls than cases, however this difference was not significant. Presence of VUE in cases had no association with birth weight, BW: PW or maternal BMI.

#### Delayed villous maturation

DVM was more common in cases compared with controls, this was statistically significant. There was no

**Table 1** Participant characteristics. Data presented as mean (SD), median (IQR) and number (%)

| Demographics | Cases (*n* = 74) | Controls (*n* = 98) |
|---|---|---|
| Gestational age, weeks | 39.5 (1.7) | 39.6 (1.1) |
| Birth weight, gram | 3514 (539) | 3548 (409) |
| Female | 31 (42%) | 45 (46%) |
| Maternal BMI (kg/m$^2$) (*n* = 58, 93)' | 27.2 (4.8) | 25.9 (4.3) |
| Mode of delivery * | | |
| Vaginal | 23 (31%) | 68 (70%) |
| Assisted Vaginal | 15 (20%) | 17 (17%) |
| Emergency CS | 35 (48%) | 13 (13%) |
| Elective CS | 1 (1%) | 0 (0%) |
| Apgars^ | | |
| 1-minute | 1.5 (1,4) | 9 (9,9) |
| 5-minute | 4 (1,7) | 10 (10,10) |
| Grade of Encephalopathy | | |
| Moderate | 40 (54%) | |
| Severe | 34 (46%) | |
| Intrapartum Sentinel Event | 32 (43%) | |
| Therapeutic Hypothermia (TH) | 53 (72%) | |
| Pre TH era | 19 | |
| Did not meet criteria of TH - | 2 | |
| Brain MRI (*n* = 63) | | |
| Abnormal | 33 (52%) | |
| Cord UV blood gas | | |
| pH (*n* = 61) | 7.2 (7.0, 7.2) | |
| BE (*n* = 49) | -9 (-11.6, -5.0) | |
| Cord UA blood gas pH (*n* = 64) | 7.0 (6.8, 7.1) | |
| BE (*n* = 51) | -11.6 (-16.1, -7.7) | |
| Postnatal blood gas | | |
| pH (*n* = 57) | 7.0 (6.9, 7.1) | |
| BE (*n* = 55) | -13.5 (-20.9, 10.9) | |
| Lactate (*n* = 52) | 12.3 (4.9) | |

*More cases were delivered by emergency Caesarean section compared with controls ($p < 0.001$). ^More cases had lower Apgar scores at 1 and 5 min compared with controls ($p < 0.001$), 'cases had a higher maternal BMI (p = 0.039). - One case did not meet the criteria within the 6-hour window and the second case had a seizure however was not treated with therapeutic hypothermia as the cord gases and Apgars score did not meet the pre-defined criteria

association between presence of DVM in cases and birth weight, BW: PW or maternal BMI.

Differences in BW: PW, CI, incidence of MVM and VUE were not statistically significant between case and control groups (Table 2).

## Discussion

This study provides evidence that placental pathology is more common in newborn infants with moderate or severe HIE than healthy controls and is in keeping with other studies that have compared placentae of infants with HIE and controls [9, 10, 16]. Several specific placental pathologies, classified used the Amsterdam criteria [15], had an increased incidence in cases compared with controls, including HCA, FVM and DVM. This suggests

**Table 2** Case and control placental histology

| Placenta Histology | Cases (*n* = 74) | Controls (*n* = 98) | Statistical Analysis | |
|---|---|---|---|---|
| | | | Risk Ratio (95% CI) | *P* value |
| Placental Weight, grams | 519 (127) | 501 (85) | | 0.135 |
| Birth Weight: Placental Weight Ratio (range 5–7) | 7.0 (5.8, 8.1) | 7.2 (6.5, 7.7) | | 0.325 |
| Coiling Index (CI) (range 0.1–0.3) | 0.21 (0.10) | 0.20 (0.08) | | 0.230 |
| Fetal Vascular Malperfusion | 18 (24%) | 11 (11%) | 1.6 (1.1–2.2) | 0.038 |
| Low-Grade | 9 (12%) | * | | |
| High-Grade | 9 (12%) | 7 (7%) 5 (5%) | | |
| Maternal Vascular Malperfusion | 11 (15%) | 25 (26%) | 0.66 (0.4–1.1) | 0.129 |
| Mild | 10 (14%) | 25 (26%) | | |
| Severe | 1 (1.4%) | 0 (0%) | | |
| Chorioamnionitis | 36 (49%) | 28 (29%) | 1.6 (1.1–2.2) | 0.007 |
| If yes, FIRS | 22 (61%) | 5 (18%) | | |
| FIRS | | | 2.3 (1.7–3.0)# | 0.001 |
| Villitis of Unknown Etiology | 9 (12%) | 22 (22%) | 0.6 (0.4–1.1) | 0.061 |
| Low-Grade | 6 (8%) | 13 (13%) | | |
| High-Grade | 3 (4%) | 9 (9%) | | |
| Delayed Villous Maturation | 24 (30%) | 10 (10%) | 2.0 (1.4–2.7) | 0.003 |
| Any Placental pathology | 58 (78%) | 68 (69%) | 1.3 (0.9–2.1) | 0.187 |

Data presented as mean (SD), median (IQR), number (%), risk ratio (RR) and 95% confidence interval (95% CI). ~CI was not available for all participants, the data shown for CI represents 46 cases and 98 controls. *One control had both high and low grade FVM. #RR calculated for FIRS is based on full cohort

**Table 3** Coiling index greater than 0.3 association with presence of FVM

| | Cases (*n* = 10) | | Controls (*n* = 12) | |
|---|---|---|---|---|
| Coiling Index > 0.3 | No FVM | Any FVM | No FVM | Any FVM |
| 0.31 | *1* | *1* | *0* | *0* |
| 0.32 | *2* | *0* | *1* | *0* |
| 0.33 | *1* | *0* | *4* | *0* |
| 0.34 | *1* | *0* | *1* | *1* |
| 0.35 | *0* | *0* | *1* | *0* |
| 0.36 | *0* | *1* | *0* | *0* |
| 0.38 | *0* | *1* | *1* | *0* |
| 0.4 | *0* | *1* | *1* | *0* |
| 0.44 | *0* | *0* | *1* | *0* |
| 0.48 | *0* | *1* | *0* | *0* |
| 0.52 | *0* | *0* | *0* | *1* |
| Total | 5 (50%) | 5 (50%) | 10 (83%) | 2 (17%) |

Data presented as number (%). CI > 0.3 was considered to represent a hypercoiled umbilical cord

that these placental pathologies itself could be contributing to the development of hypoxic ischaemic brain injury or due to reduced placental reserve, resulting in earlier and more significant fetal decompensation in the setting of intrapartum hypoxic ischaemia.

The incidence of FVM was higher in infants with moderate or severe HIE compared with controls. This finding supports the results of other studies [9, 16]. There was also a higher incidence of FVM in cases without an intrapartum sentinel event compared to those with an intrapartum sentinel event (31% v 16%). This is based on very small numbers and was not statistically significant. This suggests that FVM may have a larger role in cases of unexplained HIE.

Cases with FVM were more likely to demonstrate hyper-coiling compared with controls (Table 3). FVM occurs with obstructed blood flow within the fetal circulation. Therefore, cords with higher coiling indexes are likely to be a contributory factor to the development of FVM and subsequent HIE. However, hyper-coiling alone is unlikely to be the sole cause of FVM as controls with FVM had a lower incidence of hyper-coiling compared to the cases. The cases with hyper-coiling may have experienced additional factors influencing the development of FVM, such as cord compression. The difference in incidence of hyper-coiling between case and control groups with FVM suggests that hyper-coiling could represent a risk factor for FVM and subsequent hypoxic ischaemia of the fetus, but perhaps in isolation it exerts less of an influence. Due to the small numbers, this study is limited in its ability to investigate this potential association in more detail for the whole case group or for individual cases.

This study demonstrates an increased incidence of HCA in infants with HIE compared to healthy controls. The incidence of HCA in cases in this study is also higher than the incidence of HCA reported in a healthy population in others studies [10]. This has been reported in studies previously, including in a cohort study by Novak et al. where they found HCA was more common in infants with HIE with an unexplained cause [17].

An inflammatory response on the fetal side of the placenta implies that the fetus was affected by inflammation. This is more commonly known as Fetal Inflammatory Response Syndrome (FIRS) [18]. For cases in this study, FIRS was present for 61% of cases affected by HCA. Bingham et al. also found cases with HCA had a much higher incidence of FIRS than controls with 100% of their cases with HCA having FIRS, although they did report a higher incidence of HCA in their control group compared to the current study [16]. This may be due to selection bias within their control group which included infants admitted to NICU for a reason other than HIE, and likely does not represent a control cohort of healthy term infants. Bingham et al. conducted an additional study to highlight the difference in placental pathology depending on the cohort being analysis [19]. This study highlighted the importance of using a true healthy control group for comparison with HIE to facilitate more accurate results and links between placental pathology and HIE.

McDonald et al. and Mir et al. conducted cohort studies for infants with HIE and found that HCA, particularly HCA with FIRS, was associated with encephalopathy and an increased severity of encephalopathy [20, 21]. The HEAL trial found 39% of their cohort had HCA [22]. Naisell et al. performed a case-control study and found no association between HIE and HCA, however their study only had 41 cases with placental findings and included infants with mild, moderate and severe HIE. Details of the number of each grade of HIE and their placental pathologies were not included in their report. Placental findings in infants with mild HIE may differ from infants with moderate or severe HIE. FIRS is associated with increased neonatal mortality and neonatal, childhood and adult morbidity [23–25]. HCA, particularly in the setting of FIRS, has potentially led to a preconditioning of the fetal brain. Inflammation may have a direct effect on the growth and developing of the fetal brain [25–27] and/or act as a primer for fetal brain injury in the setting of intrapartum hypoxic ischemia [23, 28].

FIRS can lead to impaired perfusion, oxygen delivery and/or disseminated intravascular coagulation, leading to micro-thrombi in the capillaries, culminating in hypoxic tissue [29]. This process may increase tissue vulnerability to reduced delivery of oxygen in the setting of labour and delivery, even if hypoxic ischaemia is within the limits of a typically progressing intrapartum course. This potentially represents a 'multiple hits' model which is implicated by others in FIRS related brain injury [26]. This may explain the pathogenesis of HIE for some infants with a seemingly normal intrapartum course. The ongoing inflammation from FIRS may also contribute to postnatal brain dysmaturation and impact brain recovery after HIE, with or without therapeutic hypothermia.

DVM was also significantly increased in cases. Some studies have found no association between DVM and HIE [16, 21, 30]. However, Harteman et al. looked at the relationship between brain injury on MRI and placental findings in HIE. They found placental immaturity to be associated with white matter brain injury [31].

In contrast, MVM was more common in controls than cases but this was not statistically significant. Some studies have found features of MVM to be associated with HIE [16, 21], in contrast to the findings in this study. Unfortunately, MVM has not been routinely reported in many placental pathology studies on HIE so it if difficult to determine if this study is an outlier in this respect or not. This study did find that where MVM was present in

cases, birth weight was lower than in all cases and lower than controls with MVM. This may suggest that where MVM is present, and contributes to suboptimal fetal growth it may impair tolerance of labour.

### Strengths

A major strength of this study is that it reports on a good sample size of cases with moderate or severe HIE compared with other studies on placenta pathology in HIE. It also includes a control group of neurologically healthy term infants without medical illness or clinical indication for placental assessment, which has been identified as a limitation in other similar studies [19]. CTG from the control group were not reviewed prior to consenting participants for inclusion in the study. This was to avoid selection bias within this group. Therefore, CTG findings had no influence on whether or not a control was approached for consent.

### Limitations

Recruitment of controls in this study was limited by the capacity of the histopathology department at this institution to process the additional workload for placental analysis and were collected over a period of one year. It was not possible to blind the reviewer to whether the placenta slides were from a case or control. Case placenta slides were archived slides that were retrieved from storage. Control placenta slides were stored on site until they were reviewed.

There were only a small number of cases and controls with hyper-coiling. This study has reported the number of those with FVM however due to the small numbers, statistical analysis was not appropriate. It is also not possible to comment on the role hyper-coiling in individual cases as other factors that may have contributed to the development of FVM cannot be accounted for.

Due to resource limitations, we were unable to have a second reviewer to analyse the placentae leading to an inability to determine the presence of any bias within the reporting.

Due to the low incidence of HIE (1–3/ 1,000 births) [7], it was not feasible to recruit cases and controls prospectively to facilitate the analysis of fresh placental slides for both groups.

Recruiting a control group from infants born at the same time as cases who had placental histology performed would not reflect a healthy control group. Placental histology is not performed routinely for healthy MFP triads and thus would represent a cohort of high-risk MPF triads.

The need for CTG excluded newborns born by elective section or vaginal delivery where CTG was not in place. This may have introduced some bias however as the aim was to identify pathology associated with poor tolerance of labour including groups with a sufficient period of labour to warrant continuous monitoring may have improved specificity of findings.

Data on maternal morbidity was collected for cases but not for controls. Therefore, it was not possible to analysis the influence of material morbidity on placental histology.

Although the placentae were analysed in detail (with grading and staging of each pathology), it was not possible to analyse the influence of grade and stage for each pathology due to the small sample size and frequency of each pathology. The analysis was done using the binary variable of present or absent.

## Conclusion

This case-control study provides evidence for differences in placental histology between infants with moderate or severe HIE and a convenience sample of healthy controls. Infants with HIE had a higher incidence of pathology overall, and specifically for HCA, FVM and DVM. This suggests that placental pathology may be a risk factor for poor tolerance of labour and/or may be a contributing factor in the pathogenesis of HIE, particularly in the absence of an intrapartum sentinel event. Further research is required to further delineate the role of the placenta in the pathogenesis of HIE.

#### Abbreviations

| | |
|---|---|
| BE | base excess |
| CI | confidence interval |
| DVM | delayed villous maturation |
| FIRS | fetal inflammatory response syndrome |
| FVM | fetal vascular malperfusion |
| HCA | histological chorioamnionitis |
| HIE | hypoxic ischemic encephalopathy |
| MPF | maternal-placental-fetal |
| MVM | maternal vascular malperfusion |
| NE | neonatal encephalopathy |
| RR | risk ratio |
| VUE | vilitis of unknown etiology |

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#### Author contributions

AF contributed to the design of the study, collected data, statistical analysis, interpretation of results and wrote and edited the manuscript. ED reviewed all the placental slides, provided expert knowledge and contributed to the interpretation of results, reviewed intellectual content and edited the manuscript. AR contributed to the design of the study, collected data, interpretation of results, reviewed intellectual content and edited the manuscript. MG contributed to the design of the study and edited the manuscript. RC contributed to the design of the study, scoring MRI images, interpretation of results, reviewed intellectual content and edited the manuscript. BH contributed to the design of the study, interpretation of data, reviewed intellectual content and edited the manuscript, supervisor of study.

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**Data availability**
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**
The study received ethical approval from the Rotunda Hospital Research and Ethics Committee (REC-2015-009). Approval was given to waiver consent for patients who died or have significant disability. All other families, including controls gave informed consent for their data to be included. Specifically, controls gave consent of placental analysis. The study was performed in accordance with the Declaration of Helsinki.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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