Placental pathology of neonates diagnosed with encephalopathy soon after birth: A retrospective analytical study

K L Sebolai,[1] FCPaed(SA), MMed (Paediatrics); **O Mekgoe,**[1] FCPaed(SA); **C A Wright,**[2,3] FCPath (Anat Path), PhD; **K Thandrayen,**[4] FCPaed(SA), PhD; **S C Velaphi,**[4] FC Paed(SA), PhD

[1] *Department of Paediatrics and Child Health, Klerksdorp/Tshepong Complex, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[2] *Division of Anatomical Pathology, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[3] *National Health Laboratory Services, Nelson Mandela Bay, South Africa*
[4] *Department of Paediatrics and Child Health, Chris Hani Baragwanath Academic Hospital, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*

Corresponding author: *K L Sebolai (lorrainelebopaul@gmail.com)*

Background. Placental pathology has been linked to neonatal encephalopathy (NE). Despite the high prevalence of NE in low- and middle-income countries (LMICs), there are limited published studies exploring this association from LMICs.
Objective. To describe and analyse the histopathology of placentas from neonates diagnosed with encephalopathy shortly after birth.
Methods. A retrospective analytical study was conducted on neonates diagnosed with encephalopathy at Klerksdorp/Tshepong hospital complex, South Africa. Placentas from term and near-term neonates (birthweight ≥2 000 g) diagnosed with encephalopathy within the first 24 hours of life were sent for histopathological examination. Neonates were grouped into those with encephalopathy with or without intrapartum hypoxia (IH) (base deficit ≥12 mmol/L). The severity of NE was assessed as mild, moderate or severe, according to Sarnat staging. The types and extent of placental lesions were compared between those with mild and moderate-to-severe NE, and between cases with or without IH.
Results. Of 16 336 live births, 271 neonates were diagnosed with NE, and of these, 193 (71.2%) had NE with IH. Placental histopathology results were available for 239 neonates (88.2%). The median placental weight was 428 g, with 46.6% of placentas weighing below the 10th percentile. Cord abnormalities were observed in 27.2% of placentas. Nearly all placentas (98.2%) exhibited at least one histopathological lesion. The most common microscopic placental lesions identified were maternal vascular malperfusion (MVM) (55.6%), fetal vascular malperfusion (55.1%), acute chorioamnionitis (41.2%) and villitis of unknown aetiology (28.9%). There was a significant association between NE with IH and the presence of MVM, with an adjusted odds ratio of 3.24 (95% confidence interval 1.19 - 8.79). No significant association was found between the presence or number of different placental lesions and the severity of NE. Factors associated with severity of any NE (with and without IH) included an Apgar score <7 at 10 minutes (p<0.001) and pH <7.00 (p<0.001).
Conclusion. A high proportion of neonates with encephalopathy showed evidence of IH. Approximately half of the placentas were below the 10th percentile in weight, and about a quarter had macroscopic cord abnormalities. Almost all neonates with encephalopathy displayed ≥1 microscopic placental lesion. A strong association was found between the presence of MVM and NE with IH.

Keywords: neonatal encephalopathy, placental pathology, intrapartum hypoxia, low Apgar score

S Afr Med J 2026;116(6):e3811. https://doi.org/10.7196/SAMJ.2026.v116i6.3811

Neonatal encephalopathy (NE) is a clinically defined disorder characterised by impaired neurological function in neonates born at term or near-term gestation. One of the causes of NE is hypoxic-ischaemic encephalopathy (HIE), which is due to impaired fetal cerebral blood flow and oxygen delivery. Globally, HIE is considered to be a major contributor to perinatal mortality.[1] The incidence of HIE has been reported to be significantly higher in low- and middle-income countries (LMICs), as high as 14.9 per 1 000 live births,[2] compared with high-income countries at 1.3 - 1.7 per 1 000 live births.[3] In South Africa (SA), studies from different provincial regions have also indicated noticeable variability. Two studies conducted at two separate academic institutions in Gauteng Province reported an incidence of 3.6 - 15.2 per 1 000 live births.[4,5] There was a vast contrast in the findings from a similar population demographic to these Gauteng studies, with incidences reported as 2.3 - 4.3 per 1 000 live births in the Western Cape Province.[6]

Placental pathology has been associated with increased risk for the development of NE.[7] According to the 2016 Amsterdam Placental Workshop Group Consensus Statement,[8] there are four significant microscopic lesions that have been associated with NE: acute chorioamnionitis (ACA), villitis of unknown aetiology (VUE), maternal vascular malperfusion (MVM) and fetal vascular malperfusion (FVM).[8] These lesions have been described in previous studies as contributing to poor neurological outcome in neonates. With regard to predictors of the outcome of NE, VUE has been shown to be the most significant predictor of abnormal long-term outcomes, while ACA is associated with the severity of NE.[9] Neonates with NE have been shown to have a higher likelihood of placental inflammatory and flow-restrictive lesions, which may predispose the neonatal brain to hypoxic ischaemia.[9,10]

There is still a substantial lack of data on the risk profile of neonates with NE, and especially the contribution of placental histopathology.

This is especially important in LMIC settings, where the incidence of NE is relatively high. Bhorat *et al.*,[11] writing from a SA obstetric perspective, now recommend that placental histopathological evaluation be part of the assessment when investigating causes of cerebral palsy where NE was a suspected cause.[11] The aim of the present study was to describe the histopathology of placentas from neonates born with encephalopathy, and to determine whether there is an association between the type or extent of placental pathology and the severity of NE.

Methods

Study design

This was a retrospective, analytical study of neonates born at or near term diagnosed with NE, who had placentas sent for histopathology.

Study setting

The study was conducted in the Klerksdorp/Tshepong (KT) hospital complex, North West Province, SA. The KT hospital complex is a provincial and a satellite teaching hospital for the University of the Witwatersrand. It is the referral hospital for patients from Nic Bodenstein district hospital and 30 local clinics in North West Province. The hospital conducts ~6 000 births per year. All neonates diagnosed with NE are admitted and managed in the neonatal unit, which has a capacity of 49 beds, including 12 neonatal intensive care unit and 12 high care beds.

In December 2019, the hospital implemented a protocol that recommended that all placentas from neonates born with encephalopathy should be sent for histopathological evaluation to assist in identifying factors that might contribute to NE. The following criteria were used to establish the diagnosis of NE: requirement for resuscitation at birth, defined as the need for at least bag-valve-mask ventilation (BMV); and signs suggestive of NE.

Study population

Neonates born in KT hospital complex, weighing ≥2 000 g, with a diagnosis of NE, with placentas sent for histopathological assessment from 1 December 2019 to 31 October 2022, were enrolled in the study. Neonates who were born outside the hospital facility, had major congenital anomalies, or did not have a placenta sent for histopathology were excluded.

Study procedures

Maternal and infant hospital records of neonates diagnosed with NE were retrieved and reviewed for analysis. Maternal data included maternal age, gravidity, antenatal care, HIV status, mode of delivery, intrapartum monitoring, and presence of meconium-stained amniotic fluid. Intrapartum monitoring was performed by assessing the maternal clinical condition, plotting the progress of labour on a Partogram, and using a cardiotocograph (CTG) to determine fetal heart rate. CTG tracings were reported as normal with reactive tracings, or pathological, according to the National Institute for Health and Care Excellence guidelines.[12]

Neonatal data collected included anthropometry, sex, Apgar scores, resuscitation details, cord blood or arterial blood gas done within the first hour of birth, Thompson score, and Sarnat staging and outcome at hospital discharge. The Thompson score and/or Sarnat staging were used to assess the severity of NE.[13,14] NE was classified as mild, moderate, or severe. NE was also classified as with or without intrapartum hypoxia (IH), defined as a blood gas with base deficit ≥12 mmol/L.

Placental histopathology was performed and reviewed by an experienced pathologist (CAW). All placentas were reported on a standardised template and reported according to a globally accepted classification system.[8] The placental lesions were divided according to macroscopic and microscopic characteristics. The macroscopic abnormalities included placental weight and cord abnormalities. All macroscopic and microscopic lesions were reviewed and reported by an experienced pathologist. The major significant microscopic lesions were identified and categorised into ACA, MVM, FVM and VUE. Further analysis was conducted, categorising ACA into maternal or maternal and fetal response as well as dividing FVM and MVM according to different grades. To assess the significance of these microscopic lesions, all placentas were further evaluated based on the total microscopic lesions that each had, and their correlation with severity of NE and type of NE (with or without evidence of IH).

Data analysis

Statistical analysis was conducted using Stata version 17.0 (StataCorp, USA). Neonates were divided into two groups based on the severity of NE: mild, and moderate to severe. Additionally, they were classified based on the presence of IH, with some having NE with IH and others without. Descriptive statistics were used to summarise data related to maternal and infant demographics, as well as placental characteristics. To compare infants based on the severity of encephalopathy, χ^2 tests with Fisher's exact test were used for categorical variables, while Student's *t*-tests or Mann-Whitney U-tests were applied for continuous variables. For multivariate analysis, all significant microscopic histopathological lesions and cardiotocographical findings were incorporated into the model, along with variables that had $p<0.20$ in the univariate analysis. Statistical results from both univariate and multivariate analyses were reported as crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Associations were deemed statistically significant if the 95% CI of the OR did not include the value 1, and if $p<0.05$.

Ethical approval

Permission to conduct the study was obtained from the hospital's chief executive officer. Ethical approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (ref. no M220119).

Results

Incidence

There were 16 336 live births during the study period, of which 271 were diagnosed with NE, with an incidence of 16.5/1 000 live births (Fig. 1). There were 270 singletons and one set of twins. Among the 216 neonates who had arterial blood gases within an hour of delivery, 193 (89.4%) were assessed as having NE due to IH (base deficit ≥12 mmol/L), giving an incidence of HIE at 11.8 per 1 000 live births.

Maternal characteristics

The median maternal age was 23 years, with 56.7% of mothers being primigravidas (Table 1). Most (95.4%) had attended antenatal care, with 58.1% attending before 20 weeks' gestation. A quarter (24.8%) of mothers were positive for HIV. Among the mothers who had comorbidities, the most common diagnosis was hypertensive disorders (32.2%), followed by urinary tract infections (26.9%). Among the 233 (97.8%) mothers who had monitoring with CTG, 103 (44.2%) had pathological CTGs. Meconium-stained amniotic fluid was observed in 40.3% of the births. Among the 238 mothers enrolled in the study, 11.3% (27/238) had induced births and 40.7% (11/27) failed induction and were delivered by caesarean section. The caesarean section rate was 36.1%.

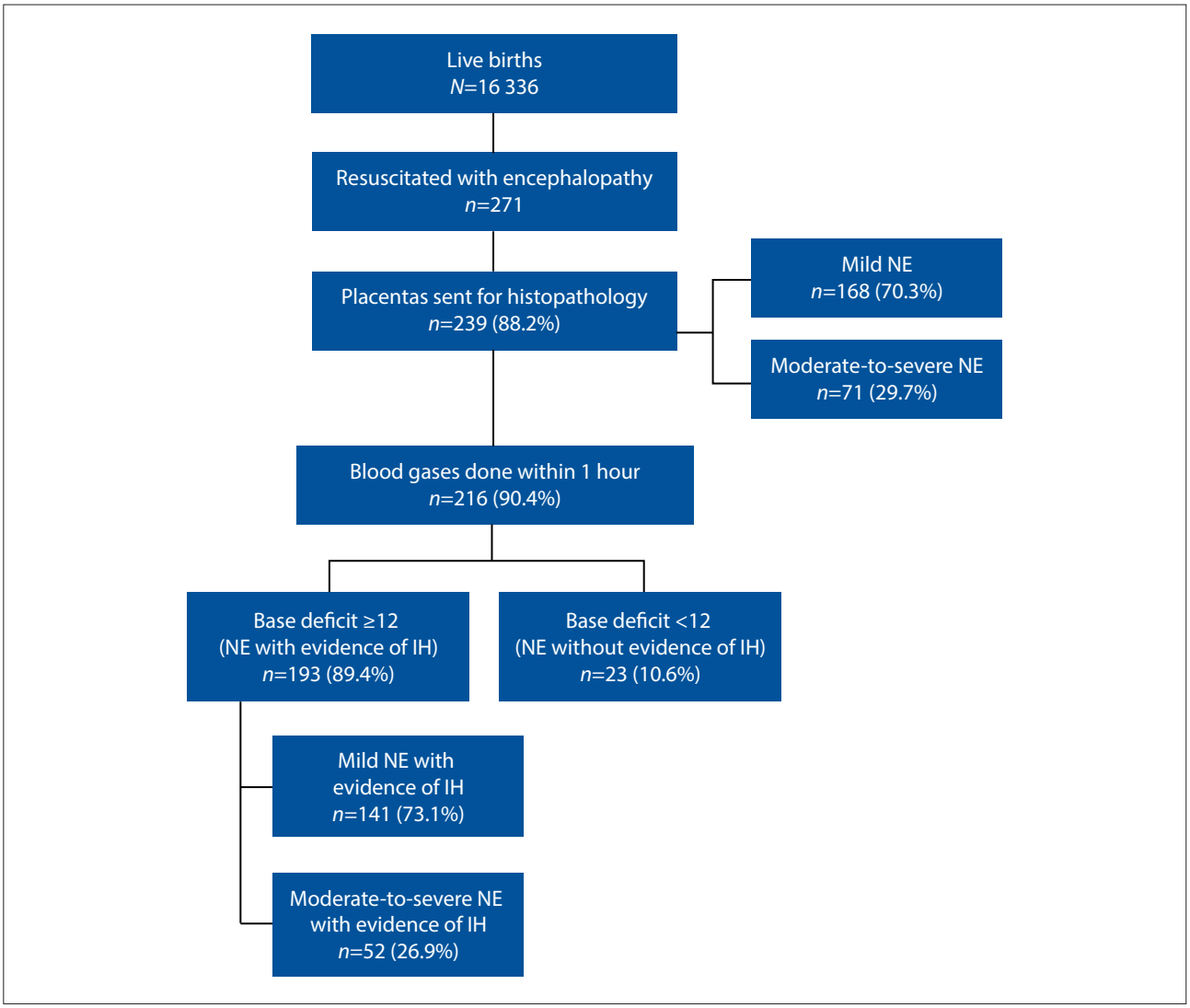

Fig. 1. Flow chart of neonates with encephalopathy enrolled in the study. (NE = neonatal encephalopathy; IH = intrapartum hypoxia.)

Table 1. Maternal age and clinical and delivery characteristics (*N*=238)

Variable	*n* (%)*
Maternal age, years, median (IQR)	23 (20 - 29)
Primigravida	135 (56.7)
Attended antenatal care	227 (95.4)
HIV positive	59 (24.8)
Hypertensive	77 (32.2)
Urinary tract infection	64 (26.9)
Pathological cardiotocograph	103 (44.2)
Meconium-stained amniotic fluid	96 (40.3)
Mode of delivery caesarean section	86 (36.1)

IQR = interquartile range.
*Unless otherwise indicated.

Neonatal characteristics

The median birthweight and gestational age were 3 100 g and 39 weeks, respectively. All neonates required a modality of resuscitation. The majority (75.2%) responded to BMV only, 18.9% required chest compressions, and 5.9% required chest compressions and intravenous adrenaline (Table 2). Apgar score at 10 minutes was <7 in 31.5% and <5 in 8.8% of neonates. Among the 216 neonates who had arterial blood gas performed within the first hour of birth, the median pH and base deficit were 7.11 and 17.4 mmol/L, respectively, with 20.1% having a pH <7.00 and 89.4% with a base deficit ≥12 mmol/L. Therapeutic hypothermia was offered to 45.2% of the neonates. Overall, the mortality rate at hospital discharge was 2.9%.

Placental histology

Reports for histopathology were available for 239 of the 271 (88.2%) neonates diagnosed with NE. The median placental weight was 428 g, with 111 (46.6%) placentas below the 10th percentile (Table 3). Cord abnormalities were present in 27.2% of placentas. These included hypercoiled umbilical cords, and abnormal insertions such as marginal cord insertions and velamentous cord insertions. Among the neonates with NE with available placental pathology, 98.3% (235/239) had significant microscopic lesions on histopathology. The common microscopic placental lesions observed were MVM (55.6%), FVM (53.1%), ACA (41.4%), VUE (28.9%), abruptio placentae (11.7%) and delayed villous maturation (11.7%). The remaining 4 placentas (2.8%) with no identified microscopic lesions had macroscopic pathology such as cord abnormalities and abnormally sized placentas (larger or smaller than gestational age or nonspecific features of intrauterine compromise).

Comparing the number of microscopic placental lesions according to the type and severity of NE

As shown in Table 4, there was a marginally significant difference in the proportion of placentas with ≥2 microscopic lesions in NE with IH compared with the group without IH (p=0.084). There were no significant differences in the proportion of placentas with ≥2 lesions with severity of NE for all those with any NE (mild v. moderate-to-severe NE, p=0.248) and for those with NE with IH (mild v. moderate-to-severe NE, p=0.401).

Comparison of maternal and neonatal characteristics and placental histopathology between neonates with mild and moderate-to-severe NE

In both univariate and multivariate analysis, the factors that were associated with moderate-to-severe NE were Apgar score <7 at 10 minutes (p<0.001) and pH <7.00 (p=0.001) (Appendix Table S1). There was no association with placental histopathology and severity thereof (p>0.05).

Comparison of maternal and neonatal characteristics, and placental pathology between NE with and without evidence of IH

On multivariate analysis the odds of neonates having NE with IH were nearly 13-fold greater if the mother attended antenatal care (OR 12.91; 95% CI 2.08 - 80.0), and three-fold greater if the placental lesion was MVM (OR 3.04; 95% CI 1.04 - 8.88); p=0.042) compared with those with NE without IH (Appendix Table S2).

Table 2. Neonatal characteristics, including management and outcome at hospital discharge

Variable	*n/N* (%)*
Birthweight, g, median (IQR)	3 100 (2 800 - 3 400)
Gestational age, weeks	39 (39 - 40)*
Sex, male	153/239 (64.0)
Apgar score at 10 minutes†	
<7	75/238 (31.5)
<5	21/238 (8.8)
Type of resuscitation required	
BMV only	179 (75.2)
BMV with chest compressions	45 (18.9)
BMV with chest compressions and adrenaline	14 (5.9)
Arterial blood gas within 1 hour of life‡	
Blood gas pH, median (IQR)	7.11 (7.01 - 7.19)
pH <7	48/216 (20.1)
Base deficit, in mmol/L, median (IQR)	17.4 (13.9 - 21.0)
Base deficit ≥12 mmol/L	193/216 (89.3)
All neonates with encephalopathy	239
Mild	168 (70.3)
Moderate to severe	71 (29.7)
Encephalopathy without IH (base deficit <12 mmol/L)	23/216 (10.6)
Encephalopathy with IH (base deficit ≥12 mmol/L)	193/216 (89.4)
Mild	141/193 (73.1)
Moderate to severe	52/193 (26.9)
Seizures	56/239 (23.4)
Thompson score >7	237/239 (99.2)
Managed with induced hypothermia (cooling)	108/239 (45.2)
Died	7/239 (2.9)

IQR = interquartile range; BMV = bag-valve-mask ventilation; IH = intrapartum hypoxia.
*Unless otherwise indicated.
†1 neonate had no Apgar score recorded.
‡23 had blood gases missing.

Table 3. Placental characteristics of neonates with encephalopathy (*N*=239)

Characteristic	*n* (%)*
Placentas with microscopic histopathology	235 (98.3)
Placental weight, g, median (IQR)	428 (360 - 490)
Placental weight <10th percentile	111 (46.6)
Cord abnormalities	65 (27.2)
ACA present	99 (41.4)
Maternal and fetal response	61 (61.6)
Maternal response only	38 (38.4)
FVM	127 (53.1)
Low grade	63 (49.6)
High grade	64 (50.4)
MVM	133 (55.6)
VUE	69 (28.9)
Low grade	39 (56.5)
High grade	30 (43.5)
Abruptio placentae	28 (11.7)
Delayed villous maturation	28 (11.7)
Meconium associated vascular necrosis	6 (2.5)
Intrauterine compromise	75 (31.4)

IQR = interquartile range; ACA = acute chorioamnionitis;
FVM = fetal vascular malperfusion; MVM = maternal vascular malperfusion;
VUE = villitis of unknown aetiology.
*Unless otherwise indicated.

Table 4. Number of placental lesions in comparison with severity and type of encephalopathy

Placental lesions, *n*	Severity of NE and/or presence of IH, *n* (%)		*p*-value
	Mild (*n*=168)	**Moderate to severe (*n*=71)**	
1	51 (30.6)	27 (38.0)	0.248
≥2	117 (69.4)	44 (62.0)	
	NE with IH (*n*=193)	**NE without IH (*n*=23)**	
1	58 (30.1)	11 (47.8)	0.084
≥2	135 (69.9)	12 (52.2)	
	Mild NE with IH (*n*=141)	**Moderate to severe NE with IH (*n*=52)**	
1	40 (28.4)	18 (34.6)	0.401
≥2	101 (71.6)	34 (65.4)	

NE = neonatal encephalopathy; IH = intrapartum hypoxia.

Comparison of maternal and neonatal characteristics and placental pathology between neonates with mild and moderate-to-severe NE with IH.

On univariate analysis, factors associated with moderate-to-severe NE with IH were maternal hypertension (p=0.021), Apgar score <7 at 10 minutes (p<0.001) and pH <7.00 (p<0.001). On multivariate analysis, the odds of having moderate-to-severe NE with IH were almost four-fold greater if the Apgar score was <7 at 10 minutes, three-fold greater if the pH was <7.00 and two-fold higher if the mother had hypertension (Appendix Table S3).

Discussion

Placental histopathology is important in identifying the causes of various neonatal adverse outcomes. Its inclusion and analysis in supporting diagnosis is now recommended as part of the investigation of neonates with NE.[11] In this study, we assessed for macroscopic and microscopic abnormalities in placentas of neonates with NE in a LMIC setting. The main findings indicated that, on a macroscopic level, approximately half of the placentas weighed below the 10th percentile, and around a quarter exhibited abnormal cord abnormalities. Microscopically, nearly all placentas showed abnormalities during histopathological assessment. The most identified placental lesions were MVM, FVM, ACA and VUE. The types, severity and quantity of these placental lesions did not change based on the severity of encephalopathy. Additionally, there was an independent association between the presence of MVM and NE with IH. The proportion of neonates with NE with IH and ≥2 histopathological lesions was marginally greater than those without IH (69.9% v. 52.2%, p=0.084). This 'placental lesion multiplicity' finding has been identified as a risk factor in other neonatal conditions such as intrauterine growth restriction (IUGR) and abnormal cranial ultrasound findings.[15]

The proportion of placentas below the 10th percentile was much higher in the neonates who were small for gestational age. The majority (87%) of the neonates weighed ≥2 500g, with 30 (12.6%) being small for gestational age (SGA). The type of SGA (symmetrical or asymmetrical) was not documented. Of these SGA neonates, 23 (76.7%) had ≥2 significant microscopic lesions. This finding correlates with previous studies that implicated multiple placental lesions with IUGR.[15] Most cases of NE occurred among mothers aged 21 - 35 years, which likely reflects the typical age distribution for women in childbearing years. However, no specific age group was associated with a higher incidence of NE. Mothers who received antenatal care were nearly 13 times more likely to have neonates with encephalopathy associated with IH compared with those who did not receive antenatal care. This finding may seem counterintuitive; it is possible that these mothers had high-risk pregnancies and an underlying predisposition to encephalopathy. It would have been helpful to know the total number of antenatal visits to better understand the potential underlying conditions.

The two chronic maternal conditions recognised to increase the risk of placental insufficiency or MVM, along with potential complications at the time of delivery, are hypertension and diabetes mellitus. A previous descriptive analysis conducted in SA found that the prevalence of hypertensive disorders among first-time (primigravid) women was 12.5%.[16] Another study by Yang *et al.*[17] concluded that maternal hypertensive disorders carried a 2.4-fold risk of NE with hypoxia. In our study population, hypertensive conditions were noted in 32.2% of the overall group. MVM was the most prevalent microscopic lesion in our study, occurring in >50% of placentas. We found that neonates born to mothers with hypertensive disorders also had an increased risk of moderate-to-severe NE with IH. There was no difference in the proportion of MVM in hypertensive v. non-hypertensive mothers (57% v. 56%). This may imply that hypertensive disorders predispose the placenta to vascular injury, even in the absence of perinatal hypoxia. An international consensus published in 1999 concluded that IH was unlikely to be the cause of cerebral palsy in >90% of affected children.[18]

Neonatal factors associated with moderate-to-severe HIE were Apgar score <7 at 10 minutes and pH <7.00. The four specific placental histopathological lesions (ACA, MVM, FVM and VUE) did not differ between the mild and moderate-to-severe HIE neonate groups with regard to the severity of NE. There were no significant differences in placental histopathology in the different groups and severity of encephalopathy. However, it was clear that certain microscopic lesions were more common in moderate-to-severe NE, as seen in previous studies.[10,19] The most significant microscopic lesions noted in all groups were MVM and FVM. Additionally, MVM was associated with a three times greater risk of developing encephalopathy with IH on the multivariate model, after adjusting for other confounding factors such as FVM, VUE, ≥2 placental lesions and ACA. MVM is diagnosed on a constellation of findings, and a minimum of three macroscopic and/or microscopic items are required to confirm the diagnosis.

MVM has been implicated in studies in neonates with HIE/NE, either alone or more frequently in combination with other pathologies such as FVM or VUE. All three of these pathological entities may contribute to a placenta that is small, further compromising the ability of the fetus to withstand the hypoxic stress of labour. This chronic intrauterine injury primes the fetal brain for additional injury in the immediate perinatal period, potentially leading to poor neurological outcomes, and this may be identified using early brain imaging.[20,21] Although our cohort did not show any association between severity of NE and cord abnormalities, just over a quarter of placentas had cord abnormalities. These included hypercoiled umbilical cords, as well as abnormalities of cord insertion such as marginal and velamentous cord insertions. These may cause intermittent or partial umbilical cord compression and obstruction of fetal blood flow. Although this may be associated with FVM, the microscopic lesion may not be identified due to sampling. In previous studies, FVM has been seen in 20 - 30% of cases of presumed HIE.[19] When present in the placenta, FVM may predict resistance to head cooling.[24] Our cohort did not show any association of FVM with the severity of NE or the presence of NE with IH. Microscopically, FVM is seen as extensive avascular villi, vascular obstructive lesions and vascular thrombi, and can often be accompanied by umbilical cord abnormalities. ACA or involvement of the chorionic membranes is a maternal response to ascending infection or cell death, while funisitis or chorionic vasculitis indicates a fetal inflammatory response, causing release of cytokines and chemokines into the fetal blood. It is an acute lesion in most cases, present for 12 - 48 hours prior to delivery. ACA is a common pathology in the placenta and may be present in 21 - 24% of placentas delivered between 21 and 24 weeks.[22] ACA was the third most common lesion (41.2%), with maternal and fetal responses more prevalent. There was no association drawn between the occurrence of ACA and the type or severity of NE.

VUE is a diagnosis made after infectious causes have been reasonably ruled out, which occurs predominantly in the third trimester, and is dependent on placental sampling. It is thought to be a graft-v.-host immune rejection phenomenon and is associated with NE and neonatal seizures, among other conditions.[23] Of the microscopic lesions in this study, VUE accounted for 28.9%. Although this was not statistically significant, it carries important

clinical implications. It is a chronic lesion, present for at least 1 week prior to delivery of the placenta.[24] An increased frequency of basal ganglia and thalamic injury has been found with VUE compared with other placental lesions.[19] Additionally, some studies have made an association between resistance to therapeutic hypothermia by the neonate and VUE in the placenta.[10]

NE is linked to both morbidity and mortality, with more severe cases predicting worse outcomes. This condition is a significant and prevalent issue in LMICs. Parameters that were significantly associated with the severity of NE were intuitive: lower Apgar scores at 5 and 10 minutes, level of resuscitation required, lower blood pH, occurrence of seizures and the Thompson score all predicted the severity of NE. As these are well-described criteria for NE and have associations with NE, they are expected findings. Death occurred only in those categorised as moderate-to-severe NE. While the factors associated with NE are known and can be targeted for intervention, many cases occur at birth without any warning. Limited resources are a major barrier to addressing these modifiable factors. This study shows that sending placentas for histopathological examination in all newborns with encephalopathy is feasible. Additionally, examining placental pathology can play a crucial role in identifying the factors that contribute to the development of NE.

Study strengths and limitations

The strength of this study is that we reviewed many placentas from neonates with NE. The diagnosis of encephalopathy was based on the need for resuscitation and the presence of signs of encephalopathy, and differentiated those with NE with or without evidence of IH based on an arterial blood gas taken within an hour of birth. The placentas were reviewed, and standard evaluation was used to determine the pathology.

The main limitation of this study was that there were no controls or placentas from neonates who did not have NE and were healthy. Therefore we were unable to assess whether the prevalence of histopathological lesions observed in this study was out of proportion to healthy neonates. Secondly, this was a single-centre study; therefore, we are unable to generalise the findings.

Previous studies have looked at the frequency and type of histopathological lesions in placentas delivered by women with no adverse pregnancy outcomes. Most placentas from these seemingly normal pregnancies had lesions consistent with inflammatory or vascular lesions.[25] This finding warrants a follow-up case-control study to our current research. The inclusion of a control group would assist in determining whether it is indeed worthwhile to continue evaluating placental histopathology in our setting, and may lead to new implementations in managing at-risk pregnancies to prevent adverse outcomes.

Conclusion

Placental histopathology with features of MVM is associated with NE and IH. Furthermore, most placentas from neonates with NE exhibited abnormalities, indicating that placental pathology may play a significant role in the development of NE. This study underscores the significance of placental histopathological evaluation for all births that required neonatal resuscitation, as this may assist in determining whether NE is attributed to inadequate perinatal care or to underlying placental pathology. Future research on the association between placental histopathology and NE should consider conducting case-control studies, as this could help to clarify the role of placental histopathology in the development of NE.

Data availability. The data used for this study are available from the first author on request.

Declaration. This study was conducted by KLS in partial fulfilment of an MMed (Paediatrics) at the University of the Witwatersrand.

Acknowledgements. Lancet Laboratories Johannesburg and the National Health Laboratory Service for permission to use the material and assistance in retrieving the data. Klerksdorp/Tshepong hospital complex for permission to use the maternal and neonatal data for the study.

Author contributions. KLS conducted the study, gathered the data and wrote the article. CAW examined all placentas, and contributed to the writing of the article. SV and OM contributed to the writing of the article, preparations of conference presentations and revision of the article before submission. OM, CAW and SV were supervisors of the of the study. KT played a major role in the data analysis and writing up of results.

Funding. University of the Witwatersrand School of Clinical Medicine (SOCM) research fund provided publication funds.

Conflicts of interest. None.

1. Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: When? Where? Why? Lancet 2005;365(9462):891-900. https://doi.org/10.1016/S0140-6736(05)71048-5
2. Lee ACC, Kozuki N, Blencowe H, et al. Intrapartum-related neonatal encephalopathy incidence and impairment at regional and global levels for 2010 with trends from 1990. Pediatr Res 2013;74(Suppl 1):S50-S72. https://doi.org/10.1038/pr.2013.206
3. Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. Early Hum Dev 2010;86(6):329-338. https://doi.org/10.1016/j.earlhumdev.2010.05.010
4. Bruckmann EK, Velaphi S. Intrapartum asphyxia and hypoxic ischaemic encephalopathy in a public hospital: Incidence and predictors of poor outcome. S Afr Med J 2015;105(4):298. https://doi.org/10.7196/SAMJ.9140
5. Ballot DE, Padayachee N. Outcomes of neonates with perinatal asphyxia at a tertiary hospital in Johannesburg, South Africa. S Afr J Child Health 2013;7(3):87-94. https://doi.org/doi.org/10.7196/sajch.574
6. Horn AR, Swingler GH, Myer L, et al. Defining hypoxic ischemic encephalopathy in newborn infants: Benchmarking in a South African population. J Perinat Med 2013;41(2):211-217. https://doi.org/10.1515/jpm-2012-0107
7. Vik T, Redline R, Nelson KB, et al. The placenta in neonatal encephalopathy: A case-control study. J Pediatr 2018;202:77-85.e3. https://doi.org/10.1016/j.jpeds.2018.06.005
8. Khong TY, Mooney EE, Ariel I, et al. Sampling and definitions of placental lesions: Amsterdam Placental Workshop Group Consensus Statement. Arch Pathology Laboratory Med 2016;140(7):698-713. https://doi.org/10.5858/arpa.2015-0225-CC
9. Nelson KB, Penn AA. Is infection a factor in neonatal encephalopathy? Arch Dis Child Fetal Neonatal Ed 2015;100(1):F8-F10. https://doi.org/10.1136/archdischild-2014-306192
10. Mir IN, Johnson-Welch SF, Nelson DB, Brown LS, Rosenfeld CR, Chalak LF. Placental pathology is associated with severity of neonatal encephalopathy and adverse developmental outcomes following hypothermia. Am J Obstet Gynecol 2015;213(6):849.e1-7. https://doi.org/10.1016/j.ajog.2015.09.072
11. Bhorat I, Buchmann E, Soma-Pillay P, Nicolaou E, Pistorius L, Smuts I. Cerebral palsy and criteria implicating acute intrapartum hypoxia in neonatal encephalopathy – an obstetric perspective for the South African setting. S Afr Med J 2021;111(3b):277-279. https://doi.org/10.7196/SAMJ.2021.v111i3b.14923
12. O'Heney J, McAllister S, Maresh M, Blott M. Fetal monitoring in labour: Summary and update of NICE guidance. BMJ 2022;379:o2854. https://doi.org/10.1136/bmj.o2854
13. Thompson CM, Puterman AS, Linley LL, et al. The value of a scoring system for hypoxic ischaemic encephalopathy in predicting neurodevelopmental outcome. Acta Paediatr 1997;86(7):757-761. https://doi.org/10.1111/j.1651-2227.1997.tb08581.x
14. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol 1976;33(10):696-705. https://doi.org/10.1001/archneur.1976.00500100030012
15. Viscardi RM, Sun CC. Placental lesion multiplicity: Risk factor for IUGR and neonatal cranial ultrasound abnormalities. Early Hum Dev 2001;62(1):1-10. https://doi.org/10.1016/s0378-3782(01)00114-1
16. Moodley J, Onyangunga OA, Maharaj NR. Hypertensive disorders in primigravid black South African women: A one-year descriptive analysis. Hypertens Pregnancy 2016;35(4):529-535. https://doi.org/10.1080/10641955.2016.1193190
17. Yang W, Wang L, Tian T, et al. Maternal hypertensive disorders in pregnancy and risk of hypoxic-ischemia encephalopathy. J Matern Fetal Neonatal Med 2021;34(11):1754-1762. https://doi.org/10.1080/14767058.2019.1647529
18. MacLennan A. A template for defining a causal relation between acute intrapartum events and cerebral palsy: International consensus statement. BMJ 1999;319(7216):1054-1059. https://doi.org/10.1136/bmj.319.7216.1054
19. Harteman JC, Nikkels PGJ, Benders MJNL, Kwee A, Groenendaal F, de Vries LS. Placental pathology in full-term infants with hypoxic-ischemic neonatal encephalopathy and association with magnetic resonance imaging pattern of brain injury. J Pediatr 2013;163(4):968-995.e2. https://doi.org/10.1016/j.jpeds.2013.06.010
20. Hagberg B, Hagberg G, Beckung E, Uvebrant P. Changing panorama of cerebral palsy in Sweden. VIII. Prevalence and origin in the birth year period 1991-94. Acta Paediatr 2001;90(3):271-277.
21. Cowan F, Rutherford M, Groenendaal F, et al. Origin and timing of brain lesions in term infants with neonatal encephalopathy. Lancet 2003;361(9359):736-742. https://doi.org/10.1016/S0140-6736(03)12658-X

22. Redline RW, O'Riordan MA. Placental lesions associated with cerebral palsy and neurologic impairment following term birth. Arch Pathol Lab Med 2000;124(12):1785-1791. https://doi.org/10.5858/2000-124-1785-PLAWCP
23. Nowak C, Joubert M, Jossic F, et al. Perinatal prognosis of pregnancies complicated by placental chronic villitis or intervillositis of unknown aetiology and combined lesions: About a series of 178 cases. Placenta 2016;44:104-108. https://doi.org/10.1016/j.placenta.2016.04.017
24. Redline RW. Placental pathology: Pathways leading to or associated with perinatal brain injury in experimental neurology. Special issue: Placental mediated mechanisms of perinatal brain injury. Exp Neurol 2022;347:113917. https://doi.org/10.1016/j.expneurol.2021.113917
25. Romero R, Kim YM, Pacora P, et al. The frequency and type of placental histologic lesions in term pregnancies with normal outcome. J Perinat Med 2018;46(6):613-630. https://doi.org/10.1515/jpm-2018-0055

Received 21 June 2025; accepted 12 November 2025.