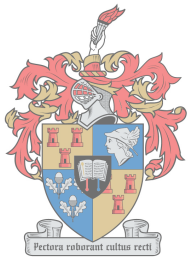
The correlation between the placental pathology and the neurological outcome of neonates ≥ 36 weeks with neonatal encephalopathy treated with therapeutic hypothermia.

By Ilhaam Abrahams

Dissertation presented in partial fulfilment of the requirements for the degree Master of Medicine Degree in Paediatrics at Stellenbosch University



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Abstract

Introduction

Perinatal asphyxia resulting in neonatal encephalopathy (NE) remains one of the commonest causes of death and morbidity in term infants in low and middle income countries. The cause of NE frequently remains unknown and its clinical presentation unanticipated. Numerous researchers are looking for biomarkers to predict the development of NE.

Aim

The aim of this study was to determine the relationship between placental pathology in neonates with NE treated with therapeutic hypothermia (TH) at Tygerberg Hospital (TBH) Neonatal Intensive Care Unit (NICU) and their neurodevelopmental outcome.

Methods

Cases were derived from a prospectively collected database of 224 neonates ≥ 36 weeks with NE who underwent TH at TBH, between January 2010 and September 2014. The study sample comprised of 17 cases remaining once 23 deaths, 173 cases with no placental pathology and 11 cases with no neurodevelopmental assessment were excluded. Placental samples from high risk neonates delivering at TBH with no evidence of NE (n=30), were derived from a list of 1787 placental samples provided by the National Health Laboratory Service (NHLS) for comparison. All placentas were re-reviewed by an experienced pathologist and all neurodevelopmental assessments were done by a single specialist.

Results

Cerebral palsy (CP) occurred in 44% of the NE group. Villitis of unknown aetiology (VUE) was the single significant placental lesion associated with both neonatal encephalopathy (NE) (p=0.01) and CP (p=0.005) while chorioamnionitis, the commonest placental lesion in both groups, was not significantly different between the 2 groups. The survival to one year in the NE group was 89.9%. The placental pathology submission rate was only 13%.

Conclusion

As VUE was demonstrated to have a significant association with NE and CP, placental histopathology is an important predictor of neurodevelopmental outcome in neonates being treated for NE with therapeutic hypothermia. Improved placental submission needs attention.

(Word count=298)

Opsomming

Inleiding

Perinatale asfiksie wat neonatale ensefalopatie (NE) veroorsaak bly een van die algemeenste oorsake van dood en morbiditeit in voltydse neonate in lae en middel inkomste lande. Die oorsake van NE bly in menige gevalle onbekend en die kliniese voorkoms word dikwels nie voorsien nie. Vir die rede soek navorsers biomerkers wat die voorkoms van NE voorspel.

Doel:

Die doel van die studie is om die verwantskap tussen plasentale patologie in neonate met NE, wat behandel word met terapeutiese hipotermie (TH) in die Neonatale Intensiewe sorgeenheid, Tygerberg Hospitaal (TBH), en neuro-ontwikkelings uitkoms te bepaal.

Metodes:

Die gevalle is gekies van 'n prospektiewe versamelde databasis van 224 neonate ≥ 36 weke wat NE onderlêde het en TH ondergaan het tussen Januarie 2010 en September 2014. 'n Groep van 17 gevalle het oorgebly nadat 23 sterftes, 173 gevalle sonder plasentale patologie en 11 gevalle sonder 'n neuro-ontwikkelingsondersoek uitgesluit is. Neonate van hoë risiko swangerskappe met geen tekens van NE (n=30) is verkry van 'n lys van 1787 plasentale monsters wat deur die Nasionale Gesondheid Laboratoriumdiens (NHLS) voorsien is. Al die plasentale monsters is herondersoek deur 'n senior patoloog en al die neuro-ontwikkelingsondersoeke is deur 'n senior spesialis uitgevoer.

Resultate:

Serebrale verlamming (SV) het in 44% van die NE groep voorgekom. Villitis van onbekend oorsaak (VOO) was die enkel plasentale letsel wat geassosieer is met NE (p=0.01) en SV (p=0.005). Chorioamnionitis, die algemeenste plasentale patologie in beide groepe, het nie statisties verskil tussen die 2 groepe nie. Die een jaar oorlewing in die NE groep was 89.9%. Die proporsie van plasentas gestuur vir ondersoek was 13%.

Gevolgtrekking:

Omdat VOO 'n betekenisse assosiasie het met NE en SV bevestig dit dat plasentale patologie 'n belangrike voorspeller is van neuro-ontwikkeling in neonate wat vir NE deur middel van TH behandel word. Verbeterde verwysing van plasentas vir ondersoek moet aandag kry.

(Woord telling=307)

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Table of Contents

Contents

List of Abbreviations

- aEEG- Amplitude integrated electroencephalogram
- BGT- Basal ganglia and thalami
- CRF- Case recording form
- C/S- Caesarean section
- CTG- Cardiotocograph
- ECM- Enterprise content management
- HIE- Hypoxic ischaemic encephalopathy
- HIV- Human Immunodeficiency Virus
- HREC- Health Research Ethics Committee
- MRI- Magnetic resonance imaging
- MSL- Meconium stained liquor
- MVM- Maternal vascular malperfusion
- NE- Neonatal Encephalopathy
- NHLS- National Health Laboratory Service
- NICU- Neonatal Intensive Care Unit
- NS- Not significant
- NVD- Normal vertex delivery
- PET- Pre-eclamptic toxaemia
- PROM- Prolonged rupture of membranes
- Rh- Rhesus
- RPR- Rapid plasma reagin
- SD- Standard Deviation
- TBH- Tygerberg Hospital
- TOP- Termination of pregnancy
- VUE- Villitis of unknown aetiology

Glossary

- **Cerebral Palsy** - a non-progressive disorder of posture and movement caused by a defect or insult to the developing central nervous system
- **Chorioamnionitis** – an inflammatory (maternal/foetal) response to microbial organisms in the amniotic fluid
- **Neonatal encephalopathy** - a clinical syndrome characterized by altered neurological function in the early days of life in infants ≥ 35 weeks gestation
- **Neonatal mortality rate** - the number of deaths in neonates less than 28 days of life per 1 000 live births in a given year or period.
- **Nulliparity**- no previous deliveries
- **Perinatal asphyxia** - impaired gas exchange leading to hypoxaemia, hypercapnia and a metabolic acidosis in a newborn
- **Perinatal mortality** - the number of stillbirths and deaths in the first week of life per 1,000 total births
- **Primigravida**-first pregnancy
- **Prolonged second stage of labour**- in primiparous women, three hours with an epidural or two hours without while in parous women two hours with an epidural and one hour without
- **Small placenta** - placental weight < 10th centile for birth weight and gestational age
- **Therapeutic hypothermia** - the core body temperature (measured by the oesophageal or rectal probe) is cooled down to 33.0–35°C for 72 hours
- **Under five mortality** - number of deaths between birth and exactly five years of age per 1,000 live births
- **Villitis of unknown aetiology** – presumably an immune mediated maternal response at foetal antigens in the villous stroma

1 Introduction

Perinatal asphyxia is defined as a condition of impaired gas exchange that leads to hypoxaemia, hypercapnia and a metabolic acidosis.[1] While all foetuses experience asphyxia, those subjected to severe asphyxia are at a greater risk of developing neonatal encephalopathy (NE).[2]

NE is a clinical syndrome characterized by altered neurological function in the early days of life in infants ≥ 35 weeks gestation. This includes an altered level of consciousness with or without seizures, depressed tone and reflexes and disturbances in maintaining respiration and feeding. In 1976 Sarnat and Sarnat developed a staging guideline for neonatal encephalopathy to stage the severity of neurological involvement. This guideline has been modified since then and is still in use today (Appendix A). [3]

The Millennium Development Goals 2015 Report shows that worldwide neonatal mortality has dropped, between 1990 and 2015, from 33/1000 live births to 19/1000 live births. Of concern was that 24% of neonatal deaths still arise from complications during labour and delivery.[4] The global incidence of NE was estimated to be 1.15 million cases in 2010 with 85% of this occurring in low to middle income countries. Here the highest incidence of NE at 14.9/1000 live births was in Sub-Saharan Africa.[5] On the contrary, the incidence of NE was 1.3/1000 live births in New Zealand[6] and moderate to severe hypoxic ischaemic encephalopathy (HIE), 0.37/1000 live births in Japan .[7]

Perinatal asphyxia remains one of the commonest causes of death and morbidity in term infants in low and middle income countries. In a retrospective study looking at the outcome of neonates treated at Charlotte Maxeke Academic Hospital in Gauteng over a 5 year period, the incidence of perinatal asphyxia was calculated to be 4.7/1000 live births/year.[8] Similarly in a study conducted in the Southern Cape Peninsula the incidence of HIE ranged from 2.3-4.3/1000 live births and the incidence varied according to the criteria used to define birth asphyxia and HIE.[9] In contrast to this a higher incidence of birth asphyxia and HIE was reported from Chris Hani Baragwanath Hospital in 2011. The incidence of birth asphyxia was 8.7-15.2/1000 live births and HIE 8.5-13.3/ 1000 live births.[10]

The burden of disease lies in those who survive with varying degrees of long term disability, with a survival rate of 86.7% found in a South African study at a tertiary academic centre looking at the outcomes of neonates with perinatal asphyxia.[8]

Until recently there were limited successful therapeutic interventions available to treat neonates with neonatal encephalopathy. Mild therapeutic hypothermia (TH) in infants with moderate encephalopathy if started within the first six hours of life has shown promise in studies done in both developing and developed countries to decrease mortality and long-term severe neurodevelopmental disabilities.[11][12]

As the cause of NE is frequently unknown and its clinical presentation unanticipated various researchers are looking for biomarkers to understand the development of NE. It has been postulated that placental histology may give clues as to the cause of the encephalopathy. The placental pathology may also provide an aid to risk assessment for an abnormal neurological outcome. The placenta can also provide information prompting urgent care for both mother and baby. There have been numerous studies performed in high income countries correlating placental pathology and the outcome from neonatal encephalopathy. Badawi et al found that a placenta with abnormal findings doubled the risk of developing neonatal encephalopathy.[13] This finding was supported by a study examining the placentas from 125 neonates ≥ 36 weeks gestation from a medicolegal registry who had NE and subsequently developed cerebral palsy (CP) or long-term neurological impairment. The authors compared the findings of the placentas to the placentas of 250 consecutive singleton deliveries at >36 weeks without neurological impairment. Severe foetal vascular lesions were found in more than half of placentas from index cases but were present in only 10% of the control group. This amounts to a 5 fold increase in the risk of developing neonatal encephalopathy if abnormal placental lesions are present ($p<0.0001$).[14] Similarly, in a study of 40 placentas in a medico-legal review of neonates with neurological impairment compared to the placentas from neonates with meconium stained liquor with no neurological impairment, severe foetal chorioamnionitis, extensive avascular villi and diffuse chorioamnionic haemosiderosis were found to be independently associated with NE. The risk of NE increased as the number of placental lesions increased. [15]

Hayes et al., also looked at placental changes, the grade of NE and long-term neurological outcome in infants >36 weeks gestation who had NE and underwent TH in their unit. In a study of 245 infants with NE in which only 141 placentas were sent for pathology, and 8 were excluded due to incomplete notes, 15 deaths and 13 cases of cerebral palsy were reported. The study reported that placental haemorrhage at any site, was associated with NE across all grades of severity. Meconium and haemorrhagic placental changes had a significant impact on the infants' neurodevelopmental outcome. An additional finding in the study was that a higher placenta to birth weight ratio was associated more significantly with grade 1 and 2 NE. Infection/inflammation was found to be associated with a low grade encephalopathy while villitis and funisitis with a higher grade of encephalopathy. As the number of lesions increased,

the neurodevelopmental outcome worsened. Surprisingly, there was no relationship between placental lesions and specific patterns of brain injury on Magnetic Resonance Imaging (MRI).[16]

More recently, Mir et al., looked at placental pathology in neonates requiring TH and the association of NE within the first six hours of life and more long-term adverse neurodevelopmental outcomes[17] An abnormal neurodevelopmental outcome was defined as death or a Bailey-III Score <85.[18] Placental abnormalities were present in 95% of cases, with 65% of cases meeting the criteria for major placental pathology. Placental pathology findings increased as the severity of NE increased (P<0.001), with chorioamnionitis being present in 54% of cases. Chronic patchy villitis/diffuse villitis was the single placental finding significantly associated with an abnormal neurological outcome. Placental villitis was identified in 13 neonates, 92% of these neonates had an abnormal neurological outcome. Five of these neonates demised, the survivors had severe delays with a Bailey III score < 70.[17]

In a systematic review of papers, over an 18 year period, looking at placental pathology and related neonatal outcome and neurological development, both foetal thrombotic vasculopathy and funisitis were found to be associated with neonatal encephalopathy. A weakness of this review was that it excluded studies done in developing countries. There might also have been publication bias towards the correlation between placental pathology and neonatal encephalopathy in highly developed countries. [19]

How these findings relate to neonatal encephalopathy in neonates born in middle and low income countries remains uncertain as all of these studies were done in highly developed countries.

In 2000 only 6 placentas were submitted for histology at TBH. By 2004, the submission rate had improved, an audit done over a 25 month period yielded 848 placentas accounting for 15% of all deliveries. This audit compared the proposed clinical diagnosis to the histopathological diagnosis. Where there was an adverse pregnancy outcome without a clinical cause, histopathology in most cases revealed acute chorioamnionitis or uteroplacental insufficiency or both. Thirty placentas were submitted for suspected intrapartum hypoxia or death and 70% of theses placentas showed acute chorioamnionitis.[20][21]

2 Study Justification

2.1 Gaps in the Literature

Sub-Saharan Africa carries a large portion of the global burden of under-five mortality, perinatal mortality and NE yet there is very little data on NE, the factors associated with possible causes of NE and how these factors might influence the long-term outcome of these neonates treated with TH. Most research on this aspect of neonatal care has been performed in high income countries. The research from middle and low income countries has mostly focused on the incidence and mortality associated with perinatal asphyxia. Furthermore, the study design of research studies on the long-term outcome of neonatal encephalopathy has limitations which make the data of limited value to neonates being cared for in middle and low income countries. These limitations are further complicated by the disease profiles that commonly occur in middle and low income countries which include HIV and puerperal sepsis, syphilis and tuberculosis. The incidence of maternal malnutrition, chorioamnionitis and pre-eclamptic toxaemia (PET) is also higher in low and middle income countries. All these factors could influence placental function and therefore might be responsible for the high incidence of neonatal encephalopathy in low and middle income countries. The developing world also struggles with poorer obstetric care, a greater incidence of obstructed labour, lack of skilled personnel and basic equipment for resuscitation and Neonatal Intensive Care Units (NICU's) with ventilator capacity.

Therefore, a study is required to address some of the gaps in the literature concerning neonatal encephalopathy in low and middle income countries. This study is designed to attempt to fill the knowledge gap in the association of placental pathology with severe neonatal encephalopathy

2.2 Null Hypothesis

That neonates with perinatal asphyxia have normal placental pathology.

2.3 Problem statement

Neonates with NE treated with TH, as compared to non-NE neonates, the neurodevelopmental outcome is associated with placental pathology findings.

2.4 Research Question

In neonates with NE treated with TH, when compared to non-NE neonates, is the neurological outcome associated with placental pathology findings?

2.5 Study Aim

We aim to study the relationship between placental pathology and the neurological outcome in infants with NE treated with TH.

2.6 Primary Outcomes

- Describe placental pathology findings in our NE and non-NE groups.
- Describe an association between placental findings and clinical outcomes in patients with NE.

2.7 Secondary outcomes

- Correlate placental pathology findings with MRI findings in those infants that were scanned.
- Describe findings that may be predictive of possible recurrence and could guide care in subsequent pregnancies.

3 Materials and Methodology

3.1 Study Design

This is a descriptive study of infants with NE treated with TH at Tygerberg Hospital (TBH) NICU from January 2010 and September 2014. Due to the anticipated small yield we propose that this be a pilot study.

3.2 Study Site

Tygerberg Children's Hospital forms part of the larger TBH. It services the immediate surrounding areas and provides tertiary care to the Metro East and the more rural Northern and Eastern regions of the Western Cape. Neonates with NE who qualify for TH are treated in the NICU. The NICU is an 8 bedded intensive care unit with an additional 4 high care beds which are also sometimes used for TH if there are no NICU beds available. The NICU provides care to 506 neonates/year (2015).

Once discharged these infants are followed up at a high risk baby clinic based in the community or a neonatal clinic at TBH. They also receive a follow up appointment for a 12-15 week assessment by a neurodevelopmental specialist at a high risk clinic situated in the outpatient clinic block of TBH. They are then followed up to 1 year of age.

3.3 Study period

The study was conducted from January 2010 to September 2014.

3.4 Study population

3.4.1 The NE group

There is an existing database of all neonates with NE who undergo TH in our NICU at TBH, we accessed this database between January 2010 and September 2014, and it comprised 224 cases. Eligibility criteria for TH at TBH are based on the UK TOBY cooling criteria. (Appendix B)

Figure 3-1

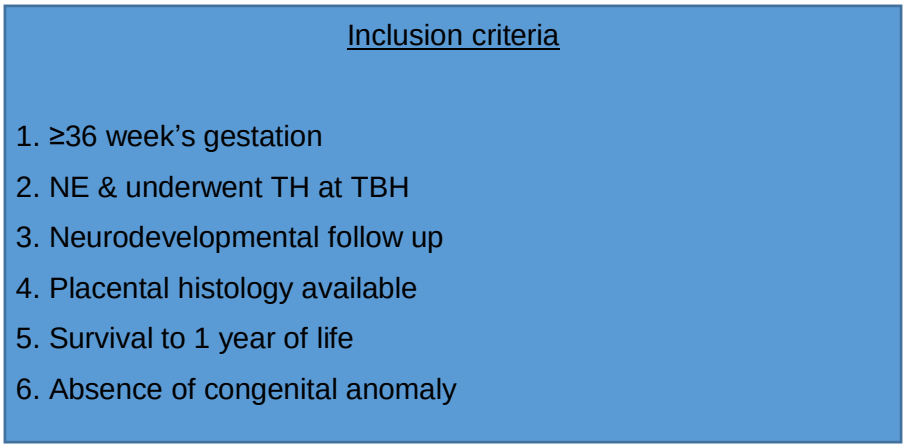

Figure 3-1 Inclusion criteria for NE group. Abbreviations: NE= neonatal encephalopathy, TH= therapeutic hypothermia, TBH= Tygerberg Hospital

3.4.2 The non-NE group

A comparative group of non-NE patients were selected from a database provided by the NHLS, which comprised of a list of 1787 placental samples submitted during the study period for various indications (miscarriages, stillbirths, intrauterine deaths, molar pregnancies, premature deliveries, maternal illness, suspected congenital infection, suspected chorioamnionitis, twin pregnancies and NE). From this list neonates of ≥36 weeks gestation with no signs of encephalopathy were extracted. This was determined by reviewing the Apgar scores (≥7 at 5 minutes), documentation on routine clinical examination following C/S deliveries, birth records, nursing and medical notes where infants were admitted. Exclusion criteria were: infants <36 weeks gestation, twins with fused placental plates, placental histopathology not available, congenital anomalies and unavailable clinical records.

3.5 Data Collection

From the database of all neonates who underwent TH during our study period at TBH and the list of placentas we were able we were able to identify those patients who were cooled and also had a placenta sent for histology.

We then accessed Enterprise Content Management (ECM) for electronic records, patient folders from medical records at TBH, cooling booklets which are routinely collected data on all patients who are cooled our hospital setting and Clinicom, the hospitals electronic database which tracks admission status, previous admissions or clinic visits attended. This enabled us to determine if patients had attended neurodevelopmental follow up at the TBH high risk clinic. Clinical data collection comprised a folder review of notes found on ECM, accessing the cooling data booklets used for routine monitoring of cooled patients and folder reviews at our Records Department.

Clinical data from the non-NE group was also sourced from ECM.

3.5.1 Patient data collected for NE group

- Maternal data: age, gravidity and parity, maternal illness, booking bloods: Rapid plasma reagin (RPR)/ Rhesus (Rh)/Human Immunodeficiency Virus (HIV)
- Delivery data: prolonged rupture of membranes (PROM), meconium stained liquor (MSL), abnormal cardiotocograph (CTG), mode of delivery, inborn/out born
- Patient data: gestational age (GA), birth weight (BW), sex, Apgar score, head circumference (HC), length, blood gas analysis within one hour of life
- Data in the postnatal period: HIE score and grade according to the Thompson score[22] (Appendix C) where HIE grade 1 ≤10; HIE grade 2=11-14; HIE grade 3 ≥15, were done within the first 6 hours and then at least daily. Seizures, amplitude integrated electroencephalogram (aEEG) findings, need for ventilation and inotropic support, evidence/proven infection. A proven infection was defined by the gold standard, a positive blood culture, while evidence of infection was defined as a CRP value above 10mg/ml.
- Placental factors: placental weight, placental histopathology findings
- Imaging: MRI if available
- Neurodevelopmental outcome was assessed using the Bayley Scales of Infant and Toddler Development, 3rd Edition, screening tool and this by done by a single specialist. A score of less than 70 was abnormal while below 85 was deemed suspect and required further follow up.
- Mortality

3.5.2. Patient data collected for the non-NE group

- Maternal data: age, gravidity and parity, booking bloods RPR/Rh/HIV, maternal illness
- Delivery data: PROM, MSL, Abnormal CTG, mode of delivery, inborn/out born
- Patient factors: GA, BW, sex, Apgar score, HC, length, blood gas analysis within one hour of life if available, reason for admission if admitted
- Placental factors: placental weight, placental histopathology report

The Department of Anatomical Pathology re-reviewed the placental pathology of both groups. The re-review was carried out by an experienced anatomical pathologist (PS) who was blinded to the neurological outcome. Placental examination findings were recorded using a modification of the Amsterdam Criteria,[23] The TBH Department of Anatomical Pathology Placenta Cluster Diagnosis Expanded Version (Appendix C). All infants in the NE group were examined using the Bayley Scales of Infant and Toddler Development, 3rd edition screening tool, at 12 months by a single examiner (JVZ) with experience in neurodevelopmental assessments and were classified as having normal, suspect or abnormal neurology.

3.6. Data management:

The data was collected on case recording form (CRF) using a patient study number only and then transcribed onto an electronic database (Excel) with this patient study number.

Data was handled in accordance with the Good Clinical Practice requirements. A laptop in a locked office was used to store the database which was password protected. Analysis and calculations were done from copies. All paper based documents will be kept in a locked cupboard for 5 years.

3.7. Data analysis:

A statistician was enlisted to assist with analysis of data. The results were fed back to the researcher, values where then further analysed.

3.8. Statistical Methods

The two sided Fisher's Exact test was used to test the null hypothesis.

Categorical variables were reported as number and percentages.

Continuous variables were reported as means and standard deviation.

3.9. Ethical Considerations

This protocol was submitted to the Stellenbosch University Health Research Ethics Committee for ethics approval (approval number S16/04/064).

This is a retrospective review of routinely collected data and a waiver of individual informed consent was granted by the HREC and Hospital Management.

Patients were allocated study numbers, and the results will be presented/published in an anonymous fashion. There were no undue investigations imposed on the study population, no infringement on personal time for questionnaires or travel to hospital for investigations. The care given to patients was in no way influenced by this study. This study will also bring no benefit or harm to this group of patients.

As described earlier the burden of HIE in our setting is huge with great cost to the families of those who demise and survive. Survivors are often disabled and mostly rely on our over-burdened health care system. Facilities for children who are disabled and access to these facilities vary greatly from region to region.

We aim to investigate the issue of perinatal–related HIE which has not been adequately reviewed in Africa before. It is our hope that by reviewing and assessing maternal and antenatal factors, placental histology characteristics and neurological outcomes we can identify modifiable factors which can assist in reducing the incidence, morbidity and mortality associated with this debilitating condition and that our findings will benefit future generations and lessen the burden of HIE.

4 Results

4.1 The group with NE

During the study period 224 neonates with NE underwent cooling. There were a total of 23 deaths in this group when followed up until one year of life, resulting in a survival rate of 89.8% (n=201) (Figure 4.1). Of the remaining 201 cases, only 28 (13.9%) placentas were submitted for histology. A further 11 cases were excluded in the NE group as there was no neurodevelopmental assessment.

Figure 4-1

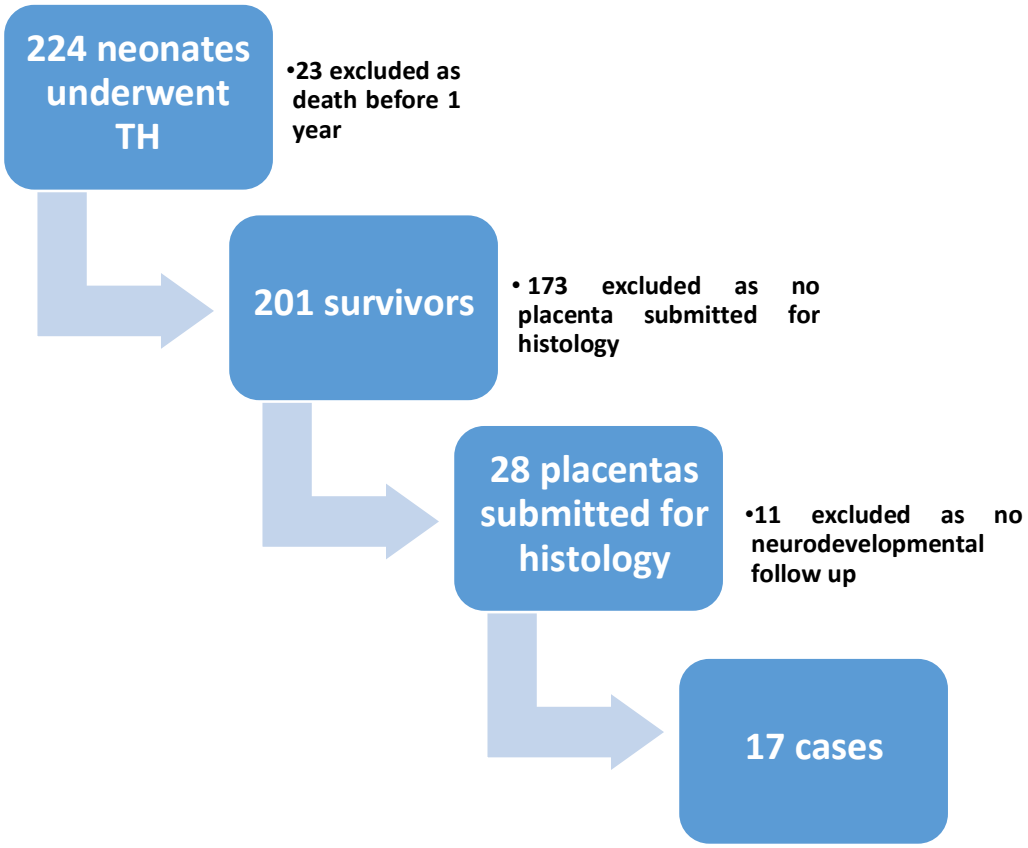

Figure 4-1 The recruitment of the patients enrolled in the study. TH= therapeutic hypothermia

4.2 The non- NE group

From the list provided by the NHLS, 1107 were screened before we met the target of 34 non-NE neonates, however once the placentas were reviewed a further 4 cases were excluded, as there were two sets of twins where there was a single placental plate.

4.3 Demographics and baseline characteristics

The demographics of our 2 groups are depicted in Table 4.1. There were significant differences in mean gestational age (p=0.005), mean birthweight (p=0.003), male sex (p=0.01), mean parity (p=0.01) and head circumference (p<0.0001).

Small for gestational age (SGA) was not a significant (p=0.3) finding. The mean parity was 1.2 in the NE group and 1.9 in the Non-NE group (p=0.01). The maternal illnesses which we looked at included hypertension, HIV and diabetes (p=0.3) and there were no significant (NS) differences in these

Table 4-1

Demographics	NE group		Non-NE group		P value
	n	%	n	%	P
Total	17		30		
Inborn	8	47	30	100	<0.0001
Male	14	82	13	45	0.01
Mean BW (grams)	3209(406)		2780(465)		0.003
Mean Gestational Age (weeks)	39.5(1.5)		38(1.8)		0.005
Mean head circumference (centimetres)	36.5(1.76) #n=13		33.3(1.38) #n=21		<0.0001
Mean maternal age (years)	24.1		26.2		0.3
Mean parity	1.2		1.9		0.01
Maternal HIV positive	2	11.8	8	26.7	0.7
Maternal hypertension	5	29	12	40	0.5

Table 4-1 : Description of the demographics and baseline characteristics of NE and non-NE groups. Where indicated values are a mean (±SD) or n (%). # Data not available due to incomplete notes. Abbreviations: NE= neonatal encephalopathy, BW= birth weight, HIV= human immunodeficiency Virus

4.4 Labour and delivery

The only significant finding during labour and delivery was the presence of a prolonged second stage (P<0.0001) as documented in the clinical notes. There was no significant difference between the two groups in the mode of delivery, although C/S approached significance (P=0.06).

4.5 Birth and the postnatal period

During the immediate postnatal period (IPP) 69% (n=13) of the NE group had a time to spontaneous respiration of ≥ 5 minutes. During the IPP the mean pH and mean Apgar score were significantly different when comparing the 2 groups (p<0.0001). Ten (59%) neonates in the NE group required ventilation with one needing inotropic support. The majority of infants treated with TH were scored as grade 2 NE (47%), followed by 6 (35%) with Grade 1 NE and 3 (18%) with Grade 3 NE. Twelve (71%) neonates in the NE group developed seizures, clinical or electrical (P<0.0001) and met our crititeria for presumed sepsis (p-value=0.0004).

Of those 12 neonates who had seizures, 11 were also in the sub-group with presumed sepsis and 9 had a lumbar puncture, with no CSF sample meeting the criteria for bacterial or viral meningitis.

Nine (30%) neonates in the non- NE group were admitted in the nursery. There were 3 (10%) cases of transient tachypnoea of the newborn, with one based on clinical grounds and 2 on CXR changes. 6 (20%) patients were admitted with suspected sepsis; none had positive blood cultures, 5 neonates had a raised C-reactive protein (CRP) and one had neither. (Table 4.2)

Table 4-2

Labour, delivery& postnatal period	NE group N=17		No NE group N=30		P-value
	n	%	n	%	P
CTG available	10	58	24	80	0.2
CTG normal	3 #n=10	30	13 #n=24	56	0.3
MSL	7	41	5	17	0.08
PROM	3	18	3	10	0.6
Delayed 2nd stage	9	53	0	0	<0.0001
NVD	8	47	3	20	0.09
C/S	8	47	23	76.7	0.06
Assisted delivery	1	5.8	1	3.3	1.0
Apgar at 1 min	3.1(1.36)		7.4(1.47)		<0.0001
Apgar at 5 min	4.7(1.26)		9.1(0.88) #n=29		<0.0001
Apgar at 10 min	5.7(1.27) #n=15		9.6(0.48) #n=26		<0.0001
Admitted	17	100	9 #n=27	33	<0.0001
Blood gas within 1 hour of birth	16	94	4	13	
pH	6.96(0.18) #n=14		7.24(0.05) †n=5		<0.0001
BE	-16.7(4.21) #n=14		-6.9(2.32) †n=4		<0.0001
Ventilated	10 #n=16	62.5	0	0	<0.0001
Presumed sepsis	12 #n=16	75	6	20	0.0004
Seizures	12	71	0	0	<0.0001

Table 4-2 : Labour, delivery, and the post-natal period. Where indicated values are a mean (±SD) or n (%). Abbreviations: NE= Neonatal Encephalopathy, CTG= cardiotocograph, NVD= normal vertex delivery, C/S= caesarean section, BE= base deficit, PROM= prolonged rupture of membranes, MSL= meconium stained liquor. #Data not available due to incomplete notes. †Data incomplete as not routinely collected in this group of patients

4.6 Neurodevelopmental follow up and outcome

Sixteen (94%) of those in the NE group had a neurodevelopmental assessment at 12 months. Seven (44 %) infants had a normal examination at 12 months, while 9 (56%) infants had an

abnormal neurological assessment. Of those with an abnormal examination: 7 (78%) had CP, 1 (11%) had an isolated fine motor delay and 1 (11%) an isolated speech delay. Only one patient in the NE group did not have a 12 month neurodevelopmental assessment but this patient examined normally at 3 months. None of the non-NE group had long term follow-up. (Table 4.3)

Table 4-3

Neurological assessment in NE group (n=16)		
	n	%
Normal examination	7	44
Abnormal neurology	9	56
• Cerebral Palsy	7/9	[78]
• Speech delay	1/9	[11]
• Fine motor delay	1/9	[11]

Table 4-3 : 12 month neurodevelopmental outcome.

4.7 Placental pathology

Sixteen (53.3%) of placentas submitted in the non-NE group where in patients with a clinical suspicion of chorioamnionitis, 10 (33%) in twin pregnancies, 2 (6.7%) in suspected congenital infection, 1 (3.3%) maternal TB and 1 (3.3%) patient where a C/S was done for foetal distress. The neonate, however, had no features of NE and was discharged to the mother post-delivery.

Significantly more of the placentas in the NE group (24%) had villitis of unknown aetiology (VUE) when compared to the placentas in the non- NE group, in which not a single case of VUE was described (p=0.01).

There was no significant difference when comparing chorioamnionitis (p=0.5), mean placental weight (p=0.5) or number of placental lesions (p=1.0) between the 2 groups. (Table 4.4)

Table 4-4

Placental Characteristics	NE group (N=17)		Non- NE group (N=30)		P-value
	n	%	n	%	P
Placental weight (grams)	499.06 (122.5)		472.97 (131.34)		0.5
PW:BW	0.156 (0.033)		0.171 (0.045)		0.3
• Chorioamnionitis	7	41	16	53	0.5
• maternal response only	0	0	4	13	0.3
• maternal and foetal response	7	41	12	40	0.3
• severe foetal response	5	29	10	33	1.0
VUE	4	24	0	0	0.01
Subacute foetal hypoxia with compensatory response	3	18	9	30	0.5
• -focal villous oedema	1	5.8	2	6.7	1.0
• -chorangiosis	0	0	5	16	0.1
• -increased nucleated red blood cells	3	18	4	13	0.7
Small placenta	3	18	3	10	0.7
Complete MVM	0	0	0	0	
Some Features of MVM					
• small placenta	5	29	12	40	0.5
• Accelerated villous maturation	0	0	1	3.3	1.0
• Retroplacental haemorrhage	1	5.8	3	10	1.0
• increased syncytial knots	0	0	1	3.3	1.0
Features of FVM	0	0	0	0	
Chorioamnionic Haemosiderosis	0	0	0	0	
Haematogenous infection	0	0	0	0	
Presence of meconium laden macrophages	3	18	6	20	1.0
Normal placenta	0	0	6	20	0.07
Multiple placental lesions	9	56	16	53	1.0

Table 4-4 Placental pathology and characteristics in the NE and non-NE groups. Where indicated values are a mean (±SD) or n (%) Abbreviations: NE= neonatal encephalopathy, VUE= Villitis of unknown aetiology, PW= placental weight, BW= birth weight, MVM= maternal vascular malperfusion, FVM=foetal vascular malperfusion.

When comparing the severity of chorioamnionitis there was no significant difference between the 2 groups, with a severe foetal response present in 5 (29%) of the NE group and 10 (33%) of the non-NE group.

When assessing the association with placental lesions in the subgroup with abnormal neurology, all cases of CP (n=7) had either a diagnosis of VUE, chorioamnionitis or a small placenta (Table 7). Only one case of CP was associated with more than one placental lesion. The one infant who had an isolated speech delay had a placenta that met the criteria for chorioamnionitis, and the one infant who had isolated fine motor delay had placental changes meeting criteria for a small placenta.(Table 4.5)

Table 4-5

Placental Lesions In CP (n=7)	No of cases	P-Value
VUE	3	0.005
Chorioamnionitis	2	0.4
Small placenta	1	0.4
Small placenta + chorioamnionitis	1	0.2

Table 4-5 : Placental lesions found in cases of cerebral Palsy.

Abbreviations: VUE = villitis of unknown aetiology, CP = cerebral palsy

4.8. MRI

MRI scans were only performed in five (29%) of the NE group and 4 of those who were imaged went on to develop CP. The findings are summarized in table below describing the placental pathology, the CP sub-type and MRI findings if available.(Table 4.6)

Table 4.6

Patient	Cerebral Palsy type	MRI findings	Placental pathology
1.	Dystonic	Left caudothalamic haemorrhage	VUE
2.	Spastic diplegia	Leukoencephalopathy	VUE
3.	Dystonic	Global white matter loss	• Chorioamnionitis • Small placenta • Meconium laden macrophages
4.	Spastic quadriplegia	Encephalomalacia	Chorioamnionitis

Table 4-6 : Description of CP sub-type, MRI findings and placental lesions. Abbreviations: CP=Cerebral Palsy, MRI=magnetic resonance imaging, VUE=villitis of unknown aetiology

5 Discussion

In this study examining the association between the neurodevelopmental outcome of neonates with neonatal encephalopathy (NE) and placental pathology, the primary outcome of the study demonstrated a significant association between villitis of unknown origin (VUE) and NE (p= 0.01) and CP (p=0.005) at 12 months. The calculated proportion of placentas submitted for histopathology in neonates with NE was 13%.

VUE is postulated to be a non-infectious, immune mediated process characterized by a maternal lymphocytic response within foetal vascular structures. VUE more commonly occurs in term pregnancies, being present in 5-15% of all placentas at term with the majority of these pregnancies having a normal outcome.[24] The recurrence rate is high, with up to 37% in one study reporting VUE in subsequent pregnancies.[25] VUE has been found to be significantly associated with neonatal encephalopathy[16] and high grade VUE with an abnormal neurodevelopmental outcome [14][17] which is similar to the findings of this study. A 2016 Dutch study reported that there was no association between VUE and a poor neurodevelopmental outcome but in this study population there were no cases of CP.[26] Although there have been no previous reports of low grade VUE and a poor neurodevelopmental outcome, in this study one of our cases with low grade VUE developed CP. While the association was not statically significant and it is acknowledged that the development of CP is multifactorial, further studies are required to look into the association of low grade VUE and CP.

The most common lesion in both the NE and the non-NE groups was chorioamnionitis, although there was not a statistical difference in chorioamnionitis between the 2 groups (p=0.5). Chorioamnionitis is recognized as a risk factor for cerebral palsy, specifically spastic quadriplegia in term and near term deliveries.[27] It is thought that a foetal inflammatory response leads to the production of pro-inflammatory cytokines and that this results in many sequelae including brain injury. [28] Chorioamnionitis was common in most studies reviewed, with varying significance. Similar to findings in our study, a 2016 Dutch study found no significant association between chorioamnionitis and an abnormal neurological outcome.[26] Two different studies by Redline showed that severe foetal chorioamnionitis [15] and chorioamnionitis [14] were significantly associated with neurological impairment. This was supported by studies by Mir et al. and Hayes et al., who found chorioamnionitis to be a significant precursor in NE [17] (specifically grade 1 NE) and funistis to be associated with grade 3 NE. [16] The findings demonstrating the association between chorioamnionitis and NE as reported by Redline[14][15] might reflect a sampling bias as the cases in their 2 studies originate from a medicolegal review. These 2 studies also did not include neonates managed with TH

which has been shown to decrease mortality and long term neurodevelopmental impairment in moderate NE.[11][12][14][15]

NE is widely accepted as an indication for placental submission for histopathological examination to investigate possible causes of NE. [29] The rate of placental submission in this study was 13% in the group with NE. This finding is similar to the 2004 general submission rate of 15% at TBH, whereas four years prior to this (in 2000) only 6 placentas were submitted the entire year.[20][21] Internationally, submission rates varied between 4.9% in a 2011 study in Yemen [30] and 81.8% in an American study in 2010.[31] The poor submission rates in Yemen were ascribed to a number of reasons, namely: (1) lack of hospital guidelines (2) College of American Pathologists (CAP) guidelines not in place (3) decision for placental submission lying with the attending doctor (4) poor communication between clinicians & pathologists (5) failure to recognize the benefit of submitting placentas and (6) lack of understanding of pathology terms. [30] The success in the American study is attributed to adoption of the CAP guidelines, and consideration of whether placental submission is necessary in each delivery.[31] Although the obstetric and neonatal services at TBH use criteria for placental submission which have been established and agreed upon by obstetricians, pathologists and neonatologists these guidelines are clearly not adhered to. [20] The importance of submitting the placentas for histopathology is demonstrated by the fact that all of the placentas in the sub-group with CP had some histopathological abnormality. This is similar to Mir et al's findings, with 95% of NE cases having some histological abnormality[17] and Hayes et al finding a placental lesion in 92.3% of their CP cases.[16]

The only significant finding relating to delivery was a delayed second stage in the NE group ($p<0.0001$), with C/S in the no NE group approaching significance ($p=0.06$). This is in contrast to the literature reviewed, where emergency C/S was found to be a significant factor in those with brain injury on MRI [32] and across all grades of encephalopathy [16] . An Apgar score of < 7 at 5 minutes in the NE group was significantly different when compared to the non-NE group in this study ($P<0.0001$), similar to findings by Redline [14][15] and those of Mir who found lower median 5 min Apgar scores of 5 in the group with moderate to severe NE.[17] Ph in the NE group was also significantly lower ($p<0.0001$), similar to findings by Mir et al where pH differed significantly between mild and moderate to severe cases of NE. [17]

Demographics which were of significance in NE included a greater birth weight ($p=0.003$), gestational age ($p=0.005$), head circumference ($p<0.0001$) and greater proportion of male infants ($p=0.01$), while mothers were more likely to be primigravida ($p=0.01$). Some studies reviewed also found birthweight[14] , gestational age[14][16][17] and primiparity[14] to be associated

with NE, with primiparity significantly associated with an abnormal neurodevelopmental outcome.[26]

Markers of inflammation were reviewed and a raised CRP was statistically significant in those with NE (p=0.004). This is problematic since the gold standard for sepsis is a positive blood culture and the CRP increase may be a consequence of therapeutic hypothermia[33] or represent a systemic inflammatory response in those with severe NE.[34]

Survival to one year in the NE group was 89.9%, while most studies commented on survival in the neonatal period or to discharge, reporting 86.7% in another South African study [8] and 93% [17] , 89%[16] and 83%[14] in other studies reviewed. Sixteen of the NE group had a 12 month neurodevelopmental assessment, with 7(43%) subsequently diagnosed with CP. The high incidence of CP in our group was similar to the 43% in a study by Redline[14], while Hayes found CP in 13.7% [16] of her study population. The findings in Redline's study could result from these cases originating from a medicolegal review and the absence of TH as a therapeutic measure in that study.

MRI imaging is not routine in all cases of NE at TBH and too few studies were done to demonstrate the significance of this investigation. Significant associations in the literature include VUE and brain injury, specifically injury of the basal ganglia and thalami (BGT)[26] or hemispheric devastation/white matter injury.[17] Although chorioamnionitis was a common finding in those with no evidence of brain injury and those with the most extensive injuries, there was no significant difference between groups.[32] Similarly, Hayes et al found no significant associations with chorioamnionitis but numbers in that study were small. [16]

The strengths of this study lie in it being unique in the African setting, as we have limited data on this subject with most studies being set in developed countries.[14][15][16][17][26][32] The placental findings were described based on the terminology used in the newer Amsterdam Classification[23] which is an attempt to standardize macro and micro sampling of placentas, whereas most studies in the literature have based their terminology on the Redline Classification.[17][32][35][36] All neurodevelopmental follow up was done by a single examiner, and all placentas were re-reviewed by a single senior pathologist who was blinded to outcomes while in some studies only a subgroup were re-reviewed[14][15][17] . We had a comparative group while a few studies lacked this.[17][32] One study excluded non-Caucasians, high risk pregnancies and HIV infected patients, all of which were included in this study.[16]

The greatest limitation in this study is the small number of placentas available as a result of the poor submission rate of placentas for histology. Possible reasons for this include

knowledge gaps relating to appropriate placental submission and no available resources for placental pathology examination in the outborn population. The large proportion of outborn infants, some from far outlying areas, may have also made follow up at TBH difficult and contributed to the loss to follow up which limited the knowledge on their neurodevelopmental outcome. Cooling booklets and clinical notes were often not adequately completed which prevented patients from being eligible for this study. The non-NE group was entirely inborn and consisted of a fair amount of twin studies which does add selection bias as those delivered at TBH mostly constitute high risk pregnancies who were referred for delivery at a tertiary institute. The non-NE group was not randomized and had no long-term neurodevelopmental follow up but this limitation is similar to that in other published studies.

6 Conclusion:

VUE has been shown to be a significant risk factor for the development of NE and CP, similar to international studies.[14][16][17] VUE has a high recurrence rate and its effect on neurodevelopment in siblings has yet to be determined.[25] As of yet there are no treatment or preventative measures for VUE, thus increased surveillance of a subsequent pregnancy may be warranted given the high recurrence rate and association with an adverse neurodevelopmental outcome. Submission rates for placental pathology vary greatly but were unacceptably low in this study population.

7 Recommendations:

A larger study of this nature is needed to determine the true role of VUE and other placental lesions in our population. For an optimal study to take place we will have to vastly improve placental submission rates. Possible ways of achieving this include: increased awareness in undergraduate and postgraduate training, improving visibility of guidelines for placental pathology submission and identifying a responsible healthcare practitioner involved in the delivery team who ensures accountability in deciding whether a placenta needs to be submitted at each delivery.

Appendix A: Sarnat and Sarnat Grading of Neonatal Encephalopathy

Level of consciousness	Stage 1 (mild) Hyperalert	Stage 2 (moderate) Lethargic/obtunded	Stage 3 (severe) Stuporous
Neuromuscular control			
Muscular tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch	Overactive	Overactive	Decreased/absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak/absent	Absent
Moro	Strong	Weak	Absent
Oculovestibular	Normal	Overactive	Weak/absent
Tonic neck	Slight	Strong	Absent
Autonomic function			
Pupils	Mydriasis	Miosis	Variable
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial/salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal/decreased	Increased/diarrhea	Variable
Seizures	None	Common/focal or multifocal	Uncommon
EEG	Normal/decreased	Early low voltage continuous delta and theta, later periodic, seizues focal 1–1.5 Hz spike-wave	Early periodic pattern with isopotential phases, later isopotential
Duration	<24 h	2–14 days	Hours–weeks

EEG, electroencephalogram.

Appendix B: TBH cooling criteria based on the UK TOBY Cooling Register Clinician's Handbook, section 2.1

Infants with suspected birth asphyxia who have **spontaneous respiration by 30 minutes** of age should be assessed to determine whether they meet the criteria for cooling (Criteria A & B below), and should be discussed with the attending consultant.

1 Criteria for considering treatment with cooling

A. ***Infants >36 completed weeks gestation*** *with at least* ***one*** *of the following*:

- Apgar score of <7 at 10 minutes
- Continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth
- Acidosis within 60 minutes of birth (defined as any occurrence of umbilical cord, arterial or capillary pH <7.00)
- Base Deficit ≥ 16 mmol/L in umbilical cord or any blood sample (arterial, venous or capillary) within 60 minutes of birth

Infants that meet criteria A should be assessed for whether they meet the neurological abnormality entry criteria (B):

B. ***Seizures or moderate to severe encephalopathy****, consisting of:*

- Altered state of consciousness (reduced or absent response to stimulation) *and*
- Abnormal tone (focal or general hypotonia, or flaccid) *and*
- Abnormal primitive reflexes (weak or absent suck or Moro response)

The severity of encephalopathy can be assessed using the table below. Infants should have abnormalities in at least 3 categories (e.g. tone, LOC, reflexes, autonomic function).

Parameter	**Moderate Encephalopathy (Sarnat 2)**		**Severe Encephalopathy (Sarnat 3)**	
Level of consciousness	Lethargic		Stupor or coma	
Spontaneous Activity	Decreased Activity		No activity	
Posture	Distal flexion, complete extension		Decerebrate	

Tone	Hypotonia (focal or general)		Flaccid	
Suck	Weak		Absent	
Moro	Incomplete		Absent	
Pupils	Constricted		Deviated, dilated or non-reactive	
Heart rate	Bradycardia		Variable	
Respiration	Periodic or shallow breathing		Apnoea	

∗ We use the Thompson HIE score now as that is what everyone is familiar with, & take a score of ≥ 7 as significant encephalopathy.

2. AEEG assessment

The amplitude integrated EEG (aEEG) should ideally be recorded in all infants with suspected birth asphyxia, preferably before cooling is started. **However, cooling need not be delayed until the aEEG is initiated.**

An apparently normal aEEG record **may not necessarily guarantee a good outcome**, and should therefore not be used to exclude infants from cooling if they have clear signs of moderate/severe encephalopathy on clinical grounds.

IV anticonvulsant therapy may cause transient suppression of EEG activity. Ideally the aEEG should be commenced before administering anticonvulsant therapy.

3. When is cooling not appropriate?

Cooling is not appropriate if:

- The infant is likely to require surgery during the first 3 days after birth
- There are other abnormalities indicative of poor long term outcome

Ongoing cooling needs to be reviewed as it may not be appropriate if the infant appears moribund or has persisting extremely severe encephalopathy such that further treatment is likely to be futile, for example if the aEEG/EEG is isoelectric beyond 48 hours of age.

Cooling may produce adverse respiratory or cardiovascular effects and should be used with **caution in infants with an unstable respiratory or cardiovascular condition (e.g. PPHN)**.

4. When to start cooling?

Cooling should be started **as soon as possible** after resuscitation is completed, ideally **within 6 hours of birth**.

(Current evidence suggests that cooling is unlikely to be beneficial if started more than six to eight hours after birth.)

5. Protocol

If the decision is made to treat with cooling, then the following steps should be followed:

I. Admission

Arrange admission to ICU if not already in ICU ASAP.

Switch off radiant/incubator heater - discontinue active warming.

II. On admission to neonatal ICU

a. I. Switch off radiant/incubator heater - discontinue active warming (if not already done)

ii. Monitor rectal temperature (see nursing guidelines)

iii. Start CFM/aEEG

b. General management as per HIE guidelines.

III. Treatment with cooling

a. Follow the Tecotherm system (or specific cooling system) guidelines (See separate sheet)

i. Initial mattress temperature set to 28°C – adjust according to response

ii. Record time of starting cooling, initial temperature, and target date & time for stopping (72 hrs. from start).

iii. NB: Make sure there are **22** pages in observation pack (excluding front reminder tick sheet).

b. Aim for rectal temp of 33-34°C (if whole body cooling)

c. If baby shows signs of distress during cooling (e.g. relative tachycardia, shivering), sedation should be considered (if not already on sedation):

- Phenobarbitone 10-20mg/kg, may be repeated up to 40mg/kg. OR
- Lorazepam (Ativan) 0.05mg-0.1mg/kg/dose. OR

- Morphine 50mcg/kg slow IV bolus over 10 minutes, then 50mcg/kg bolus 6 hourly or infusion at 8mcg/kg/hr. Can double dose for +- 6 hours if still distressed, then review.

IV. Re-warming

Cooling will be stopped 72 hours from when it was initiated.

b. Rate of re-warming should **not be more than 0.5°C/hour**

c. If clinical condition deteriorates during re-warming

i. Stop re-warming

ii. Discuss with consultant

V. When to stop cooling?

If a decision is made by the attending medical/nursing team to withdraw intensive care, cooling should be discontinued and, if time allows, the baby re-warmed before intensive care is withdrawn.

NB. Cooling & re-warming should be completed in ICU.
Ensure all documentation completed before discharge from IC

Appendix C: Thompson Score

Sign	Score				Day 1	Day 2	Day 3
	0	1	2	3			
Tone	Normal	Hypertonic	Hypotonic	Flaccid			
Level of consciousness	Normal	Hyper alert stare	Lethargic	Comatose			
Fits	None	Infrequent <3/day	Frequent > 2/day	Decerebrate			
Posture	Normal	Fisting, cycling	Strong distal flexion	IPPV (apnea)			
Moro	Normal	Partial	Absent				
Grasp	Normal	Poor	Absent				
Suck	Normal	Poor	Absent ± bites				
Respiration	Normal	Hyperventilation	Brief apnea				
Fontanelle	Normal	Full, not tense	Tense				
				Total score per day			

Appendix D: TBH Department of Anatomical Pathology Placenta Cluster Diagnosis Expanded Version

Department of Anatomical Pathology
Placenta Cluster Diagnosis Expanded Version:

A) Maternal vascular Malperfusion: D8-00104

Criteria:

- Small placenta (below the 10th centile for gestational age)
- Cord <8mm in diameter at term
- Infarction:
  - Any infarction in pre-term
  - >5% of non-peripheral parenchyma at term (inner 2/3)
- Extensive infarction – microscopically.
- Accelerated villous maturation
- Distal villous hypoplasia
- Decidual vasculopathy: mural hypertrophy / fibrinoid necrosis / acute atherosis / absence of spiral artery remodeling / arterial thrombosis / persistence of intramural endovascular trophoblast in the 3rd trimester.
- Retroplacental haematoma
- Increased syncytial knots (>33% of villi)
  - Uncertainty over:
    - Increase in perivillous fibrin
    - Increase in extravillous trophoblast
    - Placental pseudocysts
    - Chorionic laeve pseudocysts
    - Membranous decidual necrosis

Diagnosis: Minimum of 3 criteria (preferably 4) – MVM

Need a small placenta (below 10th centile) with 2 (preferably 3) more features.

If >1 but <3 or if ≥3 but placenta within normal ranges → placental compromise.

G-0182

If only 1 – isolated finding (e.g. decidual vasculopathy) – other causes)

B) Foetal Vascular Malperfusion : D8-61540

- Low Grade
- High Grade:
  - >1 focus of avascular villi (total ≥45 villi over 3 sections or an average of >15 villi per section with or without thrombosis or
  - ≥2 occlusive or non-occlusive thrombi in chorionic plate or major stem villi, or
  - multiple non-occlusive thrombi
- Segmental: thrombotic occlusion of chorionic or stem villous vessels or stem vessel obliteration.
- Global (indicating partially obstructed umbilical blood flow with
  - Venous ectasia
  - Intramural fibrin deposition in large vessels
  - Small foci (<5 villi per focus) of avascular villi or
  - Karyorrhectic villi.

C) Placental Insufficiency: D8-00122

a. Maternal floor infarction
    i. Villi of the entire maternal floor are embedded in fibrin, to a thickness of at least 3mm, evident on at least one slide.
b. Massive perivillous fibrin deposition disease
    i. Entrapment of at least 50% of the villi as seen on at least 1 slide.
c. Massive histiocytic intevillositis
d. Diffuse villous oedema
e. Maturation arrest

Each entity is a diagnosis on its own.

D) Placental Abruption: D8-0012A

- Criteria need 2 major:
    - Clinical diagnosis of abruption placenta
    - Macroscopic abruption: >15% adherent retroplacental haematoma or indentation
    - Microscopic abruption – need at least 2 minor:
        - Retroplacental &/or retromembranous &/or marginal sinus haemorrhage
        - Dissection into the decidua and placental parenchyma
        - Overlying infarction/ crowding / agglutination / ischaemic damage to the syncytiotrophoblast.
        - Intravillous haemorrhage / congestion

E) Chorioamnionic Haemosiderosis (chronic/venous abruption): D6-31250

- Iron deposits in the membranes, chorionic plate or decidua.

F) Subacute Fetal Hypoxia with compensatory response: D8-720F8

- Focal villous oedema
- Chorangiosis (focal or diffuse)
- Increase in fetal nucleated red blood cells

G) Ascending Infection - chorioamnionitis: D8-22202

- Criteria: clusters of at least 5 neutrophils in the subchorionic layer.
- Maternal Stage:
    - Stage 1 : acute subchorionitis or chorionitis
    - Stage 2 : acute chorioamnionitis: polys extend into fibrous chorion and or amnion
    - Stage 3 : necrotizing chorioamnionitis: karyorrhexis of polys, amniocyte necrosis and/or amnion basement membrane hypereosinophlia
- Maternal Grade:
    - Grade 1: not sever as defined
    - Grade 2: severe – confluent poly or with subchorionic microabscesses
- Foetal Stage:
    - Stage 1: chorionic vasculitis or umbilical phlebitis
    - Stage 2: involvement of umbilical vein and one or more umbilical arteries
    - Stage 3: necrotizing funisitis
- Foetal Grade:
    - Grade 1: not severe as defined
    - Grade 2: severe – near-confluent intramural poly with attenuation of vascular smooth muscle.
- Association:
    - minor component in intervillositis and
    - chorionic plate, stem villous or umbilical cord vascular thrombosis.
- Intensity:
    - Confluent - continuous inflammatory infiltrate over an entire chorionic plate on a slide.

- Non-confluent – noncontinuous inflammatory infiltrate.
- Microabscess formation: microabscess >20 cells in diameter – maternal response
- Necrotizing funisitis – umbilical cord necrosis with acute inflammation.

H) Haematogenous infection: R-1004D

- Acute Villitis – neutrophils in the villi (major pattern) ± overspill into the intervillous space. Prominent numbers of neutrophils in the villous vessels.
- Chronic villitis – lymphocytes, histiocytes &/or plasma cells in the villi ± villous lysis ± overspill into the intervillous space. Characterized by focal areas of inflammation with monoculear cells and areas of fibrinoid necrosis in chorionic villi.
  - Lymphocytic villitis, Lymphoplasmacytic villitis, Lymphohistiocytic villitis, Histiocytic villitis and Granulomatous villitis.
  - Obliterative vasculopathy – when avascular villi are caused by inflammation (Infective or VUE)
- Acute invervillositis – neutrophils in the intervillous space ± secondary overspill into the villi.
- Intervillous micro abscesses are defined: when the acute intervillous inflammatory aggregate (intervillositis) starts to push apart neighbouring villi.
- SNOMED:
  - CMV : DE-32610
  - Syphilis : DE-14505
  - Herpes : DE-32115
  - Chicken pox : DE-32390
  - Toxoplasma : DE-51200
  - Parvovirus : DE-30006

I) Immunological damage: R-1004C

a. Chronic villitis of unknown aetiology, VUE:
   i. High grade VUE - >10villi involved / focus, >1 focus on >1 slide. Either patchy or diffuse
      Either:
      Patchy: >1 focus with one focus >10 villi in one or more slides.
      Diffuse: >30% of distal villi are involved.

   ii. Low grade VUE - <10 villi involved / focus. >1 focus need.
      Either
      focal: only 1 slide or
      multifocal: >1 slide involved

J) Small placenta, nos : F-03BED

K) Within normal limits / no pathological diagnosis : M-00100

SNOMED codes:

A) Maternal vascular Malperfusion: D8-00104
B) Foetal Vascular Malperfusion : D8-61540
C) Placental Insufficiency: D8-00122
D) Placental Abruption: D8-0012A
E) Chorioamnionic Haemosiderosis (chronic/venous abruption): D6-31250
F) Subacute Fetal Hypoxia with compensatory response: D8-720F8
G) Ascending Infection - chorioamnionitis: D8-22202
H) Haematogenous infection: R-1004D
    a. CMV : DE-32610
    b. Syphilis : DE-14505
    c. Herpes: DE-32115
    d. Chicken pox : DE-32390
    e. Toxoplasma : DE-51200
    f. Parvovirus : DE-30006
I) Immunological damage (Villitis VUE): R-1004C
J) Small placenta, nos : F-03BED
K) Within normal limits / no pathological diagnosis : M-00100
L) Diabetic changes in a placenta: DB-61400

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