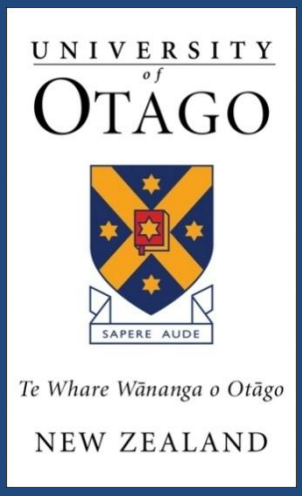

School of Medicine and Health Sciences
University of Otago, Wellington

2012/2013

SUMMER STUDENTSHIP PROGRAMME

Reports

Hamish Green

The Surgical Research Trust

UNIVERSITY of OTAGO

Te Whare Wānanga o Otāgo

NEW ZEALAND

PATHOLOGICAL FINDINGS IN FATAL PERINATAL ASPHYXIA

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DATE November 2012 - February 2013

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PATHOLOGICAL FINDINGS IN FATAL PERINATAL ASPHYXIA

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Sponsor: The Surgical Research Trust

Background: Birth asphyxia occurs when infants are deprived of oxygen at birth. When infants die of birth asphyxia a clinical review of the case may follow which may lead to concerns about malpractice. As well as new lesions, autopsies may reveal older lesions which are thought to develop before birth. This suggests that these infants are not completely normal prior to birth. It is important that these prenatal lesions are understood when these cases are reviewed clinically.

Aim: We aimed to document the demographics and pathology found in infants with birth asphyxia. We compared the relationship between the presence of brain lesions thought to have developed during the pre-natal period, clinical features and acute catastrophic events occurring during labour. We also examined the relationship between the presence of pre-natal brain lesions and placental or umbilical cord pathology in these infants.

Methods: We reviewed autopsy reports from a period of 12 years for infants who died of birth asphyxia. Clinical factors and pathology from 60 cases were analysed. We calculated rates of pre-natal brain lesions and compared these amongst infants with and without acute catastrophic events during labour and in infants with placental or cord pathology.

Results: Forty-eight percent of infants had pre-natal brain lesions. We found that the longer infants survived for, the more likely they were to have developed visible evidence of new brain lesions by the time they died. As expected, infants with clinically detectable brain damage had evidence of new lesions at autopsy. There was no difference in the rate of pre-natal brain lesions in infants experiencing an acute catastrophic event during labour compared to those not experiencing such an event. There was also no significant difference in the rate of pre-natal lesions found in infants with placental or cord pathology compared to those without.

Conclusion: The presence of pre-natal brain lesions found at autopsy in infants with birth asphyxia suggests an injury may have occurred prior to labour. Our findings indicate that there is still much to be understood about the cause of this pathological finding in term infants who have died of asphyxia.

LAY REPORT

ABSTRACT

Aim: The aim of this study was to document the demographics and pathology associated with perinatal asphyxia. We sought to determine the relationship between the presence of gliosis, clinical features and sentinel events associated with birth. We also examined the relationship between the presence of gliosis and placental or cord pathology in infants with perinatal asphyxia.

Methods: A retrospective review of autopsy reports from the Wellington Hospital Mortuary from January 2000 to December 2011 was conducted. Clinical information and pathology from 60 cases of perinatal asphyxia was extracted from autopsy reports for analysis. Rates of gliosis were compared amongst infants with and without peri-partum sentinel events and in infants with placental or cord pathology.

Results: Forty-eight percent of infants had gliosis. Histological evidence of acute hypoxic-ischaemic neuronal injury was positively correlated with the infants age at death ($p=0.0009$). Infants with an encephalopathy had histological evidence of acute hypoxic-ischaemic neuronal changes ($p=0.016$). There was no difference in the rate of gliosis in infants experiencing a sentinel event compared to those not experiencing a sentinel event. There was no statistically significant association between the presence of placental or cord pathology and gliosis in the brain.

Conclusion: The presence of gliosis at autopsy in infants with perinatal asphyxia can indicate the presence of brain injury prior to the onset of labour. The failure to demonstrate a relationship between placental and cord pathology and gliosis and the finding that gliosis can also be present in infants who experienced acute peri-partum asphyxia indicate that there is still much to be understood about the aetiology of the histopathological finding in term infants who have died of asphyxia.

INTRODUCTION

The American College of Obstetricians and Gynaecologists has defined foetal asphyxia as a condition of "impaired blood gas exchange leading to progressive hypoxaemia and hypercapnia with significant metabolic acidosis."[1]

Intra-partum foetal asphyxia occurs at a rate of around 25/1000 live term births with moderate and severe foetal asphyxia at a rate of 4/1000 live term births.[2] Not all infants experiencing foetal asphyxia will progress to neonatal encephalopathy (NE). NE is characterised by respiratory depression, depressed tone and reflexes, reduced level of consciousness, and seizure activity.[3] Hypoxic ischaemic encephalopathy (HIE) is a subset of NE where the cause is attributed to an asphyxial event. A recent systematic review of several older studies reported the incidence of HIE to be between 1.2-7.7/1000 live births with an overall incidence around 2.5/1000 live births.[4] More recent studies have shown the incidence to be around 0.27-0.86/1000 live term births.[5, 6]

HIE is an uncommon event but contributes to a significant proportion of neonatal mortality. A recent local study classifying the cause of all neonatal deaths over a 10 year period found that HIE/perinatal asphyxia was the most common diagnosis assigned at death with a rate of 16.9% of all neonatal deaths and prevalence of 0.54/1000 live births.[7]

Studies have shown that infants who experience fatal birth asphyxia have evidence of prenatal brain damage,[8, 9] with some infants showing evidence of recent lesions superimposed on old lesions.[8] This suggests these infants are compromised prior to the onset of labour and are further compromised during labour. Others, however, have reported no relationship between NE and the presence of established lesions.[10]

Placental pathology has also been associated with neonatal neurologic impairment[11-13] and it has been hypothesised that placental lesions predispose the foetus to intra-partum brain injury.[11] Others, however, have found no association between placental and brain pathology.[8]

The aim of this study was to review the demographics of and pathology found in local cases of fatal perinatal asphyxia. We focused on documenting the presence of old CNS lesions, specifically gliosis in the brain, and major placental pathology. We examined correlations between pathology found at autopsy and significant clinical events related to labour.

We hypothesised that infants with post mortem evidence of old CNS lesions (gliosis) would be more likely to have associated placental pathology but less likely to have experienced a sentinel event related to the birth than infants without evidence of gliosis. Furthermore, we hypothesised that this would be more apparent in infants surviving for less than 72 hours as gliosis resulting from an intra-partum insult would not have had time to develop.[14]

METHODS

A retrospective review of all autopsy records for perinatal deaths documented in the Wellington Hospital Mortuary, New Zealand was conducted. This included reports for both hospital and Coronial autopsies and some cases where the autopsies were conducted elsewhere. All autopsies were undertaken by one experienced perinatal pathologist (JZ). Attention was focused on live births successfully resuscitated and transferred from the delivery suite to a secondary care area such as neonatal intensive care unit or special care baby unit where the pre-mortem diagnosis was perinatal asphyxia. Only infants at term (≥ 37 weeks gestation) were included. An initial data set of 77 cases of perinatal asphyxia was produced for deaths between January 2000 and December 2011. Fourteen cases were excluded because the infants were not successfully resuscitated. These infants died following the withdrawal of initial resuscitative measures. Of the 14, three had been transferred to a secondary care area where resuscitation attempts were discontinued. A further three cases were live-born concealed pregnancies where resuscitation was not attempted. This left 60 cases to be reviewed.

Data were predominantly extracted from the clinical summary and final pathological diagnoses section of the autopsy reports as this was considered to contain the main relevant findings from each case. Data were tabulated into a Microsoft Excel database and analysed using pivot tables. Data were reviewed by an experienced neonatologist and an experienced perinatal pathologist to ensure the relevant clinical information and pathology was included.

Rates of gliosis were compared between those cases with a documented peri-partum sentinel event and those without. Sentinel events included: antepartum haemorrhage (five), feto-maternal haemorrhage (one), antepartum foetal haemorrhage (one), umbilical cord events (two), umbilical cord prolapse (two), shoulder dystocia (two), and uterine rupture (one). In one of these cases, both shoulder dystocia and a cord event were present. We also calculated rates of gliosis amongst pregnancies that had been apparently normal and those pregnancies that were not.

P values were calculated using a Chi-squared test to provide an estimate of statistical significance. In addition, a Wilcoxon rank-sum test was used to calculate p values

where time was a variable to allow it to be measured as a continuous variable. A p value < 0.05 was considered significant.

Birth weight centiles were calculated using the Australian national birth weight percentiles tables.[15] Infants weighing less than the 10th centile for gestation and sex at birth were considered growth retarded.

The 2006 National Maternity Data Set was selected as a control comparison for demographic variables as this represented the middle year of our data set.[16]

Ethical approval was not required as this study fulfilled criteria for a clinical audit.

RESULTS

Demographics

Thirty-three (55%; 95% CI 41-68%) cases were male and taking the confidence interval into account this was consistent with the national average of 51.1%.[16] Mean gestation (figure 1) was 39 completed weeks (range 37-42) and median age at death was 2 days (IQR 1-4.25). With regard to ethnicity, information was unavailable for one case. Of the remaining cases, 38 (64%) were NZ European, 13 (22%) NZ Maori, three (5%) Pacific, and five (9%) other; which included Asian and Indian. There was a higher proportion of NZ European (55.6% nationally) and a lower proportion of Pacific (10.3% nationally) compared to the national average.[16] Median birth weight was 3585 g (IQR 3078-3875). Mean birth weight was 3509 g, compared with the national average of 3420.[16] The median post mortem weight was 3620 g (IQR 3070-4291). Mean maternal age (figure 2) was 28 (range 15-45); information on maternal age was unavailable for one case.

Obstetric data

With respect to the number of previous pregnancies, information was unavailable in six cases. Of the remaining 54 cases, 32 (59%) mothers were primigravida. Fifty-nine (98%) pregnancies were singletons and only one (2%) was a twin pregnancy: this was consistent with the national average.[16]

Table 1 contains information on the course of the pregnancy and summarises the complications present.

There was a higher rate of Caesarean deliveries, 42% compared to a national rate of 24.9%; and a lower rate of normal vaginal deliveries, 42% to 64.7%.[16] There were eight (13%) assisted vaginal deliveries and two (3%) breech deliveries, which was consistent with national rates.[16]

Excluding two cases for which information was unknown, there was a lower rate of inductions of labour, 8.6% compared to 19.8% nationally.[16] However, when the number of augmented deliveries was combined with those induced (17.2%) the rate of inductions was similar.

Fifty-five (92%) babies were delivered in a hospital; three (5%) were delivered at home; and two (3%) were planned home deliveries but were transferred to hospital during established labour due to complications (one umbilical cord prolapse and one failure to progress in second stage). A slightly lower percentage of infants were born in tertiary facilities, 35% compared to the national rate of 41.7%.[16] However, the rate of infants born in secondary facilities was increased compared to the national average of 41.9%.[16] Usually term infants are more likely to be born in either a secondary or a tertiary level facility[16] and the combined rate of deliveries in a secondary or tertiary facility was higher than the national average, 92% compared to 83.6%.[16]

Fourteen (23%) cases had a recognised sentinel event during labour (table 2). A further seven (12%) had a definite cord event at delivery; and eight (13%) had a suspected cord event. With respect to whether meconium was present at birth, information was unavailable in 10 cases. Of the remaining cases, 33 (66%) infants had meconium present at birth.

Neonatal data

Eight (13%) infants were less than the 10th centile for gestational age and sex. Relevant clinical information was not available to calculate a grade of encephalopathy for four cases. Of the remaining, 44 (79%) infants were diagnosed with grade 3 HIE, six (10%) with grade 2, and one (1.7%) with grade 1. Five (9%) had no evidence of encephalopathy.

Cases were evaluated and a decision was made on which organ system made the greatest contribution to final demise (table 3). The majority of infants died because of the severity of their brain injury and withdrawal of care was the final step for these infants.

Pathology

Information on the final pathological diagnoses assigned at autopsy can be found in table 4. Of note, in six (10%) cases sepsis was thought to be the probable or definite reason for death. In a further case metabolic abnormality could not be ruled out. All other final diagnosis confirmed the pre-mortem diagnosis of perinatal asphyxia.

Brain pathology

At autopsy 53 (88%) infants had evidence of acute hypoxic ischaemic neuronal changes. Of these 12 (20%) had focal changes and 41 (68%) global changes. Twenty-nine (48%) infants had gliosis. Of these, six (10%) had early gliosis, and 23 (38%) extensive white matter gliosis. There was no significant difference in the age at death between those with gliosis and those without (p=0.60 Wilcoxon rank-sum test).

Placental pathology

Placental pathology reports were available for 19 cases. Fourteen (34%) had significant pathology. Information on cord pathology was unavailable in 20 cases. Of the remaining, 18 (45%) infants had cord pathology.

Lung pathology

Fifteen (25%) infants had evidence of massive meconium inhalation, 9 (15%) moderate meconium inhalation, 11 (18%) minor meconium inhalation, and 25 (42%) no evidence of meconium inhalation. Fifteen (25%) infants had evidence of massive fresh pulmonary haemorrhage, and nine (15%) minor fresh pulmonary haemorrhage. Eighteen (30%) infants had findings of bronchopneumonia; 10 (17%) congenital pneumonia; five (8%) aspiration pneumonia; one (1.7%) extensive collapse; and 26 (43%) did not have other lung pathology.

Other organ pathology

With respect to the heart, seven (12%) infants had massive myocardial necrosis, 14 (23%) focal myocardial necrosis, and 39 (65%) a normal myocardium. Seventeen (28%) infants had evidence of either liver necrosis or haemorrhage or both at autopsy, whilst 43 (72%) were normal. Ten (17%) infants had a two-tone liver indicating that asphyxia occurred while the foetus was dependent on umbilical arterial blood flow. With regard to the kidney, 30 (50%) infants had acute tubular necrosis (ATN), 14 (23%) had evidence of either resolving or resolved ATN, and 16 (27%) had no evidence of ATN. Twenty-three (38%) infants had either adrenal necrosis or haemorrhage or both, and 37 (62%) had no adrenal pathology. Three (5%) infants had definite infection, 11 (18%) were suspected to have infection, 45 (75%) had no evidence of infection and it was not possible to rule infection out in one (2%) case. Eight (13%) infants experienced birth trauma. Seven (12%) infants were diagnosed at autopsy with intrauterine growth restriction (IUGR), and six (10%) with foetal malnutrition.

Correlations between clinical and pathological findings (tables 5 and 6)

As expected survival for longer than 24 hours was associated with the presence of acute hypoxic-ischaemic neuronal injury (p=0.0009). Also, the majority of infants who had a clinical diagnosis of encephalopathy also had histological evidence of acute hypoxic-

ischaemic neuronal changes (p=0.016). There was a positive correlation between the HIE grade and the degree of gliosis found (p=0.016).

Gliosis was found in 52.5% of infants surviving for less than 72 hours. There was no statistically significant difference in the rate of gliosis in infants experiencing a sentinel event and those not experiencing a sentinel event. Also, no statistically significant association was found between the rate of gliosis and the type of pregnancy course (normal versus abnormal), or the presence of acute hypoxic-ischaemic neuronal changes.

There was a higher rate of gliosis in infants where there was placental pathology compared with those without (57% versus 44%). In infants where there was cord pathology the rate of gliosis was lower, 39% compared to 55% when there was no cord pathology. When placental pathology and cord pathology were considered together the rate of gliosis was similar to the overall rate of gliosis. None of these differences were statistically significant.

DISCUSSION

Perinatal asphyxia is an important clinical problem in obstetrics and midwifery. If the affected infant dies then a clinical review of obstetric and midwifery practice may follow and this may in turn lead to concerns about malpractice. As well as recent pathology, autopsy may reveal evidence of older previously unrecognised CNS insults that may indicate the foetus was compromised prior to the onset of labour. The significance of these insults is not currently understood. It is important that the possible implications of these insults are considered when these cases are reviewed clinically.

At least 18 hours is required for acute neuronal changes to become apparent by light microscopy.[2, 14] Gliosis is reported to occur from 36 to greater than 72 hours following the insult.[8, 14] It is the presence of gliosis that is of particular importance when evaluating evidence for prenatal brain damage. Overall 48% of infants in the current study had evidence of gliosis. This is consistent with previous studies reporting the rate of white matter gliosis in asphyxiated term infants to be 48%.[8] Although not statistically significant, our rate of gliosis in infants surviving for less than 72 hours is consistent with a previous Scottish study reporting a rate of white matter gliosis at 52% in infants surviving less than 3 days.[8]

Cowan et al reported that infants with encephalopathy have evidence of lesions acquired in the perinatal period.[10] However, they found a low rate of established lesions considered to develop prior to birth. In regard to encephalopathy being associated with established lesions our data are consistent. Given that gliosis requires around 3 days to become evident histologically[14] we would expect to find a low rate of

gliosis in infants surviving less than 3 days and its presence suggests that a prenatal insult had occurred. The main difference between this study of Cowan et al and our own was the reliance on MRI to detect lesions. Not all infants in this study died and as such it is likely that they were less severely affected clinically. Furthermore, histology will accurately detect lesions seen on MRI but not all lesions detected histologically will be evident on MRI.[17]

We set out to examine the relationship between placental pathology and gliosis in the brain. It is important to note that our focus was solely on significant primary placental and umbilical cord pathology. Previous studies have examined the relationship of placental pathology to neonatal neurologic impairment.[11-13] These studies examined specific lesions whilst our study combined all placental lesions that were considered by the pathologist to be significant. We found no statistically significant difference between the rate of gliosis and the presence of placental or cord pathology. The Scottish study also found no relationship between placental and brain pathology[8] however this study utilised different methods namely the inclusion of preterm infants.

Milsom et al reported that being a primigravida is a risk factor for birth asphyxia.[18] The rate of primigravidas in our study was the same as in this study. There was a higher rate of Caesarean sections in our cases compared to the national rate. Caesarean sections have been associated with an increased risk of HIE but of course are often the end point of a response to foetal distress in labour.[18, 19] Oxytocin augmentation has been reported as a risk factor for birth asphyxia,[18, 20] however our rate of augmentation was less than in both of these studies. Although we found no difference in the rate of gliosis in infants experiencing a sentinel event, sentinel events have been shown to be associated with an increased risk of developing HIE.[21]

A limitation of this study was that this was not a geographic cohort as the pathologist in this centre conducted perinatal autopsies for infants from centres around New Zealand. This was a retrospective review and as such has the same limitations of other retrospective reviews in that there was often missing data, thus making analysis more difficult. Due to the nature of the study, it is not possible to have a control group. We therefore we do not have information on the rate of gliosis in infants that survived an asphyxial event or in infants that did not experience asphyxia.

Taking data from 12 years of records provided us with good numbers for analysis, however, clinical practice changes over time. For instance, during the study period therapeutic hypothermia for NE was introduced. It is not clear what impact this has on findings at autopsy. Autopsies were conducted by one pathologist therefore ensuring consistency in the histological interpretation. The exclusion of infants where initial

resuscitation failed was necessary as from the information available it was not always possible to determine which of these were live born and which were still born.

With many of the reported risk factors[18, 20, 22] being absent from the cases in this study it makes it difficult to identify a point in the clinical course for intervention. All infants involved in this study struggled from birth; they all had low Apgar scores and were admitted to secondary care facilities from birth. Placentae often shed light on possible contributors to an infant's condition so it is imperative that these are sent for pathologic examination. Thirty-two percent of placentae were not available for analysis in this study. Many of these had been discarded at birth.

This study sought to document the pathology of neonatal asphyxia and particularly associations between the presence of gliosis and other clinical and pathological factors. No clear associations were found between the presence of gliosis and placental and cord pathology and clinical events. Clearly further research is required to determine the aetiology of this pathological feature and to understand what, if any, significance it has in the foetal response to asphyxia.

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ACKNOWLEDGMENTS

I would like to thank The Surgical Research Trust for sponsoring this research. I would like to thank my supervisors Associate Professor Dawn Elder and Dr Jane Zuccollo for their guidance. I would also like to thank the kind mortuary staff for being so obliging in allowing me to access their records.

Conflicts of Interest, The authors have no conflicts to declare.

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APPENDIX:

Figure 1: Gestation at birth

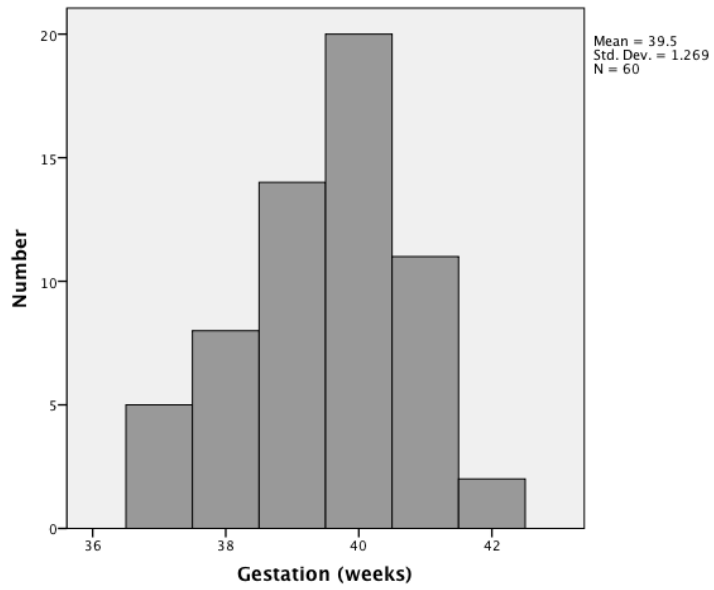

Figure 2: Maternal age

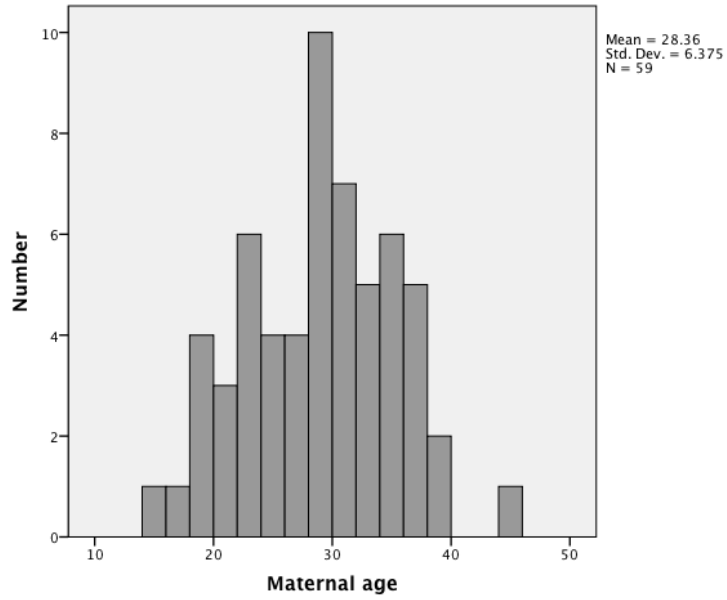

Table 1: Pregnancy course

Pregnancy course*	Number (%)
Apparently normal	38 (66)
Reduced foetal movements†	5 (9)
Diabetes mellitus	3 (5)
Decreased foetal growth velocity	2 (3.4)
In-vitro fertilisation	2 (3.4)
Little antenatal care	2 (3.4)
Major congenital anomaly	1 (1.7)
GBS bacteraemia	1 (1.7)
Unstable lie	1 (1.7)
Twins and threatened pre-term labour	1 (1.7)
Pre-eclampsia	1 (1.7)
Maternal kidney problems^	1 (1.7)
Total‡	**58‡ (100)**

*Prior to the onset of labour
†From 24-96 hours prior to labour
^No cause found
‡ Information was unavailable for 2 cases

Table 2: Sentinel events

Sentinel event	Number (%)
No sentinel event	46 (77)
Sentinel event	14 (23)
Total	**100 (100)**

Table 3: Organ system responsible for final demise

Organ system responsible for final demise	Number (%)
CNS*	44 (73)
Respiratory	4 (7)
Coagulopathy	4 (7)
Multi-organ failure	4 (7)
CNS and cardiorespiratory	2 (3)
CNS and coagulopathy	1 (1.7)
Cardiorespiratory	1 (1.7)
Total	**60 (100)**

*The majority of these cases had their care withdrawn as a result of their significant encephalopathy

Table 4: Final diagnosis assigned at autopsy

Final diagnosis	Number (%)
Perinatal asphyxia	29 (48)
Intra-partum asphyxia	12 (20)
Antepartum asphyxia	6 (10)
Antenatal asphyxia	4 (7)
Perinatal asphyxia (secondary to infection)	3 (5)
Perinatal asphyxia (with congenital pneumonia)	1 (1.7)
Congenital pneumonia	1 (1.7)
Probable sepsis	1 (1.7)
Perinatal and antenatal asphyxia	1 (1.7)
Perinatal asphyxia and birth trauma	1 (1.7)
?Congenital metabolic abnormality*	1 (1.7)
Total	**60 (100)**

*Facilities were not available at the time to properly diagnose this case

Table 5: Relationship of acute hypoxic-ischaemic neuronal injuries to survival time of the infants and the extent of HIE

	Acute hypoxic-ischaemic neuronal injury		Total	Wilcoxon rank-sum test
	Y (%; 95% CI)	N (%; 95% CI)		
Age (hours)				p=0.0009
≤23	7 (54; 95% CI 24.13-80.78)	6 (46; 95% CI 19.22-74.87)	13 (22)	
24 – 47	14 (100; 95% CI 76.84-100)	0 (0; 95% CI 0-23.16)	14 (23)	
48 – 71	13 (100; 95% CI 75.29-100)	0 (0; 95% CI 0-24.71)	13 (22)	
≥72	19 (95; 95% CI 75.13-99.87)	1 (5; 95% CI 0.13-24.87)	20 (33)	
TOTAL	**53 (88; 95% CI77.43-95.18)**	**7 (12; 95% CI 4.82-22.57)**	**60 (100)**	
HIE (grade)				p=0.016†
Unknown†	4* (100)	0 (0)	4*	
0	0 (0; 95% CI 0-52.18)	5 (100; 95% CI 47.82-100)	5 (9)	
1	1 (100; 95% CI 2.5-100)	0 (0; 95% CI 0-97.5)	1 (2)	
2	6 (100; 95% CI 54.07-100)	0 (0; 95% CI 0-45.93)	6 (11)	
3	42 (95; 95% CI 84.53-99.44)	2 (5; 95% CI 0.56-15.47)	44 (78)	
TOTAL	**49 (88; 95% CI 75.93-94.82)**	**7 (12; 95% CI 5.18-24.07)**	**56 (100)**	

*Not included as part of a percentage of the total
†Where information was unavailable this was excluded from analysis

Table 6: Relationship of gliosis to various parameters within the study

	Gliosis		Total (%)	Chi^2 P value	Wilcoxon rank-sum test
	Y (%; 95% CI)	**N (%; 95% CI)**			
Age (hours)					p=0.60
≤23	5 (38; 95% CI 13.86-68.42)	8 (62; 95% CI 31.58-86.14)	13 (22)		
24 – 47	6 (43; 95% CI 17.66-71.14)	8 (57; 95% CI 28.86-82.34)	14 (23)		
48 – 71	10 (77; 95% CI 46.19-94.96)	3 (23; 95% CI 5.04-53.81)	13 (22)		
≥72	8 (40; 95% CI 19.12-63.95)	12 (60; 95% CI 36.05-80.88)	20 (33)		
TOTAL	**29 (48; 95% CI 35.23-61.61)**	**31 (52; 95% CI 38.39-64.77)**	**60 (100)**		
Sentinel event				p=0.89	
Y	7 (50; 95% CI 23.04-76.96)	7 (50; 95% CI 23.04-76.96)	14 (23)		
N	22 (48; 95% CI 32.89-63.05)	24 (52; 95% CI 36.95-67.11)	46 (77)		
TOTAL	**29 (48; 95% CI 35.23-61.61)**	**31 (52; 95% CI 38.39-64.77)**	**60 (100)**		
HIE (grade)					p=0.016†
Unknown†	2‡ (50)	2‡ (50)	4‡		
0	1 (20; 95% CI 0.51-71.64)	4 (80; 95% CI 28.36-99.49)	5 (9)		
1	0 (0; 95% CI 0-97.5)	1 (100; 95% CI 2.5-100)	1 (2)		
2	1 (17; 95% CI 0.42-64.12)	5 (83; 95% CI 35.88-99.58)	6 (11)		
3	25 (57; 95% CI 41.03-71.65)	19 (43; 95% CI 28.35-58.97)	44 (78)		
TOTAL	**27 (48; 95% CI 34.66-61.97)**	**29 (52; 95% CI 38.03-65.34)**	**56 (100)**		
Pregnancy course				p=0.064†	
No information†	1‡ (50)	1‡(50)	2‡		
Apparently Normal	15 (39; 95% CI 24.04-56.61)	23 (61; 95% CI 43.39-75.96)	38 (66)		
Abnormal	13 (65; 95% CI 40.78-84.61)	7 (35; 95% CI 15.39-59.22)	20 (34)		
TOTAL	**28 (48; 95% CI 34.95-61.78)**	**30 (52; 95% CI 38.22-65.05)**	**58 (100)**		
Acute hypoxic-ischaemic				p=0.27	

neuronal injury					
Y	27 (51; 95% CI 36.84-64.94)	26 (49; 95% CI 35.06-63.16)	53 (88)		
N	2 (29; 95% CI 3.67-70.96)	5 (71; 95% CI 29.04-96.33)	7 (12)		
TOTAL	**29 (48; 95% CI 35.23-61.61)**	**31 (52; 95% CI 38.39-64.77)**	**60 (100)**		
Placental pathology*				p=0.44†	
No Information†	9‡ (47)	10‡ (53)	19‡		
No Pathology	12 (44; 95% CI 25.48-64.67)	15 (56; 95% CI 35.33-74.52)	27 (66)		
Pathology	8 (57; 95% CI 28.86-82.34)	6 (43; 95% CI 17.66-71.14)	14 (34)		
TOTAL	**20 (49; 95% CI 33.83-63.9)**	**21 (51; 95% CI 35.13-66.17)**	**41 (100)**		
Cord pathology^				p=0.32†	
No Information†	10‡ (50)	10‡ (50)	20‡		
No Pathology	12 (55; 95% CI 32.21-75.61)	10 (45; 95% CI 24.39-67.79)	22 (55)		
Pathology	7 (39; 95% CI 17.3-64.25)	11 (61; 95% CI 35.75-82.7)	18 (45)		
TOTAL	**19 (47.5; 95% CI 31.51-63.87)**	**21 (52.5; 95% CI 36.13-68.49)**	**40 (100)**		
Placental* and cord^ pathology				p=0.94†	
No Information†	9‡ (47)	10‡ (53)	19‡		
No Pathology	16 (48; 95% CI 30.8-66.46)	17 (52; 95% CI 33.54-69.2)	33 (80)		
Pathology	4 (50; 95% CI 15.7-84.3)	4 (50; 95% CI 15.7-84.3)	8 (20)		
TOTAL	**20 (49; 95% CI 33.83-63.9)**	**21 (51; 95% CI 35.13-66.17)**	**41 (100)**		
Placental* or cord^ pathology				p=0.65†	
No Information†	9‡ (47)	10‡ (53)	19‡		
No Pathology	9 (53; 95% CI 27.81-77.02)	8 (47; 95% CI 22.98-72.19)	17 (41)		
Pathology	11 (46; 95% CI 25.55-67.18)	13 (54; 95% CI 32.82-74.45)	24 59)		
TOTAL	**20 (49; 95% CI 33.83-63.9)**	**21 (51; 95% CI 35.13-66.17)**	**41 (100)**		

*Only major Primary Placental Pathology

^Only major Primary Cord Pathology

†Where information was unavailable this was excluded from analysis

‡Not included as part of a percentage of the total