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ORIGINAL ARTICLE

Perinatal antecedents of moderate and severe neonatal hypoxic ischaemic encephalopathy: An Australian birth cohort study

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Background: Neonatal hypoxic ischaemic encephalopathy (HIE) is the most common cause of encephalopathy in the neonatal period and carries a high risk of mortality and long-term morbidity.

Aim: The aim of this study was to investigate key antecedents of moderate and severe HIE in a large contemporary birth cohort.

Methods: A retrospective cohort study of births meeting criteria was conducted between 2016 and 2020 at the Mater Mothers' Hospital, Brisbane, Australia. This is a quaternary perinatal centre and Australia's largest maternity hospital. Univariate and multivariate Firth logistic regression were used to account for imbalanced frequency classes between non-HIE and HIE groups. Maternal variables and intrapartum factors were investigated for associations with neonatal moderate and severe HIE.

Results: Overall, 133 of 46 041 (0.29%) infants were diagnosed with HIE: 77 (0.17%) with mild HIE and 56 (0.12%) with moderate/severe HIE. Nulliparity, type 1 diabetes mellitus and maternal intensive care unit admission were associated with increased odds of moderate/severe HIE. Intrapartum risk factors included emergency caesarean birth, emergency caesarean for non-reassuring fetal status or failure to process, intrapartum haemorrhage and an intrapartum sentinel event (shoulder dystocia, cord prolapse, uterine rupture and placental abruption). Neonatal risk factors included male sex, late preterm gestation (35^{+0}–36^{+6} weeks), Apgar score less than four at 5 min, severe respiratory distress requiring ventilatory support and severe acidosis at birth.

Conclusions: This cohort study identified a series of potentially modifiable maternal and obstetric risk factors for HIE. Risk factors for HIE do not appear to have changed significantly with evolution in modern obstetric care.

KEYWORDS

cerebral palsy, fetal distress, fetus, hypoxic ischaemic encephalopathy, intrapartum hypoxia, pregnancy

INTRODUCTION

Neonatal encephalopathy (NE) is a heterogeneous condition of diverse aetiology that results in impairment of an infant's central nervous system soon after birth.[1] Hypoxic ischaemic encephalopathy (HIE), a subset of NE, is characterised by clinical, laboratory and imaging evidence of acute or subacute brain injury, as a result of a perinatal hypoxic, ischaemic or asphyxial event. In late preterm and term infants, HIE accounts for approximately 15–35% of all cases of encephalopathy and carries a high risk of mortality and long-term morbidity such as epilepsy and motor and cognitive impairment. This has significant impact on families and the healthcare system.[2] Severity of HIE, graded according to the Sarnat criteria,[3] closely correlates with future neurodevelopmental impairment. Infants with moderate or severe HIE are most at risk of future adverse outcomes. There is now good evidence that therapeutic hypothermia is neuroprotective and significantly reduces short- and long-term morbidity and mortality.[4]

Risk factors for HIE are varied and include pre-eclampsia, small-for-gestational-age (SGA) infants and nulliparity[5] as well as acute intrapartum events[2] such as placental abruption, cord prolapse and uterine rupture. However, much of the available evidence is based on data that are often more than 20 years old – there is a clear need for information more reflective of current obstetric practice where intrapartum fetal monitoring and management of labour complications have significantly evolved over recent decades.

The aim of this study thus was to determine the potential antecedents of moderate/severe HIE using a contemporary data set from a major quartenary Australian perinatal centre.

MATERIALS AND METHODS

Design and setting

This was a five-year retrospective cohort study (January 2016 to December 2020) of non-anomalous, singleton liveborn infants, ≥35 + 0 weeks' gestation with moderate or severe HIE, at the Mater Mothers' Hospital in Brisbane, Australia. Ethical and governance approvals were obtained from the Mater Research Human Research Ethics Committee and Governance office, respectively (reference number: HREC/18/MHS/46).

Participants

Only infants meeting criteria (Table 1) for moderate or severe HIE based on level of consciousness, activity, tone, reflexes and respiration were included. Infants delivered <35 + 0 weeks, those with major congenital anomalies or genetic syndromes and all stillbirths were excluded.

Maternal demographical, obstetric and neonatal variables were extracted from the institution's maternity database. Where necessary individual chart review was also undertaken. Data regarding maternal age, ethnicity, smoking during pregnancy, use of illicit drugs during pregnancy, nulliparity, body mass index, diabetes mellitus (DM) (type 1 or type 2 or gestational), hypertension (essential or gestational hypertension or pre-eclampsia), thyroid disease, Socio-Economic Index for Areas (SEIFA) score, intensive care unit (ICU) admission, mode of birth (caesarean section (CS), instrumental vaginal (vacuum or forceps)), onset of labour (spontaneous or induction of labour), Apgar score less than seven at 5 minutes, Apgar score less than four at 5 minutes and acidosis at birth (cord umbilical artery pH <7) were used for analysis.

The SEIFA score is an Australian area-based score reflective of socio-economic status, where an average score is 1000 and a lower score reflects relative socio-economic deprivation.[6] Total length of labour was calculated as the duration of stages one and two. Gestational age was estimated using the last menstrual period or earliest ultrasound measurements and categorised as late preterm (35^{+0}–36^{+6}), term (37^{+0}–41^{+6}) and post-term (≥42^{+0}). Birthweight centiles were categorised using an Australian reference cohort.[7] Severe respiratory distress was defined as the need for any additional respiratory support beyond bag and mask. Ethnicity, smoking and illicit drug use during pregnancy were self-reported variables.

Statistical analysis

Continuous data are reported as mean (standard deviation) or median (interquartile range (IQR)), and categorical data are reported as proportions and percentage. Associations between variables were assessed using Pearson's χ^2 test, Student's *t*-test or Wilcoxon rank-sum test as appropriate. Logistic regressions are presented as odds ratios (OR) or beta coefficient (β) with 95% confidence intervals (CI). Univariate Firth logistic regression was used to account for imbalanced frequency classes between non-HIE and HIE groups.[8] Multiple logistic Firth regression analyses were performed, accounting for significant maternal characteristics where indicated, guided by event per variable ≥10 as previously described.[9] Variables were treated as continuous where possible. No assumptions were made regarding the use of missing data. Results are reported according to the STROBE guidelines and checklist (https://www.equator-network.org/reporting-guidelines/strobe/).

All hypothesis were tested two sided, and statistical significance was determined by *P*-values ≤0.05. Stata SE, Release 15 (StataCorp LP, College Station, TX, USA), was used to perform all statistical analyses.

RESULTS

Selection of the study cohort is shown in Figure 1. Over the study period, there were 46 041 non-anomalous, singleton infants, ≥35 + 0 weeks, who met all criteria for analysis. Of these, 133 (0.29%) were diagnosed with HIE: 77 (0.17%) with mild HIE and 56 (0.12%) with moderate/severe HIE. Of the 56 moderate/severe

TABLE 1 Maternal factors

			HIE			
		All	**No HIE**	**Moderate/severe HIE**		
		(*n* = 45 964)	**(*n* = 45 908)**	**(*n* = 56)**	**OR or *β* (95% CIs)**	***P*-value**
Age (years)	Mean (SD)	31.6 (5.0)	31.6 (5.0)	30.8 (6.1)	−0.03 (−0.08 to 0.02)	0.228
	<20	551/45 964 (1.2%)	550/45 908 (1.2%)	1/56 (1.8%)	2.41 (0.47–12.39)	0.291
	20–34	32 384/45 964 (70.5%)	32 348/45 908 (70.5%)	36/56 (64.3%)	REF	
	≥5	13 029/45 964 (28.3%)	13 010/45 908 (28.3%)	19/56 (33.9%)	1.33 (0.77–2.30)	0.312
BMI	Median (IQR)	23 (21–27)	23 (21–27)	24 (20–27)	0.01 (−0.04 to 0.06)	0.658
	Underweight	2846/45 671 (6.2%)	2841/45 615 (6.2%)	5/56 (8.9%)	1.77 (0.71–4.41)	0.218
	Normal	27 059/45 671 (59.2%)	27 030/45 615 (59.3%)	29/56 (51.8%)	REF	
	Overweight	9510/45 671 (20.8%)	9496/45 615 (20.8%)	14/56 (25.0%)	1.40 (0.75–2.62)	0.295
	Obese	6256/45 671 (13.7%)	6248/45 615 (13.7%)	8/56 (14.3%)	1.25 (0.58–2.67)	0.572
Ethnicity	Asian	11 261/45 943 (24.5%)	11 250/45 887 (24.5%)	11/56 (19.6%)	REF	
	Aboriginal and/or Torres Strait Islander	1086/45 943 (2.4%)	1084/45 887 (2.4%)	2/56 (3.6%)	2.26 (0.57–8.87)	0.244
	Caucasian	26 970/45 943 (58.7%)	26 937/45 887 (58.7%)	33/56 (58.9%)	1.22 (0.62–2.38)	0.566
	Other	6626/45 943 (14.4%)	6616/45 887 (14.4%)	10/56 (17.9%)	1.55 (0.67–3.59)	0.303
Nulliparous		21 042/45 889 (45.9%)	21 007/45 833 (45.8%)	35/56 (62.5%)	1.95 (1.14–3.33)	0.014
Type 1 diabetes mellitus		192/45 964 (0.4%)	189/45 908 (0.4%)	3/56 (5.4%)	15.33 (5.14–45.76)	<0.001
Type 2 diabetes mellitus		167/45 964 (0.4%)	167/45 908 (0.4%)	0/56 (0.0%)	2.48 (0.15–40.35)	0.524
Gestational diabetes mellitus		4460/45 964 (9.7%)	4456/45 908 (9.7%)	4/56 (7.1%)	0.84 (0.32–2.20)	0.720
Gestational hypertension		891/45 964 (1.9%)	891/45 908 (1.9%)	0/56 (0.0%)	0.45 (0.03–7.25)	0.572
Pre-eclampsia		711/45 964 (1.5%)	710/45 908 (1.5%)	1/56 (1.8%)	1.69 (0.33–8.55)	0.529
Any thyroid disease		4560/39 960 (11.4%)	4553/39 913 (11.4%)	7/47 (14.9%)	1.44 (0.66–3.14)	0.361
Hypothyroidism requiring treatment		3243/45 964 (7.1%)	3237/45 908 (7.1%)	6/56 (10.7%)	1.70 (0.75–3.84)	0.205
Smoking		4600/45 936 (10.0%)	4593/45 880 (10.0%)	7/56 (12.5%)	1.36 (0.63–2.94)	0.431
Alcohol use		1749/45 728 (3.8%)	1748/45 673 (3.8%)	1/55 (1.8%)	0.69 (0.14–3.50)	0.656
Illicit drug use		2751/45 720 (6.0%)	2747/45 664 (6.0%)	4/56 (7.1%)	1.34 (0.51–3.51)	0.553
SEIFA score		1038 (1000–1073)	1038 (1000–1073)	1036 (999–1065)	−0.00 (−0.00 to 0.00)	0.496
SEIFA lowest quintile		4999/45 731 (10.9%)	4995/45 675 (10.9%)	4/56 (7.1%)	0.70 (0.27–1.83)	0.464
Assisted reproduction technology		4194/45 964 (9.1%)	4189/45 908 (9.1%)	5/56 (8.9%)	1.06 (0.44–2.56)	0.891
Antepartum haemorrhage		553/45 964 (1.2%)	553/45 908 (1.2%)	0/56 (0.0%)	0.73 (0.04–11.75)	0.821
Maternal ICU admission		154/45 964 (0.3%)	153/45 908 (0.3%)	1/56 (1.8%)	8.06 (1.58–41.10)	0.012
Admission for hypertensive complications		58/154 (37.7%)	57/153 (37.3%)	1/1 (100.0%)		
Admission for haemorrhagic complications		53/154 (34.4%)	53/153 (34.6%)	0/1 (0.0%)		
Admission for sepsis		9/154 (5.8%)	9/153 (5.9%)	0/1 (0.0%)		
Admission for other indication		34/154 (22.1%)	34/153 (22.2%)	0/1 (0.0%)		

Data are presented as % (*n*), mean (SD) or median (IQR) as appropriate.
BMI, body mass index (kg/m^2); CI, confidence interval; HIE, hypoxic ischaemic encephalopathy; ICU, intensive care unit; IQR, interquartile range; OR, odds ratio; REF, reference group; SEIFA, Socio-Economic Index for Areas; SD, standard deviation.

cases eligible for therapeutic hypothermia, 49 (87.5%) were cooled; 40 of those cases were cooled for 72 h or longer (83.33%), eight were cooled for less than 72 h and one case did not record duration of cooling. Of the remaining seven infants that were not cooled, six were diagnosed >6 h after birth or were <36 weeks' gestation at birth. One infant received palliative care.

Table 1 summarises maternal risk factors. Nulliparity (OR: 1.95, 95% CI 1.14–3.33), type 1 DM (OR: 15.33, 95% CI 5.14–45.76)

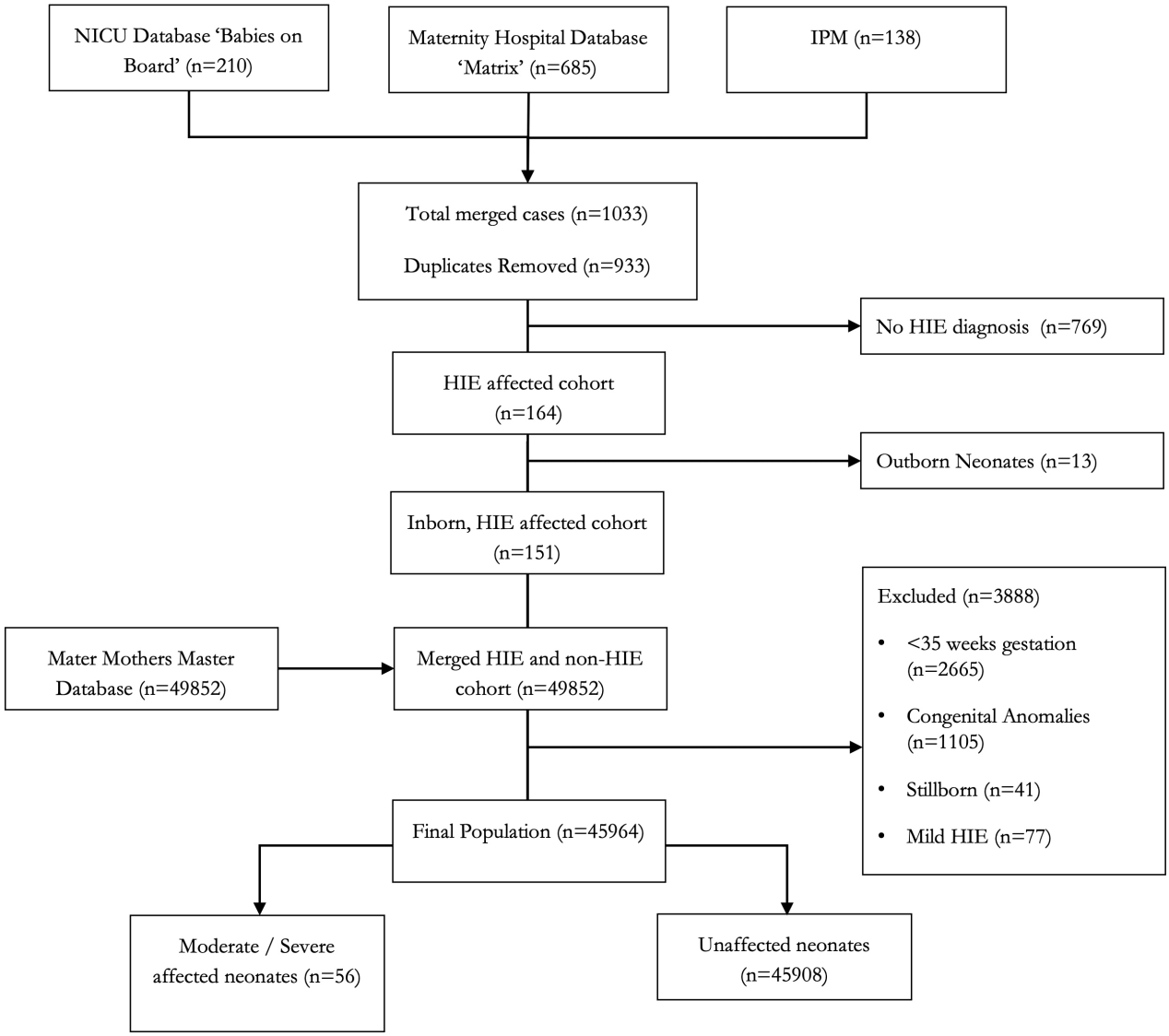

FIGURE 1 Study participant selection diagram.

and ICU admission for any reason (OR: 8.06, 95% CI 1.58–41.10) were all associated with increased odds for moderate/severe HIE.

Table 2 presents intrapartum risk factors related to moderate/severe HIE. Emergency CS, emergency CS for non-reassuring fetal status or failure to progress, intrapartum haemorrhage, placental abruption, cord prolapse, uterine rupture and shoulder dystocia were all associated with higher odds of moderate/severe HIE. Length of labour in the moderate/severe cohort was significantly longer than in controls (median [IQR] 8.80 h [5.80–11.57] vs 4.52 h [2.60–7.20], $P = 0.006$).

Table 3 presents neonatal characteristics associated with moderate/severe HIE. Male sex, birth at late preterm gestation (35^{+0}–36^{+6} weeks), Apgar score less than four at 5 min, severe respiratory distress and severe acidosis at birth were all associated with higher odds of moderate/severe HIE. Birthweight <5th or <10th percentile or >90th or >95th percentile was not associated with increased risk of HIE.

DISCUSSION

Main findings

In this large contemporary cohort from a single Australian quaternary centre, we demonstrate that nulliparity, type 1 DM, antenatal maternal ICU admission for any indication, prolonged labour, emergency CS, emergency CS for non-reassuring fetal status, intrapartum haemorrhage, placental abruption, cord prolapse, uterine rupture, severe shoulder dystocia and late preterm birth were all strongly associated with moderate/severe HIE. From a neonatal perspective, Apgar score less than seven at 5 min, severe respiratory distress and severe acidosis at birth were also linked to this complication. Overall major intrapartum causative factors (placental abruption, cord prolapse, uterine rupture and shoulder dystocia) accounted for 28.6% of cases.

TABLE 2 Intrapartum factors

Intrapartum risk factors		All (*n* = 45 964)	HIE: No HIE (*n* = 45 908)	HIE: Moderate/severe HIE (*n* = 56)	Unadjusted: OR or β (95% CIs)	Unadjusted: *P*-value	Adjusted†: OR or β (95% CIs)	Adjusted†: *P*-value
Length of labour	Hours	4.52 (2.60–7.20)	4.52 (2.60–7.20)	8.80 (5.80–11.57)	0.13 (0.08–0.19)	<0.001	0.11 (0.03–0.20)	0.006
	>95th percentile	1447/29 025 (5.0%)	1443/29 006 (5.0%)	4/19 (21.1%)	5.54 (1.94–15.86)	0.001	3.33 (1.14–9.72)	0.028
Induction of labour		16 662/45 964 (36.3%)	16 645/45 908 (36.3%)	17/56 (30.4%)	0.78 (0.44–1.37)	0.384	0.75 (0.42–1.35)	0.341
Use of oxytocin		19 919/45 947 (43.4%)	19 900/45 891 (43.4%)	19/56 (33.9%)	0.68 (0.39–1.17)	0.166	0.57 (0.32–1.03)	0.062
Vaginal breech birth		1932/45 964 (4.2%)	1930/45 908 (4.2%)	2/56 (3.6%)	0.84 (0.21–3.46)	0.814	0.60 (0.12–3.07)	0.544
Method of birth	SVD	22 115/45 964 (48.1%)	22 108/45 908 (48.2%)	7/56 (12.5%)	2.49 (1.02–6.04)	0.107	0.43 (0.16–1.16)	0.096
	Instrumental (forceps or vacuum)	6091/45 964 (13.3%)	6080/45 908 (13.2%)	11/56 (19.6%)	2.49 (1.02–6.04)	0.044	1.63 (0.62–4.26)	0.322
	CS elective	11 181/45 964 (24.3%)	11 173/45 908 (24.3%)	8/56 (14.3%)	REF		REF	
	CS emergency	6577/45 964 (14.3%)	6547/45 908 (14.3%)	30/56 (53.6%)	6.12 (2.86–13.10)	<0.001	5.90 (2.63–13.21)	<0.001
	CS emergency – NRFS	1908/6585 (29.0%)	1887/6555 (28.8%)	21/30 (70.0%)	5.60 (2.60–12.03)	<0.001	6.67 (2.89–15.39)	<0.001
	CS emergency – FTP	2280/6596 (34.6%)	2278/6566 (34.7%)	2/30 (6.7%)	0.17 (0.05–0.60)	0.006	0.22 (0.06–0.84)	0.027
Pyrexia in labour		1637/45 964 (3.6%)	1633/45 908 (3.6%)	4/56 (7.14%)	2.09 (0.75–5.77)	0.157	1.57 (0.52–4.69)	0.422
Premature rupture of membranes		184/12 562 (1.46%)	184/12 543 (1.47%)	0/19 (0.0%)	1.72 (0.10–28.56)	0.706	2.04 (0.12–34.69)	0.622
Intrapartum haemorrhage		1654/45 964 (3.6%)	1647/45 908 (3.6%)	7/56 (12.5%)	4.07 (1.89–8.79)	<0.001	2.94 (1.21–7.14)	0.017
Placental abruption		151/45 964 (0.3%)	146/45 908 (0.3%)	5/56 (8.9%)	33.36 (13.64–81.57)	<0.001	28.98 (10.81–77.71)	<0.001
Cord prolapse		41/45 964 (0.1%)	40/45 908 (0.1%)	1/56 (1.8%)	30.61 (5.87–159.51)	<0.001	25.98 (4.46–151.39)	<0.001
Uterine rupture		8/45 964 (0.0%)	6/45 908 (0.0%)	2/56 (3.6%)	323.94 (73.55–1426.78)	<0.001	609.40 (127.00–2924.12)	<0.001
Shoulder dystocia		2083/45 962 (4.5%)	2075/45 906 (4.5%)	8/56 (14.3%)	3.70 (1.78–7.68)	<0.001	3.88 (1.86–8.11)	<0.001

Data are presented as % (*n*), mean (SD) or median (IQR) as appropriate.

†Adjusted for nulliparity, type 1 diabetes mellitus

CI, confidence interval; CS, caesarean section; FTP, failure to progress; HIE, hypoxic ischaemic encephalopathy; IQR, interquartile range; NRFS, Non-reassuring fetal status; OR, odds ratio; SD, standard deviation; SVD, spontaneous vaginal delivery.

TABLE 3 Neonatal risk factors

Neonatal risk factors		All (*n* = 45 964)	HIE: No HIE (*n* = 45 908)	HIE: Moderate/severe HIE (*n* = 56)	Unadjusted: OR or β (95% CIs)	Unadjusted: *P*-value	Adjusted† : OR or β (95% CIs)	Adjusted† : *P*-value
Male sex		23 702/45 942 (51.6%)	23 662/45 886 (51.6%)	40/56 (71.4%)	2.31 (1.30–4.09)	0.004	2.10 (1.17–3.75)	0.013
Gestational age (weeks + days)	Median (IQR)	274 (268–280)	274 (268–280)	274 (262–286)	−0.04 (−0.23–0.15)	0.678	0.03 (−0.18 to 0.24)	0.798
	Late preterm (35^{+0}–36^{+6})	2568/45 964 (5.6%)	2557/45 908 (5.6%)	11/56 (19.6%)	4.27 (2.23–8.16)	<0.001	3.31 (1.61–6.83)	0.001
	Term (37^{+0}–41^{+6})	43 257/45 964 (94.1%)	43 212/45 908 (94.1%)	45/56 (80.4%)	REF		REF	
	Post-term (≥42^{+0})	139/45 964 (0.3%)	139/45 908 (0.3%)	0/56 (0.0%)	3.40 (0.21–55.53)	0.390	3.11 (0.19–50.85)	0.426
Birth weight (g)		3357 (3044–3669)	3357 (3044–3669)	3274 (3060–3720)	−0.00 (−0.00 to 0.00)	0.690	0.00 (−0.00 to 0.00)	0.954
Birthweight centiles	<5th	1760/45 937 (3.8%)	1758/45 881 (3.8%)	2/56 (3.6%)	1.32 (0.36–4.85)	0.674	0.82 (0.16–4.31)	0.816
	<10th	4005/45 937 (8.7%)	4002/45 881 (8.7%)	3/56 (5.4%)	0.81 (0.27–2.49)	0.716	0.62 (0.17–2.30)	0.475
	≥90^{th}	4251/45 937 (9.3%)	4243/45 881 (9.3%)	8/56 (14.3%)	1.99 (0.84–4.70)	0.119	1.91 (0.75–4.85)	0.172
	≥95^{th}	2019/45 937 (4.4%)	2015/45 881 (4.4%)	4/56 (7.1%)	2.04 (0.67–6.25)	0.211	1.38 (0.38–5.10)	0.624
Apgar score <7 at 5 min		608/45 772 (1.3%)	569/45 720 (1.2%)	39/52 (75.0%)	231.98 (124.37–432.70)	<0.001	227.17 (118.39–435.88)	<0.001
Apgar score <4 at 5 min		81/45 772 (0.2%)	63/45 720 (0.1%)	18/52 (34.6%)	385.56 (208.22–713.93)	<0.001	395.05 (207.21–753.17)	<0.001
Severe respiratory distress		9265/45 964 (20.2%)	9214/45 908 (20.1%)	51/56 (91.1%)	37.29 (15.47–89.86)	<0.001	74.97 (21.02–267.47)	<0.001
Severe acidosis		320/45 964 (0.7%)	292/45 908 (0.6%)	28/56 (50.0%)	155.95 (91.63–265.43)	<0.001	136.22 (77.78–238.57)	<0.001

Data are presented as % (*n*), mean (SD) or median (IQR) as appropriate.
†Adjusted for nulliparity, type 1 diabetes.
CI, confidence interval; HIE, hypoxic ischaemic encephalopathy; IQR, interquartile range; OR, odds ratio; SD, standard deviation.

Interpretation

Our study identified an overall HIE rate of 2.9 per 1000 births, which is consistent with other studies reporting a rate of 1–4 per 1000 live births in high-income regions.[10,11] Our findings are also very similar to those from two earlier landmark studies from Western Australia.[10,12] The rate of moderate/severe HIE in our study was 1.2 per 1000 births, also comparable with contemporary data from other large cohort studies from Sweden[13] (1.7 per 1000 births), and Canada which report an overall neonatal asphyxia rate of 2.3 per 1000 births, and a rate of 0.9 per 1000 births for moderate/severe HIE respectively.[14]

Similar to our study, nulliparity regardless of socio-economic setting has been reported as a risk factor for HIE.[15] We did not find any difference in socio-economic disparity between the HIE cohort and controls, and similarly in other studies,[15] socio-economic deprivation has not been consistently linked with HIE.

Although previous data suggest an association between SGA infants and HIE,[16] we did not find a similar relationship. Our results, however, are in keeping with the findings of Parker *et al*[17] but may, nonetheless, be limited by the relatively small numbers of infants with moderate/severe HIE. Interestingly, whereas our results suggest that male infants are at double the risk (OR: 2.1, 95% CI 1.17–3.75), a large meta-analysis from Rossi and Prefumo[18] did not show an association between infant sex and HIE. Nevertheless, as there are good data to show that male infants are more prone to adverse outcomes of HIE,[19] including higher rates of cerebral palsy,[20] investigating this potential sex-specific vulnerability is an increasingly important field of research. We found a clear association between late preterm birth (35^{+0}–36^{+6} weeks' gestational age) and moderate/severe HIE, again consistent with other studies[5,14] highlighting the increased vulnerability of this cohort for peripartum brain injury. Why this group of preterm infants is at risk is a current knowledge gap as it is unclear if the neuropathology of hypoxic–ischaemic injury is secondary to selective neuronal necrosis (as is observed in term infants), the arrest of maturation of pre-oligodendrocytes (typical in preterm infants) or a combination of both.[21]

In our study almost one in three cases of moderate/severe HIE was attributable to a sentinel event in labour, very similar to other studies suggesting that intrapartum factors may be responsible for approximately 15–35% of cases of severe HIE. Acute intrapartum complications such as cord prolapse, uterine rupture, placental abruption or severe shoulder dystocia, although rare, have been reported to be strongly associated with HIE.[11] Indeed, a recent retrospective study from North America found that 36% of cases of HIE were preceded by a sentinel event despite occurring in only 3% of the entire study cohort.[17] Although other studies have shown that instrumental birth and emergency CS[15] are associated with increased risk of moderate/severe HIE, our data suggest that only emergency caesarean birth increases this risk. Possible reasons for this discrepancy include variations in outcome potentially influenced by institutional guidelines and/or the type of fetal monitoring or classification systems used during labour.[22,23] Nevertheless, the relevance of an acute intrapartum event causally associated with HIE remains somewhat uncertain, with some earlier studies reporting relatively low rates compared to others[24] documenting rates as high as 62%.

The issue of vaginal breech birth and NE is problematic. In our study, we were unable to show a significant association between vaginal breech birth and moderate/severe HIE. Any investigation of association between vaginal breech birth and HIE is a major challenge, first because HIE at term is rare and second only a very small proportion of the 3–4% of women with breech presentation at or close to term tend to elect for a vaginal breech birth. Using Norwegian birth data from 1996 to 1998, Andersen *et al*.[25] showed that after controlling for gestational age, assisted conception, SGA and sex, singleton vaginal breech infants had an OR of 3.3 (95% CI 1.6–6.7) for cerebral palsy compared with cephalic infants. However, the authors themselves and an accompanying comment[26] acknowledge that causality was very difficult to prove because of the possibility that antenatally acquired brain injuries were more likely in the breech cohort.

An interesting finding of our study is the longer median overall length of labour in the HIE cohort (8.80 vs 4.52 h), which was associated with the development of acidosis at birth. Blankenship *et al*.[27] reported an increased risk of maternal and neonatal morbidity in pregnancies with first-stage labour length above the 90th percentile. It is certainly plausible that overall longer length of labour may cumulatively increase the duration of intrapartum hypoxia and increase the likelihood of hypoxic cerebral injury.

Although we did not identify SGA as a risk factor, other studies have highlighted its association with HIE.[16] Prenatal identification of SGA and/or aberrant fetal growth is important as this cohort is at increased risk of intrapartum and neonatal complications, including hypoxic brain injury and longer-term neurodevelopmental sequelae.[28] Most cases of HIE occur because of prolonged intermittent fetal hypoxaemia resulting from reduced uteroplacental perfusion during contractions in labour.[29] Uterine contractions reduce uteroplacental perfusion by as much as 60%, and although most fetuses are able to tolerate the reduction in placental blood flow, there exists a cohort that is unable to and thus at risk of hypoxic injury.[30] Identifying infants at risk is difficult as many have no obvious risk factors.[31] There is evidence that infants with a low fetal cerebroplacental ratio (CPR) on ultrasound have increased vulnerability to intrapartum fetal distress.[32] Women with low prelabour levels of placental growth factor (PlGF) are also at a similar risk.[33] However, neither the CPR, PlGF nor computerised analysis of fetal heart rate patterns or fetal ECG[34] has been shown to improve important clinical outcomes, such as HIE, indicating why better methods for identifying the at-risk infant are critical areas of unmet need.

There are some interventions on the horizon that have the potential to reduce the risk of severe birth asphyxia secondary to progressive severe intrapartum hypoxia. In a recent phase 2, double-blind, randomised controlled trial,[35] maternal oral

sildenafil during labour reduced the risk of pathological fetal heart rate patterns and halved the rate of operative birth for fetal compromise. Further larger trials are required to determine if this novel therapy can also reduce rates of birth injury attributable to intrapartum hypoxia. More broadly, regular staff training to recognise abnormal fetal heart rate patterns, careful and judicious use of oxytocin particularly in the context of a previous CS, careful selection of candidates for trial of labour after caesarean, early recognition of malpresentation and other risk factors for cord prolapse, timely and judicious intervention with operative birth and regular shoulder dystocia drills could also potentially reduce the risk of hypoxic birth injury.

Strengths and limitations

Despite its single-centre focus, our study cohort of 56 cases of moderate/severe HIE is large and comparable to other series.[18] We minimised ascertainment bias by carefully screening electronic health and neonatal ICU notes and correlating these with other relevant health records.

We were not able to assess the role of suboptimal clinical care, maternal or infant thrombophilia disorders or aberrant fetal growth. In addition, the lack of placental histopathology data and details regarding maternal pyrexia in labour limited our analyses. Our study was also constrained because we used routinely collected clinical data with the accompanying challenges of missing or incomplete data. Finally, inherent to our quartenary centre focus, our institution has a significant load of high-risk pregnancies, which may affect the generalizability of our results. However, given the ubiquity of electronic fetal heart rate monitoring and clear guidelines regarding intrapartum management, in other similar quartenary centres our results remain pertinent and may be useful for practitioners and women in these settings.

CONCLUSION

Our results suggest that antecedents for HIE in a high-income setting have not significantly changed compared to studies several decades earlier despite changes in obstetric practice. The contribution of acute, sentinel or catastrophic intrapartum events remains at approximately one in three of all cases. Although better intrapartum care may mitigate some of these risk factors, not all are predictable and thus preventable. Areas that warrant further research include the utility of pharmacological agents to improve uteroplacental perfusion during labour and better prenatal screening techniques to identify infants at risk.

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