Supplementary Online Content

Trends in the Incidence and Management of Hypoxic-Ischaemic Encephalopathy in the Therapeutic Hypothermia Era: A national population study

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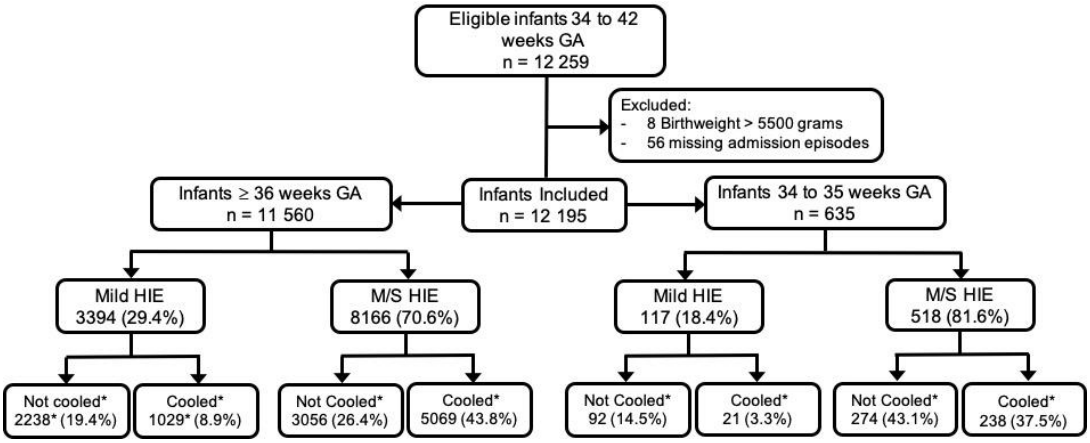
Content:

Supplementary Figure 1. Flowchart of study participants demonstrating included/excluded infants and rate of hypoxic ischaemic encephalopathy for each gestational subgroup



* Therapeutic hypothermia data not available for all infants within each subgroup
GA, gestation age; m/s moderate/severe; HIE, Hypoxic Ischaemic encephalopathy

Supplementary Table 1. National Neonatal Research Database Hypoxic Ischaemic Encephalopathy and Therapeutic Hypothermia data identifiers

Principal Diagnosis at Discharge database entry
Severe HIE : - HIE Grade 3 - Severe Neonatal Encephalopathy - Hypoxic ischaemic brain damage ; Severe - Severe perinatal asphyxia (with 1 minute Apgar <4) - Severe Neonatal Encephalopathy - Gr.3 - Hypoxic Ischaemic Encephalopathy (Gr 3) - Severe Neonatal Encephalopathy – Grade 3 HIE Moderate HIE: - HIE Grade 2 - Moderate Neonatal Encephalopathy - Hypoxic ischaemic brain damage ; Moderate - Moderate perinatal asphyxia (with 1 minute Apgar 4-7) - Moderate Neonatal Encephalopathy - Gr.2 - Hypoxic Ischaemic Encephalopathy (Gr 2) - Moderate Neonatal Encephalopathy - Grade 2 HIE Mild HIE: - HIE Grade 1 - Mild Neonatal Encephalopathy - Hypoxic ischaemic brain damage ; Mild - Mild perinatal asphyxia (with 1 minute Apgar >7) - Mild Neonatal Encephalopathy - Gr.1 - Hypoxic Ischaemic Encephalopathy (Gr 1) - Mild Neonatal Encephalopathy - Grade 1 HIE - Very mild perinatal asphyxia - clinically normal by 24 hours Unspecified - Birth Asphyxia - Anoxic Brain Damage Therapeutic Hypothermia - Therapeutic Hypothermia - Therapeutic Hypothermia (whole body cooling) - Hypothermia Therapeutic
Principal procedures during stay
Therapeutic Hypothermia - Therapeutic Hypothermia - Therapeutic Hypothermia (whole body cooling) - Hypothermia Therapeutic

Shipley L, *et al. Arch Dis Child Fetal Neonatal Ed* 2021;0:1–6. doi: 10.1136/archdischild-2020-320902

Supplementary Table 2. Comparison of antenatal and delivery characteristics between epochs (2011-13 and 2014-16) for infants ≥36 weeks gestational age with moderate/severe hypoxic ischaemic encephalopathy who died without therapeutic hypothermia

Variables	Number of infants (n=120)*	Missing n (%)
Antenatal Characteristics		
Diabetes mellitus	0	0
Gestational diabetes	4 (3.3)	0
Preeclampsia	2 (1.7)	0
Risk factors of early infection[a]	22 (18.3)	0
Delivery Characteristics		
Gender (male)	61 (50.8)	0
Gestational age (weeks)	39 (37 - 40)	0
Birth weight (grams)	3252 (2840 - 3576)	0
> 98th Centile	3 (2.5)	0
Intrapartum events[b]	13 (10.8)	0
Apgar 1 minute	2 (0 - 5)	9 (7.5)
Apgar 5 minute	5 (1 - 8)	9 (7.5)
Significant resuscitation[c]	58 (38.1)	0
Venous Cord pH	7.23 (7.09 - 7.32)	55 (45.8)
Day of death (days)	0.7 (0.37 - 2.0)	0

* Data are n (%) or median (interquartile range)
[a] Maternal fever, Chorioamnionitis, prolonged rupture of membranes, urinary tract infection
[b] Cord prolapse, shoulder dystocia, abruption, reduced fetal movements
[c] Chest compressions, intubation, drugs
Data items diabetes mellitus, gestational diabetes, preeclampsia, risk factors for sepsis, intrapartum events and significant resuscitation variables are collected using a tick box, so not possible to accurately determine missing data from absence of a characteristic

Supplementary Table 3. Comparison of antenatal and delivery characteristics between epoch 1 (2011-13) and 2 (2014-16) for infants ≥36 weeks gestational age with moderate/severe hypoxic ischaemic encephalopathy undergoing therapeutic hypothermia

	Infants ≥36 weeks GA with moderate/severe HIE and TH				
Variables	Epoch 1 (n=2286)*	Missing n (%)	Epoch 2 (n=2783)*	Missing n (%)	p value**
Diabetes mellitus	13 (0.6)	0	46 (1.7)	0	<0.001
Gestational diabetes	63 (2.8)	0	123 (4.4)	0	0.002
Preeclampsia	111 (4.9)	0	122 (4.3)	0	0.43
Risk factors of early infection[a]	384 (16.8)	0	732 (26.3)	0	<0.001
Delivery Characteristics					
Gender (male)	1244 (54.4)	0	1528 (54.9)	0	0.70
Gestational age (weeks)	40 (38 – 41)	0	40 (38 – 41)	0	0.04
Birth weight (grams)	3355 (2958 – 3760)	0	3330 (2940 – 3750)	0	0.29
> 98th Centile	131 (5.7)	0	158 (5.6)	0	0.94
Intrapartum events[b]	278 (12.2)	0	351 (12.6)	0	0.63
Apgar 1 minute	1 (0 – 3)	156 (6.8)	1 (1 – 3)	209 (7.5)	0.37
Apgar 5 minute	4 (2 – 6)	159 (7.0)	4 (2 – 6)	198 (7.1)	0.03
Significant resuscitation[c]	1136 (51.9)	0	1934 (71.3)	0	<0.001
Venous Cord pH	7.11 (6.93 – 7.25)	698 (30.5)	7.13 (6.97 – 7.26)	803 (28.8)	0.009

GA, Gestational age; HIE, Hypoxic-ischaemic encephalopathy; TH, Therapeutic hypothermia
* Data are n (%) or median (interquartile range)
** Categorical data analysed using Chi Squared test; Non-normally distributed continuous data analysed using Mann U Whitney test
[a] Maternal fever, Chorioamnionitis, prolonged rupture of membranes, urinary tract infection
[b] Cord prolapse, shoulder dystocia, abruption, reduced fetal movements
[c] Chest compressions, intubation, drugs
Data items diabetes mellitus, gestational diabetes, preeclampsia, risk factors for sepsis, intrapartum events and significant resuscitation variables are collected using a tick box, so not possible to accurately determine missing data from absence of a characteristic

Supplementary Table 4. Comparison of antenatal and delivery characteristics between epoch 1 (2011-13) and 2 (2014-16) for infants ≥36 weeks gestational age with mild hypoxic ischaemic encephalopathy undergoing therapeutic hypothermia

	Infants ≥ 36 weeks GA with mild HIE and TH				
Variables	Epoch 1 (n=426)*	Missing n (%)	Epoch 2 (n=603)*	Missing n (%)	p value**
Antenatal Characteristics					
Diabetes mellitus	1 (0.2)	0	6 (1.0)	0	0.14
Gestational diabetes	8 (1.9)	0	18 (3.0)	0	0.27
Preeclampsia	10 (2.3)	0	23 (3.8)	0	0.19
Risk factors of early infection[a]	69 (16.2)	0	142 (23.5)	0	0.004
Delivery Characteristics					
Gender (male)	243 (57.0)	0	347 (57.5)	0	0.85
Gestational age (weeks)	40 (39 – 41)	0	40 (39 – 41)	0	0.60
Birth weight (grams)	3405 (2970 – 3760)	0	3330 (2950 – 3705)	0	0.10
> 98th Centile	16 (3.8)	0	17 (2.8)	0	0.40
Intrapartum events[b]	37 (8.7)	0	52 (8.6)	0	0.97
Apgar 1 minute	2 (1 – 4)	38 (8.9)	3 (1 – 5)	58 (9.6)	0.02
Apgar 5 minute	5 (4 – 7)	40 (9.4)	6 (4 – 7)	50 (8.3)	0.04
Significant resuscitation[c]	163 (38.3)	0	270 (44.8)	0	0.04
Venous Cord pH	7.14	120 (28.2)	7.14	161 (26.7)	0.78

	(6.98 – 7.25)	(6.99 – 7.25)

GA, Gestational age; HIE, Hypoxic-ischaemic encephalopathy; TH, Therapeutic hypothermia
* Data are n(%) or median (interquartile range)
** Categorical data analysed using Chi Squared test; Non-normally distributed continuous data analysed using Mann U Whitney test
[a] Maternal fever, Chorioamnionitis, prolonged rupture of membranes, urinary tract infection
[b] Cord prolapse, shoulder dystocia, abruption, reduced fetal movements
[c] Chest compressions, intubation, drugs
Data items diabetes mellitus, gestational diabetes, preeclampsia, risk factors for sepsis, intrapartum events and significant resuscitation variables are collected using a tick box, so not possible to accurately determine missing data from absence of a characteristic

Supplementary Table 5. Comparison of antenatal and delivery characteristics between infants ≥36 weeks with moderate/severe and mild hypoxic ischaemic encephalopathy undergoing therapeutic hypothermia

	Infants ≥ 36 weeks GA with M/S versus mild HIE and TH				
Variables	M/S HIE (n=5069)*	Missing n (%)	Mild HIE (n=1029)*	Missing n (%)	p value**
Antenatal Characteristics					
Diabetes mellitus	59 (1.2)	0	7 (0.7)	0	0.17
Gestational diabetes	186 (3.7)	0	26 (2.5)	0	0.07
Preeclampsia	233 (4.6)	0	33 (3.2)	0	0.05
Risk factors of early infection[a]	1116 (22.0)	0	211 (20.5)	0	0.28
Delivery Characteristics					
Gender (male)	2772 (54.7)	0	590 (57.3)	0	0.12
Gestational age (weeks)	40 (38 – 41)	0	40 (39 – 41)	0	<0.001
Birth weight (grams)	3340 (2950 – 3760)	0	3360 (2965 – 3740)	0	0.98
> 98th Centile	289 (5.7)	0	33 (3.2)	0	0.001
Intrapartum events[b]	629 (12.4)	0	89 (8.6)	0	0.001
Apgar 1 minute	1 (0 - 3)	365 (7.2)	3 (1 – 5)	96 (9.3)	<0.001
Apgar 5 minute	4 (2 – 6)	357 (7.0)	5 (4 – 7)	90 (8.7)	<0.001
Significant resuscitation[c]	3070 (60.6)	0	433 (42.1)	0	<0.001
Venous Cord pH	7.13 (6.96 – 7.25)	1501 (29.6)	7.14 (6.99 – 7.25)	281 (27.3)	0.06

GA, Gestational age; m/s, moderate/severe; HIE, Hypoxic-ischaemic encephalopathy; TH, Therapeutic hypothermia

* Data are n (%) or median (interquartile range)

** Categorical data analysed using Chi Squared test; Non-normally distributed continuous data analysed using Mann U Whitney test

[a] Maternal fever, Chorioamnionitis, prolonged rupture of membranes, urinary tract infection

[b] Cord prolapse, shoulder dystocia, abruption, reduced fetal movements

[c] Chest compressions, intubation, drugs

Data items diabetes mellitus, gestational diabetes, preeclampsia, risk factors for sepsis, intrapartum events and significant resuscitation variables are collected using a tick box, so not possible to accurately determine missing data from absence of a characteristic

Supplementary Table 6. Incidence rates for the whole study population by gestational age for any grade of hypoxic ischaemic encephalopathy (HIE), moderate/severe HIE and mortality with moderate/severe HIE

Gestation (weeks)	Any grade HIE (n=12195)	Rate per 1000 live births	M/S HIE & TH (n=5307)	Rate per 1000 live births	Died & M/S HIE (n=843)	Rate per 1000 live births
34	255	6.22	76	1.85	41	1.00
35	380	6.31	162	2.69	40	0.66
36	615	5.04	319	2.61	66	0.54
37	977	3.50	483	1.73	81	0.29
38	1344	2.38	612	1.09	109	0.19
39	1989	1.97	858	0.85	129	0.13
40	3319	2.94	1456	1.29	212	0.19
41	2837	3.63	1163	1.51	144	0.18
42	479	3.49	178	1.34	21	0.15
Total						
34-35 weeks	635	6.27	238	2.35	81	0.80
≥36 weeks	11560	3.03	5069	1.26	762	0.19

M/S, moderate/severe; TH, Therapeutic Hypothermia

Supplementary Table 7. Comparison of antenatal and delivery characteristics between epoch 1 (2011-13) and 2 (2014-16) for infants 34 to 35 weeks with hypoxic ischaemic encephalopathy undergoing therapeutic hypothermia

	Infants 34 to 35 weeks GA with HIE and TH				
Variables	Epoch 1 (n=103)*	Missing n (%)	Epoch 2 (n=156)*	Missing n (%)	p value**
Antenatal Characteristics					
Diabetes mellitus	1 (1.0)	0	10 (6.4)	0	0.03
Gestational diabetes	6 (5.8)	0	14 (9.0)	0	0.35
Preeclampsia	8 (7.8)	0	17 (10.9)	0	0.40
Risk factors of early infection[a]	24 (23.3)	0	40 (25.6)	0	0.67
Delivery Characteristics					
Gender (male)	60 (58.3)	0	92 (59.0)	0	0.91
Gestational age (weeks)	35 (34 – 35)	0	35 (34 – 35)	0	0.38
Birth weight (grams)	2275 (2030 - 2650)	0	2370 (2122 – 2640)	0	0.14
> 98th Centile	6 (5.8)	0	12 (7.7)	0	0.56
Intrapartum events[b]	21 (20.4)	0	37 (23.7)	0	0.53
Apgar 1 minute	1 (0 – 3)	7 (6.8)	1 (0 – 3)	8 (5.1)	0.79
Apgar 5 minute	4 (1 – 5)	8 (7.8)	3 (1 – 6)	8 (5.1)	0.64
Significant resuscitation[c]	56 (54.4)	0	119 (76.3)	0	<0.001
Venous Cord pH	7.03 (6.85 – 7.23)	40 (38.8)	7.08 (6.85 – 7.26)	60 (38.5)	0.56

GA, Gestational age; HIE, Hypoxic-ischaemic encephalopathy; TH, Therapeutic hypothermia
* Data are n(%) or median (interquartile range)
** Categorical data analysed using Chi Squared test; Non-normally distributed continuous data analysed using Mann U Whitney test
[a] Maternal fever, Chorioamnionitis, prolonged rupture of membranes, urinary tract infection
[b] Cord prolapse, shoulder dystocia, abruption, reduced fetal movements
[c] Chest compressions, intubation, drugs
Data items diabetes mellitus, gestational diabetes, preeclampsia, risk factors for sepsis, intrapartum events and significant resuscitation variables are collected using a tick box, so not possible to accurately determine missing data from absence of a characteristic