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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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

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# 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  |
**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 | Missing |
|-----------------------------------------------|-------------------|---------|
| **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       |
| > 98\(^{th}\) 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       |

\(^a\) Data are n (%) or median (interquartile range)

\(^b\) 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.

| 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**

| Variables                              | Epoch 1 (n=2286)* | Missing n (%) | Epoch 2 (n=2783)* | Missing n (%) | p value** |
|----------------------------------------|--------------------|---------------|--------------------|---------------|-----------|
| 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               | 0             | 3330               | 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)          | 0             | 156 (6.8)          | 1 (1 – 3)     | 209 (7.5) |
| Apgar 5 minute                         | 4 (2 – 6)          | 0             | 159 (7.0)          | 4 (2 – 6)     | 198 (7.1) |
| Significant resuscitation c            | 1136 (51.9)        | 0             | 1934 (71.3)        | 0             | <0.001    |
| Venous Cord pH                          | 7.11               | 0             | 7.13               | 0             | 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

| 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 infectiona  | 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             | 0             | 3330             | 0             | 0.10      |
| (2970 – 3760)                     |                  |               | (2950 – 3705)    |               |           |
| > 98th Centile                    | 16 (3.8)         | 0             | 17 (2.8)         | 0             | 0.40      |
| Intrapartum eventsb               | 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 resuscitationc        | 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      |
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.

| 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**        | 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              | 0             | 3360              | 0             | 0.98      |
| > 98th Centile                          | 289 (5.7)         | 0             | 33 (3.2)          | 0             | 0.001     |
| Intrapartum events**                     | 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**              | 3070 (60.6)       | 0             | 433 (42.1)        | 0             | <0.001    |
| Venous Cord pH                           | 7.13              | 1501 (29.6)   | 7.14              | 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  
** Maternal fever, Chorioamnionitis, prolonged rupture of membranes, urinary tract infection  
** Cord prolapse, shoulder dystocia, abruption, reduced fetal movements  
** 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

| 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 |
|--------------------------|---------------------------|------------------------|---------------------------|------------------------|---------------------------|
| 34-35 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

| 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*              | 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          | 0.14      |
| > 98th Centile                                | 6 (5.8)          | 0             | 12 (7.7)         | 0             | 0.56      |
| Intrapartum events*                           | 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*                    | 56 (54.4)        | 0             | 119 (76.3)       | 0             | <0.001    |
| Venous Cord pH                                 | 7.03             | (6.85 – 7.23) | 0               | 7.08          | 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
* Maternal fever, Chorioamnionitis, prolonged rupture of membranes, urinary tract infection
* Cord prolapse, shoulder dystocia, abruption, reduced fetal movements
* 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