Treatment Of Asphyxiated Newborns With Moderate Hypothermia In Routine Clinical Practice: How Cooling Is Managed In The UK Outside A Clinical Trial

D. Azzopardi¹, B. Strohm², A. D. Edwards¹, H. Halliday³, E. Juszczak², M. Levene⁴, M. Thoresen⁵, A. Whitelaw⁶, P. Brocklehurst² on behalf of the Steering Group and TOBY Cooling Register Participants

¹ Hammersmith Campus, Imperial College, London, UK
² National Perinatal Epidemiology Unit, University of Oxford, UK
³ Royal Maternity Hospital, Belfast, Northern Ireland
⁴ Leeds General Infirmary, Leeds, UK
⁵ St. Michael's Hospital, Bristol, UK
⁶ Southmead Hospital, Bristol, UK

Corresponding author:
Dr Denis Azzopardi
Division of Clinical Sciences
Hammersmith Campus
Imperial College
London
W12 0NN
d.azzopardi@imperial.ac.uk
Tel: +44 208 383 3326
Fax +44 208 740 5281
Keywords: Induced hypothermia, asphyxia, newborns, encephalopathy, register

Abbreviations:
aEEG: Amplitude integrated electroencephalography
CFM: Cerebral Function Monitor
MRI: Magnetic Resonance Imaging
Abstract

Background

This is a phase 4 study of infants registered with the UK TOBY Cooling Register from December 2006 to February 2008. The registry was established on completion of enrolment to the TOBY randomised trial of treatment with whole body hypothermia following perinatal asphyxia at the end of November 2006.

Methods

We collected information about patient characteristics, condition at birth, resuscitation details, severity of encephalopathy, hourly temperature record, clinical complications and outcomes before discharge from hospital.

Results

120 infants born at median 40 (IQR 38, 41) weeks’ gestation and weighing median 3287 (IQR 2895, 3710) grams at birth were studied. Cooling was started at median 3 h 54 min (IQR 2 h, 5 h 32 min) after birth. All but three infants underwent whole body cooling. The mean (SD) rectal temperature from 6 to 72 hours of the period of cooling was 33.57 °C (0.51 °C). The daily encephalopathy score fell: median (IQR) 11 (6, 15), 9.7 (5, 14), 8 (5, 13) and 7 (2, 12) on each of days 1-4 after birth. 51% of the infants established full oral feeding at a median (range) of 9 (4-24) days. 26% of the study infants died. MRI was consistent with hypoxia-ischaemia in most cases. Clinical complications were not considered due to hypothermia.

Conclusion

In the UK, therapeutic hypothermia following perinatal asphyxia is increasingly being provided. The target body temperature is successfully achieved and the clinical complications observed were not attributed to hypothermia. Treatment with hypothermia may have prevented the worsening of encephalopathy that is commonly observed following asphyxia.
Introduction

Many clinicians are encouraged by the positive short-term results of the first randomised clinical trials of treatment with moderate hypothermia following perinatal asphyxia, as well as the generally supportive commentaries and systematic reviews, and have started or are considering offering therapeutic hypothermia. [1-6] In the UK, 35 centres participated in the Medical Research Council TOBY trial of moderate whole body hypothermia following perinatal asphyxia (www.npeu.ox.ac.uk/TOBY). On completion of enrolment of the TOBY study at the end of November 2006, the study investigators recognised that, based on the already published evidence, many clinicians would consider offering therapeutic hypothermia as part of clinical care whilst awaiting the results of the TOBY trial, which are expected at the end of 2008. The TOBY investigators therefore developed clinical guidelines, information material for clinicians and parents, and a case record form, and set up a national registry, the UK TOBY Cooling Register of treatment with hypothermia, to monitor uptake of this intervention within the UK (www.npeu.ox.ac.uk/tobyregister).

This study reports the clinical details, temperature control and complications in infants reported to the registry from December 2006 to February 2008. We hypothesised that moderate hypothermia following asphyxia could be provided safely and effectively even when used outside the setting of a clinical trial, as part of routine clinical care.

Methods

The operational group (DA, BS, PB) of the UK TOBY register of therapeutic hypothermia produced guidance and case record forms which were derived from those used in the TOBY study but differ in some respects: firstly, unlike in the TOBY study when enrolment had to be completed and cooling initiated within 6 hours of birth, clinicians are still advised to initiate hypothermia as soon as possible after birth but also to consider therapeutic hypothermia up to 12 hours after birth since the exact duration of the ‘therapeutic window’ is uncertain [7,8]; secondly, clinicians are advised not to delay starting therapeutic hypothermia in infants meeting the clinical criteria if the amplitude integrated EEG (aEEG) is not available, although clinicians are still advised to record the aEEG throughout the period of treatment with cooling; and thirdly, the need for parental consent for treatment of infants with hypothermia is guided by local hospital policies.

In other respects the guidance is the same as that of the TOBY protocol: eligible infants should be at least 36 weeks gestation, with clinical evidence of birth asphyxia and moderate to severe encephalopathy, as defined in the TOBY protocol (www.npeu.ox.ac.uk/TOBY); and the target rectal temperature is 33.5°C for 72 hours, using a certified or locally approved cooling device followed by gradual re-warming, at a rate no faster than 0.5°C/hour.

All TOBY cooling register material is available publicly and copies are also sent to centres that have indicated their intention to offer therapeutic hypothermia. A monthly reminder and notification card is sent out to all centres that have registered infants. The register is managed by the TOBY study coordinator (BS) using the facilities of the National Perinatal Epidemiology Unit, Oxford, UK.
Each case is given a unique identification number but no patient identifying information is collected on the registry, which avoids the need to obtain consent for data collection. Information is collected about patient characteristics, condition at birth, resuscitation details, daily assessment of severity of encephalopathy assessed on a scale of 0-22 [9], hourly temperature record, clinical complications and outcomes at hospital discharge. Clinicians are asked to obtain a magnetic resonance image (MRI) before the infant is discharged and are informed that they will be contacted when the child reaches 2 years to obtain standardised information on clinical outcome. The definitions of the terms used in the data forms are given in the Appendix.

Since this was an observational study, data analysis was limited to descriptive analysis only. We used SPSS (release 12.0.1) to enter and manage data and STATA (release 9.2) for analysis. Demographic factors and clinical characteristics were summarised with counts (percentages) for categorical variables, mean (standard deviation [SD]) for normally distributed continuous variables, or median (interquartile or entire range) for other continuous variables. We restricted the analysis of time within the optimal range when cooling, to the period from 6 hours to 72 hours.

Results

120 infants from 28 hospitals that participated in the TOBY trial in the UK were reported to the registry from December 2006 to February 2008 (Figure 1). Registered infants were born at median (IQR) 40 weeks’ gestation (38-41), weighing median (IQR) 3287 (2895-3710) grams at birth (Table 1). In five infants conditions other than hypoxic ischaemic encephalopathy were subsequently diagnosed: One had a chromosomal disorder, one an undiagnosed neuromuscular disorder, two infants had early onset group B streptococcal meningitis and one had group B streptococcal septicaemia diagnosed on day 3.

Before cooling was started clinical seizures were reported in 74/110 (67%) of the infants but were noted on aEEG in only 33/115 (29%) infants. 44/82 (53.6%) infants had a severely suppressed aEEG, 23/82 (28%) a moderately suppressed aEEG and 15/82 (18%) a normal or mildly suppressed aEEG on initial recording. The age when cooling was started was available for 114 infants. Cooling was started at median 3 h 54 min (IQR 2 h, 5 h 32 min) after birth; it was started within 2 hours of birth in 31 infants (27%), after 2 to 4 hours in 31 infants (27%), after 4 to 6 hours in 31 infants (27%) and after 6 to 8 hours in 15 infants (13%) and after 8 to 12 hours after birth in 6 infants (0.6%), (Figure 2). Three of the infants received selective head cooling using the Cool Care head cooling system (Olympic Medical, Seattle, Washington, USA); three were treated with the CritiCool servo controlled whole body cooling system (CritiCool, MTRE, Charter Kontron, UK); and the remaining infants were treated with the Tecotherm whole body cooling equipment (Tecotherm, Inspiration Healthcare, UK). The mean (SD) rectal temperature from 6 to 72 hours of the period of cooling was available for 117 infants and was 33.57 °C (0.51 °C), (Figure 3), and the temperature profiles for two individuals treated with a manually controlled and servo controlled device are shown in Figure 4. The daily encephalopathy score progressively fell during the first 4 days after birth: median (IQR) 11 (6, 15), 9.7 (5, 14), 8 (5, 13) and 7 (2, 12) on days 1-4 after birth (Figure 5). 51% of the infants
established oral feeding before discharge or transfer from the treating hospital at a median of 9 (4-24) days. 26% of the infants died.

MRI was performed in 71/120 study infants (60%) but reports were unavailable for 18 infants. MRI findings could be classified as normal or consistent with mild hypoxic ischaemic injury in 30 infants, and consistent with moderate or severe hypoxic ischaemic injury in the other 23 infants. Additional findings were: middle cerebral artery infarction in one infant; white matter cysts in two infants; diffuse white matter injury in one infant; and two infants had extensive cerebral, subdural and subgaleal haemorrhage, both following traumatic deliveries. One infant had a haemorrhagic cavity in the left frontal lobe and one infant a small subgaleal haemorrhage. One other infant born by forceps assisted delivery following a failed ventouse extraction and who did not undergo an MRI, had a large subgaleal haemorrhage and skull fracture noted at autopsy.

Table 2-3 lists the clinical complications recorded during the cooling period and at discharge; none was considered related to therapeutic hypothermia by the treating physicians.

Discussion

These data suggest that therapeutic moderate hypothermia can be carried out safely and effectively in clinical practice: the desired rectal temperature was achieved and although clinical complications were often recorded they were not apparently related to treatment with hypothermia. However, all the treating centres had participated in the TOBY trial and were familiar with the intervention and study protocol; therefore it remains uncertain whether these findings will apply to centres that are newly introducing therapeutic hypothermia into clinical practice. It is still important that centres intending to introduce therapeutic hypothermia ensure that medical and nursing staff are familiar with the published protocols such as that produced by the UK TOBY Cooling Register and receive appropriate training in the use of the cooling equipment.

Although the randomised controlled trials so far have not reported significant complications with moderate hypothermia in newborns, one of the chief aims of a phase 4 study such as this is to identify complications that may be associated with the introduction of the new intervention into routine clinical practice. Many of the clinical complications reported in this study could be due to asphyxia or a cause other than moderate hypothermia. A coagulopathy commonly occurs following asphyxia and may be worsened by hypothermia.[3,10] In this study it was observed in several infants, especially in the first 24 hours after birth (Table 2), but it was not considered by the clinicians to have caused significant bleeding. Three cases of severe intracranial, subdural or subgaleal haemorrhage were reported, all following traumatic ventouse extraction, and associated with other injuries. Three infants suffered from pulmonary haemorrhage but the coagulation tests were normal. All three infants were receiving mechanical ventilation and it is likely that the pulmonary haemorrhage was due to cardiac dysfunction associated with asphyxia. Hypothermia causes prolongation of the QT interval which potentially may induce arrhythmias, especially following inadvertent excessive hypothermia.[11] Sinus bradycardia is the most common electrocardiographic observation in infants treated with moderate
A small number of infants developed an arrhythmia during cooling (Table 2). The type of arrhythmia was not described on the case record forms but was most likely a sinus bradycardia since no intervention was required in any case. Pulmonary hypertension is a further possible complication of therapeutic hypothermia. Seven infants were reported to develop pulmonary hypertension; meconium aspiration syndrome was also reported in four of these cases. Infection, especially pneumonia, has been reported to occur more commonly in adults treated with moderate hypothermia. In our study of 120 infants only one infant developed pneumonia and a further three infants had late onset sepsis. It seems unlikely therefore that therapeutic hypothermia in newborns greatly increases the risk of sepsis or pneumonia. Two of the 120 infants developed necrotizing enterocolitis; both infants survived. Perinatal asphyxia is a recognised risk factor for necrotizing enterocolitis in full term infants. One of the two infants also had hypotension and the other a coagulopathy; both complications are also risk factors for necrotizing enterocolitis. Therapeutic hypothermia was not associated with necrotizing enterocolitis in the randomised trials, and it seems unlikely therefore that treatment with hypothermia contributed to the condition in these two infants. Ten infants were wrongly reported as having a major cerebral anomaly, which was pre-defined as evidence of parenchymal haemorrhage as determined by ultrasound, ventricular dilatation (defined as >97th centile for gestational age) or the presence of porencephalic cysts or cystic leukomalacia. In fact none of these infants had such findings or evidence of congenital abnormalities on cranial ultrasound or MRI and therefore these data are not included in table 3.

Experimental evidence suggests that the interval from termination of the hypoxic ischaemic insult to initiation of therapeutic hypothermia influences the neuroprotective response. In the two large randomised controlled trials of therapeutic hypothermia in newborns, cooling was initiated at approximately 4.5 hours after birth, mainly because of the need to obtain parental consent. The median age at initiation of cooling for the infants notified to the registry was earlier than in the randomised trials and was within 4 hours after birth in 54% of the infants. However, some infants were cooled after 6 hours from birth, when any neuroprotective benefit from hypothermia may be diminished and it is important that clinicians develop local arrangements to reduce delay in initiating treatment.

Temperature control during the period of cooling was excellent in the study: the mean rectal temperature for the infants treated with whole body cooling was on target (33.57 ± 0.5 °C) although almost all infants were treated using a manually controlled cooling device adjusted by the carer according to changes in the infant’s rectal temperature (Tecotherm, Inspiration Healthcare, UK). The three infants receiving whole body cooling with the CritiCool servo-controlled device, which uses a cooling jacket wrapped around the body rather than a blanket or mattress, achieved a stable temperature control (Figure 4), unlike in the American National Institutes for Health cooling trial, where the chosen servo-controlled device required the addition of an adult sized blanket to the system to achieve a steady temperature control. Just three infants were treated with a selective head cooling system, which in the UK has only recently become commercially available.

It is usually stated that following asphyxia, neonatal encephalopathy worsens over the first 48-72 hours after birth before gradually improving. This deterioration is
presumed to be due to evolving pathophysiological processes that culminate in secondary energy failure and delayed cell death, which follow a similar time course. It is interesting therefore that this pattern of progression of encephalopathy was not observed in this study: encephalopathy was most severe during the first 24 hours and gradually improved subsequently (Figure 5). The proportion of infants in the study who died was similar to that reported in the randomised trials of therapeutic hypothermia, suggesting that the study infants suffered a similar severity of asphyxia. Study infants had a similar encephalopathy score at 24 hours as the abnormal outcome group reported by Thompson et al.[9] However, whereas the encephalopathy score in the abnormal outcome group reported by Thompson subsequently worsened, in the study infants the encephalopathy score reduced over the next 3 days and approximated to that of the normal outcome group reported in Thompson’s study (Figure 4). In experimental studies moderate hypothermia has been shown to prevent the onset of secondary energy failure, secondary cytotoxic oedema and increase in epileptic activity and apoptosis [20-24]; we hypothesise that treatment with moderate hypothermia may have altered the processes leading to secondary energy failure and delayed cell death thus preventing a worsening of the encephalopathy.

In conclusion, this study shows that in the UK, therapeutic hypothermia is increasingly being provided following completion of enrolment of the TOBY whole body hypothermia study; treated infants have a similar severity of asphyxia as those reported by the randomised trials of moderate hypothermia; target body temperature was achieved successfully; and the clinical complications observed could mostly be attributed to asphyxia or other conditions. The National Institute for Clinical Excellence is currently assessing treatment with moderate hypothermia in newborns following asphyxia, but it is important that even if therapeutic hypothermia became the standard of care, surveillance of its use in clinical practice is continued, so as to identify complications that may arise when therapeutic hypothermia is used more widely and newly introduced into neonatal units.

Steering group members:

Acknowledgements
The following centres have provided the data used for this paper [in order of number of cases reported]: Professor Marianne Thoresen and Dr James Tooley, St Michaels Hospital Bristol [13]; Dr Andrew Currie and Marie Hubbard, Leicester Royal Infirmary [12]; Professor Andrew Whitelaw, Southmead Hospital [10]; Dr Denis Azzopardi and Professor David Edwards, Queen Charlottes and Chelsea Hospital [9]; Professor Michael Weindling and Andrew Burke, Liverpool Women’s Hospital [8]; Professor Neil Marlow and Tim Styche, Queen’s Medical Centre Nottingham [8]; Dr Phil Amess, Royal Sussex County Hospital Brighton [8]; Dr Shobha Cherian, University Hospital Wales Cardiff [8]; Dr Elia Maalouf and Claudia Harris, Homerton Hospital [7]; Dr Julian Eason, Derriford Hospital Plymouth [5]; Dr Michael Smith, Jessop Wing Sheffield [5]; Dr Paul Clarke, Norfolk and Norwich University Hospital [4]; Dr Sarah Skinner and Yvonne Millar, Luton & Dunstable Hospital [3]; Dr Bov Jani and Karina Vandertak, Medway Maritime Hospital [3]; Dr Janet Berrington,
Royal Victoria Infirmary Newcastle [3]; Dr Simon Mitchell and Dr Ruth Gottstein, St Marys Hospital Manchester [3]; Dr Lesley Jackson, Princess Royal Maternity Hospital Glasgow [2]; Dr Jean Matthes, Singleton Hospital [2]; Dr Stephen Rose and Charmaine Mabor, Birmingham Heartlands Hospital [1]; Dr Sue Chatfield, Bradford Royal Infirmary [1]; Professor Sunil Sinha and Jan Gavey, James Cook University Hospital [1]; Dr Baby Kumararatne and Lyndola Greig, New Cross Hospital [1]; Dr Paul Munyard, Royal Cornwall Hospital Truro [1]; Professor Henry Halliday and Dr David Sweet, Royal Jubilee Maternity Hospital Belfast [1]; Dr Nikki Robertson and Dr Sudhin Thayyil, University College Hospital London [1]

Financial Support
This paper reports on an independent study which is part-funded by the Policy Research Programme in the Department of Health. The views expressed are not necessarily those of the Department.

The UK TOBY Cooling Register is currently administered as part of the MRC funded TOBY Study (Whole body cooling as a treatment for perinatal asphyxial encephalopathy)

Statement of competing interests

None

Copyright license statement

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in Archives of Disease in Childhood editions and any other BMJPGL products to exploit all subsidiary rights, as set out in our licence
<table>
<thead>
<tr>
<th>Infants included in the study, N=120</th>
<th>Median</th>
<th>Range</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (grams)</td>
<td>3287</td>
<td>1790-5200</td>
<td>2895, 3710</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>40</td>
<td>34-44</td>
<td>38, 41</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>35</td>
<td>32-37.7</td>
<td>33.8, 35.8</td>
</tr>
<tr>
<td>Time to first gasp (min)</td>
<td>7</td>
<td>0-60</td>
<td>3, 14.5</td>
</tr>
<tr>
<td>Apgar at 5 min</td>
<td>3</td>
<td>0-8</td>
<td>1, 4</td>
</tr>
<tr>
<td>Apgar at 10 min</td>
<td>4</td>
<td>0-10</td>
<td>2, 6</td>
</tr>
<tr>
<td>First pH</td>
<td>6.85</td>
<td>6.54-7.48</td>
<td>6.7, 7</td>
</tr>
<tr>
<td>First BE</td>
<td>-19.6</td>
<td>1.4 / -30</td>
<td>-23.4, -15.3</td>
</tr>
</tbody>
</table>
Table 2

Proportion of infants with complications during the first 4 days after birth

<table>
<thead>
<tr>
<th></th>
<th>Day</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>90 (75%)</td>
<td>59 (49.2%)</td>
<td>40 (33.3%)</td>
<td>28 (23.3%)</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>41 (34.2%)</td>
<td>33 (27.5%)</td>
<td>22 (18.5%)</td>
<td>11 (9.2%)</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>20 (16.7%)</td>
<td>16 (13.3%)</td>
<td>15 (12.5%)</td>
<td>11 (9.2%)</td>
<td></td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>32 (26.7%)</td>
<td>22 (18.3%)</td>
<td>15 (12.5%)</td>
<td>7 (5.8%)</td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>28 (23.3%)</td>
<td>13 (10.8%)</td>
<td>5 (4.2%)</td>
<td>1 (0.8%)</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>3 (2.5%)</td>
<td>2 (1.7%)</td>
<td>3 (2.5%)</td>
<td>1 (0.8%)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>99 (82.5%)</td>
<td>75 (62.5%)</td>
<td>59 (49.2%)</td>
<td>40 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>support</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Definitions for all items may be found in the Appendix and the Clinician’s Handbook (www.npeu.ox.ac.uk/tobyregister)
Table 3  
Diagnoses recorded during admission

<table>
<thead>
<tr>
<th>Diagnoses recorded during admission (total number of infants =120)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meconium aspiration</td>
<td>13 (10.8%)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>7* (5.8%)</td>
</tr>
<tr>
<td>Air leak</td>
<td>4* (3.3%)</td>
</tr>
<tr>
<td>Late sepsis</td>
<td>4 (3.3%)</td>
</tr>
<tr>
<td>Pulmonary haemorrhage</td>
<td>3 (2.5%)</td>
</tr>
<tr>
<td>NEC</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (0.8%)</td>
</tr>
</tbody>
</table>

*4 of the infants with pulmonary hypertension and 2 of those with air leak also had meconium aspiration

Definitions for all items may be found in the Appendix and in the Clinician’s Handbook (www.npeu.ox.ac.uk/tobyregister)
Figure 1  
UK TOBY Cooling Register Registrations  
A: Number of registrations  
B: Centres registering babies

Figure 2  
Age when cooling started

Figure 3  
Hourly rectal temperature from 117 infants treated with moderate whole body hypothermia

Figure 4  
A: Hourly rectal temperature from an infant treated with manually controlled cooling mattress  
B: Hourly rectal temperature from an infant treated with servo controlled cooling wrap

Figure 5  
Mean encephalopathy score during the first 4 days after birth, compared with mean scores reported by Thompson et al [9]
References


Figure 1

UK TOBY Cooling Register Registrations

Figure 1A

Figure 1B
Figure 2

Age when cooling started showing median and interquartile ranges

114 cases
Figure 3
Hourly rectal temperature from 117 infants treated with moderate whole body hypothermia.
Figure 4
A: Hourly rectal temperature from an infant treated with manually controlled cooling mattress
B: Hourly rectal temperature from an infant treated with servo controlled cooling jacket
Figure 5
Mean encephalopathy score during the first 4 days after birth, compared with mean scores reported by Thompson et al [9]
Appendix

Definitions Of Terms In Data Collection Form

**Arrhythmia**
Sinus bradycardia below 80 bpm and other arrhythmias identified on ECG

**Coagulopathy**
Any disorder requiring treatment in order to maintain or recover normal haemostasis

**Delivery complications**
This can include prolapsed cord, abruption, shoulder dystocia, ruptured uterus, head entrapment etc.

**Diabetes**
Existing diagnosis of diabetes, or gestational diabetes requiring treatment.

**EDD**
Use the best estimate (dates or ultrasound) based on a 40 week gestation.

**Head entrapment**
Severely delayed second stage during breech delivery, vaginally or at caesarean section

**Hypoglycaemia (infant)**
Blood glucose below 2.6 mmol/litre

**Hypotension (infant)**
Persistent mean blood pressure of < 40 mmHg

**Illicit drug use**
Recorded drug or alcohol use that may lead to social, occupational, psychological, or physical problems.

**Late onset sepsis (>72 hours after birth) confirmed by blood or CSF culture.**
Any evidence of infection requiring antibiotic therapy which is confirmed on culture.

**Major cerebral anomaly**
Including evidence of parenchymal haemorrhage as determined by ultrasound, ventricular dilatation (defined as >97th centile for gestational age) or the presence of porencephalic cysts or cystic leukomalacia.

**Maternal seizure**
Convulsions due to eclampsia or other causes, e.g. epilepsy

**Meconium aspiration syndrome**
The presence of meconium stained liquor at birth and severe respiratory distress within 1 hour of birth and compatible X-ray changes.

**Necrotising enterocolitis**
Infants with abdominal distension, gastric aspirate and/or blood in stools together with abdominal X-ray showing bowel oedema, pneumatosis or pneumoperitoneum, i.e. Bell’s staging 2 or 3.

**Placental abruption**
Separation of a normally situated placenta after 28th week of pregnancy.

**Placenta Praevia**
Placenta partially or wholly covering the internal cervical os.

**Pre-eclampsia**
Hypertension greater than 140/90 mmHg, during pregnancy.

**Pregnancy complications**
This can include: pre-eclampsia, maternal seizure, thyroid disorder, diabetes, placenta praevia, known illicit drug use etc.

**Prolapsed cord**
Cord presentation following rupture of membranes.

**Pulmonary airleak**
Any radiologically confirmed airleak serious enough to affect management (including pneumothorax, pulmonary interstitial emphysema, pneumopericardium, pneumoperitoneum and pneumomediastinum).

**Pulmonary haemorrhage**
Copious bloody secretions with clinical deterioration requiring change(s) in ventilatory management.

**Pulmonary hypertension**
Severe hypoxaemia disproportionate to the severity of lung disease and evidence of a right to left shunt.

**Respiratory support**
Use of mechanical ventilation, CPAP or supplementary oxygen.

**Ruptured uterus**
Spontaneous full-thickness tear in the uterine wall due to existing scar, obstructed labour, etc.

**Seizures**
Clinical or subclinical, identified on CFM /EEG.

**Sepsis**
Any evidence of infection requiring antibiotic therapy which is confirmed on culture.

**Shoulder dystocia**
Failure of the shoulders to rotate into the anteroposterior diameter of the pelvis following delivery of the head, resulting in a substantial delay in delivery.

**Maternal Thyroid disorder**
Thyroid dysfunction requiring treatment during pregnancy.