Neonatal Therapeutic Hypothermia in Ireland

Annual Report | 2018

Aggregate Report 2016–2018

National Neonatal Therapeutic Hypothermia Development Project

Prepared by the National Clinical Programme for Paediatrics and Neonatology, the National Women and Infants Health Programme and the National Perinatal Epidemiology Centre

HSE

NATIONAL PERINATAL EPIDEMIOLOGY CENTRE

National Women & Infants Health Programme

National Clinical & Integrated Care Programmes

Person-centred, co-ordinated care

Citation for this report:

Meaney S, McGinley J, Corcoran P, McKenna P, Filan P, Greene RA, Murphy J on behalf of Neonatal Therapeutic Hypothermia Working Group. Neonatal Therapeutic Hypothermia in Ireland, Annual Report 2018. Cork: National Perinatal Epidemiology Centre, 2020.

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List of Acronyms and Abbreviations

aEEG – Amplitude Integrated Electroencephalogram
APGAR – Appearance, Pulse, Grimace, Activity, Respiration
ARM – Artificial Rupture of Membranes
BMI – Body Mass Index
CTG – Cardiotocograph
EDD – Estimated Due Date
FVM – Fetal Vascular Malperfusion
FGR – Fetal Growth Restriction
GROW – Gestation Related Optimal Weight
HIE – Hypoxic Ischaemic Encephalopathy
MDT – Multi-Disciplinary Team
MRI – Magnetic Resonance Imaging
MVM – Maternal Vascular Malperfusion
NCPPN – National Clinical Programme for Paediatrics and Neonatology
NE – Neonatal Encephalopathy
NG – Nasogastric Tube
NICU/SCBU – Neonatal Intensive Care Unit/ Special Care Baby Unit
NNT – Number Needed to Treat
NNTP – National Neonatal Transport Programme
NPEC – National Perinatal Epidemiology Centre
NWIHP – National Women and Infants Health Programme
SHO – Senior House Officer
TH – Therapeutic Hypothermia

Foreword

This is the Neonatal Therapeutic Hypothermia in Ireland report for 2018. It is a collaborative initiative undertaken by the National Clinical Programme for Paediatrics and Neonatology (NCPPN), the National Perinatal Epidemiology Centre (NPEC) and the National Women and Infants Health Programme (NWIHP). The Therapeutic Hypothermia steering committee has overseen the governance of the project.

We thank all 19 maternity sites in Ireland for their willingness to contribute to this project and their help with the data collection process. This report would not have been possible without the valued support of each hospital and its staff.

Work continues to progress in the development of the Electronic-Register. It is anticipated that the E-Register will be in operation from January 2020, whereby all 2019 data will be collected using the E-Register. Data will be collected using a refined dataset, on the E-Register, compared to that of the current data collection tool. National data collected on the E-Register will continue to be analysed from a number of perspectives; antenatal, labour management, resuscitation of the neonate and the overall clinical management of this cohort. The NPEC has been instrumental in progressing this work.

From 2020 onwards, we will begin the collection of national data on the formal developmental assessment carried out at two years of age. It has been previously advocated for and recommended in the 2016/2017 TH report that all babies who require treatment should be followed up for their formal developmental assessment. A data set has been designed using a Multi-Disciplinary Team approach to extract pertinent data on the developmental data of these infants. Once again in our request to gain this information hospital sites have been very receptive and are demonstrating a commitment to assist the Therapeutic Hypothermia steering committee on this important endeavour.

This report serves as a valuable resource to Medical, Midwifery and Nursing staff who are striving to make quality changes in the services we deliver to mothers and their babies. The recently formed National Neonatal Encephalopathy Action Group reflects this. The group comprises representatives from the Department of Health, the States Claims Agency, and the Health Service Executive, the NWIHP, the NPEC, Clinical Leads and patient advocates. The group acknowledges the long-lasting consequences caused by Neonatal Encephalopathy. The group aims to reduce avoidable instances of Neonatal Encephalopathy through the identification of known causes and risk factors and plans to drive initiatives to eliminate or mitigate them. The aspiration is a reduction in cases requiring therapeutic hypothermia intervention in our national maternity units/ hospitals. This working group has been endorsed by the Minister for Health Mr Simon Harris.

We look forward to working with all stakeholders in 2020.

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Executive Summary

Therapeutic Hypothermia (TH) has been found to be protective in those infants presenting with moderate or severe Neonatal Encephalopathy (NE) by inhibiting various events in the cascade of this injury. The effectiveness of TH in preventing brain injury to hypoxic infants is a welcomed development, whilst the number need to treat remains at 7 (only 1 in 7 will benefit from therapy), major Randomised Clinical Trials (RCT) involving induced neonatal hypothermia have demonstrated a reduction in death and disability. The RCTs have shown improved outcomes for this cohort of babies if they are cooled within 6 hours of birth to a targeted core temperature of between 33°C - 34°C for a duration of 72 hours. Rewarming to normothermic temperature occurs over a 12-hour period. TH has been considered the standard of care since 2009 for infants with moderate and severe NE.

This Report, pertaining to Neonatal Therapeutic Hypothermia (TH) serves two purposes. Firstly, it documents the maternal and infant clinical data for the cases requiring TH which occurred in Ireland in 2018. Secondly, it provides the composite data for all TH cases in the three-year period 2016-2018. The strength of the report is that it is based on a geographically defined region, namely the Republic of Ireland. All cases of TH have been captured. This makes the findings representative and eliminates selection bias. In 2018, 60% of TH infants who received TH were born in one of the four tertiary maternity hospitals and 40% of TH infants were born in one of the other 15 maternity hospitals. This is consistent with the pattern observed from the composite data from 2016-2018. In 2018 there were 69 TH cases and there were 61,016 births nationally. The incidence rate was 1.07 per 1,000 births; which suggests that one in one in every 884 infants born required TH. The composite data for 2016-2018 was 209 TH cases and there were 186,966 births nationally in this timeframe amounting to an overall incidence of 1.11 per 1,000 births (one in every 899 births required TH).

The annual incidence of TH was consistent during 2016-2018.

- A Maternity unit with 2,700 births would expect to encounter three cases annually.
- A Maternity unit with 5,400 births would have six cases annually.
- A Maternity unit with 8,100 births would anticipate nine cases annually.

These figures provide units with a guide on how to benchmark their activity in relation to the annual rate of TH cases.

In 2018 there were seven deaths among the 69 infants who recieved TH, a mortality rate of 10%. The composite number for 2016-2018 was 24 infants' deaths, which equates to a mortality rate of 12%. NE requiring TH is the commonest cause of death in normally formed term new-born infants. A unit with 2,700 births would expect to encounter a death from NE once every three years, a unit with 5,400 births once every 18 months whereas a unit with 8,100 births will have one TH death per year.

In 2018, 18% of TH infants were postnatally found to be small for dates. In the composite data 2016-2018 19% were born small for dates. In 2018 a diagnosis of Intrauterine Growth Restriction (IUGR) was made in 7% of the TH cases. The composite 2016-2018 data reported a diagnosis of IUGR in 8% of TH cases. These findings demonstrate that poor fetal growth is a factor in some TH cases. Currently less than half are being identified antenatally. The diagnostic criterion for IUGR needs to be reviewed and the diagnostic rate improved.

In 2018, 57% of TH cases were born to primiparous women and 43% born to multiparous women. The composite data 2016/17/18 shows that 59% of TH cases were born to primiparous mothers and 41% TH cases were born to multiparous women. These figures show that the incidence of a baby requiring TH in primiparous women is 1:577 and in multiparous women it is 1:1347. This represents a 2.3 times increased risk in first time mothers. Recognition of this finding should be appreciated by all units and translated into labour ward acuity management.

In 2018, 9% of TH cases were associated with assisted reproductive treatment (ART), in which 83% of these cases had IVF. As to be expected given this cohort, in terms of parity the majority of women were nulliparous (83%). The composite 2016-2018 data found that 7% TH cases had fertility treatment. It is estimated that 2.5% of births in Ireland are from ART pregnancies. This would mean that over the same three year period (2016-2018) 4,674 births were from ART resulting in the TH incidence in this group of 1:311 which represents a three-fold increased risk.

In 2018, 9% of TH cases were associated with an endocrine disorder in the mother during pregnancy which is consistent with the findings from the composite data 2016-2018 at 8%. This finding supports the importance that mothers with these disorders need frequent thyroid function tests and dosage adjustment during the pregnancy in perinatal medicine clinics or endocrinology clinics.

In 2018, 48% of mothers of infants treated with TH laboured spontaneously, 33% were induced and 19% were never in labour. The composite data for 2016-2018 was: Spontaneous labour 49% cases Induction 34.0% cases and Never in labour 17.2% cases. The significant number of TH cases in mothers who were never in labour needs further investigation.

In 2018, 4% of the TH cases were associated with pyrexia in labour. The corresponding findings for 2016 and 2017 were 22% of cases and 16% of cases. This improvement may in part be due to improved knowledge around sepsis recognition and treatment.

In 2018, 4% of TH cases were associated with a uterine rupture. In the three years 2016-2018 4% of TH cases occurred secondary to a uterine rupture. Previous caesarean section and uterine rupture in the subsequent labour is a recognised entity; the woman should be clearly counselled about these risks to ensure informed choice to undertake labour following a previous caesarean section.

Caesarean Section continues to be a common mode of delivery; accounting for almost half of the 209 infants 45% over the three year period 2016-2018. Of these deliveries, 3% were planned Caesarean Sections. Over the three year period a slightly higher proportion of women had a Caesarean Section after the onset the labour.

- 49% of mothers had a Caesarean Section pre-labour
- 51% of mothers had a Caesarean section after the onset of labour

Over the three year period, 34% of deliveries required instrumental assistance, and of these women 26% required both forceps and ventouse to deliver. The median interval from time of decision to delivery for instrumental delivery was 16 minutes.

The umbilical cord pH measures the degree of acidosis caused by hypoxia. The normal value is 7.25. A value less than 7.0 is indicative of severe hypoxia, and readings between 7.0 and 7.25 are in keeping with moderate hypoxia. In 2018 Cord pH was recorded for 63 of the 69 TH infants, and 59% of these infants had a Cord pH <7.0. The composite data 2016-2018 found that 63% infants had a Cord pH <7.0. It is important that the umbilical cord blood gases are measured in all TH cases.

In 2018, 60% of infants required tracheal intubation during resuscitation. One in three infants needed chest compressions and 16% were administered Adrenaline. These findings are consistent across the three year period, demonstrating that two-thirds of TH infants require intensive resuscitation at birth. It further illustrates the necessity that all maternity units have a fully trained team capable of performing neonatal resuscitation on a 24 hours basis.

In 2018, 81% of TH infants achieved the target temperature range 33°C -34°C within six hours of birth. The composite data 2016-2018 shows that 82% TH infants achieved the optimum temperature range within six hours of birth. It is important to note that the process of therapeutic hypothermia

had begun in all but 1% of the cases. The timing of the decision about when to start therapeutic hypothermia is an important factor in determining whether the target is reached within six hours.

In 2018, the severity of encephalopathy among the affected infants was severe 27%, moderate 57%, and mild 16%.The composite data 2016-2018 was severe 29%, moderate 58% and mild 14%. Over three-quarters of the infants are moderately/severely impaired in the early hours and days after birth. The findings confirm that this is a critically ill cohort of infants.

The Sarnat score is a clinical tool that quantifies the neurological status of an infant with NE. In keeping with 2016/2017, documentation of the infant's Sarnat Score remains sub-optimal in 2018. The level of consciousness is undocumented in 19% of cases on day 1, 40% of cases on day 2 and 52% of cases on day 3. The pattern is similar for the other components of the Sarnat score. For example, the pupil responses are undocumented in 41% of cases on day 1, 69% of cases on day 2, and 70% cases on day 3. Daily documentation of the Sarnat score during the days of TH is important and should be adopted as an essential standard of care in all units providing TH.

In 2018, 15% of infants had a clinical seizure on day 1 and 13% of infants had a clinical seizure on day 2. No infant had a clinical seizure documented on day 3. Electrographic seizures were recorded on aEEG and were reported for 20% of infants on day 1, 15% on day 2 and 6% on day 3. The composite 2016/17/18 data illustrate that 24% of infants had a seizure on day 1, 20% infants on day 2, and 13% on day 3. The electrographic seizure rate was 31% on day 1, 20% on day 2 and 9% on day 3. The higher electrographic seizure identified on aEEG rate compared to the clinical seizure rate confirms that many seizures are sub-clinical. These findings underscore the importance of aEEG/EEG monitoring of all TH infants.

In 2018, MRI findings were available for 85% of TH infants of which 74% were normal. The proportion of cases which were abnormal were slightly lower in 2018 (26%) compared to the findings from the three years of data from 2016-2018 where 32% of cases were abnormal.

In 2018, the placenta was retained for histological analysis in three-quarters of TH cases (77%). Placentas of infants with NE that underwent TH, showed over a 6-fold increase in fetal vascular malperfusion (29%) and a similar increase in maternal vascular malperfusion (17%) compared to the general population (5% and 3% respectively).

Analysis of the data provides information on how the management of TH cases could be improved. It identifies risk factors for the development of NE. As the collection of TH cases gets larger, it may be possible to quantify these risks in a manner that can influence clinical practice. The process of reducing the incidence of NE requiring TH treatment will be an aggregation of marginal gains. While sentinel events may be difficult to predict, improved risk assessment (maternal disease) and better risk identification and stratification (IUGR, male fetus, primigravida woman, induction of labour) will identify at risk babies including sentinel event risks. Clear, agreed national care pathways and the standardisation of multidisciplinary training should achieve improvements and lead to increasing positive outcomes for infants including a reduction in NE. Furthermore, the findings will enable us to contribute to the international consensus and expertise in the development of evidence-based quality improvements initiatives.

Key Messages

- During 2016-2018, 209 NE infants were treated with TH, indicating that one in 900 infants born in Ireland are treated with TH. Consistent data collection, analysis and action is needed to reduce the incidence of NE.

- NE is a significant cause of enduring morbidity and is the largest cause of mortality in normally formed term infants. The total survival rate for infants in the TH cohort for the time period 2016-2018 was 89% with 24 infant deaths.

- The antenatal detection of intrauterine growth restriction is important. During the 3-year period 18% of infants who underwent TH were small for dates (<10th centile) for their gestation at birth but this was rarely (4%) detected at birth.

- The standardisation of the interpretation of CTG and subsequent clinical response should be encouraged.

- The diagnosis and appropriate management of maternal pyrexia, shoulder dystocia and uterine rupture are recurrent challenges.

- There should be a heightened awareness of antecedent obstetric risk factors including primiagravida mothers, endocrine disorders, assisted reproduction and previous caesarean section.

- Over the three year period, 82% of infants achieved optimum core temperature range within six hours of birth. The cooling candidacy checklist is an effective, reliable tool in the identification of infants requiring TH treatment with moderate and severe encephalopathy. Through the maintenance of an annual register evolving evidence of therapeutic creep will be captured.

- In total 40% of TH infants were born in a peripheral hospital and required transfer to one of the four tertiary centres that administer TH. The National Neonatal Transport Programme (NNTP) plays an important role in the retrieval of NE infants from peripheral hospitals.

- Placental examination was undertaken in 54% of NE cases. The commonest abnormalities were chorioamnionitis (30%) and maternal vascular malperfusion (MVM) (27%). In many cases the placental findings provides an explanation of the cause of NE.

Recommendations

1. **Enhanced awareness of the risk factors for NE (first time mothers, induced mothers, IUGR etc.) through standardisation of care pathways and multidisciplinary training among front line staff is needed.**
   The findings from this report provide additional information to help improve the understanding of the risk factors associated with NE. Improving knowledge through the introduction of training programmes and tools for front line staff to help develop strategies for minimising delays and initiating interventions if appropriate.

2. **Appropriate counselling for informed consent and standardised care pathways for labour management of mothers with previous caesarean sections should be introduced at a national level.**
   Caesarean section has become an increasingly common method of delivery, with one in three women being delivered by caesarean in the Republic of Ireland per annum. When women, who have had a previous caesarean section delivery, are being counselled either for VBAC or repeat elective caesarean section they must be provided with comprehensive standardised information about the associated risks and adverse outcomes and document the discussion.

3. **A National standardised assessment for the diagnosis of fetal growth restriction (FGR) is warranted and should include multidisciplinary training.**
   International evidence illustrates that suboptimal fetal growth is linked to both short and long-term adverse outcomes. Findings from this report illustrates there was some evidence of poor fetal growth with almost 20% of the infants born below the 10th centile. The establishment of a multidisciplinary working group to address a national standardised approach for the detection of FGR is warranted.

4. **Multidisciplinary skills and drills training to deal with obstetric sentinel events are required.**
   Sentinel events; such as uterine rupture, placental abruption and shoulder dystocia, are acute events that are associated with NE. Training, with 1-2 yearly re-certifications, on the management of major obstetric situations is required for all levels.

5. **Front line staff responsible for CTG interpretation must undertake annual training.**
   Fetal monitoring, including continuous cardiotocography (CTG), requires expert knowledge and interpretation and should be undertaken by skilled front line staff. Anonymised CTG reports should be submitted to the NPEC as part of this audit to facilitate interpretation from an expert panel of Midwives and Obstetricians.

6. **An Umbilical cord pH measurement and the retention of the placenta for histopathology assessment are required in each case where an infant requires resuscitation and is treated with TH.**
   The findings from this report have indicated that a cord pH measurement was not taken in 13% of cases and placenta histology was not undertaken in 25% of cases where an infant is treated with TH.

7. **The Neonatal Resuscitation Programme (NRP) needs to be a requirement with 2 yearly re-certification for all staff working in birthing areas. This should be implemented with appropriately trained personnel.**
   It is important that trained personal attend these births. A national NRP Coordinator is advocated in order to manage and provide governance for the NRP programme within the 19 maternity units.

8. **All therapeutic hypothermia infants require daily Sarnat grading assessment as a standard of care.**
   The Sarnat grading scale is an internationally recognised classification assessment tool for Neonatal Encephalopathy in the newborn infant. Regular assessment is prudent to determine the progression of encephalopathy, exclude other causes of encephalopathy and provide prognostic information to families. This subsequent 2018 TH report mirrors the findings of the 2016/2017 report in which there is incomplete data for Sarnat scoring on TH day 1,2,3 and upon discharge.

9. **aEEG training required to accurately determine neurophysiological status of infant undergoing TH.**
   Seizures are a common feature of neonatal encephalopathy. aEEG monitoring is important in order to assess the severity of encephalopathy. Training is required for optimal interpretation of the aEEG findings. An aEEG elearning programme is in the final stage of development in collaboration with the Royal College of Physicians (RCPI).

10. **Brain MRIs should be performed between days 5-10 for optimal imaging results.**
    MRI is the modality of choice for assessment of brain injury severity in cases of NE. Timing of the MRI scan is important in the identification of the initial diffusion changes. If there is a delay in undertaking the scan the early findings can be missed because of pseudo normalisation.

11. **Neurodevelopmental follow-up.**
    All TH infants should be followed up to assess their motor, cognitive and speech and language development. Future reports will provide two year follow-up data on Bayley assessment outcomes.

12. **Continuous yearly reviews are needed for TH cases using the electronic register to enhance knowledge and learning.**
    The development of the national e-register in 2020 will facilitate benchmarking against international registries and databases. The register will enable us to evaluate new adjunctive therapies. Furthermore, the maintaining of a yearly register will contribute to a body of evidence which will have the ability to develop risk profiles, standardise clinical practice, inform public health interventions and service planning.

Introduction

The NCPPN in collaboration with NPEC and NWIHP presents its successive report on Neonatal TH in the Republic of Ireland for 2018. We now have three years, 2016-2018, cumulative comprehensive data to determine the current status and outcomes for infants who underwent TH during this time frame.

This report presents the 2018 data alongside the 2016/2017 data for comparative analysis. By laying out the report in this format it is anticipated that patterns and trends will begin to emerge.

Going forward the implementation of the electronic register in 2020 will serve as a much needed platform to inform clinicians of identified maternal and infant trends alongside clinical risk factors which will assist in the development of maternal risk profiles leading to a change in their antenatal and delivery management. Furthermore an e-register will facilitate benchmarking of TH in Ireland against international standards and thus ensure continuous quality improvement.

TH is an evolving treatment and by maintaining a constant record of the data on the e-register, the value of the adjunctive therapies during TH treatment can be accurately assessed with measured outcomes.

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Maternal Characteristics
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SECTION 2
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Methods

Purpose of this report

The primary aim of this report is to present an overview and national statistics on Neonatal Therapeutic Hypothermia in the Republic of Ireland for the year 2018. Therapeutic Hypothermia (TH) is administered in four centres only (National Maternity Hospital, Rotunda, Coombe Women and Infants University Hospital and Cork University Maternity Hospital). All babies born in other local and regional hospitals needing this treatment are transferred to one of these four centres.

The audit will examine the clinical details around each case of Neonatal Therapeutic Hypothermia. This will include the mothers' antenatal details, labour, delivery, resuscitation, neurological assessment, treatment of seizures, the supportive clinical care the examination of the placenta and post mortem, if applicable.

Data Collection

Retrospective reviews of inpatient medical records have been used as a gold standard approach when assessing multiple outcomes and rates of adverse events. Therefore, for the purposes of the National Neonatal Therapeutic Hypothermia Audit, medical records were considered the primary source of information. Data were collected on site in the 19 maternity units/hospitals and neonatal intensive care units or special care baby units (NICU/SCBU) in the Republic of Ireland. The NCPPN and NPEC collected data on all cases of neonatal therapeutic hypothermia in 2018 by taking an active case ascertainment approach.

Processing of the data

Data on all infants who received therapeutic hypothermia were collected on site in the 19 maternity units/hospitals. The data were submitted by paper to the NPEC and were processed in a pseudonymised format. No hospital identifiers were included in the dataset, which means these data cannot be attributed to a specific hospital or to a specific individual.

Missing data

To ensure accuracy of information, missing or incomplete data were sought from the respective maternity hospitals/units by the Therapeutic Hypothermia Co-Ordinator. For analysis purposes, cases with missing data were excluded from calculations. However, the extent of missing data is reported in the results section.

Comparison to National Statistics

Comparisons are made with the most recent publications available, including the Central Statistics Office's Vital Statistics Fourth Quarter and Yearly Summary report as well as from the Healthcare Pricing Office.

Definitions & Terminology

Neonatal Encephalopathy (NE) is a clinical condition in the term infant defined by abnormal neurological behaviour, with the onset occurring at or shortly after birth.

NE is manifested by an abnormal level of consciousness, with or without the presence of seizures and is often accompanied by difficulty initiating and maintaining respirations, depressed tone and depressed reflexes, poor suck and swallow.

NE incidence is estimated as 3.0 per 1000 live births and for HIE is 1.5.[1] NE is graded as mild, moderate or severe using the Sarnat grading system.

A subgroup of infants with NE have been exposed to a hypoxic-ischaemic insult in-utero and therefore they are assigned a diagnosis of Hypoxic-Ischaemic Encephalopathy (HIE). In a proportion of these cases, a sentinel event is identified i.e. placental abruption, uterine rupture etc.

Suggested criteria for an intrapartum hypoxic-ischaemic insult[2] include:

(i) Evidence of metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH < 7 and base deficit ≥ 12 mmol/L).

(ii) Early onset of severe or moderate NE in infants ≥ 34/40.

(iii) A sentinel hypoxic event occuring immediately before or during labour e.g. uterine rupture, placental abruption, cord prolapse etc.

(iv) A sudden and sustained fetal bradycardia or the absence of fetal heart rate variability in the presence of persistent late or persistent variable decelerations on cardiotocography, usually after a hypoxic sentinel event when the pattern was previously normal.

(v) Apgar scores of 0-3 beyond 5 minutes.

(vi) Onset of multisystem involvement within 72 hours of birth.

(vii) Early imaging study showing evidence of acute non-focal cerebral abnormality.

(viii) Exclusion of other identifiable aetiologies e.g. trauma, coagulation disorders, infection or genetic disorders.

TH has been found to be protective in those infants presenting with moderate or severe NE by inhibiting various events in this cascade of HIE injury. Major randomized clinical trials[3-5] involving induced neonatal hypothermia have demonstrated a reduction in death and disability.[6-8] These trials have shown improved outcomes for babies with NE if they are cooled within six hours of birth to a targeted core body temperature of between 33°C to 34°C for a duration of 72 hours. Rewarming to normothermic temperature occurs over a 6-12 hour period. TH is considered to be the standard of care for infants with moderate-to-severe NE who meet inclusion criteria.

The inclusion criteria for TH are:

- ≥ 36 weeks completed gestation with a weight ≥ 1800grams.
- Acidosis (pH<7.0) present in the umbilical cord, or any blood sample taken within 60 minutes of birth.
- Base deficit ≥ -16.0 mmol/L in umbilical cord or any blood sample taken within 60 minutes of birth.
- History of acute perinatal event (such as but not limited to cord prolapse, placental abruption or uterine rupture).
- Apgar score ≤ 5 at 10 minutes or at least 10 minutes of positive-pressure ventilation.
- Evidence of moderate-to-severe encephalopathy, demonstrated by the presence of seizures OR at least one sign in three or more of the six categories shown In the Modified Sarnat Table (see Table 38).

Main Findings

The following analysis is based on 69 infants who underwent neonatal therapeutic hypothermia treatment in 2018.

Maternal Characteristics

Age

The age of mothers whose infants underwent therapeutic hypothermia was known for 68 of the 69 mothers in 2018. The mothers whose infants underwent therapeutic hypothermia ranged in age from teenage years (the youngest being 17 years of age) through to early-forties (the eldest being 42 years of age). Their age distribution broadly reflected that of the population of mothers who gave birth in Ireland in 2016 (Table 1). There was a higher proportion of mothers aged 24 or younger years (14.7%) whose babies were cooled in 2018, than all mothers who gave birth in 2016 (9.6%)[9]. Over half of the population (52.3%)[9] who gave birth in 2016 were aged 25-34 years, whereas a slightly lower proportion of mothers whose infants underwent therapeutic hypothermia between 2016-2018 were in this age group (50.9%).

Table 1: Age distribution of mothers whose infants underwent therapeutic hypothermia in 2016-2018 versus all births in 2016

Age group	TH cases N=63 2016	TH cases N=77 2017	TH cases N=68 2018*	TH cases N=208 2016-2018	All births[9] N=64,133 2016 (%)
<20yrs	1(1.6)	0(0.0)	3(4.4)	4(1.9)	1.7
20-24yrs	8(12.7)	8(10.4)	7(10.3)	23(11.1)	7.9
25-29yrs	9(14.3)	15(19.5)	10(14.7)	34(16.3)	17.3
30-34yrs	23(36.5)	24(31.2)	25(36.8)	72(34.6)	35.0
35-39yrs	18(28.6)	25(32.5)	18(26.5)	61(29.4)	28.6
>40yrs	4(6.3)	5(6.5)	5(7.4)	14(6.7)	6.7

Note: Values are shown as N(%) unless otherwise stated. *Age unknown for one mother.

Ethnicity

Assessment of risk associated with ethnic group is impeded by the absence of national data on ethnicity for the pregnant population in Ireland. The majority of mothers whose infants underwent therapeutic hypothermia in 2018 were of white Irish ethnicity (72.1%, n=49 of 68; missing data for one mother) (Table 2). This is similar to the proportion of white Irish women in the female population aged 15-49 years, enumerated by the National Census 2016. While the numbers involved were small, Irish Traveller, Asian and Black ethnicities were overrepresented in the mothers whose infants underwent therapeutic hypothermia in 2018 (8.8%) compared to 5.3% of the female 15-49-year-old population from the National Census in 2016.

Table 2: Ethnicity of mothers whose infants underwent therapeutic hypothermia in 2016-2018 versus 15-49 year-old female population, 2016

Ethnicity	TH cases N=63 2016	TH cases N=75 2017*	TH cases N=68 2018**	TH cases N=206 2016-2018	15-49 year-old female population, 2016*** (%)
White Irish	53(84.1)	52(69.3)	49(72.1)	154(74.8)	79.2
Irish Traveller	0(0.0)	2(2.7)	1(1.5)	3(1.5)	0.7
Other white background	6(9.5)	14(18.7)	12(17.6)	32(15.5)	13.7
Asian/Asian Irish	4(6.3)	3(4.0)	2(2.9)	9(4.4)	2.9
Black/Black Irish	0(0.0)	4(5.3)	3(4.4)	7(3.4)	1.7
Other/mixed	0(0.0)	0(0.0)	1(1.5)	1(0.4)	1.9

Note: Values are shown as N(%) unless otherwise stated. *Ethnicity unknown for two mothers. **Ethnicity unknown for one mother. ***Population data from the National Census 2016.

Occupation

Table 3 provides a high-level overview of the data provided on mother's occupation, alongside data available for the most comparable occupation categories for mothers of all births in Ireland[9] and for the 15-44 year-old female population from the National Census 2016. Employment status was specified for 95.7% (n=66 of 69) of the mothers for whom data were recorded in 2018 (Table 3). It can be seen that unemployed status was recorded for 16.7% of the mothers whose infants underwent therapeutic hypothermia compared to 4.5% of all mothers and 8.2% of the female population aged 15-44 years. The proportion of mothers engaged in home duties whose infants underwent therapeutic hypothermia (4.5%) was lower than the percentage of all women engaged in home duties who gave birth (20.5%) in 2016 but was similar to the proportion of females aged 15-49 years in the Irish population (10.4%).

Table 3: Occupation at booking of mothers whose infants underwent therapeutic hypothermia in 2016-2018 versus all births in 2016 and 15-44 year-old female population in 2016

Occupation	TH cases N=53 2016*	TH cases N=65 2017**	TH cases N=66 2018***	TH cases N=184 2016-2018	All maternities[9] 2016 (%)	15-44 year-old female population, 2016* (%)
Employed	43(81.1)	48(73.8)	49(74.2)	140(76.1)	73.1	57.8
Unemployed	1(1.9)	10(13.0)	11(16.7)	22(12.0)	4.5	8.2
Home duties	5(1.9)	4(5.2)	3(4.5)	12(6.5)	20.5	10.4
Student	4(7.5)	3(3.9)	3(4.5)	10(5.4)	n/a	21.1
Others not in labour force	0(0.0)	0(0.0)	0(0.0)	0(0.0)	n/a	2.5

Note: *Data not known on employment for 10 mothers **Data not known on employment for 12 mothers ***Data not known on employment for 2 mothers. **Population data from Census 2016.

Body Mass Index

Body Mass Index (BMI) was available for 62 of the 69 women whose infants underwent therapeutic hypothermia in 2018 (Table 4). The pattern of BMI in the mothers was similar to that from the general population who participated in the 2017 Healthy Ireland Survey[10]. The BMI of 32.3% of these mothers was in the obese range (>30.0kgm^{-2}), which is higher than those from the general population.

Table 4: Body mass index of mothers whose infants underwent therapeutic hypothermia in 2016-2018 versus all participants in the Healthy Ireland Survey in 2017

BMI Category (kg/m²)	TH cases N=62 2016*	TH cases N=72 2017**	TH cases N=62 2018**	TH cases N=196 2016-2018	Healthy Ireland Survey 2017 (%)[10]
Underweight (<18.5)	1(1.6)	2(2.8)	0(0.0)	3(1.5)	2
Healthy (18.5-24.9)	22(35.5)	33(45.8)	23(37.1)	78(39.8)	36
Overweight (25.0-29.9)	22(35.5)	20(27.8)	19(30.6)	61(31.1)	39
Obese (>30.0)	17(27.4)	17(23.6)	20(32.3)	51(26.0)	23

Note: Values are shown as N(%) unless otherwise stated. *BMI value missing for six mothers.
**BMI value missing for five mothers. ***BMI value missing for seven mothers.

Smoking and substance abuse

Smoking status of the mothers at their time of booking was recorded for 68 (98.6%) of the 69 women. Of these, 10 (14.7%) were smokers at the time of booking; this is slightly lower than the prevalence of all female smokers in the Irish population in 2018 (17%)[11]. Information on smoking was available for seven of the ten smokers (70.0%). Five women were smoking between 1 and 9 cigarettes per day (n=5 of 7, 71.4%) and two were smoking 10 or more cigarettes per day (n=2 of 7, 28.6%). Of the seven women who were smoking at booking, two (28.6%) stopped smoking during pregnancy. There were no pregnancies with a documented history of alcohol abuse, but one woman had a documented history of drug abuse prior to pregnancy.

Previous pregnancy

In terms of parity of women who delivered infants requiring therapeutic hypothermia in 2018, there was an overrepresentation of women who had not previously delivered (56.5%) compared to the general population of women who gave birth in 2016 (38.2%; Table 5).

Table 5: Distribution of parity, 2016-2018

Parity	TH cases N=63 2016	TH cases N=77 2017	TH cases N=69 2018	TH cases N=209 2016-2018	All births* 2016 (%)
Nulliparous	42(66.7)	42(54.5)	39(56.5)	123(58.9)	38.2
Para 1	13(20.6)	21(27.3)	19(27.5)	53(25.4)	34.9
Para 2	5(7.9)	8(10.4)	7(10.1)	20(9.6)	17.9
Para 3+	3(4.8)	6(7.8)	4(5.8)	13(6.2)	9.0

Note: Values are shown as N(%) unless otherwise stated. *Population data from the Healthcare Pricing Office[9]

Table 6 specifies the gravidity/parity of the 69 women whose infants underwent neonatal therapeutic hypothermia in 2018. Nearly half (n=39, 56.5%) had never been pregnant before (gravida = 0). Of the 30 women who had been pregnant (gravida > 0), 96.7% (n=29) had pregnancies exceeding 24 weeks or 500g birthweight (gravida = parity, indicated by green shading). One of the women had experienced at least two pregnancies exceeding 24 weeks or 500g birthweight and one pregnancy less than 24 weeks gestation and under 500g birthweight (gravida > parity > 0, indicated by yellow shading).

Table 6: Gravidity/parity of mothers whose infants underwent therapeutic hypothermia in 2018

GRAVIDA	PARITY						
	0	**1**	**2**	**3**	**4**	**5**	**Total**
0	39						**39**
1	0	19					**19**
2	0	0	6				**6**
3	0	0	1	2			**3**
4	0	0	0	0	0		**0**
5	0	0	0	0	0	2	**2**
Total	**39**	**19**	**7**	**2**	**0**	**2**	**69**

Note: We refer to gravidity and parity prior to the pregnancy associated with neonatal therapeutic hypothermia. Green represents women with previous pregnancies that were all ≥24 weeks or ≥500g; yellow represents women who had experienced pregnancy ≥24 weeks or ≥500g and also pregnancy <24 weeks and <500g; and orange represents women whose previous pregnancies were always <24 weeks gestation and <500g birthweight.

Of the 30 women who had a previous pregnancy, 30.0% (n=9) were reported to have had a previous pregnancy-related problem (undocumented for one). Caesarean section delivery was the most common previous pregnancy-related problem, with twenty percent of mothers (n=6, 20.0%) having a previous caesarean section delivery (Table 7). Placental abruption and an infant requiring intensive care were both the second most common pregnancy-related problem in mothers who had a previous pregnancy (n=2; 6.7%). None of the mothers had an infant with Hypoxic Ischaemic Encephalopathy (HIE) in a previous pregnancy.

Table 7: Previous pregnancy-related problems in mothers whose infants underwent therapeutic hypothermia in 2018

	TH cases N=28 2016	TH cases N=47 2017	TH cases N=30 2018	TH cases N=105 2016-2018
Previous caesarean delivery	6(21.4)	8(17.0)	6(20.0)	20(19.0)
Three or more miscarriages	1(3.6)	4(8.5)	1(3.3)	6(5.7)
Infant requiring intensive care	0(0.0)	3(6.4)	2(6.7)	5(4.8)
Pre-term birth or mid-trimester loss	2(7.1)	1(2.1)	0(0.0)	3(2.9)
Neonatal death	1(3.6)	0(0.0)	1(3.3)	2(1.9)
Pre-eclampsia	2(7.1)	0(0.0)	0(0.0)	2(1.9)
Stillbirth	1(3.6)	1(3.6)	1(3.3)	3(2.9)
Other	0(0.0)	1(2.1)	2(6.7)	3(2.9)
Infant with congenital anomaly	0(0.0)	0(0.0)	(0.0)	0(0.0)
Placenta abruption	0(0.0)	1(2.1)	2(6.7)	3(2.9)
Placenta praevia	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Post-partum haemorrhage requiring transfusion	0(0.0)	0(0.0)	1(3.3)	1(0.9)
Previous infant with HIE	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Note: Percentage relates to total number of mothers who had a previous pregnancy (n=105). Categories are not mutually exclusive. Values are shown as N(%) unless otherwise stated.

Pre-existing medical problems

One in four of the women, whose infants underwent therapeutic hypothermia in 2018, had a pre-existing medical problem (n=7, 23.3%). Fifteen of the 69 women were taking prescribed medication during the pregnancy (21.7%). Four mothers had a documented family history of conditions which can affect newborn infants (5.8%, n=4). The most common type of pre-existing medical problems were endocrine disorders, with 8.7% of mothers (n=6) suffering from conditions of this type (Table 8). Psychiatric disorders also had the highest percentage of occurrence (8.7%, n=6).

Table 8: Pre-existing medical problems in mothers whose infants underwent therapeutic hypothermia in 2018

	TH cases N=63 2016	TH cases N=77 2017	TH cases N=69 2018	TH cases N=209 2016-2018
Endocrine disorder	7(11.1)	3(3.9)	6(8.7)	16(7.7)
Psychiatric disorder	4(6.3)	3(3.9)	6(8.7)	13(6.2)
Hypertension	3(4.8)	1(1.3)	0(0.0)	4(1.9)
Haematological disorder	1(1.6)	2(2.6)	0(0.0)	3(1.4)
Diabetes	1(1.6)	1(1.3)	1(1.4)	3(1.4)
Cardiac disease	0(0.0)	1(1.3)	1(1.4)	2(0.9)
Inflammatory disorder	0(0.0)	1(1.3)	0(0.0)	1(0.5)
Renal disease	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Epilepsy	0(0.0)	(0.0)	2(2.9)	2(0.9)
Other	7(11.1)	18(23.4)	9(13.0)	34(16.3)

Note: Percentage relates to total number of mothers, categories are not mutually exclusive.

Antenatal care

Currently in Ireland, there is no national data on the number of births as a result of fertility treatment. Information was available for 68 of the 69 (98.6%) whose infants underwent therapeutic hypothermia in 2018. In six of these cases (8.8%), the pregnancy was reported to be the result of fertility treatment. In vitro fertilisation was the method of fertility treatment specified for five of the six pregnancies and all bar one of these women were aged between 30-34 years (83.3%; n=5 of 6). In terms of parity the majority of women were nulliparous (83.3%; n=5 of 6).

During this pregnancy, the majority of the 69 women intended on delivering in an obstetric unit (91.3%; n=63) with obstetric-led care (89.9%; n=62). One in five women had an antenatal ultrasound scan before 12 weeks gestation (20.3%; n=14) and over half of the women had a scan between 12 and 15 weeks gestation (58.0%; n=40). Gestation at booking was unknown for five women and two women were unbooked (Table 9). Estimated date of delivery (EDD) was documented for 67 of the 69 women. EDD was calculated using ultrasound scan in the majority of cases (97.0%; 65 of 67).

Table 9: Timing of antenatal hospital booking appointment for mothers whose infants underwent therapeutic hypothermia in 2016-2018

	TH cases N=63 2016	TH cases N=77 2017	TH cases N=69 2018	TH cases N=209 2016-2018
Less than 12 weeks	16(25.4)	22(28.6)	14(20.3)	52(24.9)
12-15 weeks	40(63.5)	40(51.9)	40(58.0)	120(57.4)
15-19 weeks	5(7.9)	9(11.7)	7(10.1)	21(10.0)
20 weeks of later	2(3.2)	2(2.6)	1(1.6)	5(2.4)
Unknown	0(0.0)	4(5.2)	5(7.2)	9(4.3)
Unbooked	0(0.0)	0(0.0)	2(2.9)	2(0.9)

Note: Values are shown as N(%) unless otherwise stated.

Gestation at last antenatal hospital visit

Information on the last antenatal visit was available for 67 of the 69 women whose infants underwent therapeutic hypothermia in 2018 (97.1%). These 67 women last attended the hospital clinic between 33 and 42 weeks. Almost 90% attended at 36 weeks or later (89.6%, n=60) with 17.9% (n=12) last attending the hospital before the last routine antenatal clinic visit at 37 weeks gestation (Figure 1). Of the 69 women, one was transferred from another maternity unit with the fetus in utero at 37 gestational weeks.

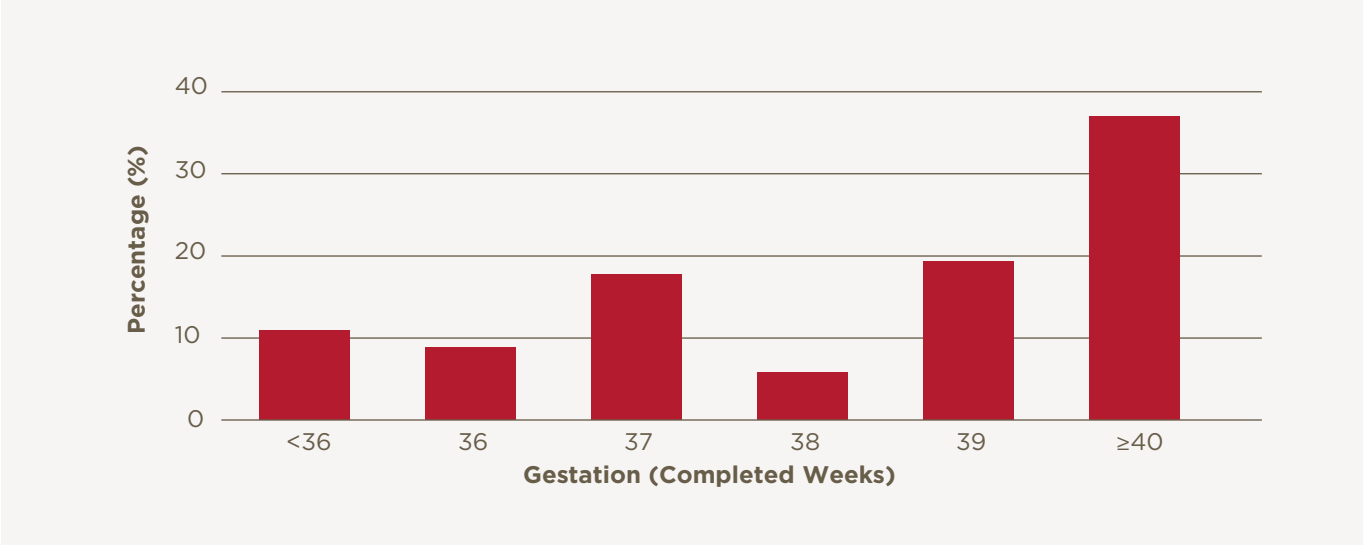

Figure 1: Weeks gestation at last antenatal visit, 2018

Concern documented during pregnancy

Of the 69 cases, there were concerns documented during the pregnancy for 26 (37.7%) of the mothers whose infants underwent therapeutic hypothermia in 2018. One in three of these women had two or more concerns documented (30.8%; n=8 of 26). The most common concern documented was gestational diabetes mellitus with 10.1% (n=7) of mothers developing this condition during pregnancy. This was followed by hypertensive disorders which had the second highest percentage of occurrence (7.2%, n=5). Polyhydramnios and infants recorded as large for gestational age were also the third most common concern documented for these pregnancies (4.3%; n=3 respectively).

Labour

Information on the onset of labour was available for all 69 women whose infants underwent therapeutic hypothermia (100%). Almost half of the women laboured spontaneously (47.8%; n=33), over a third of women were induced (33.3%; n=23) and 18.8% of women were never in labour (Table 10). Almost half of the women who laboured spontaneously had their labour accelerated (45.5%; n=15 of 33), either by artificial rupture of membranes (ARM; 53.3%, n=8 of 15) or oxytocin (26.7%; n=4 of 15). Three women (20.0%; n=3 of 15) had their labour accelerated with both (Table 11).

Table 10: Onset of labour for mothers whose infants underwent therapeutic hypothermia in 2016-2018

	Total	Nulliparous			Parous		
	N=209	2016 N=42	2017 N=42	2018 N=39	2016 N=21	2017 N=35	2018 N=30
Spontaneous	102(48.8)	19(45.2)	22(52.4)	19(48.7)	10(47.6)	18(51.4)	14(46.7)
Induction	71(34.0)	22(52.4)	13(31.0)	12(30.8)	6(28.6)	7(20.0)	11(36.7)
Never in labour	36(17.2)	1(2.4)	7(16.7)	8(20.5)	5(23.8)	10(28.6)	5(16.7)

Note: Values are shown as N(%) unless otherwise stated.

Table 11: Method of acceleration for mothers who laboured spontaneously by parity

	Total	Nulliparous			Parous		
	N=45	2016 N=11	2017 N=11	2018 N=9	2016 N=3	2017 N=5	2018 N=6
Artificial rupture of membranes	25(55.6)	3(27.3)	6(54.5	4(44.4)	3(100)	5(100)	4(66.7)
Oxytocin	17(37.8)	8(72.7)	5(45.5)	2(22.2)	0(0.0)	0(0.0)	2(33.3)
Both	3(6.6)	0(0.0)	0(0.0)	3(33.3)	0(0.0)	0(0.0)	0(0)

Note: Values are shown as N(%) unless otherwise stated.

As outlined in Table 12, liquor was clear in 27 of the 59 documented cases (45.8%). Two of every five women had meconium-stained liquor (40.7%; n=24 of 59). The grade of meconium was specified for 22 of the 24 cases (91.7%), with 31.8% of women having Grade 1 (n=7), 50.0% of women having Grade 2 (n=11) and the remaining four women having Grade 3 (18.2%).

Table 12: Liquor colour by parity

	Total	Nulliparous			Parous		
	N=209	2016 N=42	2017 N=42	2018 N=39	2016 N=21	2017 N=35	2018 N=30
Clear	95(45.5)	22(52.4)	19(45.2)	16(41.0)	11(52.4)	16(45.7)	11(36.7)
Meconium	55(26.3)	11(26.2)	10(23.8)	14(35.9)	2(9.5)	8(22.9)	10(33.3)
Other	20(9.6)	5(11.9)	5(11.9)	4(10.3)	0(0.0)	2(5.7)	4(13.3)
Missing/Non-applicable	39(18.7)	4(9.5)	8(19.0)	5(12.8)	8(38.1)	9(25.7)	5(16.7)

Note: Values are shown as N(%) unless otherwise stated.

There was a documented reason for induction for 19 of the 23 women whose onset of labour was induced. As indicated in Table 13, the common reasons to induce labour were associated with post maturity (31.6%; n=6 of 19), oligohydramnios (15.8%; n=3 of 19), hypertensive disorders (10.5%; n=2 of 19), large for gestational age (10.5%; n=2 of 19) and prolonged spontaneous rupture of membranes (10.5%; n=2 of 19). Under the "Other" category a range of indications were captured including; suspected IUGR, raised dopplers, polyhydramnios, twins, gestational diabetes mellitus and social reasons.

Table 13: Reason for induction of mothers whose infants underwent therapeutic hypothermia in 2018

	TH cases 2018 N=19*
Post maturity	6(31.6)
Oligohydramnios	3(15.8)
Hypertensive disorders	2(10.5)
Large for gestational age	2(10.5)
Prolonged SROM	2(10.5)
Other	6(31.6)

Note: Values are shown as N(%) unless otherwise stated. *Categories are not mutually exclusive.

The method of induction was known for all 23 women who were induced (100%). The majority of women had their labour induced using multiple methods of induction (56.5%; 13 of 23). As illustrated in Table 14, the most common method of induction was the use of oxytocin (60.9%; n=14 of 23), followed by prostaglandin gel (52.2%; n=12) and almost half of women had their labour induced with the artificial rupture of membranes (43.5%; n=10).

Table 14: Method of induction for mothers whose infants underwent therapeutic hypothermia in 2016-2018

	Total	Nulliparous			Parous		
	N=71	2016 N=22	2017 N=13	2018 N=12	2016 N=6	2017 N=7	2018 N=11
Oxytocin	43(60.6)	14(63.6)	9(69.2)	7(58.3)	2(33.3)	4(57.1)	7(63.6)
Artificial rupture of membranes	37(52.1)	11(50.0)	8(61.5)	6(50.0)	4(66.7)	4(57.1)	4(36.4)
Prostaglandin gel	36(50.7)	12(54.5)	6(46.2)	7(58.3)	4(66.7)	2(28.6)	5(45.5)
Propress	18(25.3)	6(27.3)	6(46.2)	4(33.3)	0(0.0)	1(14.3)	1(9.1)
Other	1(1.4)	1(4.5)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Note: Values are shown as N(%) unless otherwise stated. Categories are not mutually exclusive.

Fetal heart monitoring was undertaken for 61 of the 69 women whose infants underwent therapeutic hypothermia (88.4%). The method of fetal heart monitoring was documented for all 61 women (100%). As illustrated in Table 15, external continuous fetal heart monitoring was the most common method of monitoring used during labour (93.4%; n=57 of 61). Twelve women who underwent external continuous fetal heart monitoring also had internal continuous fetal heart monitoring (19.7%; n=12 of 61). A third of women who had external intermittent fetal heart monitoring (36.1%; n=22 of 61). Of these women, almost half also underwent external continuous fetal heart monitoring during labour (81.8%; n=18 of 22).

Table 15: Method of fetal heart monitoring for infants who underwent therapeutic hypothermia in 2016-2018

	Total	Nulliparous			Parous		
	N=171	2016 N=40	2017 N=34	2018 N=37	2016 N=13	2017 N=23	2018 N=24
External continuous	143(83.6)	36(90.0)	26(76.5)	36(97.3)	9(69.2)	15(65.2)	21(87.5)
External intermittent	62(36.3)	16(40.0)	10(29.4)	11(29.7)	5(38.5)	9(39.1)	11(45.8)
Internal continuous	16(9.4)	1(2.5)	2(5.9)	6(16.2)	0(0.0)	1(4.3)	6(25.0)

Note: Values are shown as N(%) unless otherwise stated. Categories are not mutually exclusive.

Data on cardiotocography (CTG), which could be interpreted, were available for 45 of the 69 cases (65.2%). Of these 45, half were interpreted as either pathological (44.4%; n=20) or suspicious (6.7%; n=3). A fetal blood sample was taken for 4 of the 69 infants who underwent therapeutic hypothermia in 2018 (5.8%). Fetal blood samples were three times more likely to be taken for infants with a pathological CTG (15.0%; n=3 of 20) compared to those with a normal CTG (5.6%; n=1 of 18). All four infants had a pH greater than 7.0 (Range: 7.2-7.3) from the initial fetal blood sample and the median base deficit was 2.1 (Range: 1.3-3.0).

Delivery

Information on both the day and time of birth was available for all 69 infants who underwent therapeutic hypothermia in 2018. The timing of birth was categorised between 08:00 and 19:59 hours and 20:00 and 07:59hrs. As illustrated in Figure 2, the time of birth varied across the seven days of the week. Of all the births, over half were born between 08:00 and 19:59 hours (55.1%; n=38).

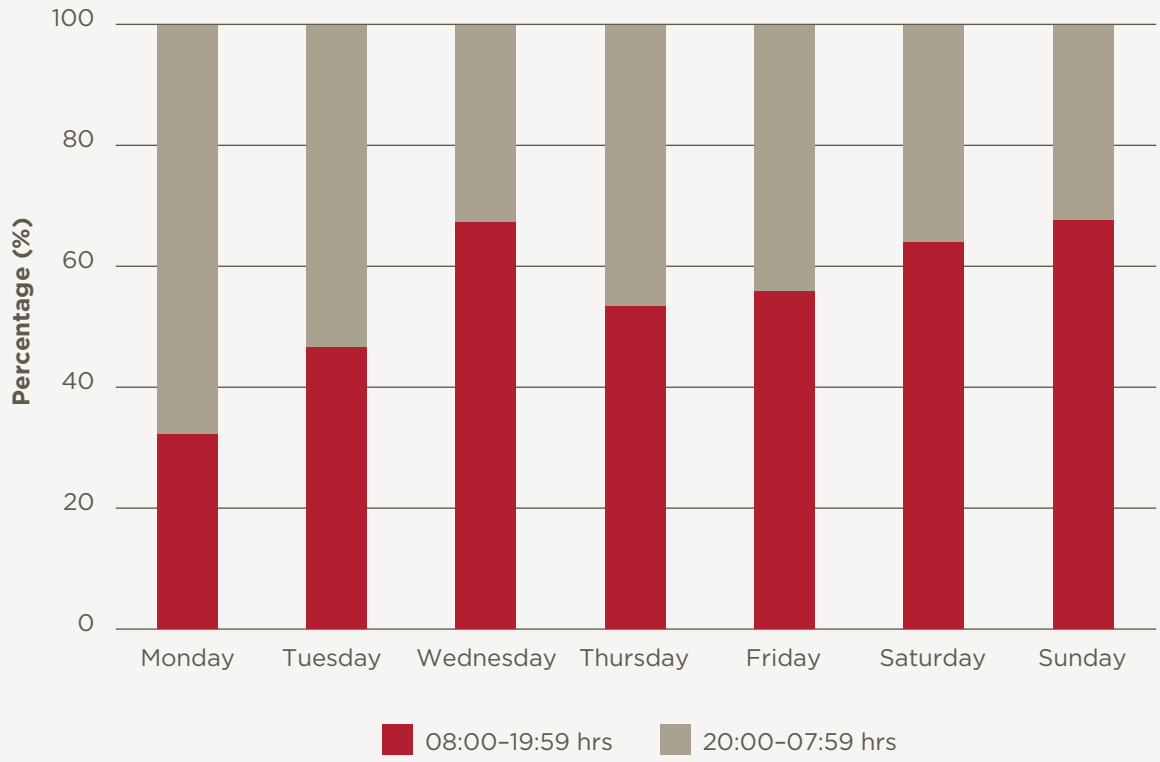

Figure 2: Day of week and time of birth (08:00 – 19:59 and 20:00 – 07:59) for infants who underwent therapeutic hypothermia in 2018

The type of care received at delivery was known for all mothers whose infants underwent therapeutic hypothermia (n=69). The vast majority of the infants (98.6%; n=68) were delivered under obstetric-led care, which is the predominant model of care in Ireland. One baby was born before arrival at the maternity unit.

Presentation at delivery was known for 92.8% of mothers whose infants underwent therapeutic hypothermia (n=64 of 69). The majority of presentations at delivery were vertex presentations (n=61 of 64, 95.3%), and in two cases the presentation was breech (n=2 of 64, 3.1%).

Mode of delivery was known for all mothers (n=69) whose infants underwent therapeutic hypothermia in 2018 (Table 16). One in five of infants had a spontaneous vaginal delivery (20.3%, n=14), which is considerably lower than the proportion of vaginal deliveries of all births occurring in 2016 (52.2%). Almost half of the deliveries were instrumental (47.8%, n=33 of 69). Of the women who had an instrumental delivery, five mothers had a combination of a ventouse and a forceps delivery. The interval time from decision to the instrumental delivery was known in 29 of the cases. The median interval time to delivery was 16 minutes and ranged from four to 45 minutes. Infants whose CTG was interpreted as suspicious or pathological were more likely to have an operative birth rather than a spontaneous vaginal delivery.

Caesarean section was the second most common mode of delivery for all 69 of these infants (42.0%, n=29), with a slightly higher percentage of caesarean sections happening pre-labour (55.2%, n=16 of 29) rather than after the onset of labour (44.8%, n=13 of 29).

Table 16: Mode of delivery for mothers whose infants underwent therapeutic hypothermia in 2018

TH cases 2018 N=69		All births 2016[1]	
Spontaneous Vaginal Cephalic Spontaneous Vaginal Breech	14(20.3) 0(0.0)	Vaginal birth[+]	52.2%
Pre-labour Caesarean Section Caesarean Section*	16(23.2) 13(18.8)	Caesarean section[++]	32.6%
Assisted breech	0(0.0)	Assisted breech	0.5%
Ventouse**	22(31.9)	Ventouse	11.1%
Forceps	11(15.9)	Forceps	3.6%

Note: Values are N(%) unless otherwise stated. Categories are not mutually exclusive. [+]Vaginal births in this category include women who had both a Spontaneous Vaginal Cephalic and a Spontaneous Vaginal Breech delivery. [++]Caesarean section in this category include women who had a pre-labour caesarean section as well as women who had a caesarean section after the onset of labour. *Two mothers had a caesarean section following failed instrumental deliveries. **Five mothers who had a ventouse delivery, also had a forceps delivery.

The type of caesarean section was documented for all 29 mothers (Table 17). One mother whose infant underwent therapeutic hypothermia in 2018 had an elective caesarean section (3.4%; n=1 of 29) and one had an urgent caesarean section (3.4%; n=1 of 29). Two mothers had a caesarean section following a failed instrumental delivery (6.9%; n=2 of 29). Emergency caesarean section delivery was the most common type of caesarean section delivery, accounting for 86.2% of cases where the infant was delivered by caesarean section (n=25 of 29). Of the women who had an Emergency caesarean section delivery, 56.0% (n=14 of 25) were pre-labour and 44.0% (11 of 25) occurred after the onset of labour.

Table 17: Type of caesarean section delivery for mothers whose infants underwent therapeutic hypothermia in 2018

	TH cases N=29 2016
Elective – planned	1(3.4)
Urgent – maternal or fetal compromise which is not immediately life threatening	1(3.4)
Emergency – immediate threat to life of woman or fetus	25(86.2)
Failed instrumental delivery	2(6.9)

Other incidences at birth and following delivery

As outlined in Table 18, 13.0% of women whose infants underwent therapeutic hypothermia had a prolonged rupture of membranes (n=9). One in twenty women experienced maternal pyrexia during labour (n=3).

Table 18: Other incidences at the birth of infants who underwent therapeutic hypothermia in 2016-2018

	TH cases N=63 2016	TH cases N=77 2017	TH cases N=69 2018	TH cases N=209 2016-2018
Maternal pyrexia in labour	14(22.2)	12(15.6)	3(4.3)	29(13.9)
Shoulder dystocia	10(15.9)	8(10.4)	9(13.0)	27(12.9)
Prolonged rupture of membranes	7(11.1)	7(9.1)	9(13.0)	23(11.0)
Subgaleal haematoma	1(1.6)	2(2.6)	0(0.0)	3(1.4)
Spontaneous premature labour	0(0.0)	1(1.3)	0(0.0)	1(0.5)
Birth trauma	1(1.6)	0(0.0)	0(0.0)	1(0.5)
Other	7(11.1)	13(16.9)	2(2.9)	22(10.5)

Note: Values are shown as N (%) unless otherwise stated. Categories are not mutually exclusive.

Uterine rupture

Over the one year period, there were three reported cases of uterine rupture which equates to a rate of 43.5 per 1,000 within this cohort. This rate is significantly higher than the incidence of uterine rupture in the Irish general population which has consistently been reported at 0.14 per 1,000 maternities since 2011[12]. All the women who experienced uterine rupture were parous. Two of the three women were reported to have had a caesarean section in a previous pregnancy. One woman had an elective caesarean section in this pregnancy, while the remaining two women had a caesarean section after the onset of labour. The birth weight of these infants ranged from 3480 grams to 4120 grams.

Shoulder dystocia infants

During delivery of the 69 infants, there were nine reported incidents of shoulder dystocia (13.0%). This rate is 9 times higher than that reported for all deliveries (1.4%) in high-income countries[13]. Of nine reported incidents of shoulder dystocia, two-thirds of the women were nulliparous (66.7%; n=6 of 9). Five of the nine women (55.6%) had an induction of labour (Table 19) and three of the four women who laboured spontaneously had their labour accelerated.

Eight of the nine women had an instrumental delivery (88.9%). The median interval time between decision and delivery was 17 minutes, ranging from 9 to 26 minutes. Of the nine women who had an instrumental delivery, two-thirds of the women (66.7%; n=6 of 9) had their birth assisted with ventouse, with one woman (11.1%; n=1 of 9) having a combination of ventouse and forceps.

The most common manoeuvre utilised for all deliveries was a combination of McRoberts and Suprapubric pressure (44.4%; n=4 of 9). The birth weight for these infants ranged from 3,695 grams to 4,595 grams, with three-quarters of these infants (77.8%; n=7 of 9) weighing 4,000-4,499 grams.

Table 19: Maternal and infants characteristics for deliveries with a reported shoulder dystocia

	Shoulder dystocia cases N=9 2018
Age Group	
<30yrs	3(33.3)
30-34yrs	3(33.3)
35-39yrs	2(22.2)
>40yrs	1(11.1)
BMI Category (kg/m²)	
Underweight (<18.5)	0(0)
Healthy (18.5-24.9)	3(33.3)
Overweight (25.0-29.9)	1(11.1)
Obese (>30.0)	5(55.6)
Parity	
Nulliparous	6(66.7)
Parous	3(33.3)
Induction of labour	5(55.6)
Mode of delivery	
Spontaneous Vaginal Cephalic	1(11.1)
Instrumental	8(88.9)
Manoeuvres*	
McRoberts	1(11.1)
McRoberts and Suprapubic pressure	8(88.9)
Other	2(22.2)
Birthweight (grams)	
3500-3999	2(22.2)
4000-4499	6(66.7)
>4500	1(11.1)

Note: Values are shown as N(%) unless otherwise stated. *Categories are not mutually exclusive.

Infant characteristics

Two-thirds of the infants who received therapeutic hypothermia in 2018 were male (76.8%; n=53 of 69). In the overall population of births in 2016, 51.3% were male and 48.7% female (Table 20). There were three infants who underwent therapeutic hypothermia from multiple births (4.3%). This is similar to the proportion of multiples among all births in 2016 (3.8%).[9]

Table 20: Sex of infants who underwent therapeutic hypothermia in 2016-2018

	TH cases N=63 2016	TH cases N=77 2017	TH cases N=69 2018	TH cases N=209 2016-2018	All births[9]
Male	32(50.8)	48(62.3)	53(76.8)	133(63.6)	51.3%
Female	31(49.2)	29(37.7)	16(23.2)	76(36.4)	48.7%

Note: Values are shown as N(%) unless otherwise stated.

Gestation at delivery

Figure 3 outlines the gestational age at delivery for infants who underwent therapeutic hypothermia in 2018 versus all infants born in 2016. The majority of infants were born between 36 and 41 completed weeks gestation (91.1%; n=62 of 68; missing data for one infant). One infant was born at 35 completed weeks (1.5%); this infant had a birthweight greater than 1,800 grams.

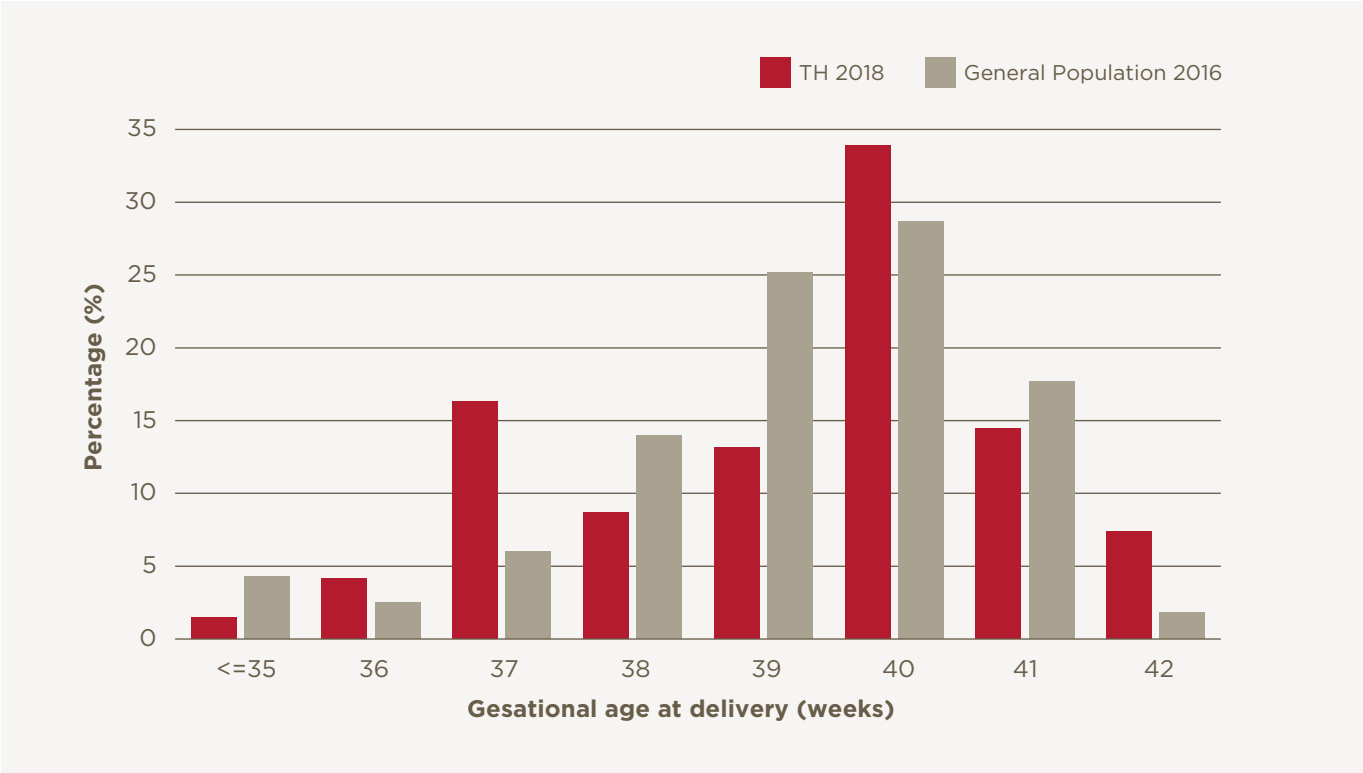

Figure 3: Gestational age at delivery (weeks) for infants who underwent therapeutic hypothermia in 2018 versus all infants born in 2016

Birthweight at delivery

The mean birthweight for infants who underwent neonatal therapeutic hypothermia in 2018 was 3,489 grams (Standard Deviation: 547 grams). The birth weight ranged from 2,210 grams to 4,620 grams. As outlined in Figure 4, almost a quarter of infants weighed 3,000-3,499 grams (21.7%, n=15). Over half of infants weighed 3,500 grams or more (55.1%, n=38). A small proportion of infants weighed between 1,800 and 2,499 grams (5.8%, n=4).

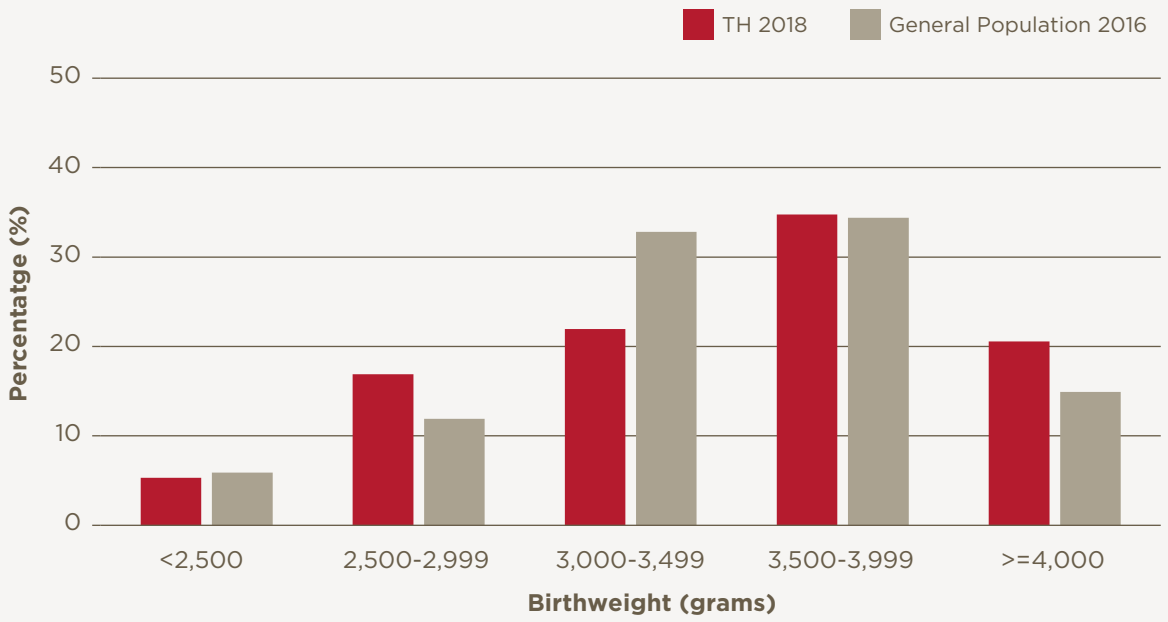

Figure 4: Distribution of birthweight for infants who underwent therapeutic hypothermia in 2018 versus all infants born in 2016

Birthweight Centiles

Gestation Related Optimal Weight (GROW) software and coefficients derived from the multiple regression analysis of data on 11,072 births in six maternity units in Dublin, Galway, Limerick and Belfast in 2008-2009[14], was used to produce Figure 5, which illustrates the optimal birthweight and normal range compared to the recorded birthweights of infants who underwent neonatal therapeutic hypothermia in 2018.

The optimal weight and normal range for all gestations are plotted with the actual birthweights of the infants in Figure 6. As can also be seen in Table 21, almost one in five of these infants were below the lower limit of the normal range (10th centile).

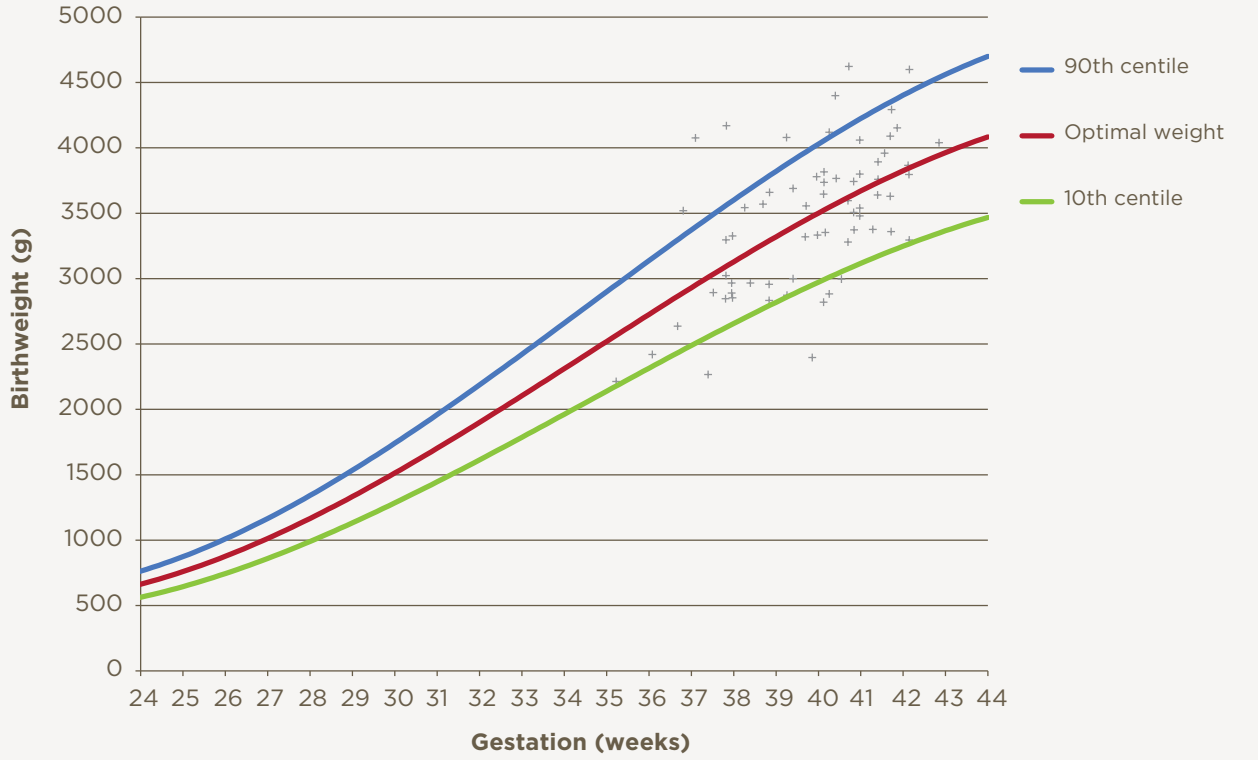

Figure 5: Optimal birthweight and normal range compared to actual birthweights for infants who underwent therapeutic hypothermia in 2018

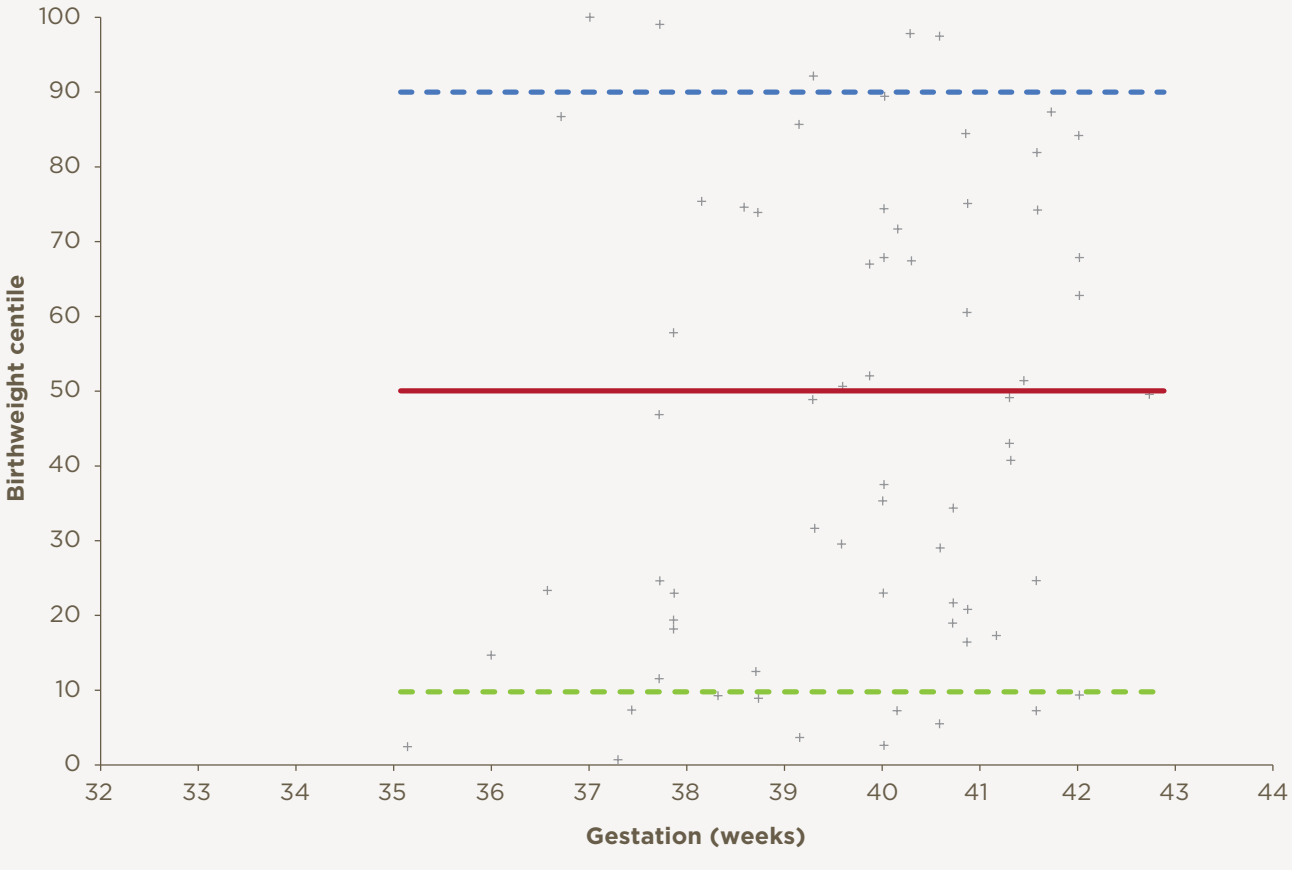

Figure 6: Distribution of customised birthweight centiles for infants who underwent therapeutic hypothermia in 2018

When examined by birth weight centile category, the distribution of the TH cohort was broadly similar to that expected but there was some evidence of poor fetal growth. Almost 20% of the infants (n=12, 17.6%) were below the 10th centile.

Table 21: Birth weight centiles for infants who underwent therapeutic hypothermia in 2016-2018

Centiles	TH cases 2016 N=63	TH cases 2017 N=77	TH cases 2018 N=69	TH cases 2016-2018 N=209
<3rd	2(3.2)	6(7.8)	4(5.8)	12(5.7)
3rd to 9th	7(11.1)	11(14.3)	8(11.6)	26(12.4)
10-49th	27(42.9)	28(36.4)	28(40.6)	83(39.7)
50-89th	17(27.0)	24(31.2)	24(34.8)	65(31.1)
>90th	10(15.9)	8(10.4)	5(7.2)	23(11.0)

Note: Values are shown as N(%) unless otherwise stated.

Diagnosis of fetal growth restriction (FGR)

Data on diagnosis of FGR were recorded for all 69 infants who underwent therapeutic hypothermia in 2018 (100%). A diagnosis of FGR was reported for five (7.2%) of the 69 infants (Table 22). In keeping with previous years, an antenatal diagnosis of FGR (as opposed to diagnosis based on observation at delivery or post-mortem) was reported for three of the five infants (60.0%).

Table 22: Diagnosis of fetal growth restriction for infants who underwent therapeutic hypothermia in 2016 -2018

	TH cases 2016 N=63	TH cases 2017 N=74*	TH cases 2018 N=69	TH cases 2016-2018 N=206*
No diagnosis documented	60(95.2)	66(89.2)	64(92.8)	190(92.2)
Diagnosis of fetal growth restriction	3(4.8)	8(10.8)	5(7.2)	16(7.8)
Fetal growth restriction suspected antenatally	1 of 3(33.3)	5 of 8(62.5)	3 of 5 (60.0)	9 of 16(56.3)

Note: Values are shown as N(%) unless otherwise stated. *Missing data for three infants.

Resuscitation

Neonatal or paediatric support was called prior to the delivery of the majority of cases (81.2%; n=56 of 68; one infant born before arrival). As outlined in Table 23, a Registrar was present at the vast majority of births for resuscitation (88.2%; n=60 of 68; data missing for one infant). A Senior House Officer (SHO) was also present at the majority of births for resuscitation (92.6%; n=63 of 68). A Neonatal Nurse was present at over half of births (52.9%; n=36 of 68) with a Midwife present for one in six births for resuscitation (16.1%; n=11 of 68). A Consultant was present for a third of births for resuscitation (34.8%; n=48).

Table 23: Who was present at the time of birth for the resuscitation of infants who underwent therapeutic hypothermia in 2016-2018

	TH cases 2016 N=61*	TH cases 2017 N=77	TH cases 2018 N=68**	TH cases 2016-2018 N=206
Consultant(Neonatology/Paediatrics)	21(34.4)	27(35.1)	28(41.2)	76(36.4)
Registrar	56(91.8)	73(94.8)	60(88.2)	189(91.7)
Senior House Officer	48(78.7)	68(88.3)	63(92.6)	174(83.3))
Neonatal Nurse	22(36.1)	37(48.1)	36(52.9)	95(46.1)
Midwife	16(26.2)	17(22.1)	11(16.1)	44(21.4)

Note: Values are shown as N(%) unless otherwise stated. *Data missing for two infants. **Data missing for one infant.

As indicated in Table 24, at one minute after birth three quarters of infants (75.0%; n=51 of 68) had an Apgar score of between zero and three. At ten minutes, infants with an Apgar score of between zero and three had reduced to 13.1% (n=8 of 61). At twenty minutes, only six infants had an Apgar score recorded; only one of these had a score of eight or greater (16.7%; n=1 of 6).

Table 24: Apgar Scores at 1, 5, 10 and 20 minutes for infants who underwent therapeutic hypothermia in 2018

	1 minute N=68	5 minutes N=67	10 minutes N=61	20 minutes N=6
0	11(16.2)	4(6.0)	2(3.3)	1(16.7)
1	21(30.9)	5(7.5)	1(1.6)	0(0)
2	10(14.7)	10(14.9)	2(3.3)	1(16.7)
3	9(13.2)	5(7.5)	3(4.9)	1(16.7)
4	4(5.9)	14(20.9)	12(19.7)	0(0)
5	3(4.4)	11(16.4)	14(23.0)	1(16.7)
6	7(10.3)	7(10.4)	9(14.8)	0(0)
7	0(0)	5(7.5)	10(16.4)	1(16.7)
8	2(2.9)	2(3.0)	4(6.6)	1(16.7)
9	1(1.5)	2(3.0)	4(6.6)	0(0)
10	0(0)	2(3.0)	0(0)	0(0)

Note: Values are shown as N(%) unless otherwise stated.

Spontaneous breath was initiated and sustained by half of infants (52.2%; n=36 of 69). Of these infants, the age at which spontaneous breathing was sustained was recorded for 33 of the 36 infants (91.7%) and began between 1 and 15 minutes (median 4 minutes).

As illustrated in Table 25, almost all infants were resuscitated in 2018 (94.2%; n=65 of 69). Over half of the 69 infants were intubated (59.4%; n=41) which occurred between 1 and 20 minutes (median 5 minutes). One third of infants had chest compressions (33.3%, n=23), which began at between 1 and 20 minutes (data missing for three infants). FiO2 was administered to the majority of infants (89.7%, n=61 of 68; data missing for one infant).

Table 25: Resuscitation for infants who underwent therapeutic hypothermia between 2016-2018

	TH cases 2016 N=63	TH cases 2017 N=77	TH cases 2018 N=69	TH cases 2016-2018 N=209
Spontaneous breath initiated	37(58.7)	37(48.1)	36(52.2)	110(52.6)
Resuscitation	58(92.1)	75(97.4)	65(94.2)	198(94.7)
Intubation	32(50.8)	50(64.9)	41(59.4)	124(59.3)
Chest compressions	19(30.2)	28(36.4)	23(33.3)	70(33.5)
FiO_2	57(90.5)	72(93.5)	61(89.7)	190(90.9)

Note: Values are shown as N(%) unless otherwise stated. Categories are not mutually exclusive.

Table 26: Drugs or fluid treatment administered at birth for infants who underwent therapeutic hypothermia in 2016-2018

	TH cases 2016 N=63	TH cases 2017 N=77	TH cases 2018 N=69	TH cases 2016-2018 N=209
Adrenaline	9(14.3)	9(11.7)	11(15.9)	29(13.9)
Dextrose	2(3.2)	4(5.2)	1(1.4)	7(3.3)
Saline	21(33.3)	21(27.3)	12(17.4)	64(30.6)
O negative blood	5(7.9)	8(10.4)	2(2.9)	15(7.2)
Sodium Bicarbonate	2(3.2)	1(1.3)	1(1.4)	4(1.9)

Note: Values are shown as N(%) unless otherwise stated. Categories are not mutually exclusive.

One of the key indicators for intrapartum asphyxia is severe metabolic acidosis evident in umbilical cord blood at delivery.[15] As outlined in Table 27, at delivery, half of infants (58.7%, n=37 of 63; data missing for 6 infants) had a pH of 7.0 or lower. The median base deficit was 11.5 (Range: 0.50-26.4) from cord blood gases and was 14.7 (Range: 2.60-36.4) from initial infant blood gases.

Table 27: pH level from cord and initial infant blood gases for infants who underwent therapeutic hypothermia in 2018

	Cord blood Gas	Initial Infant Blood Gas		
	N=63	Venous N=37	Capillary N=13	Arterial N=16
pH level				
6.4-6.5	0(0.0)	0(0.0)	1(7.7)	1(6.3)
6.51-6.6	3(4.8)	0(0.0)	0(0.0)	2(12.5)
6.61-6.7	5(7.9)	1(2.7)	1(7.7)	0(0.0)
6.71-6.8	9(14.3)	8(21.6)	1(7.7)	2(12.5)
6.81-6.9	12(19.0)	2(5.4)	1(7.7)	1(6.3)
6.91-7.0	8(12.7)	8(21.6)	4(30.8)	1(6.3)
7.01-7.1	11(17.5)	8(21.6)	1(7.7)	2(12.5)
7.11-7.2	10(15.9)	7(18.9)	3(23.1)	3(18.8)
7.21-7.3	5(7.9)	3(8.1)	1(7.7)	4(25.0)
7.31-7.4	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Note: Values are shown as N(%) unless otherwise stated.

Assessment for Therapeutic Hypothermia

All 69 infants met one or more criteria for therapeutic hypothermia as outlined in Table 28. Three quarters of the women (71.0%), whose infants underwent therapeutic hypothermia in 2018, experienced an acute perinatal event. Almost half of infants experienced variable and/or late fetal heart rate decelerations during labour (49.3%; n=34).

Table 28: Assessment for therapeutic hypothermia in 2018

	TH cases 2018 N=69
≥36 completed weeks gestational age	**68(98.6)**
Apgar score ≤ 5 at 10 minutes	33(47.8)
Weight ≥ 1800 grams	69(100)
Continued need for PPV or Intubation at 10 mins	41(59.4)
Did an acute perinatal event occur?	**49(71.0)**
Variable / late fetal heart rate decelerations	34(49.3)
Prolapsed / ruptured / tight nuchal cord	2(2.8)
Uterine Rupture	3(4.3)
Maternal haemorrhage / placental abruption	6(8.6)
Maternal trauma	0(0.0)
Other	11(15.9)
Acidosis present in umbilical cord, or any blood sample within 60 minutes of birth	**44(63.8)**
Base Deficit >16.0 mmol/L in umbilical cord, or any blood sample, within 60 minutes of birth	**34(49.3)**

Note: Values are shown as N(%) unless otherwise stated.

The majority of the infants (97.1%, n=67 of 69) had a diagnosis of encephalopathy based on having an altered state of consciousness, (lethargy, stupor or coma). A grade of encephalopathy was assigned to 41.8% of infants (n=28 of 67). Table 29 illustrates that almost two thirds of infants were graded as moderately encephalopathic during assessment for therapeutic hypothermia (60.7%; n=17).

Table 29: Grade of encephalopathy during assessment for therapeutic hypothermia in 2016-2018

	TH cases 2016 N=29	TH cases 2017 N=40	TH cases 2018 N=28
Mild	3(10.3)	8(20.0)	2(7.1)
Moderate	17(58.6)	22(55.0)	17(60.7)
Severe	9(31.0)	10(25.0)	9(32.1)

Note: Values are shown as N(%) unless otherwise stated.

Transfer to Tertiary Unit

Over half of all infants who were delivered in Ireland in 2016 were born in a tertiary unit (52%).[1] Forty-one of the 69 infants who underwent neonatal therapeutic hypothermia in 2018 were born in a tertiary hospital (59.6%; Table 30). Twenty-eight infants required transfer to a tertiary unit for therapeutic hypothermia treatment (40.6%). The majority of infants were transported by the National Neonatal Transport Programme (67.9%; n=19 of 28) with the remaining nine (32.1%) infants being transported by the referring hospital's team.

Table 30: Transfer of infants to a tertiary unit for therapeutic hypothermia treatment in 2018

	TH cases 2018 N=69
Inborn at tertiary unit	41(59.6)
Out-born requiring transfer	28(40.6)
Transferred by the NNTP	19 of 28(67.9)
Transferred by referring hospital's team	9 of 28(32.1)

Note: Values are shown as N(%) unless otherwise stated.

For almost two-thirds of infants who required transfer, a referral call was made to the tertiary cooling centre within two hours of birth (73.9%, n=18 of 23; missing data for 5 infants). A call was made between two and three hours for 17.4% of infants requiring transport (n=4 of 23; missing data for five infants).

All 28 infants who required transfer to a tertiary centre, were commenced on Therapeutic Hypothermia at the referring hospital within four hours of birth, by means of passive cooling (7.1%; 2 of 28) and/or active cooling (92.9%; 26 of 28). All 28 infants who required transfer to a tertiary centre were initially passively cooled (see Table 31). Passive cooling was initiated within the first hour of birth for over half of infants (53.5%; n=15 of 28).

Table 31: Age of outborn infants at commencement of therapeutic hypothermia (passive and/or active modes) in 2018

	Passive Cooling N=28	Active Cooling N=23
Within 1 hour	15(53.5)	0(0)
1-2 hours	4(14.3)	2(8.7)
2-3 hours	4(14.3)	1(4.3)
3-4 hours	5(17.9)	4(17.3)
4-5 hours	(0)	8(34.9)
5-6 hours	0(0)	5(21.8)
Greater than 6 hours	0(0)	3(13.0)

Note: Values are shown as N(%) unless otherwise stated.

As illustrated in Figure 7, two-thirds of the infants transferred had a core temperature within the target range of 33°C to 34°C on departure from the referring hospital (67.9%, n=19 of 28) with one-quarter of infants (25.0%; n=7 of 28) having a core temperature ranging from 34.4°C to 35.9°C. Two infants had a core temperature below 33°C.

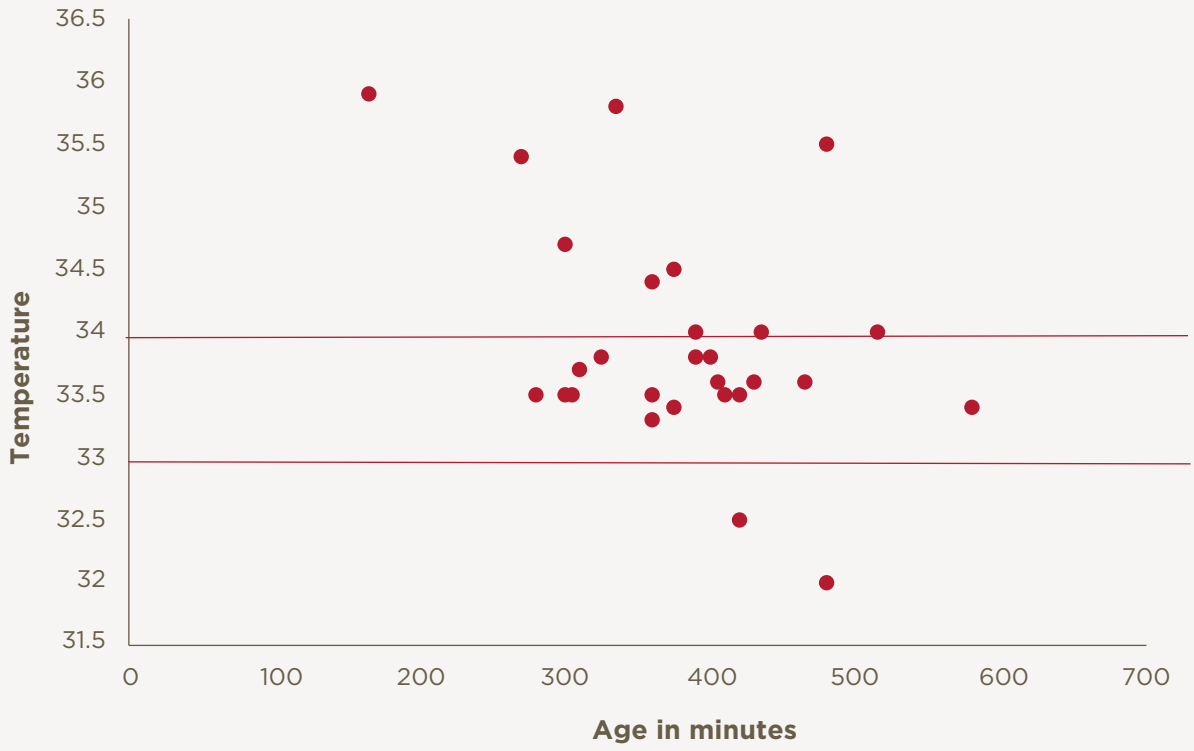

Figure 7: Temperature (°C) of infant by age (mins) on departure from referring hospital

Half of infants requiring transfer (42.9%; n=12 of 28) departed the referral hospital within six hours of birth (Table 32). Therapeutic Hypothermia was continued during transport in all cases where infants were transferred to a tertiary centre (100%; n= 28). The majority of infants transferred by the NNTP were changed from passive to active cooling for transport either before or on departure from the referral hospital (94.7%; n=18 of 19). Two infants already on active cooling at the referral centre, were changed from active to passive cooling during transfer to a tertiary centre by referring hospital teams. All bar two of the ten infants who were passively cooled during transfer had reached the optimal core temperature of between 33°C and 34°C within six hours of birth.

Table 32: Timing, from birth, of departure from a referring hospital and admission to a tertiary unit in 2018

	National Neonatal Transport Programme N=19	Own Hospital Team N=9
Departed referring unit within 6 hours	5(26.3)	7(77.8)
Admitted to tertiary unit within 6 hours	0(0.0)	2(22.2)

Note: Values are shown as N(%) unless otherwise stated. *Missing data for two infants.
**Data missing for three infants.

Over three-quarters of the 28 infants transferred for neonatal therapeutic hypothermia treatment required respiratory support (78.6%; n-22) and sedation (75.0%; n=21) en-route to a tertiary unit (Table 33).

Table 33: Management during transfer of infants for therapeutic hypothermia in 2018

	NNTP N=19	Own Hospital Team N=9
Respiratory support	**17(89.5)**	**5(55.8)**
Ventilation	13 of 15(86.7)*	4 of 5 (80.0)
CPAP	1 of 15(6.7)*	1 of 5 (20.0)
Nasal prong O_2	0(0.0)*	0(0.0)
Sedation	**17(89.5)**	**4(44.4)**
IV access	**19(100)**	**9(100)**
Peripheral	18 of 19(94.7)	8 of 9(88.9)
Umbilical	18 of 19(94.7)	6 of 9(66.7)

Note: Values are shown as N(%) unless otherwise stated. *Data missing for two infants.

Ninety three percent of the infants requiring transfer to a tertiary unit for therapeutic hypothermia treatment were admitted more than six hours after birth (92.9%; 26 of 28). One third (32.1%; n=9 of 28) of the infants requiring transfer to a tertiary unit for neonatal therapeutic hypothermia treatment were admitted nine or more hours after birth.

As illustrated in Figure 8, the majority of infants had a core temperature within the target range of 33°C to 34°C (89.3%, n=25 of 28) on admission to a tertiary unit. While 10.7% (n=3) had a core temperature ranging from 34.8°C to 36.3°C, with two of these three infants admitted to the tertiary unit before six hours of birth.

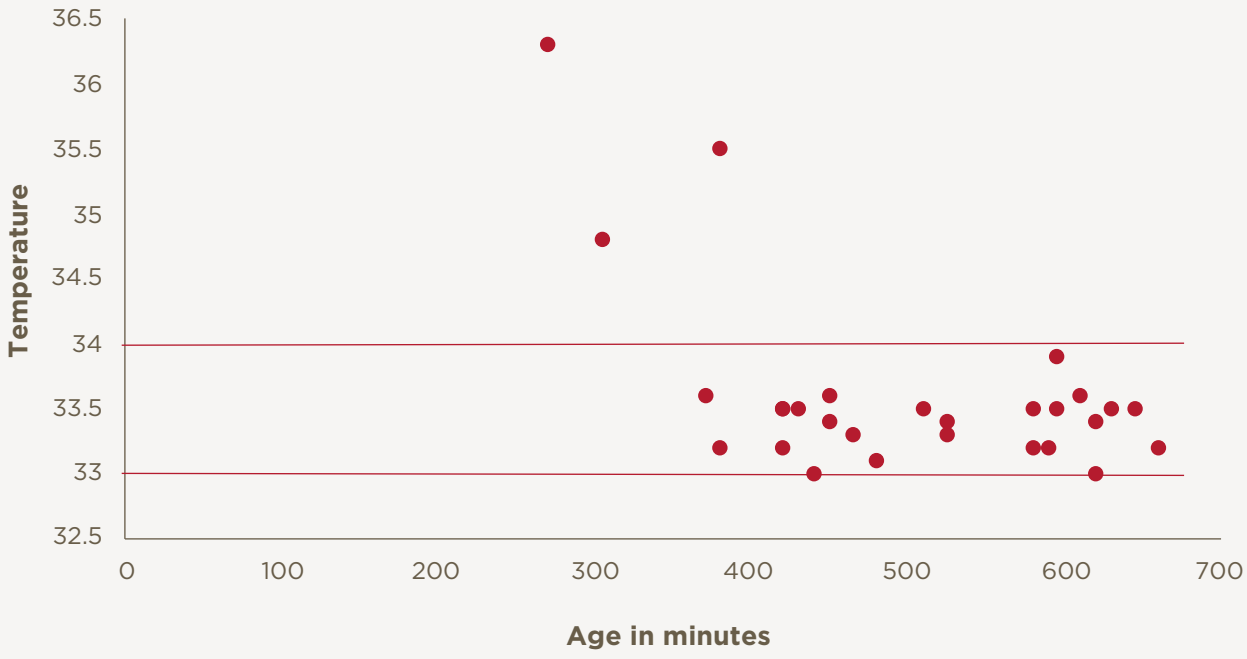

Figure 8: Temperature (°C) of infant by age (mins) on admission to a tertiary unit from a referring hospital

Initiating of Treatment

In line with practice guidelines, therapeutic hypothermia should be initiated within six hours of birth and should be continued for 72 hours. The optimum core temperature of 33°C to 34°C is targeted over this 72-hour period.

The time the decision to treat the infant with therapeutic hypothermia was not recorded in this audit. As illustrated in Table 34, almost all infants were passively cooled before active cooling was commenced (92.8%; n=64 of 69). Of these, almost two-thirds of infants were passively cooled within the first two hours of birth (60.8%; n=39 of 64). The majority of infants commenced active cooling within six hours of birth (85.5%; n=59 of 69).

Table 34: Age of infant at time of commencement of passive and active cooling for infants who underwent therapeutic hypothermia in 2018

	Passive Cooling N=64	Active Cooling N=69
Within 1 hour	28(43.6)	8(11.6)
1-2 hours	11(17.2)	11(15.9)
2-3 hours	6(9.4)	8(11.6)
3-4 hours	5(7.8)	11(15.9)
4-5 hours	3(4.7)	12(17.4)
5-6 hours	0(0.0)	9(13.0)
Greater than 6 hours	1(1.6)	10(14.5)

Note: Values are shown as N(%) unless otherwise stated.

The time when optimum core temperature was reached was recorded for 64 of the 69 infants (92.8%). Of these, 79.7% of infants (n=51) were reported to have achieved optimum core temperature within 6 hours of birth. Optimum core temperature was achieved for the remaining 13 infants (20.3%) between 6 and 16 hours of birth.

The 72-hour treatment clock should begin when the infant reaches the targeted 33-34°C rectal temperature. As illustrated in Figure 9, almost half of infants (46.9%; n=30 of 64, missing data for four infants) had their treatment started once they had achieved the optimum core temperature range. The remaining infants had begun their 72 hours of TH treatment before the optimum core temperature range was achieved (54.1%; n=34 of 64).

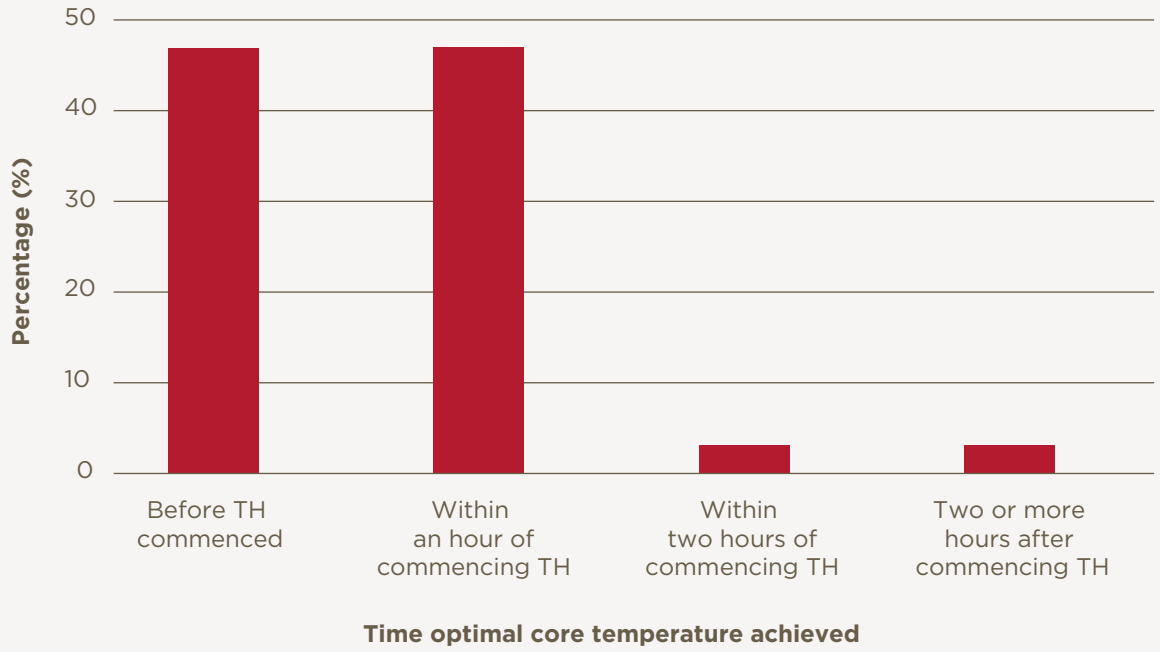

Figure 9: Time infants achieved optimal core temperature in relation to the time TH treatment commenced in 2018

Treatment Days 1-3

As outlined in Table 35, almost all infants admitted for neonatal therapeutic hypothermia received sedation on Day 1 (98.6%; n=68 of 69), Day 2 (94.2%; n=65 of 69) and Day 3 (89.9%; n=62 of 69) of treatment. The vast majority of infants were administered antibiotics on Day 1 and Day 2 of treatment, with almost half receiving antibiotics on Day 3 (43.5%; n=30 of 69). Seven infants required blood products on Day 1 of treatment (10.1%) of which the majority had fibrinogen administered (71.4%; n= 5 of 7).

Table 35: Drugs and Volume Replacement Day 1, 2 & 3 in 2018

	Day 1	Day 2	Day 3
Sedation	68(98.6)	65(94.2)	62(89.9)
Antibiotics	67(97.1)	64(92.8)	30(43.5)
Anticonvulsants	15((21.7)	10(14.5)	10(14.5)
Inotropes	17(24.6)	17(24.6)	13(18.8)
Blood products	7(10.1)	4(5.8)	2(2.9)
Volume replacement (normal saline)	12(17.4)	3(4.3)	2(2.9)
Other	11(15.9)	10(14.5)	6(8.7)

Note: Values are shown as N(%) unless otherwise stated. Categories are not mutually exclusive.

As outlined in Tables 36 and 37, a number of diagnostic investigations were undertaken during the 72 hours of therapeutic hypothermia treatment.

Table 36: Laboratory Parameters Day 1, 2 & 3 in 2018*

	Day 1 N=69	Day 2 N=69	Day 3 N=69
Acid base parameters	68(98.6)	63(91.3)	55(79.7
Coagulation	32(46.4)	8(11.6)	3(4.3)
Biochemistry	57(82.6)	48(69.6)	36(52.2)
Lumbar puncture	2(2.9)	2(2.9)	2(2.9)
Metabolic Screen	3(4.3)	0(0.0)	2(2.9)

Note: Values are shown as N(%) unless otherwise stated. Categories are not mutually exclusive. *Data for laboratory tests which may have been undertaken during assessment for therapeutic hypothermia were not recorded and therefore are not presented here.

In relation to neuro imaging, 68.1% (n=47) of infants had a cranial ultrasound in the first three days of life. Six of these 47 infants underwent more than one cranial ultrasound. Of the 56 cranial ultrasounds undertaken, 14 (29.8%) were abnormal. During the three-day period, 1.4% of infants (n=1) underwent Magnetic Resonance Imaging (MRI) of the brain in Day 3 (Table 37).

Table 37: Investigations Day 1, 2 & 3 in 2018

	Day 1 N=69	Day 2 N=69	Day 3 N=69
Cranial ultrasound	25(36.2)	16(23.2)	15(21.7)
MRI of the brain	0(0.0)	0(0.0)	1(1.4)
Echocardiography	15(21.7)	8(11.6)	2(2.9)

Note: Values are shown as N(%) unless otherwise stated. Categories are not mutually exclusive.

SARNAT Scoring

Infants were assigned a SARNAT[16] score based on clinical behaviour on Day 1, Day 2 and Day 3 of treatment (Table 38). A diagnosis of encephalopathy, consisting of an altered state of consciousness (lethargy, stupor or coma) was only assigned to half of infants who had the SARNAT completed over the 72 hour period of therapeutic hypothermia. As outlined in Table 39, over half of infants were graded as moderately encephalopathic on Day 1 (66.7%; n=28 of 42), Day 2 (58.1%; 18 of 36) and Day 3 (51.9%; n=14 of 36) of treatment.

Table 38: SARNAT Scoring on Treatment Day 1, 2 & 3 in 2018

		Day 1 N=69	Day 2 N=67	Day 3 N=64
Level of consciousness				
	Hyperalert	8 (11.6)	4 (6.0)	
	Lethargic or obtunded	24 (34.8)	18 (26.9)	13 (20.3)
	Stupor or Coma	6 (8.7)	4 (6.0)	3 (4.7)
	Normal	18 (26.1)	13 (19.4)	15 (23.4)
	Undocumented	13 (18.8)	27 (40.3)	33 (51.6)

Activity				
	Normal	24 (34.8)	20 (29.9)	17 (26.6)
	Decreased	26 (37.7)	20 (29.9)	14 (21.9)
	Absent	7 (10.1)	4 (6.0)	3 (4.7)
	Undocumented	12 (17.4)	23 (34.3)	31 (48.4)
Neuromuscular Control				
Muscle tone	Normal	9 (13.0)	11 (15.9)	10 (15.6)
	Mild hypotonia	26 (37.7)	12 (17.9)	12 (18.8)
	Flaccid	7 (10.1)	4 (5.8)	4 (6.3)
	Undocumented	27 (39.1)	40 (59.7)	38 (59.4)
Posture	Mild distal flexion	9 (13.0)	3 (4.5)	2 (3.1)
	Strong distal flexion	8 (11.6)	8 (11.6)	7 (10.9)
	Intermittent decerebration	3 (4.3)	0(0.0)	0(0.0)
	Normal	4 (5.8)	2 (3.0)	2 (3.1)
	Undocumented	44 (63.8)	53 (79.1)	53 (82.8)
Stretch reflexes	Overactive	2 (2.9)	3 (4.5)	3 (4.7)
	Decreased or absent	4 (5.8)	1 (1.5)	3 (4.7)
	Normal	4 (5.8)	7 (10.4)	4 (6.3)
	Undocumented	57 (82.6)	53 (79.1)	52 (81.3)
Complex Reflexes				
Suck	Weak	16 (23.2)	8 (11.9)	6 (9.4)
	Weak or absent	6 (8.7)	7 (10.4)	5 (7.8)
	Absent	10 (14.5)	6 (9.0)	4 (6.3)
	Normal	13 (18.8)	10 (14.9)	14 (21.9)
	Undocumented	22 (31.9)	34 (50.7)	35 (54.7)
Moro	Strong; low threshold	0(0.0)	2 (3.0)	0(0.0)
	Weak; incomplete high threshold	4 (5.8)	0(0.0)	0(0.0)
	Absent	4 (5.8)	3 (4.5)	2 (3.1)
	Normal	8 (11.6)	3 (4.5)	4 (6.3)
	Undocumented	48 (69.6)	56 (83.6)	57 (89.1)
Tonic Neck	Slight	0(0.0)	0(0.0)	0(0.0)
	Strong	0(0.0)	0(0.0)	0(0.0)
	Absent	0(0.0)	1 (1.5)	1 (1.6)
	Normal	1 (1.4)	1 (1.5)	0(0.0)
	Undocumented	66 (95.7)	61 (91.0)	63 (98.4)
Autonomic Function				
Pupils	Mydriasis	3 (4.3)	3 (4.5)	2 (3.1)
	Miosis	15 (21.7)	6 (9.0)	1 (1.6)
	Variable; often unequal, poor light reflex, fixed, dilated	6 (8.7)	4 (6.0)	2 (3.1)
	Normal	16 (23.2)	5 (7.5)	13 (20.3)
	Undocumented	28 (40.6)	46 (68.7)	45 (70.3)
Heart rate	Tachycardia	0(0.0)	0(0.0)	0(0.0)
	Bradycardia	14 (20.3)	11 (16.4)	10 (15.6)
	Variable	0(0.0)	1 (1.5)	0(0.0)
	Normal	53 (76.8)	54 (80.6)	53 (82.8)
	Undocumented	1 (1.4)	0(0.0)	0(0.0)
Seizures	None	59 (85.5)	57 (85.1)	0(0.0)
	Common; focal or multifocal	10 (14.5)	9 (13.4)	0(0.0)
	Uncommon (excluding decerebration)	0(0.0)	0(0.0)	0(0.0)
	Normal	0(0.0)	0(0.0)	0(0.0)
	Undocumented	0(0.0)	0(0.0)	0(0.0)

Note: Values are shown as N(%) unless otherwise stated.

Table 39: Grade of Encephalopathy on Treatment Day 1, 2 & 3 in 2018

	Day 1 N=42	Day 2 N=31	Day 3 N=27
Mild	4(9.5)	3(9.7)	3(11.1)
Moderate	28(66.7)	18(58.1)	14(51.9)
Severe	10(23.8)	10(32.3)	10(37.0)

Note: Values are shown as N(%) unless otherwise stated.

Over the course of the 72 hours of treatment, amplitude-integrated electroencephalography (aEEG) interpretation was documented for two thirds of cases (65.5%). As outlined in Table 40, the number of cases where the aEEG was interpreted as severely abnormal reduced from 25.0% (n=12 of 69) on Day 1 to 13.5% (n=5 of 37) on Day 3. Electrical seizures were identified in 14 of the 69 infants (20.3%) on Day 1, 10 of the infants (14.5%) on Day 2 and four of all the infants (5.8%) on Day 3.

Table 40: aEEG interpretation on Treatment Day 1, 2 & 3 in 2018

	Day 1 (n=69)	Day 2 (n=67)	Day 3 (n=64)
aEEG interpretation documented	**48(69.5)**	**46(66.7)**	**37(57.8)**
Interpretation			
Normal	21 of 48(43.8)	26 of 46(56.5)	23 of 37(62.2)
Abnormal	9 of 48(18.8)	6 of 46(13.0)	3 of 37(8.1)
Moderately abnormal	0(0.0)	6 of 46(13.0)	6 of 37(16.2)
Severely abnormal	12(25.0)	8 of 46(17.4)	5 of 37(13.5)
Electrical seizures	**14(20.3)**	**10(14.9)**	**4(6.3)**

Rewarming

Of the 69 infants who underwent therapeutic hypothermia treatment, 9 infants (13.0%) did not complete 72 hours of therapeutic hypothermia in 2018. As outlined in Table 41, two-thirds of these infants had their care redirected (62.5%; n=5 of 8).

Table 41: Indications to cease rewarming of infants who underwent TH in 2016-2018 before 72 hours completed therapy

	TH cases N=4 2016	TH cases N=9 2017	TH cases N=8* 2018	TH cases N=21 2016-2018
Redirection of care	3(75.0)	7(77.8)	5(62.5)	15(71.4)
PPHN	1(25.0)	1(11.1)	2(25.0)	4(19.0)
Sepsis	0(0.0)	1(11.1)	1(12.5)	2(9.5)

Note: Values are shown as N(%) unless otherwise stated. *Missing data for one infant.

Excluding the 5 infants whose treatment was ceased, data on rewarming was available for 57 of the 64 infants (89.1%). As outlined in Table 42, most infants were rewarmed within 12 hours (86.0%; n=49 of 57) in 2018. During the rewarming period, six of the 57 infants (10.5%) had seizures. Infants were rewarmed over periods of between 6 and 18 hours.

Table 42: Duration of rewarming for infants who underwent therapeutic hypothermia in 2016-2018

	TH cases N=59 2016	TH cases N=66 2017	TH cases N=57 2018	TH cases N=182 2016-2018
Up to 12 hours	48(81.4)	50(75.8)	49(86.0)	143(78.6)
13 – 15 hours	4(6.8)	0(0.0)	1(1.8)	5(2.7)
16 – 18	7(11.9)	14(21.2)	7(12.3)	28(15.4)
Greater than 19 hours	0(0.0)	2(3.0)	0(0.0)	2(1.1)

Note: Values are shown as N(%) unless otherwise stated.

Feeding

Data on the introduction of feeding was recorded for 63 of the 69 infants who underwent therapeutic hypothermia treatment (91.3%). None of the mothers breastfed on introduction of feed, two-thirds of infants were fed with expressed breastmilk (68.1%; n=47) and 28 were fed with formula (40.6%). As outlined in Table 43, the majority of infants had feed introduced on Day 4 (52.4%; n=33) or Day 5 (23.8%; n=15). The majority of infants reached full oral requirement (92.8%; n=61 of 69).

Table 43: Age that infants who underwent therapeutic hypothermia in 2016-2018 had feed introduced

	TH cases N=60 2016	TH cases N=66 2017	TH cases N=63 2018	TH cases N=189 2016-2018
Up to Day 3	6(10.0)	2(3.0)	11(12.7)	19(10.1)
Day 4	17(28.3)	21(31.8)	33(52.4)	71(37.7)
Day 5	25(41.7)	28(42.4)	15(23.8)	68(36.0)
Day 6	8(13.3)	11(16.7)	3(4.8)	22(11.6)
Day 7+	4(6.6)	4(6.1)	1(1.6)	9(4.8)

Note: Values are shown as N(%) unless otherwise stated.

Of these 63, two-thirds of infants were initially fed with a nasogastric tube (60.3%; n=38). Of these, one quarter of infants were fed with a nasogastric tube for less than 24 hours (23.5%; n= 8 of 34; missing data for 4 infants). As indicated in Table 44, one infant was discharged home with a nasogastric tube (2.9%).

Table 44: Duration of feeding with a nasogastric tube for infants who underwent therapeutic hypothermia in 2016-2018

	TH cases N=30 2016	TH cases N=36 2017	TH cases N=34 2018	TH cases N=90 2016-2018
Less than 24 hours	9(30.0)	7(19.4)	8(23.5)	24(26.7)
24-47 hours	6(20.0)	7(19.4)	3(8.8)	16(17.8)
48-71 hours	4(13.3)	8(22.2)	1(2.9)	13(14.4)
Greater than 72 hours	8(26.7)	6(16.7)	21(61.8)	25(27.8)
Discharged home with a nasogastric tube	3(10.0)	8(22.2)	1(2.9)	12(13.3)

Note: Values are shown as N(%) unless otherwise stated.

Specific placental conditions

Of the 69 infants who underwent TH, the placenta was retained and sent for histological analysis in 53 of the 69 cases (76.8%). Of these, 41 placental examinations were complete (77.4%, n=41 of 53). All 41 completed reports were made available to the NPEC for inclusion in this report.

Placental disease categories have been divided into subsections and, while numbers in any one year are small, it will assist in understanding the relative contribution of placental conditions. In particular, a severe fetal inflammatory response is associated with abnormal neonatal neurologic findings in cases of chorioamnionitis.

Abnormal placental findings have been classified in line with recommendations from the publication from the international consensus meeting of pathology.[18] These are presented under the following broad categories: maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), cord pathology, cord pathology with distal disease, chorioamnionitis, villitis and other. Chorioamnionitis was present in a third of cases (34.1%; n=14 of 41). Conditions within the categories of MVM (29.2%, n=12 of 41) and FVM (17.0%, n=7 of 41) were also commonly reported (see Table 45).

Placenta pathologies represent the largest category of cause of intrauterine death, with placental disease explaining up to 65% of stillbirths.[19] With the standardisation of terminology[18] the prevalence of major pathologic findings becomes clearer as national data accumulates.

Relatively few studies have examined large numbers of consecutive placentas. One such study, conducted in the National Maternity Hospital on 816 placentas[20], found what is now termed MVM in 4.5% of controls and FVM in 2.9% of controls.

Placentas of infants with NE that underwent TH, showed over a 6-fold increase in FVM (29.2% v 4.5%) and a similar increase of MVM (17.0% v 2.9%). The prevalence of MVM and FVM in placentas of stillborn infants and those needing TH shows the importance of placental examination in all cases of perinatal loss and of adverse outcome.

Table 45: Placental histology findings for infants who underwent neonatal therapeutic hypothermia in 2016-2018 versus Stillbirths in 2017

	TH cases N=72 2016/2017	TH cases N=41 2018	Stillbirth[16] N=234 2017
Maternal Vascular Malperfusion (MVM)	19(26.4)	12 (29.2)	81(34.6)
• Low Grade		11(26.8)	
• High Grade		1(2.4)	
Fetal Vascular Malperfusion (FVM)	16(22.2)	7 (17.0)	60(25.6)
• Low Grade		4(9.7)	
• High Grade		3(7.3)	
Any Cord Pathology	14(19.4)	14 (34.0)	54(23.1)
• Isolated		9(21.9)	
• Cord Pathology with distal FVM		3 (7.3)	
• Cord Pathology with distal High Grade FVM		2 (4.8)	
Chorioamnionitis	20(27.8)	14(34.1)	21(9.0)
Chorioamnionitis FIR Stage 2		1(2.4)	
Villitis	3(4.2)	4(9.7)	10(4.3)
Other Placental Condition	28(38.9)	12(29.2)	35(15.0)
Normal	–	3(7.3)	–

Note: Values are shown as N(%) unless otherwise stated. Categories are not mutually exclusive.

Discharge diagnosis and neonatal death

Of the 69 infants who underwent therapeutic hypothermia treatment, 63 infants (91.3%) had MRI of the brain undertaken. The MRI report was available in 59 of the 63 cases (93.7%). The MRI reports were assessed by adopting the Barkovich HIE scoring system.[21]

Adopting the Barkovich HIE scoring system, one quarter (25.4%; n=15 of 59) had an abnormal MRI compared to 35% (n=34 of 96) of the infants in 2016/2017 with an abnormal report. The full set of Barkovich HIE scores are outlined in Appendix A.

In 12 of the 69 cases no reference was made to HIE on discharge (Table 46). When HIE was referenced at discharge, a grade of moderate encephalopathy was assigned to almost half of cases (54.4%; n=31 of 57).

Table 46: Grade of encephalopathy on discharge in 2016-2018

	TH cases N=60 2016	TH cases N=68 2017	TH cases N=69 2018	TH cases N=197 2016-2018
HIE – no grade assigned	27(45.0)	29(42.6)	0(0.0)	56(28.4)
Mild HIE	2(3.3)	3(4.4)	4(5.8)	9(4.6)
Mild-Moderate HIE	1(1.7)	6(8.8)	4(5.8)	11(5.6)
Moderate HIE	23(38.3)	18(26.5)	31(44.9)	72(36.5)
Moderate to Severe HIE	0(0.0)	1(1.5)	3(4.3)	4(2.0)
Severe HIE	6(10.0)	5(7.4)	15(21.7)	26(13.2)
HIE not documented	1(1.7)	6(8.8)	12(17.4)	19(9.6)

Note: Values are shown as N(%) unless otherwise stated.

The survival rate for the infants who underwent therapeutic hypothermia in 2018 was 93.9%, as 7 of the 69 infants died. Three of deaths occurred within 7 completed days of birth and were classified as early neonatal deaths (42.9%; n=3 of 7). As outlined in Table 47, three deaths occurred after the 7th day and within 28 completed days of birth and were classified as late neonatal deaths (42.9%; n=3 of 7). All seven infants had an autopsy performed (100%) as they were referred to the coroner. It is important to note that data on the findings of these reports, and on the infants' respective causes of death, were not collected for this report.

Table 47: Perinatal and infant mortality for infants who underwent therapeutic hypothermia in 2016-2018

	TH cases N=6 2016	TH cases N=11 2017	TH cases N=7 2018	TH cases N=24 2016-2018
Early neonatal death	0(0.0)	5(45.5)	3(42.9)	8(33.3)
Late neonatal death	2(33.3)	4(36.4)	3(42.9)	9(37.5)
Infant death	4(66.7)	2(18.2)	1(14.3)	7(29.2)

Note: Values are shown as N(%) unless otherwise stated.

As outlined in Table 48, first infant blood lactate level was strongly associated with risk of death among infants treated with TH. As expected, higher blood lactate scores were associated with increased risk of death. Similarly, low Apgar score was an indicator of mortality risk. Twenty-one percent of the infants with an Apgar score ≤5 at 10 minutes died, which was 4.8 times higher than the risk of deaths among the other infants.

Table 48: Maternal and infant characteristics and mortality risk for infants who underwent therapeutic hypothermia in 2016- 2018

		Number of infants	Number (%) who died	Risk ratio
All		209	24(11.5)	
Parity	Nulliparous	123	11(8.9)	1.00 (ref.)
	Parous	86	13(15.1)	1.69
Pre-existing medical problems	Yes	63	10(15.9)	1.50
	No	146	14(10.6)	1.00 (ref.)
Mode of delivery	Spontaneous Vaginal	45	5(11.1)	1.00 (ref.)
	Instrumental/ Operative	164	19(11.6)	1.04
Birthweight centile	<10th	38	3(7.9)	1.03
	10-49th	83	13(15.7)	2.04
	50-89th	65	5(7.7)	1.00 (ref.)
	>90th	23	3(13)	1.70
Sex	Male	133	13(9.8)	1.00 (ref.)
	Female	76	11(14.5)	1.48
First infant blood lactate	0 to 4	7	0(0)	0
	5 to 14	120	6(5)	1.00 (ref.)
	15+	53	9(17)	3.40
	Undocumented	29	9(31)	6.21
Assessment for therapeutic hypothermia				19(9.6)
>36 completed weeks gestational age	Yes	201	24(11.9)	1.00 (ref.)
	No	8	0(0)	0
Apgar score ≤ 5 at 10 minutes	Yes	92	19(20.7)	4.83
	No	117	5(4.3)	1.00 (ref.)
Weight ≥ 1800 grams	Yes	209	24(11.5)	
	No	0	0(0)	
Continued need for PPV or Intubation at 10 mins	Yes	128	22(17.2)	6.96
	No	81	2(2.5)	1.00 (ref.)
Did an acute perinatal event occur?	Yes	123	21(17.1)	4.89
	No	86	3(3.5)	1.00 (ref.)
Acidosis present in umbilical cord, or any blood sample within 60 minutes of birth	Yes	142	22(15.5)	5.19
	No	67	2(3)	1.00 (ref.)
Base Deficit >16.0 mmol/L in umbilical cord, or any blood sample, within 60 minutes of birth	Yes	107	20(18.7)	4.77
	No	102	4(3.9)	1.00 (ref.)
Diagnosis of encephalopathy during assessment for TH	Yes	136	15(11)	0.89
	No	73	9(12.3)	1.00 (ref.)

Appendix A. Barkovich HIE Scores

Result	Watershed (WS)	Basal Ganglia/Watershed (BG/W)	Basal Ganglia (BG)
Abnormal	4	5	4
Abnormal	4	0	3
Abnormal	2	2	3
Abnormal	2	2	3
Abnormal	2	2	3
Abnormal	2	0	1
Abnormal	2	0	1
Abnormal	2	0	1
Abnormal	1	3	3
Abnormal	0	5	2
Abnormal	0	2	2
Abnormal	0	2	2
Abnormal	0	2	1
Abnormal	0	1	2
Abnormal	0	1	2
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
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Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0
Normal	0	0	0

Appendix B.

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