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Abstract

Background: The acid-base status of infants around birth can provide information about their past, current and future condition. Although umbilical cord blood pH less than 7.0 or base deficit equal to or greater than 12mmol/l is associated with increased risk of adverse outcome, there is uncertainty about the prognostic value of degree of acidosis as previous studies have used different variables, thresholds, outcomes and populations.

Methods: Retrospective review of routinely collected clinical data in all liveborn inborn infants of 35 weeks gestation or more delivered between January 2005 and December 2013 at the Simpson Centre for Reproductive Health, Edinburgh, UK. Infants were included if their lowest recorded pH was less than 7 and/or highest base deficit equal to or greater than 12mmol/l on either umbilical cord blood and/or neonatal blood gas within one hour of birth. Neurodevelopmental outcome of the infants with encephalopathy was collected from the targeted follow-up database.

Results: 56,574 infants were eligible. 506 infants (0.9%) met inclusion criteria. Poor condition at birth and all adverse outcomes increased with worsening acidosis. Combined outcome of death or cerebral palsy was 3%, 10% and 39% at lowest pH of 6.9-6.99, 6.8-6.89 and <6.8 respectively, and 8%, 14% and 59% at a base deficit of 12-15.9, 16-19.9, and 20mmol/l or more respectively.

Conclusions: There is a dose-dependent relationship between the degree of acidosis within an hour of delivery, and the likelihood of adverse neonatal and later neurodevelopmental outcome in infants born at 35 weeks gestation or more.

Introduction:

Perinatal asphyxia is an important cause of neonatal morbidity and mortality. Umbilical cord blood pH less than 7.0 or base deficit equal to or greater than 12mmol/l are thresholds beyond which the risk of adverse outcome is considered to be increased[1]. Most infants whose measurements reach these thresholds recover without sequelae, but some develop neonatal encephalopathy. The relationship between umbilical cord blood pH or base deficit at birth and the immediate condition of the infant and risk of subsequent encephalopathy is not well characterised. In perinatal litigation, considerable importance can be attached retrospectively to these measurements in infants who die or develop permanent disability, with arguments about the likely impact of earlier delivery on the outcome based on weak scientific literature.

The aim of this large population-based study was to describe relationship between pH and base deficit around the time of birth, and the immediate clinical condition of the infants after birth, the risk of neonatal encephalopathy, and the risk of death or survival with permanent disability.

Methods:

The study took place in the Simpson Centre for Reproductive Health at the Royal Infirmary of Edinburgh, UK. This is a regional referral centre with 7000 to 8000 births per annum. Data was sought for all live-born infants of 35 weeks gestation or more who were delivered between January 2005 and December 2013. It was routine practice for umbilical arterial and venous blood sampling to be attempted after all deliveries. Umbilical cord blood gases occasionally do not reflect the true acid-base status of a newborn infant (for example in cases where there has been umbilical cord obstruction). Therefore both umbilical cord blood gas and early neonatal blood gas results were collected to capture the blood gas values when infants were at their most acidotic. Hospital policy is to aim to provide routine postnatal ward care alongside the

mother to all infants who are born at 35 weeks gestation or more. Where an infant was admitted to the Neonatal Unit, blood gas data were collected from the admission blood gas sample, if it was obtained within 1 hour of birth. Infants were included in the study if the lowest recorded pH value was <7.0 or the base deficit value was equal to or greater than 12mmol/l either on an umbilical cord blood specimen or on a blood gas specimen obtained from the infant within an hour of birth.

Umbilical cord blood samples and neonatal unit admission blood gas samples were analysed at the point of care using Radiometer ABL805M Flex blood gas analysers in the delivery suite and neonatal unit. Blood gas results were entered into the clinical records. Individual infants could have umbilical arterial and venous blood gases and a neonatal unit admission blood gas (capillary, venous or arterial) obtained within the first hour after birth. Most infants therefore had more than one blood gas sample and for each infant the lowest pH and the most acidotic base deficit from any of these specimens were included. Results were excluded where a transcription error had resulted in an impossible pH or base deficit result being recorded such as with values with more digits than are reported by the analyser or a result outside the clinically observable range. We did not differentiate between umbilical arterial and venous specimens, simply taking the most acidotic specimen for each infant.

The clinical details of the infants were extracted from the electronic patient record systems (Clevermed Badger and TRAK). Data recorded for each infant included pH, base deficit, highest blood lactate level within the first hour, lowest blood glucose level in the first hour, Apgar scores at 1 and 5 minutes, need for IPPV (Intermittent Positive Pressure Ventilation) by mask or endotracheal tube during initial stabilisation, need for cardiac massage during initial stabilisation, neonatal encephalopathy as defined by Sarnat[2] and mortality (both in the labour

suite and within 2 years of birth). Neurodevelopmental follow up until 2 years of age was offered to all surviving infants diagnosed with grade 2 or 3 HIE, as these infants are at highest risk of neurodevelopmental problems. Follow up was not organised for infants with perinatal acidosis who did not develop encephalopathy. For infants diagnosed with cerebral palsy, a Gross Motor Function Classification System (GMFCS)[4] score of 1 was classed as "mild", 2 as "moderate", and 3 to 5 was classed as "severe". Development was classified as normal in infants in whom there was no concern about developmental delay and delayed in any infant with ongoing concerns.

Advice from the South East Scotland Research Ethics Service indicated that formal NHS ethical review under the terms of the Governance Arrangements for Research Ethics Committees was not needed to review routinely collected data in the neonatal records.

Results:

There were 59,092 live inborn infants during the study period, of which 56,574 were born at 35 weeks gestation or more. 4776 eligible infants (8.4%) were admitted to the neonatal unit during the study period. Overall, there were 506 infants (0.9%) who met the inclusion criteria.

pH: This included 504 infants with a lowest pH less than 7.0 of whom 468 had their lowest pH on umbilical cord blood and 37 had their lowest pH on blood gas specimen within an hour of birth. Two further infants had a pH above 7 but met inclusion criteria on base deficit.

Base Deficit: There were 223 of the 506 infants who had a base deficit equal to or greater than 12mmol/l. Of these, 151 infants had their highest base deficit on an umbilical cord blood specimen and 72 infants had their highest base deficit on a blood gas specimen within an hour of birth. Of the 504 infants with pH <7.0 there were 199 infants whose base deficit was not 12 or greater and there were 85 infants who did not have a valid base deficit value recorded.

A valid pH was recorded in 66.9% of infants. Base deficit was poorly documented in the electronic patient data record. A valid base deficit was recorded in 5.1% of eligible infants. A flowchart of data acquisition is shown in figure 1.

Neurodevelopmental Outcome

Of the 506 eligible infants, 3 (0.6%) died in the delivery suite, 271 (53.6%) were admitted to the neonatal unit, and 63 (12.4%) developed HIE grade 2 or 3. There were 24 deaths of infants overall (3 deaths in the delivery suite, and 21 in infants with a diagnosis of HIE grade 2 or 3). There were 42 surviving infants who developed grade 2 or 3 HIE (29 grade 2 and 13 grade 3). Information about developmental delay on follow up was available for 38 out of 41 cases (93%). This was to at least 2 years for 33 out of 41, and to at least 21 months for 5 out of 41. One infant (who had grade 2 HIE) had extensive cystic encephalomalacia, microcephaly, cerebral palsy and developmental delay when follow up was taken over in another service at 5 months. A further two infants were lost to follow up (1 had grade 2 HIE and 1 had grade 3 HIE). There were 15 cases of cerebral palsy in the 39 infants with grade 2 or 3 HIE with follow up data. All of the infants with cerebral palsy were also considered to have delayed development. Infants are categorised according to degree of acidosis in table 1, which details Apgar scores, resuscitation required and early mortality. For those admitted to the neonatal unit, table 2 shows highest lactate and lowest glucose within one hour, highest grade of hypoxic-ischaemic encephalopathy during admission, cerebral palsy and mortality. Long term outcomes for those diagnosed with hypoxic-ischaemic encephalopathy grade 2 or 3 is shown in table 3. Outcomes compared to degree of acidosis are in figures 2 and 3.

Worsening acidosis as measured by either pH or base deficit was associated with poor condition at birth and the development of hypoxic-ischaemic encephalopathy, and at 2 years

with death or cerebral palsy. The risk of death or cerebral palsy was 3%, 10% and 39% at a lowest pH of 6.9-6.99, 6.8-6.89 and less than 6.8 respectively, and 8%, 14% and 59% at a base deficit of 12-15.9, 16-19.9 and 20mmol/ or more respectively. When data are restricted to 2009 onwards after the introduction of therapeutic hypothermia for HIE grade 2 or 3, the findings were very similar with risk of death or cerebral palsy 3%, 9% and 35% at lowest pH of 6.9-6.99, 6.8-6.89 and less than 6.8 respectively, and 9%, 15% and 64% at a base deficit of 12-15.9, 16-19.9mmol/l, and 20mmol/l or more respectively. Long-term outcomes of infants before and after the introduction of therapeutic hypothermia are shown in table 4.

Table 1: Condition at birth categorised by pH and base deficit

	Lowest pH within an hour of birth			Worst base deficit within an hour of birth (mmol/l)			
	<6.8	6.8-6.89	6.9-6.99	≥ 20	16 to 19.9	12 to 15.9	< 12
N	53	91	360	27	50	146	199
Apgar at 1 min*	1(0-3,53)	4(2-6,83)	6(3-8,338)	1(0-2,26)	3(1-6,48)	5(2-7,132)	6(3-7,187)
Apgar at 5 mins*	4(2-6,53)	7(5-9,86)	9(7-9,342)	4(3-4,26)	6(4-8,48)	8(6-9,134)	8(7-9,189)
IPPV at birth	43 (81%)	59 (65%)	174 (48%)	23 (85%)	38 (76%)	88 (60%)	107 (54%)
Cardiac massage	23 (43%)	7 (8%)	10 (3%)	16 (59%)	7 (14%)	10 (7%)	7 (4%)
Death in DS	2	0	1	1	2	0	0
Admitted to NNU	48 (91%)	66 (73%)	157 (44%)	26 (96%)	39 (78%)	87 (59%)	90 (45%)

*median(IQR,n), IPPV: Intermittent Positive Pressure Ventilation, DS: Delivery Suite, NNU: Neonatal Unit

Table 2: Neonatal outcomes for those infants admitted to the neonatal unit and neurodevelopmental outcomes for infants undergoing targeted follow-up

	Lowest pH within an hour of birth			Worst base deficit within an hour of birth (mmol/l)			
	<6.8	6.8-6.89	6.9-6.99	≥ 20	16 to 19.9	12 to 15.9	< 12
N	53	91	360	27	50	146	199
Admissions	48 (91%)	66 (73%)	157 (44%)	26 (96%)	39 (78%)	87 (59%)	90 (45%)
Lactate* (mmol/l)	17.8 (9.0,36)	14.1 (7.1,52)	11.8 (5.0,124)	15.2 (9.7,23)	15.5 (7.9,32)	13.4 (6.5,64)	11.6 (4.8,75)
Glucose* (mmol/l)	5.5 (3.0,35)	5.4 (3.4,53)	4.4 (2.6,123)	5.0 (3.4,23)	5.8 (2.5,32)	4.5 (2.6,64)	4.7 (3.0,75)
All HIE	35 (66%)	26 (29%)	18 (5%)	19 (70%)	19 (38%)	22 (15%)	9 (5%)
HIE Grade 1	4 (8%)	9 (10%)	3 (1%)	2 (7%)	7 (14%)	5 (3%)	1 (0.5%)
HIE Grade 2	12 (23%)	11 (12%)	8 (2%)	4 (15%)	8 (16%)	7 (5%)	6 (3%)
HIE Grade 3	19 (36%)	6 (7%)	7 (2%)	13 (48%)	4 (8%)	10 (7%)	2 (1%)
CP 95% CI	9 (17%) (9-29%)	4 (4%)	2 (0.6%)	9 (33%) (19-52%)	2 (4%)	3 (2%)	0
Death 95% CI	11 (21%) (12-33%)	5 (5%)	8 (2%)	7 (26%) (13-45%)	5 (10%)	8 (5%)	1 (0.5%)
Death or CP 95% CI	21 (40%) (28-53%)	9 (10%)	10 (3%)	16 (59%) (41-75%)	7 (14%)	11 (8%)	1 (0.5%)

*mean (standard deviation,n), HIE: Hypoxic-Ischaemic Encephalopathy, CP: Cerebral palsy, Death includes early death in delivery suite, up to age 2 years. Percentages are expressed from the total number of infants in that pH or base deficit range. CI confidence intervals

Table 3: Long term outcomes for those infants who developed hypoxic-ischaemic encephalopathy grade 2 or 3

		HIE grade 2	HIE grade 3	p value*
	n	31	32	
Acid-base status	pH mean (95% CI)	6.83 (6.64-7.13)	6.72 (6.57-7.02)	.0004
	Base deficit mean (95% CI)	16.6 (11.47-21.73)	21.5 (16.65-26.35)	.0002
Follow-up	Died	2 (6%)	19 (59%)	
	Survivors with follow up data	27/29 (93%)	12/13 (92%)	
Cerebral Palsy	No cerebral palsy	22 (81%)	2 (17%)	
	Hemiplegic	1	2	
	Diplegic	2	1	
	Quadriplegic	1	5	
	Dystonic	1	2	
	Mild (GMFCS criteria)	2	2	
	Moderate (GMFCS criteria)	1	3	
	Severe (GMFCS criteria)	2	5	
Outcome	Combined Death / CP outcome	7/29 (24%)	29/31 (94%)	

*: p value from Student's T-test, CI: confidence interval, SD: standard deviation, CP: cerebral palsy, GMFCS: Gross Motor Function Classification System, HIE: hypoxic-ischaemic encephalopathy. Deaths do not include infants who died without a diagnosis of HIE.

Table 4: Long-term outcomes for those infants who developed hypoxic-ischaemic encephalopathy grade 2 or 3, pre and post the introduction of therapeutic hypothermia

	Therapeutic Hypothermia Era	Pre-Therapeutic Hypothermia Era
N	39	24
pH: mean(SD)	6.797 (0.128)	6.752 (0.142)
Base deficit: mean (SD)	19.929 (4.996)	18.747 (5.777)
Died	13 (33%)	8 (33%)
Lost to follow-up	1	2
Survivors from HIE grade II	15	12
Survivors from HIE grade III	10	2
Cerebral Palsy	10 (26%)	5 (21%)

SD: standard deviation, HIE: hypoxic-ischaemic encephalopathy, IQR: Interquartile range

Discussion:

This population study of infants born at 35 weeks gestational age or more demonstrates a dose-dependent association between the degree of acidosis around the time of birth (measured by the most acidotic result from either umbilical cord blood gas or subsequent

blood gas within one hour of birth) and adverse neonatal and later neurodevelopmental outcome. It is the largest single cohort which examines both routine umbilical samples and subsequent gases within one hour of birth, which incorporates venous pH, arterial pH and base deficit, and which includes neurodevelopmental follow-up of 93% of encephalopathy survivors.

Umbilical cord blood gas analysis is recommended in all high-risk deliveries[5] and where a baby is born in poor condition[6], and in some centres this practice is routine following all deliveries. Early identification of infants at risk of complications such as encephalopathy is important as prompt intervention can be instituted. However, there is not clear consensus on how to define fetal acidosis and there is a lack of robust umbilical cord acid-base reference values[7].

Previous observational studies have drawn inconsistent conclusions with regard to the association between cord pH and adverse outcome. These studies have used a variety of different thresholds to define significant acidosis (pH 7.0-7.24)[8], have used different variables such as arterial cord pH, venous cord pH and base deficit[9-11], have examined a variety of different neonatal and long term outcomes [12-23], and have used both selected high-risk populations[24-31] and unselected populations where umbilical sampling is routine[32-40]. This has led to uncertainty about the prognostic value of the degree of acidosis at birth, despite cord pH being used as an outcome measure in obstetric clinical trials and as a factor that may be used to support medicolegal claims[1,5].

Malin et al[8] conducted a systematic review and meta-analysis into the association between umbilical cord pH and both perinatal and longterm outcomes. They demonstrated an

association between low arterial cord pH and neonatal mortality, HIE, intraventricular haemorrhage, periventricular leucomalacia and cerebral palsy. However, both the variable and the threshold used to define significant acidosis differed significantly between papers, and the population varied including both term and preterm infants.

Yeh et al[41] conducted a large observational cohort study, including the entire pH range. They described an increased risk of adverse neurological outcome at a pH less than 7, and demonstrated that above a pH of 7 neonatal acidaemia is weakly associated with adverse outcome. Base deficit, or subsequent infant blood gases, were not analysed and the rate of acidotic infants was significantly higher (2.2%) than in our study, presumably secondary to targeted umbilical cord gas sampling.

The literature which relates outcome to a specific level of base deficit in term infants is relatively sparse. One study of cord base deficit from the 1990s in which term and preterm infants were matched with a more historic cohort, showed an increased risk of neonatal complications at a base deficit of greater than 16mmol/l[42]. A further study describes the neonatal outcomes of term infants born in the same time period in relation to various base deficit values taken in the first hour of life. Although this was a highly selected population and no mortality is described, it shows an increasing likelihood of encephalopathy with increasing acidosis, with a threshold base deficit of 14mmol/l giving 81% sensitivity for developing encephalopathy[43]. Both studies showed a higher incidence of encephalopathy than our more recent cohort perhaps reflecting less rigorous postnatal support such as effective resuscitation protocols and the absence of therapeutic hypothermia, the latter well-recognised in altering the typical trajectory of HIE[44].

In relation to longer term sequelae, only one study reports the outcome at differing buffer base values[45]. Like base deficit, buffer base measures the metabolic acid state of the fetus but from an opposite perspective (presence of base vs absence of base). This study showed a dose-dependent relationship between metabolic acidosis and both major and minor deficits at one year of age but the study was limited in being small, including both term and preterm infants, and in not describing infants who died.

The strength of this paper is that it includes a large cohort selected only by gestational age and therefore captures both high and low risk deliveries. Unlike previous studies, it also includes blood gas samples obtained within an hour of birth and therefore includes infants whose umbilical cord values may not truly reflect their degree of acidosis at the time of delivery (for example cases of cord obstruction). This study also examined both pH and base deficit, and the centre involved has a system of targeted follow up which provides neurodevelopmental follow up until 2 years of age in infants who have survived neonatal encephalopathy.

A limitation of this study is that while pH is well-recorded, base deficit data is less complete in the maternal electronic patient record. There is therefore the possibility that infants who had a high cord base deficit alone were missed from inclusion. All cases of HIE were captured from the neonatal unit admission data, but because valid cord blood gas data was only available for 66.9% it is likely that there were other acidotic infants who did not have cord gases and remained well. This means the extent to which acidosis may predict adverse outcome may be overestimated by this dataset. In this paper we have only estimated the risk associated with the degree of acidosis. Other factors which might influence outcome such as hypoglycaemia[46], intrauterine growth restriction[47] and chorioamnionitis[48] were not studied.

The risk of adverse long term outcomes associated with acidosis was broadly similar in this cohort of infants before and after the introduction of therapeutic hypothermia. The study design does not measure the efficacy of therapeutic hypothermia.

This study defines a clear dose-dependent relationship between the degree of acidosis and outcome in a cooling era. It may help to facilitate the setting of entry criteria in clinical trials and better inform medicolegal opinion as to the likely outcome had delivery been expedited and the severity of acidosis been reduced.

What is already known on this topic:

- Degree of acidosis at delivery is used as an outcome measure in obstetric clinical trials and as a factor used to support medico-legal claims
- Previous smaller studies have demonstrated a variable association between acidosis and adverse outcome of uncertain prognostic value

What this study adds:

- In more than 500 infants with severe acidosis at birth drawn from a population of 59,000 infants, pH and base deficit showed a clear dose-dependent relationship with adverse neonatal and two year outcome

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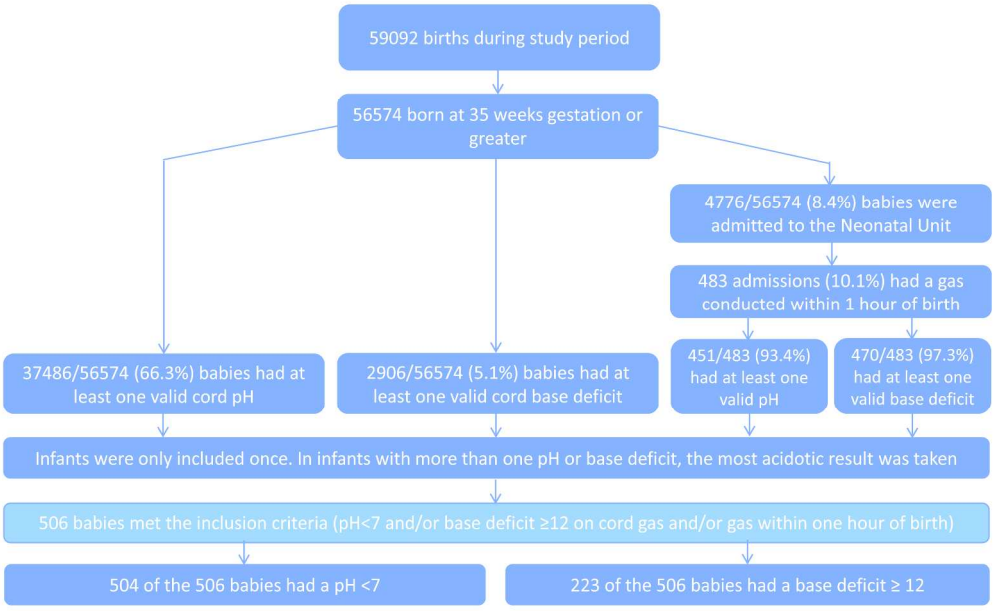
Contributorship Statement
Dr Ramaiah and Dr. Sheridan conducted an initial internal audit using data from 2005 to 2009 from unit admission records and patient notes. Dr. Kelly expanded this to a longer study period, and included data from electronic patient records (provided by Dr. Kissack), blood gas analysers and follow up data (provided by Mrs. Cruickshank and Dr. Rudnicka). Dr. Kelly wrote the manuscript under the supervision of Dr. Becher and Professor Stenson, who both conceived and refined the study design.

References:

1. MacLennan A. A template for defining a causal relation between acute intrapartum events and cerebral palsy: international consensus statement. *BMJ* 1999;319(7216):1054-9.
2. Sarnat HB and Sarnat MS.Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. *Arch Neurol.* 1976;33(10):696-705
3. Bayley N. Bayley Scale of Infant and Toddler Development – Third edition. *Journal of Psychoeducational Development.* 2007;180-198
4. Palisano RJ et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol.* 1997;39:214-223.
5. ACOG Committee Opinion No 348. Umbilical cord blood gas and acid-base analysis *Obstet Gynecol* 2006;108:1319-22
6. National Collaborating Centre for Women's and Children's Health – Intrapartum Care (NICE Clinical Guideline 190). 2014
7. Thorp JA et al Umbilical cord blood gas analysis at delivery 1996 *AJOG;*175(3):517-522
8. Malin G, Morris R, Khan KS. Strength of association between umbilical cord pH and perinatal and long term outcomes: systematic review and meta-analysis *BMJ* 2010;340:1471-83
9. Dijxhoorn MJ, Visser GH, Huisjes HJ, Fidler V, Touwen BC. The relation between umbilical pH values and neonatal neurological morbidity in full term appropriate-for-dates infants *Early Hum Dev* 1985;11:33-42
10. Van den Berg PP, Nelen WL, Jongsma HW, Nijland R, Kollée LA, Nijhuis JG, et al. Neonatal complications in newborns with an umbilical artery pH<7.00 *Am J Obstet Gynecol* 1996;175:1152-7
11. Wildschut J, Feron FJ, Hendriksen JG, van Hall M, Gavilanes-Jiminez DW, Hadders-Algra M, et al. Acid-base status at birth, spontaneous motor behaviour at term and 3 months and neurodevelopmental outcome at age 4 years in full-term infants *Early Hum Dev* 2005;81:535-44
12. Winkler CL, Hauth JC, Tucker JM, Owen J, Brumfield CG. Neonatal complications at term as related to the degree of umbilical artery acidaemia. *Am J Obstet Gynecol* 1991;164:637-41
13. Valentin L, Ekman G, Isberg PE, Polberger S, Marsál K. Clinical evaluation of the fetus and neonate. Relation between intra-partum cardiotocography, Apgar score, cord blood acid-base status and neonatal morbidity. *Arch Gynecol Obstet* 1993;253:103-15
14. Yudkin P, Johnson A, Clover LM, Murphy KW. Clustering of perinatal markers of birth asphyxia and outcome age 5 years. *BJOG* 1994;101:774-81
15. Socol ML. Depressed Apgar score, acid-base balance and neurologic outcome. Am J Obstet Gynecol 1994;170:991-9
16. Perlman JM, Risser R. Can asphyxiated infants at risk for neonatal seizures be rapidly identified by current high-risk markers? *Pediatrics* 1996;97:456-62
17. Ingemarsson I, Herbst A, Thorngren-Jerneck K. Long term outcome after umbilical artery acidaemia at term birth: influence of gender and duration of fetal heart rate abnormalities. *BJOG* 1997;104:1123-7

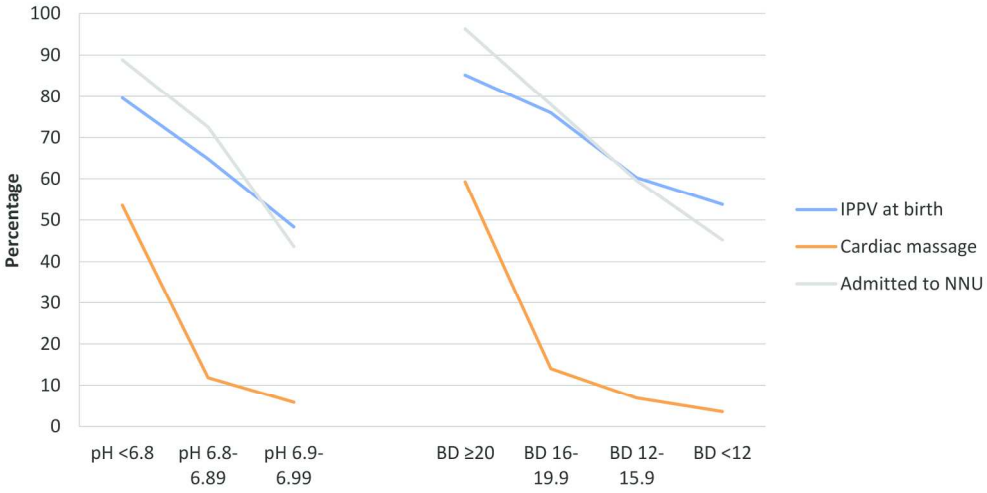
18. Wu L, Thorngren-Jerneck K, Ingemarsson I. Different types of acidemia at birth, fetal heart rate patterns and infants outcome at four years of age. *Chung-Hua Fu Chan Ko Tsa Chih* 1998;33:462-5
19. Haddad B, Mercer BM, Livingston JC, Talati A, Sibai BM. Outcome after successful resuscitation of babies born with Apgar scores of 0 at both 1 and 5 minutes. *Am J Obstet Gynecol* 2000;182:1210-4
20. Gonzalez de Dios J, Moya M, Carratala F. Neurological evolution of asphytic full-term newborns with severe umbilical acidosis (pHUA <7.00). *Rev Neurol* 2000;31:107-13
21. Graham EM, Holcroft CJ, Blakemore KJ. Evidence of intrapartum hypoxia-ischemia is not present in the majority of cases of neonatal seizures. *J Matern Fetal Neonatal Med* 2002;12:123-6
22. Silva AM, Cootauco AC, Aina-Mumuney A, Donohue PK, Graham EM. The association of hypotonia and depression in the term and near-term neonate with metabolic acidemia. *J Perinat Med* 2008;36:151-6
23. Svirko E, Mellanby J, Impey L. The association between cord pH at birth and intellectual function in childhood. *Early Hum Dev* 2008;84:37-4
24. Jurgens-van der Zee AD, Bierman-van Eendenburg MEC, Fidler V, Olinga AA, Visch JH, Touwen BC, et al. Preterm birth, growth retardation and acidemia in relation to neurological abnormality of the newborn. *Early Hum Dev* 1979;32:141-54
25. Schneider R, Tanner R. Perinatal umbilical artery pH and cerebral function disorders in twins starting school. *Z Kinder Jugendpsychiatr* 1985;13:24-30
26. Luthy DA, Shy KK, Strickland D, Wilson J, Bennett FC, Brown ZA, et al. Status of infants at birth and risk for adverse neonatal events and long-term sequelae: a study in low birth weight infants. *Am J Obstet Gynecol* 1987;157:676-9
27. Tejani N, Verma U. Correlation of Apgar scores and umbilical artery acid-base status to mortality and morbidity in the low birth weight neonate. *Obstet Gynecol* 1989;73:597-600
28. Hibbard JU, Hibbard MC, Whalen MP. Umbilical cord blood gases and mortality and morbidity in the very low birth weight infant. *Obstet Gynecol* 1991;78:768-73
29. Gaudier FL, Goldenberg RL, Nelson KG, Peralta-Carcelen M, Johnson SE, DuBard MB, et al. Acid-base status at birth and subsequent neurosensory impairment in surviving 500 to 1000 gm infants. *Am J Obstet Gynecol* 1994;170:48-53
30. Spinillo A, Fazzi E, Orcesi S. Perinatal factors and 2 year minor neurodevelopmental impairment in low birth weight infants. *Biol Neonate* 1995;67:39-46
31. Ertan AK, Tanriverdi HA, Meier M, Schmidt W. Perinatal risk factors for neonatal intracerebral hemorrhage in preterm infants. *Eur J Obstet Gynecol Reprod Biol* 2006;127:29-34
32. Thoulon JM, Varnier C, Faure M. Prognostic value of umbilical blood pH measurement in newborn infants at birth. *Lyon Med* 1972;227:699-702
33. Litschgi M, Benz JJ, Glatthaar E. Actual and prognostic value of arterial cord pH for the newborn infant. *Z Geburtshilfe Perinatol* 1974;178:23-9
34. Huisjes HJ, Aarnoudse JG. Arterial or venous umbilical pH as a measure of neonatal morbidity? *Early Hum Dev* 1979;3:155-61

35. D'Souza SW, Black P, Cadman J, Richards B. Umbilical venous blood pH: a useful aid in the diagnosis of asphyxia at birth. *Arch Dis Child* 1983;58:15-19
36. Gilstrap LC 3rd, Leveno KJ, Burris J, Williams ML, Little BB. Diagnosis of birth asphyxia on the basis of fetal pH, Apgar score, and newborn cerebral dysfunction. *Am J Obstet Gynecol* 1989;161:825-30
37. Dennis J, Johnson A, Mutch L, Yudkin P, Johnson P. Acid-base status at birth and neurodevelopmental outcome at four and one-half years. *Am J Obstet Gynecol* 1989;161:213-20
38. Loh SF, Woodworth A, Yeo GS. Umbilical cord blood gas analysis at delivery. *Singapore Med J* 1998;39:151-5
39. Thorp JA, Rushing R. Umbilical cord blood gas analysis. *Obstet Gynecol Clin North Am* 1999;26:695-709
40. Casey BM, Goldaber KG, McIntire DD. Outcomes amongst term infants when two-hour postnatal pH is compared with pH at delivery. *Am J Obstet Gynecol* 2001;184:447-50
41. Yeh P, Emary K, Impey L. The relationship between umbilical cord arterial pH and serious adverse neonatal outcome: analysis of 51 519 consecutive validated samples. BJOG. 2012;119:824-831
42. Low JA, Lindsay BG, Derrick EJ Threshold of metabolic acidosis associated with newborn complications. *Am J Obstet Gynecol* 1997;177(6):1391-4
43. Wayenberg JL Threshold of metabolic acidosis associated with neonatal encephalopathy in the term newborn *J Matern Fetal Neonatal Med* 2005;18(6):381-5
44. Shankaran S, Laptook AR, Tyson JE, et al. Evolution of encephalopathy during whole body hypothermia for neonatal hypoxic–ischaemic encephalopathy. *J Pediatr* 2012;160: 567–72
45. Low JA, Galbraith RS, Muir DW, et al. Factors associated with motor and cognitive deficits in children after intrapartum fetal hypoxia. *Am J Obstet Gynecol.* 1984 Mar 1;148(5):533-9
46. Basu SK et al CoolCap Study Group. Hypoglycaemia and hyperglycaemia are associated with unfavourable outcome in infants with hypoxic ischaemic encephalopathy: a post hoc analysis of the CoolCap Study *Arch Dis Child Fetal Neonatal Ed.* 2016;101(2):F149-5
47. Badawi N et al. Antepartum risk factors for newborn encephalopathy: the Western Australian case-control study *BMJ* 1998; 317: 1549-53
48. Mir IN et al. Placental pathology is associated with severity of neonatal encephalopathy and adverse developmental outcome following hypothermia *Am J Obstet Gynecol* 2015;213(6):849.e1-7



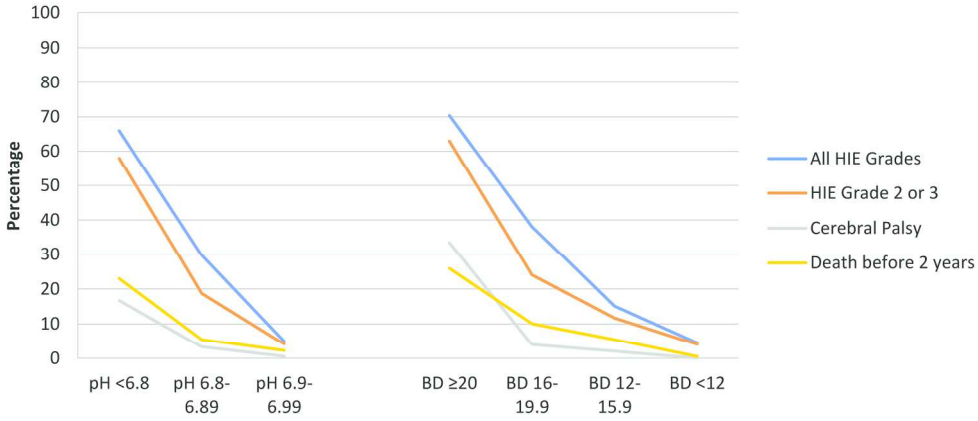
Flowchart of data acquisition from eligible infants during the study period

252x155mm (300 x 300 DPI)



Condition at birth according to acid-base status at birth
(IPPV: Intermittent Positive Pressure Ventilation, NNU: Neonatal Unit)

174x87mm (300 x 300 DPI)



Outcome at 2 years according to acid-base status at birth
(HIE: Hypoxic-Ischaemic Encephalopathy)

182x79mm (300 x 300 DPI)