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The relationship between umbilical cord arterial pH and serious adverse neonatal outcome: analysis of 51 519 consecutive validated samples

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Objective To examine the relationship between umbilical cord pH at term and serious neonatal outcomes.

Design Observational cohort study.

Settings Deliveries within the Oxford Radcliffe Hospital NHS Trust between 1991 and 2009.

Population In all, 51 519 singleton, term, nonanomalous live neonates with validated umbilical cord arterial pH values.

Methods Absolute risks, relative risks with 95% confidence intervals, and numbers needed to harm were calculated for different levels of arterial pH across the entire range.

Main outcome measures Neonatal encephalopathy with seizures and/or death, encephalopathy within 24 hours of birth, 5-minute Apgar scores and neonatal unit admission.

Results The median arterial pH was 7.22, interquartile range 7.17–7.27. The absolute risk of an adverse neurological outcome was significantly increased below 7.10 (0.36%) and was lowest between 7.26 and 7.30 (0.16%). Even below 7.00, the risk was only 2.95%. However, more than 75% of neonates with neurological outcomes examined, including seizures within 24 hours of birth, had a pH above 7.10. A small increase in risk was evident at higher pH levels.

Conclusion The threshold pH for adverse neurological outcomes is 7.10 and the 'ideal' cord pH is 7.26–7.30. Above 7.00, however, neonatal acidaemia is weakly associated with adverse outcomes. Most neonates with neurological morbidity have normal cord pH values. Other variables must influence adverse outcomes and account for more of these than acidaemia. A better understanding of these is required before intrapartum fetal monitoring can improve.

Keywords Acidaemia, encephalopathy, neonatal death, pH, seizure.

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Introduction

It is currently accepted that the role of labour in the aetiology of cerebral palsy, even after term delivery, is limited.[1] Most estimates suggest that labour accounts for only up to 15% of affected children. Yet these cases are considered potentially avoidable, account for much litigation and attempts at their prevention lead to increased intervention and consume vast resources.

This 'prevention' of intrapartum cerebral palsy addresses fetal hypoxia. The National Institute for Health and Clinical Excellence (NICE) states: 'the monitoring of babies in labour aims to identify hypoxia before it is sufficient to lead to damaging acidosis and long-term neurological sequelae for the baby'.[2] In high-risk pregnancies, this has consisted of electronic fetal monitoring (EFM); in low-risk pregnancies, monitoring has consisted of intermittent auscultation with recourse to EFM if abnormalities develop. If EFM is abnormal, assessment of fetal acidaemia by scalp sampling is advised. By convention, although the data on the relationship between scalp pH and outcomes is restricted largely to Apgar scores, a normal level of scalp pH is >7.24; at <7.20 urgent delivery is advised.[3]

Identification and prevention of fetal acidaemia is therefore the aim of intrapartum fetal monitoring; the cord pH is considered a crucial outcome measure. The risk of severe acidaemia is well documented. In an important systematic review, Malin et al.[4] reported outcomes on 481 753 infants

with known cord gases and concluded that low arterial pH was strongly associated with long-term adverse outcomes. What is unclear is what pH level is significant. Goldaber et al.[5] suggest that it is at 7.00, although even at this level, most neonates suffer no sequelae. Consensus for ascribing cerebral palsy to intrapartum hypoxia states that the arterial pH must be <7.00.[6] However, a pH of 7.00 in the umbilical artery is very much lower than would be expected following a scalp pH of <7.24, the level considered abnormal by NICE. Above 7.00, the relationship between cord pH and outcome is much less clear.

This is because the data on neonatal and longer-term outcomes are largely limited to severely acidaemic babies or unwell babies, and do not cover the entire pH range. Malin et al.[4] include some series with a wider pH range (<7.20), which also show a correlation with adverse outcome. But this does not prove that the upper values constitute the threshold, because of the effect of including the extreme values. The full range of pH has been correlated with Apgar scores, the need for ventilatory support and neonatal unit admission,[7] but not with important neurological outcomes.

This means that what constitutes clinically significant acidaemia is unclear. This is important for determining an appropriate threshold for intervention: for balancing the risks of neonatal damage against those of obstetric intervention. It is also crucial for understanding the role of intrapartum hypoxia in the aetiology of long-term handicap.

The aim of the study was to analyse a very large cohort of deliveries, across the entire pH range, to document the risk of adverse outcomes, including neurological outcomes according to arterial pH, to provide prognostic data and assess the contribution of different pH ranges to these outcomes.

Methods

Data set

This was an observational cohort study using data, prospectively entered on a maternity database (OXMAT), from all women who have delivered since 1 January 1991 in the John Radcliffe Hospital, Oxford, UK and the three community hospitals and at home and, after 12 December 2000, all women delivering in the Horton Hospital in Banbury, North Oxfordshire, UK. Deliveries between 1 January 1991 and 31 December 2009 were included if they were after 37 completed weeks of gestation and resulted in a singleton live birth. Those where the infants had major congenital abnormalities were excluded.

We further selected those who had umbilical cord vessels sampled. Unit policy is that paired cord acid–base analysis is performed on women who have been monitored electronically in labour, or where there is meconium, or antenatal complications. We validated our cord blood gas values according to the methods of Westgate et al.,[8] to obviate: (i) inadvertently sampling from the same vessel twice or (ii) transposing the vessels either when taking the samples, on introduction into the analyser, or when entering data. Therefore we excluded all where only one sample was taken, where the values were nonphysiological and where the arterial–venous pH difference was less than the fifth centile.

Cord gas analysis

The cord was double clamped immediately after delivery at a minimum length of 10 cm with the placenta *in situ* and both the artery and vein were sampled in preheparinised labelled syringes and analysed within 15 minutes: Instrumentation Laboratory BGM1312 from 1 January 1991, Radiometer ABL700 from 18 May 2002 and Radiometer ABL800 from 23 June 2005 thereafter. Routine calibrations were run every 4 hours. Rinse solution sat in the pathway between samples so any drift in accuracy could be detected in real time. Quality control solution was run automatically in the early morning on at least three levels (mimicking acidaemic, normal and alkalotic samples) and a fourth level was run on a Wednesday and a Sunday to check for exceptionally high Po_2 ranges.

Outcomes

These were (i) a composite of neonatal encephalopathy with seizures and/or death within 4 weeks, (ii) neonatal encephalopathy with seizures requiring anticonvulsant medication, (iii) neonatal encephalopathy with seizures requiring medication, within 24 hours of birth, (iv) Apgar score <7 at 5 minutes, and (v) admission to the neonatal unit. We did not include Grade 1 encephalopathy or 'hypoxic ischaemic encephalopathy' because these are subjective diagnoses, and the former at least correlates little with long-term outcome.[9] Neonatal death was not analysed alone because of its rarity.

Data abstraction

Data were entered following delivery, and again after discharge. Early neonatal complications were coded, but further examination was required for encephalopathy. Until 31 March 1995, this was coded according to the International Classification of Diseases Revision 9 (ICD-9); thereafter, this was changed according to Revision 10 (ICD-10). Cases of neonatal convulsions were suggested by 'convulsions' (ICD-9 779.0 or ICD-10 P90) or 'other disturbances of cerebral status of the newborn' (ICD-9 779.1 or ICD779.2 or ICD-10 P91). We ensured optimal case ascertainment by inspecting neonatal admission books, computerised records and neonatal discharge summaries; we double checked ICD-coded with paper notes, neonatal unit discharge summaries and electroencephalogram records to

ascertain neonates who actually had seizures and who received medication. After semi-anonymisation, OXMAT data were converted into PASW Statistics version 18 (SPSS Inc, Chicago, IL, USA) software for analysis.

Analysis

The overall incidence of all outcomes examined was calculated. The incidence of seizures was also calculated according to whether umbilical cord blood samples were taken or not. This was because we anticipated that these incidences might differ according to whether acid–base status had been determined, reflecting the higher-risk pregnancies undergoing EFM and a potential bias that cord blood would be more likely to be sampled if risk factors for our outcomes were present.

The distributions of umbilical cord arterial pH were plotted. The ranges of pHs, to two decimal places, were split into different groups in 0.05 units, i.e. ≤7.00, 7.01–7.05, 7.06–7.10, 7.11–7.15, 7.16–7.20, 7.21–7.25, 7.26–7.30, 7.31–7.35, ≥7.36. The incidence and the relative risk, with 95% confidence intervals, of the outcome measures was then calculated for each pH arterial range group, using the pH range with the lowest risk as the denominator. The percentage of all babies with each outcome was then calculated for each pH group.

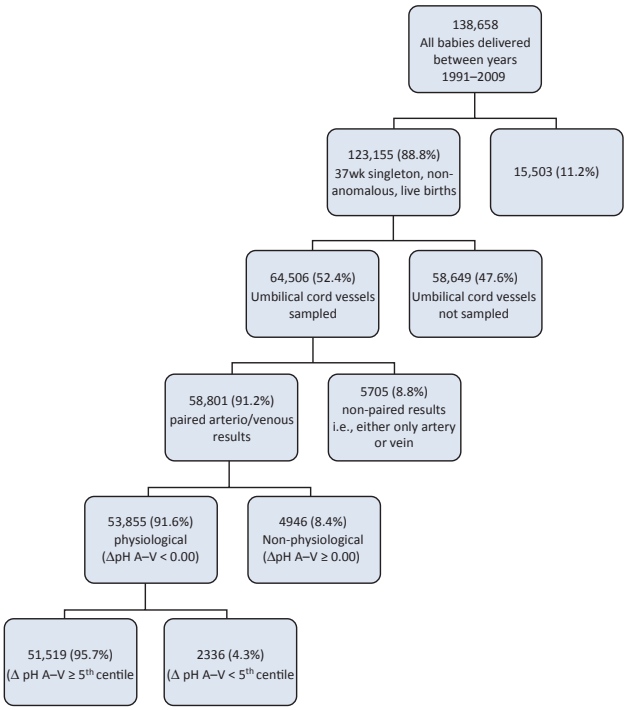

Figure 1. Summary of exclusions to identify and validate paired arterial (A) and venous (V) cord pH values.

Results

Cohort selection

This is shown in Figure 1. Between 1 January 1991 and 31 December 2009, there were 138 658 births. Of these, 123 155 (88.8%) were singleton nonanomalous live births at or over 37 completed weeks of gestation. Umbilical cord vessels were sampled in 64 506 (52.4%) deliveries. Of these, there were 58 801 (91.2%) paired samples. The arterial pH was at least equal to the venous pH in 4946 (8.4%), i.e. nonphysiological, to give 53 855 physiological cases; of these, the arteriovenous pH difference was less than the fifth centile (i.e. pH difference <0.02) in 2336, leaving 51 519 with validated umbilical cord blood pH values.

Cohort description

The Kolmogorov *D* statistic suggested that the distribution of cord arterial pH in the 51 519 validated paired samples was skewed (Figure 2). The median umbilical cord arterial pH was 7.22; range 6.55–7.52; interquartile range 7.17–7.27. An arterial pH of <7.00 occurred in 2.2% of all deliveries; the first centile was 6.94.

Neurological outcomes

The incidence of encephalopathy with seizures was 2.3/1000 for the deliveries with validated paired umbilical cord pH values (n = 51 519). For all eligible deliveries (n = 123 155), the incidence was 1.8/1000 term deliveries. According to whether cord blood gases were taken or not, the incidence was 2.2/1000 or 1.3/1000 term deliveries (n = 64 506 and n = 58 649) respectively (χ^2 = 13.4; P < 0.001). Encephalopathy with seizures or death occurred in 3.0/1000 deliveries. Neonatal death occurred in 1.1/1000, and seizures in the first 24 hours occurred in 1.1/1000.

The absolute risks, relative risks with 95% confidence intervals and numbers needed to harm, for the different outcomes at a given pH range, are shown in Table 1. The percentage of all neonates with the outcome in each pH range is also presented. The pH range 7.26–7.30, which is above the median, appears to be the 'ideal' pH range for all outcomes, and is used for comparison. The risk of adverse neurological outcomes starts to rise below a pH of 7.10. Despite this, the risk only rises sharply below an arterial pH of 7.00. A pH below 7.00 accounted for 20–24% of adverse neurological outcomes, with a further 10–15% occurring after a pH below 7.11. Even for seizures within the first 24 hours, at least half had a pH > 7.10, whereas 39% had a pH above 7.20. The data also suggest a small increase in adverse sequelae with higher pH levels. The percentage contribution of levels of neonatal acidaemia to all incidences with 'encephalopathy with seizures and/or death' is represented graphically in Figure 3. The relative risk of different levels of neonatal acidaemia for all infants with

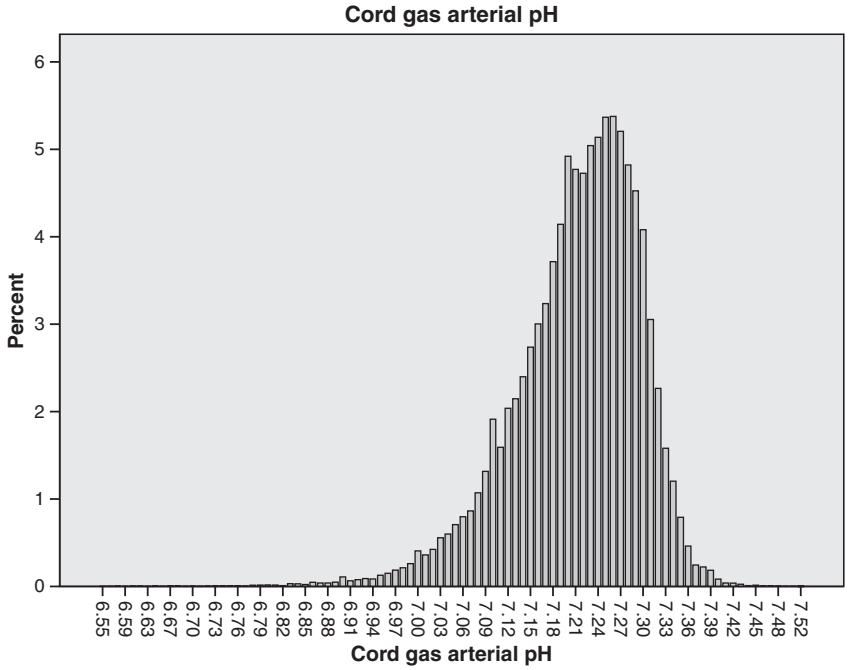

Figure 2. Percentage frequency distribution of umbilical cord arterial pH in 51 519 validated samples.

'encephalopathy with seizure and/or death' is represented graphically in Figure 4.

Apgar scores and neonatal unit admission

The absolute risks, relative risks with 95% confidence intervals and numbers needed to harm for these outcomes at a given pH range are also shown in Table 1, with the percentage of all neonates with the outcome in each pH range. The risk for neonatal unit admission is significantly raised from <7.20, but differs little until <7.00. The risk of low Apgar scores at 5 minutes also increases from around the median: a higher level than with neurological sequelae. There is a small increase in low Apgar scores with higher pH levels.

Discussion

This large cohort study provides new information on the relationship between umbilical arterial pH and neonatal outcomes. Our cohort is far larger than has been used before, and we are able to examine neurological outcomes in addition to short-term, less predictive outcomes. Using an entire cohort, rather than simply an acidaemic cohort, we provide figures for prediction of adverse neurological outcome for a given pH range, with the number needed to harm, and can assess the contribution of degrees of acidaemia to these outcomes. This shows, as expected, that 7.00 is the level where the risk is highest, although few babies with severe acidaemia appear to have sequelae. The key findings are (i) the 'threshold' for neurological sequelae is around 7.10, yet (ii) the number needed to harm at pH levels of 7.06–7.10 is very high and (iii) most neonates with adverse outcomes, even that of seizures in the first 24 hours, are not born acidaemic. In addition, (iv) it appears that the lowest risk of any adverse outcomes occurs at 7.26–7.30, rather than 'the higher the better', for (v) there may be a higher risk at higher pH levels.

We do note differences between our data and those of some other investigations, particularly Graham et al.[10] First, although our median pH is not significantly different from other studies, 2.2% of our neonates had a cord pH < 7.00. This is much higher than the 0.37% calculated by Graham et al.[10] in a systematic review of the risks of encephalopathy at an arterial pH < 7.00.[10] However, our incidence is closer to other large series: our 5th centile was 7.05, which was the 2.5th in a seminal analysis;[11] in a cohort recruited to a large randomised controlled trial, 1.0% had a pH of <7.00.[12] The differences could be related to our cord validation protocol, or obstetric policy, but ours and other data suggest that Graham et al.[10] have underestimated the incidence of severe acidaemia. Second, our risks of neurological sequelae at extreme pH levels are lower than those suggested by these authors and third, our incidence of encephalopathy (Grade 2–3), at 0.22%, may be slightly lower than is generally reported. Although both these above differences could be the result of case ascertainment, our methodology involved multiple cross checks, and we were very strict with definitions. We stipulated that anticonvul-

Table 1. Adverse outcomes according to cord arterial pH

pH range (*n*; %)	*n*	% risk	Relative risk (95% CI)	NNH*	Percentage of all**
Encephalopathy with seizures and/or death					
≤7.00 (1120; 2.17%)	33	2.95	18.20 (10.50–31.70)	36	21.71
7.01–7.05 (1364; 2.65%)	8	0.59	3.63 (1.60–8.22)	236	5.26
7.06–7.10 (3071; 5.96%)	11	0.36	2.22 (1.06–4.62)	509	7.24
7.11–7.15 (5622; 10.91%)	16	0.28	1.76 (0.91–3.39)	NS	10.53
7.16–7.20 (9797; 19.02%)	19	0.19	1.20 (0.64–2.25)	NS	12.50
7.21–7.25 (12903; 25.05%)	34	0.26	1.63 (0.94–2.83)	NS	22.37
7.26–7.30 (12369; 24.01%)	20	0.16	1.00	–	13.16
7.31–7.35 (4581; 8.89%)	8	0.17	1.08 (0.48–2.45)	NS	5.26
≥7.36 (692; 1.34%)	3	0.43	2.67 (0.80–8.96)	NS	1.97
Encephalopathy with seizures <24 hours					
≤7.00	14	1.25	30.92 (11.16–85.69)	83	23.73
7.01–7.05	6	0.44	10.88 (3.33–35.61)	251	10.17
7.06–7.10	4	0.13	3.23 (0.87–11.99)	NS	6.78
7.11–7.15	7	0.12	3.08 (0.98–9.70)	NS	11.86
7.16–7.20	5	0.05	1.26 (0.37–4.36)	NS	8.47
7.21–7.25	13	0.10	2.49 (0.89–6.99)	NS	22.03
7.26–7.30	5	0.04	1.00	–	8.47
7.31–7.35	3	0.07	1.62 (0.39–6.78)	NS	5.08
≥7.36	2	0.29	7.15 (1.39–36.79)	403	3.39
All encephalopathy with seizures					
≤7.00	21	1.88	16.86 (8.45–32.49)	57	18.10
7.01–7.05	8	0.59	5.18 (2.18–12.33)	212	6.90
7.06–7.10	9	0.29	2.59 (1.12–5.98)	556	7.76
7.11–7.15	12	0.21	1.89 (0.87–4.07)	NS	10.34
7.16–7.20	16	0.16	1.44 (0.70–2.95)	NS	13.79
7.21–7.25	26	0.20	1.15 (0.52–2.51)	NS	22.41
7.26–7.30	14	0.11	1.00	–	12.07
7.31–7.35	8	0.17	1.54 (0.65–3.68)	NS	6.90
≥7.36	2	0.29	2.55 (1.58–11.21)	569	1.72
Neonatal Unit admission					
≤7.00	392	35.00	6.38 (5.72–7.10)	4	10.68
7.01–7.05	208	15.25	1.63 (1.38–1.93)	11	5.67
7.06–7.10	287	9.35	1.70 (1.49–1.94)	26	7.82
7.11–7.15	441	7.84	1.43 (1.27–1.60)	43	12.02
7.16–7.20	644	6.57	1.20 (1.08–1.33)	93	17.55
7.21–7.25	754	5.84	1.06 (0.96–1.18)	NS	20.54
7.26–7.30	679	5.49	1.00	–	18.50
7.31–7.35	237	5.17	0.94 (0.82–1.09)	NS	6.46
≥7.36	28	4.05	0.74 (0.51–1.07)	NS	0.76
Apgar <7 at 5 minutes					
≤7.00	151	13.48	49.05 (33.98–70.79)	8	29.26
7.01–7.05	44	3.23	11.74 (7.53–18.30)	34	8.53
7.06–7.10	59	1.92	6.99 (4.59–10.64)	61	11.43
7.11–7.15	60	1.07	3.88 (2.55–5.91)	127	11.63
7.16–7.20	69	0.70	2.56 (1.70–3.86)	233	13.37
7.21–7.25	71	0.55	2.00 (1.33–3.01)	364	13.76
7.26–7.30	34	0.27	1.00	–	6.59
7.31–7.35	23	0.50	1.83 (1.08–3.10)	441	4.46
≥7.36	5	0.72	2.63 (1.03–6.70)	244	0.97

*NNH, number needed to harm; NS, relative risk not significant.

**Percentage of all in category under examination; i.e. % of all seizures or death; % of all seizures <24 hours; % of all seizures; % of all neonatal unit admissions and % of all Apgar scores <7 at 5 minutes.

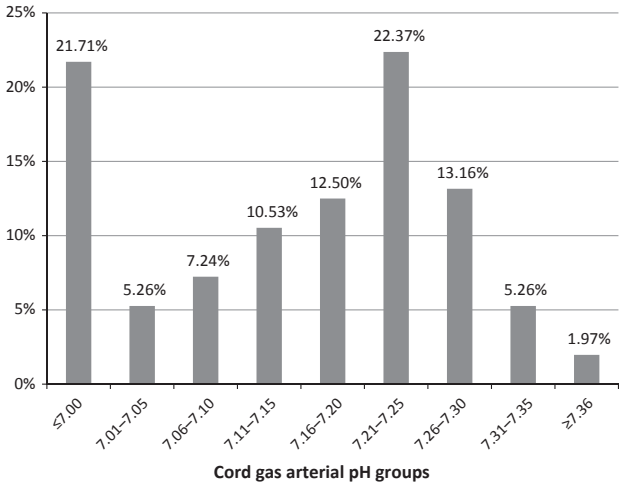

Figure 3. Percentage of all cases with encephalopathy with seizures or death in each arterial pH group.

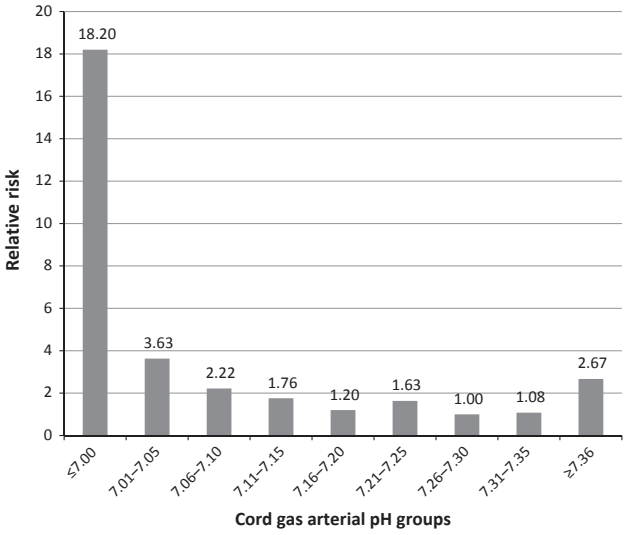

Figure 4. Relative risk of encephalopathy with seizures or death in each arterial pH group.

sants must be used, or if not, that Grade 3 encephalopathy must be present. This is because Grade 1 Sarnat is subjective, and correlates poorly with long-term outcome.[9] Importantly, we did not use the term hypoxic ischaemic encephalopathy because this is less precise, influenced by cord gases,[13] assumes causation, is confused with other risk factors such as chorioamnionitis,[14] and can lead to a circular argument where cord gas levels are associated with it because they form part of the clinical diagnosis.[13]

We acknowledge several limitations. First, cord gas sampling was incomplete (52.4% sampling rate). We confirm that bias influenced our results: seizures occurred in 2.2/1000 where samples had been taken and only 1.3/1000 where they had not. Although this could be the result of higher-risk labours undergoing EFM and therefore having cord gas analysis performed, the decision to measure cord pH is also likely to have been influenced by neonatal condition at birth. This bias probably applies more to other series of only acidotic babies or with low or unknown cord sampling rates. Indeed, even Graham et al.,[10] included, in the calculation of the incidence of seizures at low pH, one large series where cord gases were taken in only 10%.[15] Only systematic, 100% cord gas analysis rates will overcome this problem.

Second, a large database contains errors. Using additional data sources and cross-referencing between these and our database should have minimised error, particularly that of missing adverse outcomes. Third, although we were rigorous in our exclusion of potentially unphysiological cord gas values (Figure 1), indeed more so than most series reviewed by Graham et al.,[10] we were not able to analyse Pco_2 because it was not recorded, and we were therefore not as rigorous as Kro et al.[16] Fourth, we analysed only arterial pH because this is the most commonly used measure. Base deficit is also thought to be important although most severely acidotic babies have a base deficit >12 mmol. This analysis is planned, along with arteriovenous differences, but would complicate this analysis further, and investigate different questions. Finally, we do not have data on longer-term follow up, although this too is planned. Nevertheless, about a third of neonates with encephalopathy Sarnat Grade 2 or worse will develop cerebral palsy or die.[9]

The study by Victory et al.[7] was one of few to also use an entire cohort, rather than a severely acidaemic cohort, and to use both cord vessels, although they analysed only assisted ventilation, Apgar scores of <7 at 5 minutes and the need for admission to the neonatal unit. The risk of these were much higher below 7.03, but a significant relationship persisted almost to the mean, with the lowest risk actually above the mean pH and possibly a small increase in risk at alkalotic pH. These findings are in agreement with ours for Apgar scores and neonatal admission; our data on neurological outcomes suggests a higher threshold for these.

Our 'threshold', where the risk of adverse neurological outcomes rises significantly, is 7.10. Decisions regarding emergency delivery are based on an intrapartum scalp pH, and therefore capillary pH, which will be higher than a cord arterial level. Therefore, this finding broadly endorses National Guidelines recommending delivery at a scalp pH of 7.20.[2,3] Nevertheless, at this level the number needed to harm (neonatal unit admission) is 26; for 'encephalopathy with seizures and/or death' the absolute risk is only 0.36%, with a number needed to harm of 509. Whether this pH level alone constitutes the correct threshold for intervention, when that intervention is operative delivery, clearly

requires further debate. Indeed, the relatively weak relationship between arterial pH and outcome is striking.

These findings are consistent with those of Badawi et al.,[17] who analysed intrapartum risk factors rather than actual pH level, but found that 75% of neonates with encephalopathy had none. There are several possible explanations. It is not that the umbilical vein is better.[7] Although there may be some in utero recovery from hypoxia,[18] the majority of neonates with encephalopathy or death had an arterial pH > 7.00, so this would have had to occur in the majority of babies. Or, we may be witnessing the effect of the 'acidosis paradox':[19] neonates without acidaemia might still have been hypoxic but are unable to develop acidaemia as a response. This is an interpretation of the observations that neonates with so called 'birth asphyxia' (often low Apgar scores) often have a normal pH, that catastrophic intrapartum events can occur without acidaemia, and that neonates with low Apgar score who are acidaemic may do better in the long term than those who are not.[20] Indeed, a very acute insult, such as shoulder dystocia, may cause neurological damage without cord acidaemia. Yet this is likely to be because of its mechanical effects on the cerebral circulation, rather than an inability to become acidaemic. Normal cord gases, therefore, are not entirely incompatible with brain hypoxia, but this mechanism of injury is unlikely to account for the nearly 75% of neonates with encephalopathy with seizures or death born with an arterial pH > 7.00. Indeed, after cord occlusion, all sheep studied by Ikeda et al.[18] did become acidaemic.

A serious problem lies in the definition of asphyxia. In 2000, Stanley et al.[21] stated: '…in the absence of direct evidence of hypoxia, its presence is sometimes inferred from the fetal or neonatal response, such as low Apgar scores, or the outcome, such as an altered conscious state. This leads to a circular argument, when the outcome, neonatal encephalopathy, is used as evidence of exposure to intrapartum hypoxia.' An alternative explanation for the better outcome of low Apgar neonates who are moderately acidaemic is that other risk factors may be more deleterious than hypoxia.

These risk factors could be antepartum or intrapartum. An intrapartum contribution can be inferred from the finding by Badawi et al.,[17] that truly elective caesarean section was strongly protective against neonatal encephalopathy. For instance, an intrapartum fever and clinical chorioamnionitis are an important risk factor for encephalopathy, cerebral palsy and neonatal death.[17,22–24] Although this probably represents a mechanism that is partly separate from acidaemia,[25] the combination of chorioamnionitis with acidaemia poses a particular risk[25,26] with recorded odds ratios for encephalopathy above 70. This observation suggests that the 'threshold' of 'acceptable' acidaemia could be altered. Indeed, perhaps the scalp pH threshold for intervention could eventually be individualised using all known risk factors, in a manner similar to that used for screening for Down's syndrome.

Conclusion

Moderate degrees of cord acidaemia (artery <7.10) are associated with an increased risk of adverse neurological outcome, but the absolute risks are very low, and most affected babies have a higher pH than this. Intrapartum fetal surveillance that relies almost entirely on detection of acidaemia, and follows NICE Guidelines for intervention, will lead to both a failure to prevent most adverse neurological outcomes and a high obstetric intervention rate. If other intrapartum deleterious processes are involved and these further influence the degree of acidaemia that is tolerated, then a better understanding of these processes is urgently required, as is a more sophisticated and individualised way of using and interpreting pH.

Disclosure of interests

None.

Contribution to authorship

PY contributed to the design, collected and analysed the data, and contributed to the final version of the paper. KE contributed to data collection and analysis and contributed to the final version of the paper. LI contributed to the design and analysis and wrote the paper. LI acts as guarantor for the study.

Details of ethics approval

Ethical approval for the on-going development and analysis of the OXMAT database for the association between pregnancy variables and neonatal outcomes was obtained from NHS Central Oxford Research Ethics Committee (COREC) on 6 September 2005 (REC reference 05/Q1605/110) and renewed on 16 March 2010.

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