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Perinatal brain damage: predictive value of metabolic acidosis and the Apgar score

Vineta J Ruth, Kari O Raivio

Abstract

To assess the predictive value for perinatal brain damage of acidosis at birth, alone or in combination with the Apgar score at 5 minutes, a cohort of 982 liveborn infants delivered over two months was studied prospectively. The umbilical cord was double clamped, and arterial acid-base values were successfully determined in 964 infants and lactate concentration in 931. Reference values defining acidosis (mean ± 2 SD) were obtained from a subset of 127 term infants who had no complications. The incidence of a low pH was 12% (111 out of 964), high base deficit 7% (70 out of 964), high lactate concentration 9% (83 out of 931), and low Apgar score at 5 minutes (≤7) 3% (32 out of 982). Twelve of the 111 infants (11%) with acidosis had a low Apgar score, and 12 out of 29 infants (41%) with low Apgar scores had acidosis. At one year of age 35 infants were lost to follow up and 22 had an adverse outcome unrelated to asphyxia; 883 infants showed normal development but the possible sequelae of asphyxia were four deaths, slight abnormalities in 28 infants, and clear abnormalities in 10. The sensitivity and the positive predictive value of low pH for adverse outcome were, respectively, 21 and 8%, of high lactate concentration 12 and 5%, and of low 5 minute Apgar score 12 and 19%.

Metabolic acidosis determined in blood from the umbilical artery at birth is a poor predictor of perinatal brain damage.

Department of Obstetrics and Gynaecology, Helsinki University Central Hospital, and the Children's Hospital, University of Helsinki, Finland
Vineta J Ruth, MD, *research fellow*
Kari O Raivio, MD, *professor of perinatology*

Correspondence and requests for reprints to: Dr V J Ruth, Children's Hospital, 00290 Helsinki, Finland.

Introduction

Perinatal asphyxia is an important cause of mortality and morbidity in the newborn infant and of neurological disability, mainly cerebral palsy, in later life. This view is widely accepted, although asphyxia as a pathophysiological and clinical concept is quite loosely defined. Its components are hypoxia, hypercapnia, and ischaemia, but both its incidence and role in outcome are difficult to evaluate because of lack of reliable diagnostic criteria.

The Apgar score at 5 minutes after birth has been used, and often misused, as a predictor of neurological damage due to asphyxia. The American collaborative perinatal project of 1959-66, however, showed poor sensitivity of the Apgar score in this respect: only 27% of children who later developed cerebral palsy scored below 7 at 5 minutes.[1] Metabolic acidosis reflects fetal distress and asphyxia, but its relation to the Apgar score is not close. In a cohort study in Oxford in 1982 only 19% of the infants with low Apgar scores had severe acidosis at birth and 27% of the infants with acidosis had a low score at 5 minutes.[2] Determining the pH of blood in the umbilical artery has become an important measure of the infant's condition at birth and is used routinely in many delivery hospitals. The importance of acidosis at birth has not, however, been related to long term outcome in a sufficiently large unselected population that has received adequate follow up. We assessed the predictive value of acidosis at birth and the 5 minute Apgar score for perinatal brain damage in a defined delivery cohort.

Subjects and methods

The study was approved by the ethical committees of both hospitals. It was based on the deliveries over two months (April-May 1984) in the department of obstetrics and gynaecology, a unit admitting

both normal parturients and those referred because they were at high risk. All liveborn infants were included. Fetal heart rate was electronically monitored in all deliveries. All infants had an Apgar score assigned according to clinical routine by a midwife or paediatrician at 1 and 5 minutes of age.

The umbilical cord was double clamped before the first breath, and the segment of cord was immediately placed on ice. Umbilical arterial blood was drawn into a heparinised syringe and the blood gases analysed within a median time of eight minutes with a Corning 178 automatic blood gas analyser. Two aliquots of arterial blood were precipitated with perchloric acid and stored at −18°C until lactate concentration was determined by an enzymatic method (Boehringer Mannheim, kit No 149993). The procedures were performed by specialist research workers to ensure proper clamping and sampling. A form with relevant maternal, obstetric, and neonatal data was completed after the delivery and checked before the baby was discharged.

Follow up—As all infants in Finland are examined at the age of 1 year in well baby clinics by a general practitioner or paediatrician using a standardised protocol a questionnaire was sent to the clinics of the surviving infants to obtain information on development and an overall evaluation of the child. This inquiry was approved by the Ministry of Social Affairs and Health and the local health boards and presupposed parental consent. The infants were preliminarily classified into three groups: (*a*) normal, (*b*) questionable, and (*c*) abnormal. All infants in the questionable and abnormal groups were re-evaluated and reclassified by a paediatrician or neurologist, or both. Infants were considered to be clearly abnormal if they had cerebral palsy or showed a noticeable delay in development—for example, an inability to sit and stand at the age of 12 months. All clear abnormalities were confirmed in a thorough neurological examination. Infants were classified as slightly abnormal if they showed transient abnormalities in muscle tone or an abnormal pattern of development in motor functions during the first year or if a slight delay in development was noted at the age of 12 months—for example, an inability to stand up. Infants with an adverse outcome were excluded when the damage could clearly be ascribed to a disease unrelated to asphyxia.

Analysis of data—To estimate the prognostic value of the variables studied the sensitivity (percentage of abnormal test results among damaged infants), specificity (percentage of normal test results among normally developing infants), positive predictive value (percentage of damaged infants among those with abnormal test results), and negative predictive value (percentage of normally developing infants among those with normal test results) were calculated. The data were analysed with the biomedical progams (BMDP) statistical package. Analysis of variance and the χ^2 test were used in comparing the neonatal data of the infants lost to follow up with the data of those examined. Linear regression or Welch's *t* test was used in analysing the effect of several maternal and obstetric variables on umbilical arterial pH. The variables with significant effects were further analysed by the Mantel-Haenszel test to evaluate possible influences on the prognostic value of pH.

TABLE I—*Characteristics of infants studied (n=982)*

Characteristic	No of subjects
Maternal complication:	
Pre-eclampsia	69
Diabetes mellitus	32
Obstetric hepatosis	28
Twin pregnancy	13
Mode of delivery:	
Caesarean section	
Elective	128
Emergency	54
Vaginal delivery	800
Gestational age (weeks):	
>41	33
37-41	863
<37	86
Birth weight:	
<2500 g	76
Small for gestational age	50
Large for gestational age	18
Apgar score at 1 minute:	
0-3	19
4-6	27
7-10	936
Intubated at birth	37
Mechanical ventilation	26
Respiratory distress syndrome	10
Meconium aspiration syndrome	12
Hypoxic-ischaemic encephalopathy	5
Major congenital anomaly	11
Died	10

TABLE II—*Mean (SD) pH, base deficit, and lactate values in umbilical arterial blood of infants delivered vaginally and by elective caesarean section*

	Vaginal delivery (n=106)	95% Confidence interval	Elective section (n=21)	95% Confidence interval
pH	7·29 (0·07)	7·28 to 7·31	7·31 (0·03)	7·29 to 7·32
Base deficit (mmol/l)	4·7 (4·0)	3·9 to 5·5	2·5 (2·2)	1·5 to 3·5
Lactate (mmol/l)	2·9 (1·2)	2·7 to 3·2	2·0 (0·6)	1·7 to 2·3

Results

During the study a total of 982 infants were born alive. Table I shows their main clinical characteristics. The function of this hospital as a referral centre is reflected in the number of mothers with diabetes and complications of pregnancy as well as the high incidence of low birth weight (8%) and caesarean section (19%).

For defining reference values of the variables studied a subgroup of healthy infants was chosen according to the following criteria: (*a*) no maternal chronic disease, (*b*) no complication of pregnancy or delivery, (*c*) no neonatal disturbance, and (*d*) normal infant development. These criteria were met by 127 infants in the cohort. The Apgar score was not used as a criterion of selection, but all 127 infants scored 9-10 at 5 minutes of age. As the mode of delivery influences acid-base values in the blood of the umbilical artery[3] separate reference values were calculated for the 106 infants delivered vaginally and the 21 infants delivered by elective caesarean section (table II). We defined the reference range as the mean ± 2 SD. With this the lower limit of normal umbilical arterial pH was 7·16 after vaginal delivery and 7·25 after elective caesarean section, whereas the corresponding upper limits for lactate concentration were 5·4 and 3·3 mmol/l and for base deficit 12·7 and 6·8 mmol/l. As the values for base deficit were not normally distributed 5% of the reference group values exceeded the 2 SD limit.

Lactate concentration was successfully determined in 931 infants, and 83 (9%) had a raised value. Acid-base values were successfully determined in 964 infants, of whom 111 (12%) had a low pH and 70 (7%) an increased base deficit. The Apgar score at 5 minutes was 7 or lower in 32 out of 982 infants (3%). Only 12 of the 111 infants (11%) with acidosis had a low Apgar score, and 12 out of 29 infants (41%) with low Apgar scores had acidosis at birth (table III). Six infants had a pH below 7·00, and three of them had low scores (5 minute Apgar score 5-7). Three infants had an Apgar score of 0-3 at 5 minutes, of whom one had acidosis (pH 7·11).

The effect of several maternal and obstetric risk factors on umbilical arterial pH was evaluated. Significantly lower ($p<0·001$) pH values were measured with infusion of oxytocin, epidural anaesthesia for vaginal delivery, long duration of labour (over 12 hours) and

TABLE III—*Relation between Apgar score at 5 minutes and umbilical arterial pH. Values are numbers of infants*

Umbilical arterial pH	Apgar score at 5 minutes ≤7	>7	Total
Low*	12	99	111
Normal	17	836	853
Total	29	935	964

*See text for definition.

delivery (over 30 minutes), meconium staining of amniotic fluid, and cord compression. These differences were, however, considered to be clinically unimportant as the average pH was decreased by only 0·02-0·04 units. No effect of maternal diabetes, pre-eclampsia, obstetric hepatosis, or intrauterine growth retardation was observed on umbilical arterial pH. In comparison with the whole group preterm delivery (gestational age below 37 weeks) was associated with a higher incidence of a low Apgar score (12% (10 out of 86 infants)) but not of acidosis (11% (9 out 86)). All five infants with hypoxic-ischaemic encephalopathy had both a low Apgar score and acidosis at birth.

DEVELOPMENTAL OUTCOME

At 1 year of age 35 infants could not be traced because the family had moved, so the rate of response to the follow up was 96%. The umbilical arterial pH, base deficit, and lactate values and Apgar scores of the 35 infants lost to follow up did not differ from those of the reference group, and none of them had any important perinatal problems. Twenty two infants had an adverse outcome caused by a specific cause unrelated to asphyxia. Two died of a congenital malformation, two of an inborn error of metabolism, and one each of rhesus immunisation and septicaemia; abnormal development or neurological symptoms were ascribed to a congenital malformation in six infants, to genetic disease in two, to the fetal alcohol syndrome in three, to social deprivation in four, and to hypocalcaemia in one.

Of the remaining 925 infants, 883 (95%) showed normal development, 28 slightly abnormal development, and 10 clearly abnormal development, and four asphyxiated infants born preterm had died. Thus altogether 42 infants had an adverse outcome with perinatal asphyxia as a possible or the most credible cause. Table IV shows the clinical details of the four infants who died and the 10 who showed clearly abnormal development; four of the 10 had cerebral palsy. Eleven infants with transient motor impairment and 17 with a slight delay in development constituted the 28 infants with slightly abnormal development at 1 year of age. None of those with transient motor impairment but six of those with slightly abnormal development were born prematurely.

Table V shows the sensitivity, specificity, and positive and negative predictive values of the variables studied with respect to adverse outcome. The positive predictive value of a low pH (8%) did not improve in combination with the lactate value, and lactate concentration alone had a low predictive value. When low pH and low Apgar score were combined the positive predictive value increased to 27%, but this combination, although specific, was insensitive. The number of infants with severe acidosis (pH below 7·00), with or without a low Apgar score, was too few for statistical evaluation, but only one of six such infants was slightly abnormal at follow up. Death, cerebral palsy (table IV), and transient motor impairment were not predicted any better than overall adverse outcome.

TABLE V—*Prediction of adverse outcome. Values are percentages (proportions)*

	Umbilical arterial pH	Lactate concentration	Apgar score at 5 minutes	Apgar score and pH
Sensitivity	21 (9/42)	12 (4/34)	12 (5/42)	7 (3/42)
Specificity	89 (767/866)	91 (768/843)	98 (861/883)	99 (858/866)
Predictive value:				
Positive	8 (9/108)	5 (4/79)	19 (5/27)	27 (3/11)
Negative	96 (767/800)	96 (768/798)	96 (861/898)	96 (858/897)

The poor predictive value of metabolic acidosis could be due to a confounding factor that would decrease the pH without having an influence on outcome. To rule out such a possibility the relation between pH and outcome was tested separately for infants with and without the risk factors, mentioned above, that had a significant effect on umbilical arterial pH. None of these risk factors had an influence on the prognostic value of pH.

Discussion

The incidence of low umbilical arterial pH was about 6% in previous cohort studies, when the mean −1 SD (7·11) of the study group[2] or an arbitrary value of 7·15[4] was taken as the lower limit of normal pH. The limit in other studies has varied from 7·09 to 7·25,[5-7] depending on the definition of normality. The most commonly

TABLE IV—*Clinical data on infants who died or who were clearly abnormal at 1 year of age*

Case No	Gestational age (weeks)	Birth weight (g)	Umbilical arterial pH	Apgar score At 1 minute	Apgar score At 5 minutes	Neonatal diagnosis	Outcome
1	22	630	7·11	0	0	Asphyxia	Died aged 20 minutes
2	26·3	920	7·24	3	8	Respiratory distress syndrome	Died aged 12 hours
3	27·7	940	7·40	4	6	Respiratory distress syndrome, intraventricular haemorrhage	Died aged 3 days
4*	28·6	615	7·19	1	6	Respiratory distress syndrome, patency of ductus arteriosus, bronchopulmonary dysplasia	Died aged 2 weeks
5	26·1	670	7·18	4	6	Respiratory distress syndrome, intraventricular haemorrhage, apnoeic spells	Hemiplegia
6	36·9	3080	7·23	9	9	Second born twin	Developmental delay
7*	38·9	3930	7·19	9	9	None	Developmental delay
8	39·6	4720	7·15	8	9	None	Developmental delay
9	39·7	2920	7·28	10	10	Hyperbilirubinaemia	Hemiplegia
10	40·1	4920	7·24	9	9	None	Developmental delay
11	40·7	3420	7·15	0	3	Hypoxic-ischaemic encephalopathy, seizures	Tetraplegia
12	41·1	3500	7·37	9	10	None	Developmental delay
13	41·4	3940	7·28	8	9	Facial nerve palsy	Hemiplegia
14	42·3	4500	7·16	9	9	None	Developmental delay

*Delivered by elective caesarean section.

used cut off points have been derived from the total population studied and thus may be influenced by the type of hospital. We based our assessment on a reference group without any complications, separately for deliveries with and without labour. The only study defining normal values for umbilical arterial pH in a sizable group of uncomplicated vaginal deliveries at term reported a cut off point (mean −2 SD=7·18) close to ours.[8] The incidence of acidosis at birth in our study group (11%) thus gives a formally correct estimate of this abnormality but, of course, reflects the nature of the patients studied.

PREDICTING BRAIN DAMAGE

Predicting the risk of brain damage during the neonatal period would be desirable for several reasons. It may be important in certain decisions about treatment in neonatal intensive care. It would help in identifying those infants who would benefit from more frequent and detailed follow up than usual to detect as early as possible those developmental abnormalities that are amenable to early rehabilitation. These include the cerebral palsies as well as visual and hearing problems. For such purposes a predictive test should have high sensitivity, so that infants needing special supervision would not be left out, and a reasonable positive predictive value, so that among the follow up group the number of infants subsequently developing normally would not be excessive compared with those found to require special care.

The poor correlation of the Apgar score, even when recorded at 5 minutes, with neurological outcome has previously been noted. The low positive predictive value, 19% in our study, means that about 80% of a group at risk as defined by a low Apgar score will be normal on follow up. In practice this is not an unreasonable ratio of normal to abnormal. The real problem is the low sensitivity—that is, only 12% of those with an eventual adverse outcome would be subjected to special follow up if the Apgar score at 5 minutes were the only criterion. This is even less than the 27% found in a previous study.[1]

For this reason we evaluated the applicability of metabolic acidosis at birth in defining a group at risk of brain damage. Blood from the umbilical cord, either venous or preferably arterial, can easily be obtained routinely at any delivery. As umbilical arterial pH may reflect not only fetal hypoxia and anaerobic metabolism but also maternal respiratory state, although only to a small extent,[9] we considered base deficit and lactate concentration as possible predictive variables in comparison with pH, alone or in combination with the Apgar score. Unfortunately, we failed to find a variable better or even as good as the Apgar score in predicting adverse outcome. The somewhat higher sensitivity of umbilical arterial pH (21%) was offset by its lower specificity and positive predictive value. The other indices of metabolic acidosis were no better.

Previous studies on the outcome of a birth cohort in relation to metabolic acidosis have not been reported. Umbilical arterial pH in relation to outcome was studied in 121 infants with acidosis with incomplete follow up and without controls.[4] Low pH in clinically normal newborn infants was not associated with a higher risk of later neurological sequelae. In preterm infants fetal acidosis was found to be more common in damaged than in normal survivors.[10] Fetal hypoxia with more prolonged metabolic acidosis (defined on the basis of arterial buffer-base values) was interpreted to carry a higher risk of deficits in comparison with acidosis of shorter duration,[11] but the data were few and the differences not significant. In another study on term infants metabolic acidosis at birth was not associated with more neurological or developmental problems on follow up than normal acid-base values.[12]

Like the Apgar score, umbilical arterial pH is useful for clinical assessment of the newborn infant. It is also valuable to obstetricians, particularly in infants with suspected fetal hypoxia. Why is metabolic acidosis at birth such a poor predictor of perinatal brain damage? One explanation might be that the abnormal outcomes observed in our study were not related to perinatal asphyxia, even though other known causal factors were excluded. In addition, the hypoxic insult responsible for the damage may have occurred well before birth,[13] and the associated metabolic abnormalities may have been compensated for by the time of birth. In the infants with acidosis the hypoxic episode may have been short. Equally probable, however, is that metabolic acidosis simply reflects physiological adaptation to the stress of delivery and asphyxia. Redistribution of blood flow to vital organs and the switch to anaerobic metabolism are usually successful in averting permanent damage, and survivors of extremely severe asphyxia often show a full neurological recovery.[14] Therefore perhaps signs of cell or tissue damage should be sought as more reliable prognostic indicators. These may include the leakage of specific enzymes—for example, creatine kinase BB, which is specific to the brain—or other neuronal proteins, ultrasonic evidence of cerebral ischaemia,[15] or signs of irreversible energy failure detected by nuclear magnetic resonance spectroscopy.[16]

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