THE RATIONALE FOR BIOCHEMICAL MONITORING OF THE FETUS

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Although our understanding of the pathophysiology of birth asphyxia has increased considerably over the last twenty-five years, the effects of asphyxia on brain development remain controversial. In this paper I will deal with the definition and incidence of birth asphyxia, the etiology of intrapartum asphyxia and the outcome measures which have been used in randomized controlled trials of fetal intensive care. In addition, I will discuss the relationship of birth asphyxia to the subsequent development of hypoxic-ischaemic encephalopathy and cerebral palsy.

1. The Definition and Incidence of Birth Asphyxia

The definition of asphyxia as given in Webster's New World Dictionary is "loss of consciousness as a result of too little oxygen and too much carbon dioxide in the blood." Thus, the dictionary gives both a biochemical and a biophysical definition. The biochemical definition can be precisely determined in terms of pH, PCO_2 and PO_2 and usually takes the form of a combined respiratory and metabolic acidosis. However, a biophysical definition, i.e., the Apgar scoring system, has been widely used for many years exclusive of any biochemical definition.

The true incidence of birth asphyxia is difficult to determine from the literature. Only those papers in which consecutive deliveries were reported are considered here so that bias from inclusion or exclusion of specific data is avoided. Table 1 shows the results of studies which satisfy these criteria and in which a biochemical definition for birth asphyxia was used, based on the pH of umbilical cord blood at birth.

It can be seen from Table 1 that the incidence of birth asphyxia depends on the precise pH chosen to define acidosis. If the definition used is that of $pH < 7.1$, the incidence varies from 2.3% to 8.6%, whereas, if the definition is widened to $pH < 7.2$, the incidence varies from 4.8% to 21.6%. There seems to have been consistent improvement in the incidence of low pH

at birth over the years between 1972 and 1987. This is particularly evident in the figures obtained from Dr. Saling's unit (2,5). Indeed, the recent figures emerging from their unit show that less than 5% of babies are now born with a UA pH of less than 7.2.

Table I Incidence of Birth Asphyxia in Consecutive Deliveries Based on Umbilical Cord Blood pH

Source	n	UA/UV	Mean ± SD	Low pH
Kubli 1972(1)	3317	UA	7.26(median)	<7.2 -21.1% <7.1 - 4.4%
Boenisch & Saling 1974(2)	5724	UA	-	<7.2 -10.6% <7.1 - 2.3%
Sykes et al 1982(3)	899	UA	7.20 ± .08	<7.1 - 8.6%
MacDonald et al 1985(4)	1075	UV	7.30 ± .07	<7.1 - 1.5%
van den Berg et al 1987(5)	2669	UA	7.30 ± .07	<7.2 - 4.8%

UA=umbilical artery UV=umbilical vein

An exception is the data of Sykes et al (3) which shows the highest incidence of acidosis (pH < 7.1) of all the studies. However, it is possible that methodological errors may account for their low pH values since pH was not always measured immediately after collection of blood samples.

It is difficult to compare the data from MacDonald et al (4) with the remainder of the data in Table 1 since the vessel chosen for blood sampling was the umbilical vein. Umbilical venous blood will not provide a satisfactory measure of acidosis in the fetus particularly under conditions of umbilical cord compression (see later) and the low incidence of acidosis reported by this group in over 1000 consecutive deliveries may reflect this problem.

It can be concluded that there are a number of problems in the biochemical definition of birth asphyxia. Firstly, if pH is to be used as the criteria, there is no agreement on the absolute value of pH which should be considered as abnormal. Should we use a pH value of 7.2 or 7.1 and should we use other parameters in addition such as PO_2, O_2 saturation, PCO_2 or lactate values? Secondly, if umbilical cord blood is used in the biochemical determination, the

duration of asphyxia is not known and there is no clear indication of whether the acidosis is chronic and long-standing or has developed acutely over the last few minutes of labour and delivery. The long-term prognosis of these two situations may be entirely different, and continuous biochemical monitoring may be the only way to monitor the duration of an asphyxial episode.

In many centres a biophysical score, usually the Apgar score or a modification of Apgar score, is the only criterion used for a diagnosis of birth asphyxia. The data which has been obtained from consecutive deliveries has been examined (Table 2), and there are wide variations in the definition and incidence using a low Apgar score, similar to those found using pH to define asphyxia.

Table 2 Incidence of Birth Asphyxia Defined by Apgar Score

Source	n	Apgar	%
Drage et al 1964(6)	10,020	<7 at 5 min	4.0%
Boenisch & Saling 1974(1)	5,724	<7 at 1.5 min	6.7%
Sykes et al 1982(2)	895	<4 at 1 min	3.8%
Macdonald et al 1985(4)	13,084	<4 at 1 or 5 min	1.0%
van den Berg et al 1987(5)	2,669	<7 at 1.5 min	1.05%

The definition of birth asphyxia by Apgar score is complicated by the presence of both false positives and false negatives (7,8). False positives (low Apgar and normal pH) can be seen with prematurity, analgesia, anaesthesia, trauma at delivery and congenital malformations. False negatives (normal Apgar and low pH) can be seen with short term asphyxia, chronic asphyxia in which fetal adaptation has occurred, and maternal metabolic acidosis.

A combined scoring system using both low Apgar score and low pH has been advocated by some authors (2, 5) and the results of three studies in which this combined approach to scoring at birth has been used is shown in Table 3; again, only those papers in which consecutive deliveries were studied are presented here. This type of approach in which not only the biochemical definition of asphyxia is used but also the effect on the fetus and newborn is taken into consideration, seems to be the most logical one in that it considers the functional effects of the biochemical abnormality.

Table 3 Incidence of Birth Asphyxia Defined as Low pH and Low Apgar in Consecutive Deliveries

	Low UA pH	Low Apgar	Low pH + Low Apgar
Boenisch & Saling 1974(2)	<7.2 10.6%	<7 at 1.5 min 6.7%	3.2%
Sykes et al 1982(3)	<7.1 8.5%	<7 at 1 min 10.8%	2.2%
van den Berg 1987(5)	<7.2 4.8%	<7 at 1.5 min 1.5%	0.7%

2. Etiology of Intrapartum Birth Asphyxia

The underlying cause of birth asphyxia is impaired placental gas exchange and the common pathological events leading to this situation during the intrapartum course are listed in Table 4.

Not included in this list are problems which precede the intrapartum course such as acute or chronic maternal hypertension, maternal or fetal cardiac failure, intrauterine growth failure and placental insufficiency. However, impairment of placental exchange before the onset of labour will considerably increase the intrapartum risk of asphyxia.

Table 4 Intrapartum Causes of Birth Asphyxia

1. Reduction of Uterine Blood Flow
   e.g. increased uterine activity
   maternal hypotension

2. Reduction of Umbilical Blood Flow
   e.g. umbilical cord compression

3. Combined Reduction of Maternal-Fetal Blood Flow
   e.g. abruptio placenta
   second stage (increased uterine activity
   ± cord compression)

There is usually a decline in pH during the course of labour and particularly during the second stage. Kubli (1) showed that there was a shift in median pH from 7.31 in early first stage to slightly lower values in late first stage. Median values for the second stage were 7.25 with a wide scattering of values below 7.1. Our own data, obtained from a small group of healthy women (n=28) in normal labour who were followed throughout first and second

stages with multiple fetal blood samples, showed a similar decline in pH in the second stage of labour (Figure 1).

Fetal pH fell from a mean of 7.30 in scalp blood samples during labour to 7.24 in umbilical cord blood at birth. It should be noted that pH was well maintained throughout the first stage and even early second stage, only falling when the second stage had been in progress for more than thirty minutes. Note that maternal pH also fell during the second stage due to the development of a mild metabolic acidosis without any change in PCO_2, presumably due to lactic acidosis from the physical activity involved in bearing down efforts. In contrast, the acidosis which developed in the fetus was due to a combination of respiratory and metabolic acidosis (Figure 1).

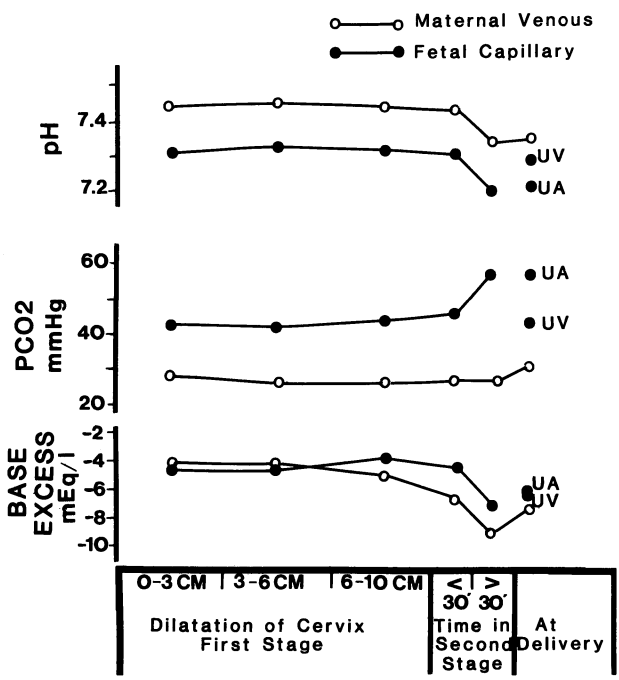


Figure 1 Mean values for pH, PCO_2 and base excess in maternal venous and fetal capillary (scalp) blood during normal labour and delivery in a group of healthy women (n=28). UA = umbilical artery; UV = umbilical vein.

Umbilical cord entanglement which was present in about 34% of 749 patients monitored in labour in our own data, is probably the commonest cause of fetal acidosis. pH values in umbilical arterial blood were significantly lower when cord entanglement was present (Table 5), although there was no difference in umbilical venous blood pH.

The explanation for maintenance of umbilical venous blood pH in the presence of umbilical cord compression is that maternal blood flow through the placenta remains uninterrupted while reduced blood flow through the umbilical circulation can satisfactorily maintain exchange with the mother at least in the early phases of cord compression. As a consequence of this, there is a significantly wider difference in pH between umbilical arterial and venous blood when cord complications are present (Table 5).

Table 5 Umbilical Arterial (UA) and Umbilical Venous (UV) Blood pH (mean ± SD) at Birth in the Presence or Absence of Cord Entanglement

	Cord Entanglement		
	Absent n=473	Present n=246	
UA pH	7.29 ± .074	7.26 ± 0.098	p<0.005
UV pH	7.35 ± .068	7.35 ± 0.077	n.s.
UV-UA pH	0.06 ± .034	0.08 ± .054	p<0.001

Cord compression has also been studied in fetal lambs (9). Figure 2 shows results from experiments in fetal lambs at 127 to 142 days gestation in which the umbilical cord was mildly compressed for a period of thirty minutes. The anticipated changes in pH, PO_2, PCO_2 and lactate can be seen from Figure 2 although the degree of compression was such that pH only fell from 7.36 to 7.26 during the thirty minute period. Changes in fetal brain electrocortical (ECoG) activity, although not significantly different, showed a trend towards increased high voltage activity during cord compression which promptly reverted to a normal percentage of time spent in high voltage and low voltage activity in the post-compression period. This suggests that even mild degrees of asphyxia may be accompanied by changes in functional activity of brain cells.

In one experiment in a fetal lamb, the umbilical cord was severely compressed for a period of twelve minutes. Figure 3 shows portions of the electrocortical (ECoG) activity from the fetal brain before, during and after compression. It can be seen that ECoG activity disappeared completely at 2-3 minutes after the start of cord compression i.e., at a time when pH had

only fallen from 7.39 to 7.30. The most significant change during this period was a dramatic fall in PO_2 from 25.6 to 5.5 mm Hg within two minutes of compression.

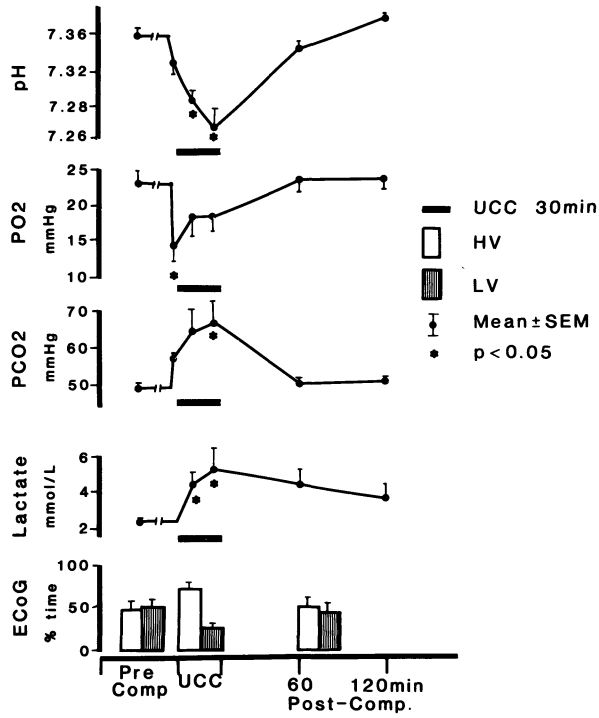
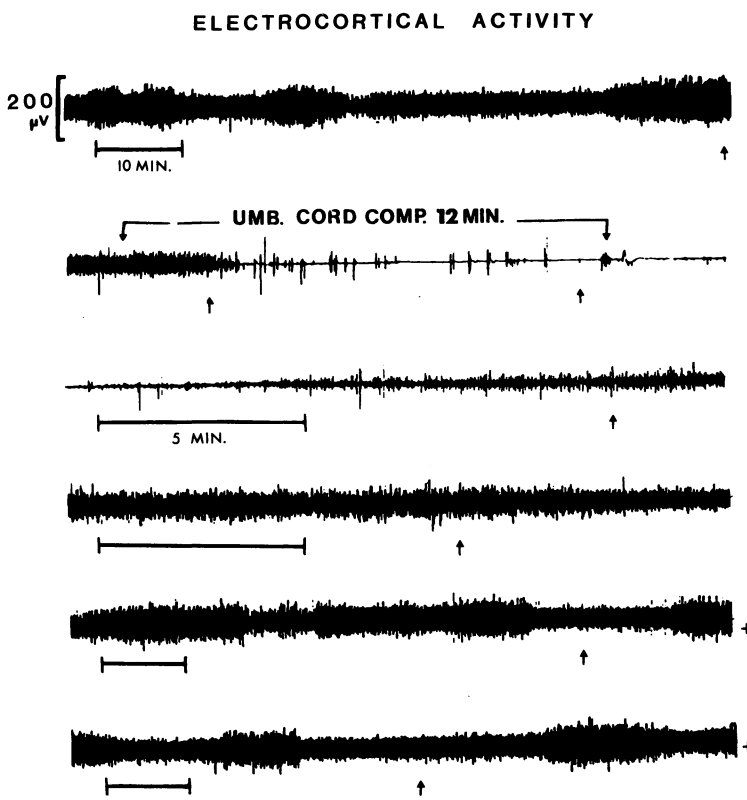


Figure 2 Effects of mild umbilical cord compression on fetal acid-base state and electrocortical (ECoG) activity in three fetal lambs at 127-142 days gestation. All experiments performed at >7 days after surgical preparation.

There was also a very large increase in lactate which only slowly resolved following compression. Lactate values remained elevated for at least three hours after the cord was released, presumably due to the slow washout of lactate from tissues once peripheral circulation was re-established during recovery from asphyxia. Similarly ECoG activity showed a slow return to its normal cyclical pattern of high voltage and low voltage activity. It is anticipated that experiments of this type will help to show how the biochemical defect in asphyxia impinges on tissue function and could provide valuable insight into the normal recovery patterns of cellular function.



	FETAL ARTERIAL BLOOD			
	pH	PCO2 mmHg	PO2 mmHg	Lactate mmol/L
PRE	7.39	48.5	25.6	2.6
U.C.C.				
2'	7.30	64.5	5.5	3.8
11'	6.84	139.0	5.0	12.5
POST				
+15'	7.04	72.6	21.5	12.1
+60'	7.26	46.7	23.5	10.4
+120'	7.34	47.6	23.1	7.9
+180'	7.38	42.6	22.0	6.8

Figure 3 Electrocortical activity, pH, PCO_2, PO_2 and lactate measurements in a fetal lamb at 133 days gestation before, during and after a 12 minute period of umbilical cord compression (U.C.C.). Arrows indicate arterial blood samples.

3. Outcome Measures in Birth Asphyxia

The effects of birth asphyxia are listed in Table 6 as modified from Fomufod et al (10) and deSa (11). Although the effects of asphyxia on the metabolism and the central nervous system are the most obvious at birth, there may be multi-organ dysfunction with widespread effects on bone marrow, kidneys, lungs, gastrointestinal tract and cardiovascular system in as many as 76% of infants affected (10). Widespread ischaemic damage may culminate in neonatal death or death in early infancy.

Table 6 Effects of Intrapartum Asphyxia on the Fetus and the Newborn Infant

Metabolic
- metabolic acidosis, hypoglycemia, hypocalcemia, hyponatremia

CNS
- hypoxic-ischaemic encephalopathy
- neonatal seizures
- brain swelling
- long term neurological handicaps

Haematologic
- thrombocytopenia, DIC

Renal Damage

Pulmonary
- hyaline membrane disease
- persistent fetal circulation

Gastrointestinal
- necrotizing enterocolitis
- liver dysfunction

Cardiovascular
- bradycardia, hyper/hypotension
- myocardial necrosis

Perinatal Death

Modified from Fomufod et al (10); deSa (11)

Much of the effort in obstetrical perinatal care over the past two decades has been directed towards development of sophisticated monitoring technics for fetal intensive care during labour. To date, the results of most randomized controlled trials using continuous fetal heart rate monitoring as a method of preventing perinatal asphyxia have been disappointing. Table

7 lists those studies which conform to the stringent criteria of truly randomized controlled trials. As can be seen, there have been no significant differences in any of the trials to date in either perinatal mortality or Apgar score.

Table 7 Randomized Controlled Trials of Continuous Fetal Heart Rate Monitoring

Source	Year	n	Perinatal Mortality	Apgar Score	Umbilical Arterial Blood pH	Neurological Outcome
Haverkamp et al(12)	1976	483	n.s	n.s	n.s	n.s
Haverkamp et al(13)	1978	695	n.s	n.s	n.s	n.s
Renou et al(14)	1976	344	n.s	n.s	$p<0.05$[1]	$p<0.001$
Kelso et al(15)	1978	504	n.s	n.s	"no diff."	n.s
MacDonald et al(4)	1985	12,964	n.s	n.s	n.s[2]	$p=0.025$

n.s = not significant [1] n = 86 [2] n = 1000; umbilical venous blood

pH has only been shown to be significantly different in one study in which pH was lower in unmonitored patients; however, the number of patients involved was small. It is unfortunate that in the Dublin randomized controlled trial (4) involving the largest number of patients, only 1000 of their patients were evaluated with umbilical cord blood pH and the vessel chosen was the umbilical vein and not the umbilical artery. Thus, no conclusions can be drawn from their data regarding the effect of monitoring on the biochemical outcome for the fetus.

In contrast, neurologic outcome has been shown to be significantly different in at least two trials (4, 14) with a higher incidence of jitteriness and early neonatal seizures in unmonitored patients. It should be noted that, in the Dublin randomized controlled trial (4), biochemical assessment of the fetus was permitted in both arms of the study. Thus, the difference in neurologic outcome was attributed to the application of continuous fetal heart rate monitoring and not to the use of fetal blood sampling.

The data from randomized controlled trials suggests that perinatal mortality and Apgar score will not be useful measures of outcome in any future trial of fetal intensive care. The current low level of perinatal mortality and its multiple etiology make it a poor choice as an outcome measure for birth asphyxia. Similarly, Apgar score alone, because of high false

negative and false positive rates in relation to fetal acidosis, is not a good measure for the presence or absence of birth asphyxia. The presence of fetal acidosis unrelated to maternal acidosis is diagnostic of impaired placental exchange and should be included in a definition of birth asphyxia. However, the absence of fetal acidosis does not exclude the possibility that episodes of asphyxia, from which the fetus has since recovered, may have preceded labour and delivery. Finally, neurologic outcome can be regarded as an important outcome measure to which we should pay close attention in the future.

Although Apgar score may not be a good measure of birth asphyxia, it is the only one that has been used for many years and a large volume of data available from the National Collaborative Perinatal Project (1955-1966) has been based on this outcome measure. Apgar scores were recorded in approximately 49,000 infants at 1 and 5 minutes and the presence or absence of cerebral palsy was known in 37,000 children who were available for follow up at 7 years of age. This data was subsequently analyzed by Nelson and Ellenberg (16) and the development of cerebral palsy compared with Apgar score at birth. The mortality rate was very high for infants <2500 gm at the time this data was collected. Furthermore, the etiology of cerebral palsy in low birth weight infants is known to be correlated with postnatal as well as prenatal factors. For these reasons, I have only considered their data from term infants of >2500 gm. Infants with very low Apgar scores of 0-3 showed an increasing mortality during the first year of life and an increasing morbidity (cerebral palsy) related to the latest time interval after birth at which an Apgar score of 0-3 was recorded (Table 8). It should be noted, however, that of the 120 children known to have cerebral palsy at 7 years of age which was not acquired postnatally, 55% had Apgar scores of 7-10 at 1 minute and 73% had scores of 7-10 at 5 minutes. Since the majority of infants will have normal Apgar scores at birth, the largest single group of children with cerebral palsy can be expected to come from this group, while a minority will come from groups with low Apgar scores.

It is clear from this data that a severely depressed infant at birth, particularly one that remains depressed and does not respond to resuscitation, has an increased risk of cerebral palsy related to the time interval over which it remains depressed after birth. However, many infants show no signs of birth asphyxia as judged by the Apgar score and it is therefore unlikely that their subsequent developmental problems can be attributed to intrapartum asphyxia. Indeed, it is more likely that, in this group, the cause of cerebral palsy antedates the intrapartum period and may or may not be related to asphyxia. The probability that factors preceding labour and delivery are very important in subsequent development of cerebral palsy has been pointed out by a multivariate analysis of the data from the National Collaborative Perinatal Project (17). This analysis showed that maternal mental retardation,

birth weight below 2001 grams and fetal malformation were among the leading predictors of cerebral palsy.

Table 8 Apgar Scores and Outcome by Latest Very Low Apgar Score (0-3) (> 2500 gm)

Apgar 0-3 (time-mins)	Liveborn	Death in First Yr (%)	Known to 7 Yrs.	With Cerebral Palsy (%)
1	1729	3.1	1330	0.7
5	286	7.7	217	0.9
10	66	18.2	43	4.7
15	23	47.8	11	9.1
20	39	59.0	14	57.1

From Nelson & Ellenberg, 1981 (16)

Breech presentation was also a predictor although breech delivery was not. Forty of the 189 survivors with cerebral palsy had evidence of birth asphyxia as judged by low Apgar score at birth. However, 23/40 or 57.5% had other factors present which were predetermined before the onset of labour such as birth weight below 2001 grams, congenital malformation etc. This data supports the idea that many fetuses are already predestined to develop cerebral palsy even before the onset of labour and that intrapartum asphyxia is responsible for a relatively small percentage of infants who eventually show neurologic developmental problems.

In 1982, Dennis and Chalmers (18) proposed that very early neonatal seizure rate could be used as a strong indicator of the quality of care based on their analysis of babies who developed seizures in the first forty-eight hours of life. They suggested that morbidity indices should be based on neonatal clinical signs which were unambiguous and strongly predictive of later morbidity such as cerebral palsy. Thus they proposed that the frequency of neonatal seizures in the first forty-eight hours of life should be considered as an index which met these criteria with respect to full term babies. The analysis of data from randomized controlled trials also suggested that, although the seizure rate did not achieve statistical significance in most of the studies, there was a trend towards a higher seizure rate in the unmonitored group. Thus, the Dublin randomized controlled trial was designed to use neonatal seizures as an outcome measure. Table 9 reproduced from that study (4) shows that there were twice as many infants with early neonatal seizures in the control (auscultated) group as in the electronic fetal monitoring group ($p < 0.025$) and the neonatal death rate following development of seizures was also twice as high ($p < 0.05$).

Table 9 Dublin RCT of Intrapartum Electronic Fetal Monitoring (EFM)

Sequelae of Neonatal Seizures	EFM	Auscultation	Significance
Neonatal death	3	6	$p < 0.05$
Survival	9	21	
Total no. of seizures	12	27	$p < 0.025$
Relative Risk (95% confid.)	.45	1.0	

From MacDonald et al. (4)

Hypoxic-ischaemic encephalopathy (HIE) is the term used to identify the cerebral problems in the full term infant following intrapartum or neonatal asphyxia. The pathological lesions are located in the peripheral and dorsal areas of the cerebral cortex and involve necrosis of the gyri at the depths of the sulci and neuronal nuclei of the basal ganglia and brain stem (19). The clinical features of HIE have been classified by Sarnat and Sarnat (20) into three stages: stage I - hyperalert: stage II - lethargic and hypotonic; stage III - stuporous and flaccid. In a careful follow up of survivors to 3.5 years of age, Robertson and Finer (21) used a similar classification into mild, moderate and severe HIE. They showed that none of the mild HIE cases died and none were handicapped at follow up (Table 10). However, with moderate and severe HIE, mortality and morbidity rates progressively increased with severity of the disorder and all survivors in the severe HIE group were handicapped.

Table 10 Outcome to 3.5 Yrs after Hypoxic-Ischaemic Encephalopathy in 226 Term Infants

HIE	n	(Lost to Follow-up)	Deaths In Hosp.	Deaths Later	Follow-up at 3.5 Yrs Not Hand.	Follow-up at 3.5 Yrs Handicapped
Mild	79	(10)	-	-	69	-
Moderate	119	(16)	3	3*	75	22
Severe	28	(0)	14	7	-	7

* 1 death from MVA

From Robertson & Finer (21)

The type of handicap described by Robertson and Finer (21) ranged from cognitive delay (58%), to cerebral palsy (53%), convulsive disorders (34%), visual loss (29%) and deafness

(11%). Thus the development of moderate or severe HIE within the first few days of life is a strong indicator of perinatal asphyxia and of subsequent morbidity.

Finally, the follow up study by Low et al (22) is the only one to date which relates careful intrapartum monitoring including acid base measurements with subsequent follow up of the child and neurologic assessment. They determined the development of intrapartum asphyxia by a measure of umbilical arterial blood buffer base and they classified their deficits at one year follow up as major or minor, motor and/or cognitive problems and showed an increasing incidence of deficits as buffer base values declined from 34 mmol/l to <22 mmol/l (Figure 4).

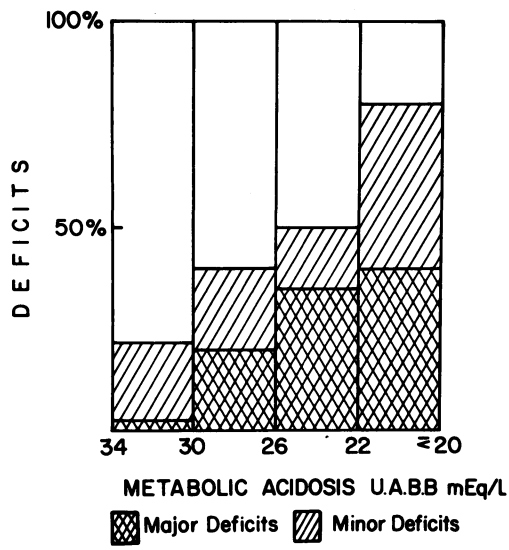


Figure 4 The incidence of major or minor, motor and/or cognitive deficits increased from 20% to 80% as the umbilical artery buffer base decreased from 30-34 to <22 mEq/l. (Reproduced with permission granted by C.V. Mosby Co. From Low, J.A. et al 1984 Am. J. Obstet. Gynecol. 148, 533-539.)

Summary

1. Rates for perinatal mortality and low Apgar scores have not been affected by fetal intensive care (electronic monitoring ± fetal blood sampling) in any randomized controlled trial to date.

2. Acidosis at birth may be susceptible to improvement by fetal intensive care but has not been tested adequately in more than a few women.
3. Birth asphyxia which is followed by evidence of cerebral dysfunction within the first 48 hours of life can be significantly altered by current technics of fetal intensive care.
4. The evidence suggests that cognitive disorders and cerebral palsy occur as long term sequelae of hypoxic-ischaemic encephalopathy in a small percentage of survivors. However, factors which predate the onset of labour are more likely to be responsible for cerebral palsy than factors associated with labour.
5. Future developments might include the following:
(i) To establish that umbilical arterial pH and/or lactate and/or Apgar score is predictive for neonatal outcome such as hypoxic-ischaemic encephalopathy or other markers of asphyxia.
(ii) To determine whether umbilical arterial pH and/or lactate is significantly different when continuous biochemical monitoring is used versus traditional intermittent fetal blood sampling, i.e. does continuous monitoring prevent acidosis?

In the present state of development of continuous biochemical monitoring technics in labour it seems unlikely that, at the present time, we could answer the larger question of whether such monitoring can prevent the neurological complications of hypoxic-ischaemic encephalopathy and the subsequent developmental problems including cerebral palsy.

Finally, we must not forget that labour and delivery represents a relatively small time period in relation to the total duration of pregnancy with a ratio of approximately 1:355. Thus, it is not surprising that many of the problems of neurologic development are difficult to trace back to a particular stage in pregnancy. Careful monitoring of labour and delivery may help to counteract the tendency to blame this period of pregnancy for all subsequent developmental problems of the child.

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