PART I

Epidemiology, Pathophysiology, and Pathogenesis of Fetal and Neonatal Brain Injury

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Perinatal asphyxia: an overview

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Although there has been a marked reduction in perinatal morbidity and mortality rates over the past four decades, asphyxia in the perinatal period, leading to major motor and cognitive disabilities, continues to be a significant health problem worldwide. With a great deal of emphasis being placed on fetal monitoring, the rapid institution of appropriate resuscitative measures in depressed infants, as well as having more precision in the diagnosis and documentation of asphyxia, the mortality rate due to intrauterine hypoxia and birth asphyxia (ICD-9 code 768) has decreased by over 70% since 1979 in the USA.[1] This trend has been noticed in Sweden[2] and in the UK[3] as well.

Despite these advances, a large number of infants with neurological abnormalities manifested by cerebral palsy, hearing or visual impairment, and mental retardation are born each year, many due to problems encountered during the birthing process. For many years, since W. J. Little's initial report linking neurological and mental handicaps in infants and children to abnormalities of labor and delivery, premature birth and asphyxia neonatorum,[4] physicians in general and the lay public in particular have considered that birth trauma and "perinatal asphyxia" were the primary causes of handicaps in children. They also felt that had appropriate obstetrical and neonatal care been provided, the majority of such handicaps could have been prevented. However, over the past 13–15 years, many epidemiological and clinical studies have demonstrated that most cases of cerebral palsy are not related to intrapartum asphyxia, and that if one eliminated infants born prematurely, as few as 7% to as many as 23% of infants born at term who developed cerebral palsy did so because of injuries sustained during this interval.[5–20] Most authorities in the field judge that the incidence is about 10% in developed countries and somewhat higher in developing countries. Nevertheless, it is the single most common cause of neurological/intellectual handicaps in children.

Major difficulties have been encountered in the inability to identify the timing, the type, the duration, and the severity of the insult that are associated with the neurological deficits. Also, the terminology used to describe the depressed or affected infant is often nonspecific and vague. Perinatal asphyxia, intrapartum asphyxia, hypoxemic–ischemic encephalopathy, neonatal neurologic dysfunctional syndrome, and fetal–neonatal acidemia have been used interchangeably to identify the affected newborn.

Several recent and excellent reviews of these problems have been published and have advanced our understanding of the incidence, the clinical manifestations, the laboratory correlates, the electroencephalographic abnormalities, and the imaging findings in infants with neonatal neurological abnormalities.[16–27] These studies have also evaluated infants who have few, if any, neonatal abnormalities but who were later found to be handicapped. While our understanding in these spheres has improved remarkably, we often lack sufficient data to understand thoroughly the mechanism or mechanisms involved in any particular affected newborn. Unfortunately, a thorough investigation attempting to identify the cause or causes of neonatal neurological

depression is often not attempted or is incomplete, and the diagnosis of perinatal asphyxia is made by default.[28] The long-term evaluation of the depressed infant is often lacking, and except for a few studies, little is known of the subsequent development of these patients.[3,20,29–32] Although severely affected infants are most likely to be enrolled in interventional and follow-up programs, those who have mild-to-moderate depression usually do not participate in long-term evaluations. Lastly, an infant or child may be identified as having neurologic or intellectual impairment, and then a retrospective analysis is instituted to identify the etiology of the abnormality. In many instances a definitive causative factor is not found, but there are suggestions that some "irregularities" of practice occurred during the perinatal period. Such suggestions sometimes provide the *only* bases for the assumptions that "perinatal asphyxia" was responsible for the child's impairment, and that if alternative approaches had been undertaken in the intrapartum period, little if any damage would have resulted. Unfortunately such reasoning has prevailed over the years despite the lack of substantive supporting data, and numerous litigations have been instituted in the belief that retrospective associations represent cause-and-effect relationships.

We readily recognize those infants who have been subjected to severe intrauterine stress, who are depressed at birth, and who remain obtunded during the neonatal period. These infants often have seizures with aberrant electroencephalographic patterns, have multiorgan abnormalities, and have a high incidence of neonatal death or subsequent neurological handicaps. These infants fit the classic clinical scenario of the neonate with hypoxemic–ischemic encephalopathy. In a number of these infants, this type of encephalopathy may not be due to intrapartum or neonatal difficulties, but may be due to other factors such as sepsis, congenital malformations, chorioamnionitis, congenital metabolic abnormalities, and various types of myotonic conditions.[11]

But what about the neonate who is depressed at birth, but who responds readily to resuscitation and has an uneventful neonatal course? If such an infant is later found to have neurological disabilities, can one implicate abnormalities in the perinatal period as being the "proximate cause" of the sequelae? The currently available data suggest that episodes of mild neonatal depression are not associated with subsequent handicaps, and that even following moderate or severe depressions, most infants, if they survive, develop normally.[29,33]

It is critical that we have a better understanding of those factors that contribute to the development of the "brain-damaged child" and that we not be unduly influenced by circumstantial evidence. It is also critical to recognize that many of the events leading to difficulties in the infant occur long before the mother has the onset of labor. With the improvement of ultrasonographic, computed tomography (CT), and magnetic resonance imaging (MRI) expertise, more and more infants are being recognized with intrauterine abnormalities that have already caused significant damage.[34–50] Careful examination of the placenta can also identify lesions that are associated with infection or anomalies that have been present for a period of time[51–53] (see Chapter 24). We recognize that these infants are often unable to tolerate the stress of labor well, may have fetal heart rate abnormalities either prior to delivery or during the early stages of labor, or have abnormal contraction stress tests or nonstress testing.[34,50] These infants are often difficult to resuscitate and show neurological features that seem excessive considering the problems that occurred during labor or the birthing process. In addition, some infants may have suffered a significant intrauterine catastrophe, recover, and may even be able to tolerate labor well enough not to have abnormalities noted on their fetal heart rate tracings.[54]

We also recognize that events leading to difficulties in the prematurely born infant may be different from those in infants born near or at term. Similarly, the preterm infant may have many more and vastly different difficulties in the postpartum rather than the intrapartum period, and will have different clinical features from those seen in the full-term infant. In attempts to evaluate etiology, pathogenesis, inter-

vention, and management one must be aware that similar events may have different consequences depending upon the patient's capacity to respond to various insults, and some of these are determined by gestational age. In addition, infants with intrauterine growth restriction make up a disproportionate share of infants with neonatal brain injury, suggesting that the underlying cause or causes of the growth restriction may have started in utero and continued through the intrapartum and postpartum periods.

Asphyxia

Asphyxia is defined as progressive hypoxemia and hypercapnea accompanied by the progressive development of metabolic acidosis. The definition has both clinical and biochemical components, and indicates that, unless the process is reversed, it will lead to cellular damage and ultimately death of the patient.[23] As stated by Stanley et al., "Birth asphyxia is a theoretical concept, and its existence in a patient is not easy to recognize accurately by clinical observation."[20] We currently do not have the sophisticated technology of routinely measuring fetal cerebral activity or the response to unfavorable conditions such as hypoxia, ischemia, or acidosis, the compensatory mechanisms that protect the brain cells, or, when such mechanisms are inadequate, the documentation of cell injury and cellular death.

In lieu of direct measurements, we have utilized indirect indicators that have been based on studies carried out in laboratory animals and extrapolated to be used in the human fetus. In a few instances, direct measurements have been possible, but have not been linked well to outcome. Indirect assessments include the biophysical profile, fetal heart rate measurements, evidence of severe metabolic acidosis, depressed Apgar scores, abnormal newborn neurological function, and development of seizures. As mentioned, the timing of the events is often unknown and difficult to ascertain as far as onset, duration, and severity are concerned.

Based on studies in monkeys by Dawes[55] and Brann and Myers,[56,57] and also substantiated to a great extent in fetal lambs by the group in Auckland,[58–62] two major types of intrauterine asphyxial conditions have been recognized. The causes of the acute total asphyxial events are listed in Table 1.1, and have been referred to as "sentinel events" by MacLennan and the International Cerebral Palsy Task Force.[24] In the acute type of asphyxia, there is a catastrophic event, the fetus is suddenly and rapidly deprived of his or her lifeline, and usually does not have the opportunity to protect the brain by "invoking the diving reflex." The conditions most commonly encountered include prolapse of the cord,[63–65] placental abruption, and fetal hemorrhage. With the increasing use of vaginal births after cesarean sections, we are also encountering more and more neonates being born following uterine rupture.[66]

Table 1.1. Acute causes of fetal brain injury (sentinel events)

Prolapsed umbilical cord
Uterine rupture
Abruptio placentae
Amniotic fluid embolism
Acute neonatal hemorrhage
Vasa previa
Acute blood loss from cord
Acute maternal hemorrhage
Any condition causing an abrupt decrease in maternal cardiac output and/or blood flow to the fetus

These infants have damage to the deep gray matter of the brain involving the thalamus, basal ganglia, and the brainstem, often with sparing of the cerebral cortex.[67–70] These infants, if successfully resuscitated, often do not have evidence of multisystem or multiorgan dysfunction. Laboratory animals, who were quite healthy prior to the onset of the acute asphyxial event, develop evidence of neurological damage as early as 8 min after the event.[55] Major irreversible lesions were found after 10–11 min,[56,57] and the animals usually succumbed if not resuscitated within 18 min. After 20 min of asphyxia, some animals could be resuscitated, but usually died of cardiogenic shock within 24–48 h even with intensive care.

Although data in humans are lacking, studies of infants following prolapsed cords suggest similar time frames,[63–65] and those infants who have occult prolapse[65] often have a better outcome than those with overt prolapse. The study from Los Angeles County University of Southern California (LAC/USC) Medical Center noted that if it required greater than 18 min to deliver the fetus after spontaneous rupture of the uterus, neurological sequelae would ensue.[66] Unfortunately, the long-term follow-up of the surviving infants in this study is not available. Thus the 30-min timing of "decision to incision," as recommended by the American College of Obstetricians and Gynecologists (ACOG), is not valid in these situations.

The infants who have suffered this type of acute event will have varying degrees of neurological injury, often manifesting extrapyramidal types of cerebral palsy and with varying degrees of mental impairment depending upon the severity and extent of the injury.[67–70]

Those infants subjected to prolonged partial asphyxial episodes and who have neurological involvement most often have lesions in the cerebral cortex in a watershed type of distribution.[27,71] They often have multiorgan involvement and have pyramidal signs of cerebral palsy.[27] The incidence and severity of cognitive impairment also depend upon the extent and severity of the lesion.

An acute event may also occur in a fetus who has already been subjected to a partial prolonged asphyxial condition or a preexisting neurological insult. That fetus may demonstrate complications of both processes and have both pyramidal and extrapyramidal neurological findings associated with varying degrees of auditory, visual, and/or cognitive abnormalities.

Incidence of asphyxia and correlation with outcome

Most authorities suggest that "perinatal asphyxia" occurs in 3–5 infants per 1000 live births, and that the incidence of encephalopathy occurs in 0.5–1 per 1000 live births.[2,20,27] Various techniques have been used to identify the asphyxiated infant including the time required to initiate spontaneous ventilation, the time that positive-pressure ventilation was required to sustain the infant before spontaneous respirations ensued, and the use of the neonatal scoring system developed by Virginia Apgar.[72–74]

The newborn scoring system which was developed by Apgar has been used in almost every delivery room to identify those infants who are depressed and who require resuscitation efforts. In addition, the use of the scoring system required an "advocate" for the neonate because someone had to evaluate the infant in the immediate neonatal period and provide a numerical score of the baby's condition. Dr Apgar did not design the scoring system to be used to evaluate neurological outcome and to identify infants early on who would subsequently develop neurological handicaps. Unfortunately, the Apgar score has been utilized in many situations for that very purpose.

It was so utilized in the National Collaborative Perinatal Project (NCPP) of the National Institutes for Neurological Disease and Stroke.[75] Unfortunately, there are many factors that can influence the Apgar score, including immaturity, maternal anesthesia and analgesia, fetal or neonatal sepsis, or neuromuscular abnormalities.[75–77] Despite these caveats, the Apgar scoring system remains the standard by which neonates are evaluated immediately after birth as well as their response to appropriate resuscitative techniques.

The long-term neurological outcome, especially in term infants, has not correlated well with low scores at 1 and 5 min, but begins to have better correlation for those infants who have scores of 0–3 for 10, 15, and 20 min after birth.[78]

If one uses an Apgar score of 6 or less at 5 min of age to indicate asphyxia, the incidence of asphyxia in the NCPP study was almost 5% (Table 1.2). Interestingly, Levene and coworkers evaluated two methods of predicting outcome in asphyxiated infants using several different Apgar ratings.[79] They found that a 10-min Apgar score of 5 or less had a sensitivity of 43% and a specificity of 95% in predicting adverse outcomes. This was in a group of infants that had postasphyxial encephalopathy.

Table 1.2. Incidence of perinatal asphyxia, mortality, and handicaps in survivors

						Outcome in survivors (%)		
Authors	Years of study	Definition of asphyxia	Number of patients	Incidence of asphyxia	Deaths (%)	Normal	Mild-to-moderate damage	Severe damage
Neligan et al. 1974:[84] community study	1960–1962	Delay greater than 5 min to establish respiration	13203	27/1000 (includes prematures)	21	95.4	0.05	4
Steiner and Neligan 1975:[87] hospital study	1961–1970	Cardiac arrest or delay greater than 20 min to establish respiration	20793	1.8/1000	52	77		23
Scott 1976[86]	1966–1971	Apparent stillborn or delay greater than 20 min to establish respiration	12389	3.8/1000	52	74		26
Nelson and Ellenberg 1981[78]	1959–1966	Apgar scores 6 or less at 5 min (all weights)	49498	47/1000	24	96.4		3.6
		Apgar scores 0–3 at 5 min (all weights)	49498	15.7/1000	42	94.7		5.3
		Apgar score 0–3 at 10 min (all weights)	49498	7.2/1000	76	76	10	14
Peters et al. 1984[82,83]	4/4–4/11/70	More than 3 min to establish respiration (all weights)	16333	45/1000	6.0	86		14
MacDonald et al.[80] and Mulligan et al 1980[81]	1970–1975	More than 1 min positive-pressure ventilation	38405	11.6/1000	46.1[a]	81.5		18.5
MacDonald et al. 1985[144]	1981–1983	Neonatal seizures	13084	3/1000	23	80		20
Jain et al. 1991[85]	1982–1986	Apparent stillborn (Apgar 0 at 1 min) all weights	81242	7.5/1000	64	61	13	26
Thornberg et al. 1995[2]	1985–1991	Apgar <7 at 5 min	42203	6.9/1000	5.7	93	1.4	5.6
Yeo and Trudehope 1994[89]	1981–1991	Apgar 0 at 1 min	64064	8.4/1000	92	63	12	25
Casalaz et al. 1998[88]	1986–1994	Apgar 0 at 1 min	94511	0.5/1000 (62% term)	7 immediate 42 total	64	16	23

Notes:
[a] 89% <30 weeks, 18% >36 weeks.
Source: Modified from Dennis.[9]

In 1980 MacDonald and coworkers evaluated 38 405 consecutive deliveries and defined neonatal asphyxia in infants who required more than 1 min of positive pressure ventilation before sustained respiration occurred.[80,81] They found 447 infants with asphyxia – an overall incidence of 1.15%. The more immature the infant, the greater the incidence, severity, and mortality associated with asphyxial episodes (Table 1.2).

Peters and coworkers evaluated 17 196 infants born during the week of 5 April 1970 through 11 April 1970 in the UK. These investigators used the time required for the onset of regular respirations to define asphyxia. The times were less than 1 min, 1–3 min (mild-to-moderate asphyxia), and more than 3 min (severe asphyxia).[82,83] The mortality rates were very low in infants who required either less than 1 min or 1–3 min to breathe; however, there was an increase in mortality in infants who required more than 3 min to institute normal respiration. The incidence of mild-to-moderate asphyxia was 18% and that of severe asphyxia was 4%. The overall mortality was most pronounced in very-low-birth-weight infants. The subsequent follow-up demonstrated an increased incidence of cerebral palsy not only in infants of low birth weight but also in larger infants, especially in those requiring more than 3 min to institute spontaneous respiration (Table 1.2).

Neligan and coworkers, using the criterion of a 5-min delay in establishing respirations, found an incidence of asphyxia of 27/1000 births, including preterm infants.[84] They also noted a mortality rate of 21%, but 95.4% of the surviving infants were normal at follow-up examination.

Jain and coworkers evaluated the outcome of infants who were apparently stillborn (Apgar scores 0 at 1 min).[85] Data from a total of 81 242 mother–infant pairs were analyzed and 613 infants were identified. Of these, 520 were classified as fetal deaths and were not resuscitated. Of the remaining 93 infants, 31 did not respond to resuscitative efforts, but 62 patients did. Twenty-six died in the neonatal period, three died after discharge, and 10 infants were lost to follow-up. Of the remainder, 61% were felt to be normal infants, 26% were abnormal, and 13% were suspected of having some neurological damage. None of the infants weighing less than 750 g at birth survived. The survival rate of the infants was 16% if the Apgar score remained 0 at 5 min and only 1.7% if it remained 0 at 10 min. Also, infants who were resuscitated at level II centers had a 50% delivery room mortality rate as compared with 26% cared for in level III centers.

Scott, defining severe asphyxia in infants who were apparently stillborn or who required more than 20 min to establish spontaneous respirations, included both preterm and term infants in the evaluation.[86] Scott also noted that, although half of the infants died, three-quarters of the survivors were apparently normal – a surprising finding considering the dire condition of the infants at birth (Table 1.2).

Steiner and Neligan, evaluating the neonates with cardiac arrest or a delay greater than 20 min for them to establish respiration, noted an incidence of 1.8/1000 births for this type of severe asphyxia. The mortality rate for these infants was 52%, but 77% of the survivors were normal at follow-up examinations.[87]

Casalaz and coworkers described 45 infants who were 24 weeks' gestation or greater who were classified as an unsuspected apparent stillborn – an incidence of 0.5/1000 live births.[88] Of these, 42 were successfully resuscitated, 52% either died or survived severely disabled, but 36% survived apparently intact. In this study, indicators of poor outcome included 5- and 10-minute Apgar scores of 3 or less, an arterial pH within the first 2 hours of life of less than 7.0, and an absent heart beat at 5 min of age.

Yeo and Tudehope described 539 infants with Apgar scores of 0 at 1 min – an incidence of 8.4/1000 births, of whom only 8.3% were successfully resuscitated.[89] Of the survivors who left the hospital, 64% had a normal outcome.

There are a few published reports that have evaluated the outcome of severely depressed infants who have required 30 min or more of assisted ventilation before they were able to initiate spontaneous respiration. Steiner and Neligan reported that all of the four patients they cared for died or had severe handicaps.[87] Scott reported 11 such infants, four of

whom were normal or had mild handicaps.[86] Koppe and Kleiverda reported that all 13 of such patients either died or had severe handicaps.[90] De Souza and Richards, on the other hand, had seven infants who required greater than 30 min to establish spontaneous respirations, and all seven survived, and were normal or had minimal disabilities.[91] Amazing.

Correlative signs of asphyxia

Several signs or findings have been correlative to some extent with the severity of asphyxia in the intrapartum period. These have included the presence of meconium in the amniotic fluid, evidence of metabolic acidosis measured either from cord blood or in the immediate neonatal period, the presence and severity of the neonatal neurological assessment, the onset of seizures within the first 3 days of life, supporting laboratory data, findings on electroencephalography, corroborative findings on imaging studies, and evidence of multiorgan dysfunction.

Meconium

The presence of meconium in the amniotic fluid has long been thought to indicate fetal stress (see Chapters 24 and 31). Meconium is found in 8–20% of all deliveries, being uncommonly encountered in preterm gestations and more frequently encountered in the postterm baby. If meconium is recognized in amniotic fluids of infants at 34 weeks' gestation or younger, significant intrauterine stress or intrauterine infection must be suspected. In term and postterm infants, meconium staining is usually light and the fetus and newborn are essentially symptom-free. However, heavy, thick meconium passed early in labor tends to have a more ominous significance than when passed more proximate to delivery.[92] But even this finding has not been substantiated in other studies.[93]

The presence of meconium *per se* in term infants is not predictive of neurological sequelae; in fact, Nelson and Ellenberg noted that fewer than 0.5% of the infants weighing more than 2500 g with meconium staining had neurological sequelae.[94] In studies in the Netherlands, the presence of meconium-stained amniotic fluid had no predictive value in regard to outcome, the development of neurologic symptoms in the newborn period, or acidosis measured by the pH of cord blood.[95–97] Even when the presence of meconium was ascertained and used in conjunction with either Apgar scores or cord pH values or both, the finding did not alter the incidence of subsequent neurological abnormalities. In Chapter 24, Dr Altshuler discusses the factors in meconium that affect the placenta and fetal circulation, and in Chapter 31, Dr Wiswell addresses the significance of meconium in amniotic fluid and its relationship to neonatal problems.

Fetal and neonatal blood gas levels

Steward Clifford was one of the first clinicians to suggest that neurologic abnormalities in the neonate are not necessarily due to birth trauma but rather to the accumulation of lactic and carbonic acids secondary to the hypoxic–anoxic episode.[98] He also noted that, in addition to damage occurring in the central nervous system, every organ and tissue in the body could be affected to some degree. Since his observations, which subsequently have been supported by studies in laboratory animals, it has been postulated that the accumulation of lactic acid is correlated with the abnormalities seen in hypoxic–ischemic encephalopathy.

Since 1967, obstetricians have utilized fetal acid–base measurements as adjuncts to fetal heart rate monitoring to evaluate the well-being of the fetus, and to identify those fetuses who were at risk for intrapartum difficulties.[99,100] However, there is a great deal of debate as to whether or not these techniques are truly helpful in the management of labor.[101,102]

Subsequently, investigators attempted to correlate the fetal acid–base status with subsequent neurological outcome. Initially it was stated that the normal umbilical arterial pH was 7.25–7.35 and defined a pH below 7.20 as acidosis. Then lower levels of pH such as 7.15 or even 7.10 were noted to be indicative of acidosis.

In the study by Sykes and coworkers only 20% of the neonates with Apgar scores of 6 or less had cord pH values of 7.10 or less.[103] Of infants whose cord pH value was 7.10 or less, 22% had Apgar scores of 6 or less. Similar results were obtained by Silverman and coworkers, who noted that the metabolic state of the fetus as measured by the umbilical artery pH level was not closely related to the Apgar score unless a severe degree of biochemical abnormality was encountered, i.e., a pH value less than 7.05.[104] Dijxhoorn and coworkers found similar results in appropriately grown neonates.[95–97] They found that measurements of the arterial or venous pH or the maternal-fetal difference in pH alone could not be used as predictors of neonatal neurological depression. However, in infants who were small-for-gestational-age, the incidence of fetal acidosis was greater than in appropriate-for-gestational-age infants, but was not necessarily correlative with severe neonatal depression.[97]

Correlative data appear when the cord arterial pH is 7.00 or less and when there is evidence of neurological abnormalities in the neonatal period as well. Also, the finding of a low pH in itself is of less prognostic significance if it is due primarily to respiratory acidosis rather than metabolic or even mixed acidosis.[105–113] Low and coworkers, who have written extensively on this subject, noted that "the threshold for significant metabolic acidosis is a base deficit between 12 and 16 mmol/liter."[23,114,115] They have found a base deficit of 12 mmol/l in 2% of all births and a base deficit of 16 mmol/l in 0.5% of the population studied. An increased number of neurological abnormalities were encountered in infants as the degree of acidosis worsened. Also, the longer the acidosis was present, the greater was the correlation with neurological deficits;[23,115–120] and a period of 1 h or greater was a critical time for the metabolic acidosis to have been present.[120]

These studies have more clinical significance and have better correlation with subsequent outcome if the acidosis is associated with abnormal neurological findings in the infant at the time of birth. Interestingly, a group of infants with metabolic acidosis (umbilical arterial base deficit of greater than 12 mmol/l) but who had either none or mild neurological complications were followed for 8 years and were found to have no greater incidence of neurological or cognitive handicaps than a control group of patients.[33]

Table 1.3. Severity of fetal acidosis and hypoxic–ischemic encephalopathy and other organ dysfunction

pH	% with encephalopathy	% with other organ damage
6.61–6.70	80	80
6.71–6.79	60	60
6.80–6.89	33	52
6.90–6.99	12	25

Source: Data from Goodwin et al.[108]

Goodwin and coworkers from LAC-USC Medical Center identified 126 term live-born singleton infants who had no major anomalies over a 4½ year period (total deliveries were 76548).[108] Of these, 109 infants were evaluated if the blood gas was documented to be arterial. The vast majority of the infants had either mixed or metabolic acidemia and the lower the pH, the greater was the risk of hypoxemic–ischemic encephalopathy (Table 1.3).

In evaluating the outcome in the 126 infants, five died (4%), 8% had major neurological deficits, 4% were suspected of having neurological problems, 6% were lost to follow-up, and 78% were normal.

In a follow-up study, these investigators noted that in the patients with an umbilical arterial pH of 7.00 or less, there was a greater incidence of seizures, hypoxic–ischemic encephalopathy, cardiac, pulmonary, and renal dysfunction and abnormal development at follow-up if the arteriovenous difference in Pco_2 was greater than 25 mmHg. The sensitivities of these clinical findings ranged from 84 to 95% and the specificities ranged from 54 to 60%. The arteriovenous difference in Po_2 correlated to a much lesser extent.[111]

Van den Berg and coworkers found an increased number of neonatal complications in newborns with an umbilical arterial pH below 7.00.[112]

Obtaining routine umbilical arterial and venous cord samples in 14 025 infants over an 8-year period, they found that 1.3% of infants who had reliable cord samples had an arterial cord pH less than 7.00. Only two of these infants died, but 32% had to be admitted to an intensive care nursery and 23% had neurological abnormalities. If the base deficit was 15 mmol/l or greater, 93% had neurological abnormalities. Interestingly, 27% of these infants had no neonatal problems. Unfortunately, the long-term evaluation of these infants is lacking.

Andres et al. found similar data in 93 infants with umbilical arterial pH of less than 7.00.[113] Nine percent of the infants died, 40% required intubation, 5% had seizures and 2% had hypoxic–ischemic encephalopathy. These authors also found a higher base deficit (>19 mmol/l) in the seriously affected infants. This was a retrospective evaluation and long-term outcome is lacking.

In an interesting study, Kruger and coworkers found a better correlation using fetal scalp lactate measurements than scalp pH in predicting low Apgar scores and moderate-to-severe hypoxic–ischemic encephalopathy. Further evaluation of this technique using microquantities of blood is warranted.[121]

Using data from numerous studies, the International Cerebral Palsy Task Force has recommended that in order to determine that an intrapartum hypoxic event has taken place, one of the three major criteria listed is a pH of less than 7.00 and a base deficit of greater than 12 mmol/l.[24]

Laboratory correlates

Various metabolic parameters have been used to identify or verify the severity of the asphyxial insult in addition to the severity of the metabolic acidosis mentioned above (Table 1.4). Goldberg and coworkers described severe hyperammonemia, usually accompanied by elevated activities of aspartate amino transferase and alanine aminotransferase, as a consequence of severe asphyxia.[122] As the condition of the infant improved, the levels of ammonia decreased as well. Table 1.4 lists the various parameters that have been measured in various body fluids. Until recently, most of these products were significantly elevated in patients who had severe and prolonged asphyxia.[123,124] Studies of creatinine kinase brain isoenzyme and neuron-specific enolase[125] in the cerebrospinal fluid (CSF) have a more correlative effect with the severity of the asphyxiated period. Even the elevation of aspartate and glutamate, the neuroexcitatory amino acids, was only increased in the severely asphyxiated infants.[126,127] Similarly, elevations of glial fibrillary acidic protein in the CSF were found in severely asphyxiated infants.[128] Hypoxanthine elevations in plasma and urine have had variable correlative effects with the degree of asphyxia.[129]

Table 1.4. Laboratory studies used to support the diagnosis and severity of perinatal asphyxia

Study	Body fluid
Ammonia	Blood
Lactate	Serum, CSF
Hypoxanthine	Serum, urine
Erythropoietin	Serum, CSF
Creatine kinase brain isoenzyme (CK-BB)	Serum, CSF
Myelin basic protein	CSF
Neuron-specific enolase	CSF
Aspartate	CSF
Glutamate	CSF
Glial fibrillary acidic protein	CSF
Lactate: creatinine ratio	Urine
Carbon monoxide	Plasma
Nitric oxide	Plasma

Notes:
CSF, cerebrospinal fluid.
Source: Modified from Volpe (27)

Similar to the findings of an elevated scalp lactate level as an adjunct to evaluating the severity of intrapartum difficulties, da Silva et al. measured lactic acid levels and base deficit at 30 min of age in 115 term infants who were suspected of having intrapartum asphyxia.[130] They found excellent correlation between the base deficit and plasma lactate levels, and when the lactate level was less than 5 mmol/l