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Pathogenesis and Prevention of Fetal and Neonatal Brain Injury

Andrew Macnab

Abstract

Recent advances in the clinical management of at-risk pregnancy and care of the newborn have reduced morbidity and mortality among sick neonates, and improved our knowledge of factors that influence the risks of brain injury. In parallel, the refinement of imaging techniques has added to the ability of clinicians to define the etiology, timing and location of pathologic changes with diagnostic and prognostic relevance to the developing fetus and newborn infant. Abnormalities of brain growth, or injury to the developing brain can occur during pregnancy; during labor and delivery, hypoxia, acidosis and ischemia pose major risks to the fetus. Defined practices for the management of pregnancy and delivery, and evidence-based strategies for care in the newborn period are influencing outcome. However, newborn infants, especially those born prematurely, remain at risk from situations that can cause or worsen brain injury. The literature reviewed here explains the mechanisms and timing of injury, and the importance of hypoxia, ischemia, hypotension and infection; describes current diagnostic strategies, neuroimaging technologies and care entities available; and outlines approaches that can be used to prevent or mitigate brain injury. Some show particular promise, and all are relevant to lowering the incidence and severity of brain damage.

Keywords: encephalopathy, hypoxia, ischemia, magnetic resonance imaging, prematurity, ultrasound, umbilical cord blood gases

1. Introduction

> *"This work must begin with the conception of man, and describe the nature of the womb and how the foetus lives in it, up to what stage it resides there, and in what way it quickens into life and feeds. Also, its growth and what interval there is between one stage of growth and another. What it is that forces it out from the body of the mother, and for what reasons it sometimes comes out of the mother's womb before the due time."—Leonardo da Vinci (1452-1519) [1].*

In a prior review (2012), literature describing the etiology of fetal brain injury, and its presentation, evolution and management in the neonate was summarized [2]. However, recent advances have considerably increased our knowledge of the nature and prognosis of brain injury, and what can be done to treat and prevent it.

The importance of maternal and fetal health throughout the nine months of intrauterine life remains. But the vulnerability of the fetus to adverse events related to labor and delivery is better understood, and more readily anticipated. Substantial progress has also been made in the care of neonates, our

understanding of the pathogenesis of injury, and protective strategies which can help to prevent or mitigate permanent injury. It is now clear that acute brain injury is a continuum; hypoxia and ischemia in particular generate a sequence of physiologic consequences where the acute phase of injury is followed by a period of latency, and then brain cells undergo secondary energy failure where a cascade of disruptive events occurs which leads ultimately to programmed cell death. This understanding is particularly valuable, as it now guides investigation linked to both the diagnosis and prognosis of injury, and provides critical opportunities for novel care strategies.

The birth and care of infants born prematurely remains challenging. The inherent immaturity of their organ systems and complex therapies they require makes them vulnerable physiologically to a spectrum of potentially adverse events; the result is a significant incidence of long-term cognitive and motor deficits. In spite of advances in obstetric and neonatal care lowering the overall prevalence of complications, the incidence of cerebral palsy has not reduced significantly. But it is clear now that a strong relationship exists between gestational age at delivery and the probability of both survival and discharge without major handicap, with every additional week in utero tending to improve the chances of a good outcome [3].

Fetal and neonatal brain injury, and the long-term neurodevelopmental handicap caused, is an extremely important problem, and especially so in premature infants, because of the large absolute number born. Research documents that infants born very prematurely (<32 weeks gestation), and those with an extremely low birth weight (<1000 g), are at increased risk for neurobehavioral impairments (cerebral palsy, blindness, deafness), lower general intelligence, specific cognitive defects, learning disabilities, and behavioral and emotional problems [2, 3]. Modern neonatal care does now enable an increasing number of these infants to survive and escape significant handicaps. Survival of extremely preterm infants (<25 weeks gestation) remains rare, but in Europe and the USA 75-90% of infants who weigh <1500 g at birth now survive, however 5-10% of them develop cerebral palsy subsequently, and many have cognitive, behavioral, attention-related or socialization deficits.

Normal fetal growth is a continuum that must be appreciated in order to fully understand the causes, evolution, and consequences of abnormalities in brain development. Key factors have been reviewed previously [2]. Genetic anomalies are the principal cause of fetal loss, and structural abnormalities are commonly evident at a macroscopic and microscopic level. Advances in genetic screening and analysis have led to genetic studies becoming an integral part of the workup of an increasing number of infants. Genetic counseling is central to prevention in situations where there is a family history of a genetic brain abnormality, birth of a prior infant with an anomaly, or predisposition to a genetic problem due to racial or age-related factors. An autopsy and placental pathology are important after fetal loss.

Embryonic development progresses rapidly after conception, so that a large proportion of the brain's structure is already formed by the time many women become aware that they are pregnant. By the end of the first trimester (3 months of gestation), all the main structures of the central nervous system are formed and so brain growth alone follows between this time and fetal maturity (40 weeks). Hence the relevance of more people understanding the concepts currently articulated in the developmental origins of health and disease (DOHaD) [4] and the importance of:

- health at the time of conception (both paternal and maternal);

- the detrimental effects on the fetal brain of drugs, alcohol and nicotine;

- the beneficial effects of a maternal diet that provides essential nutrients

- maternal nutrition and weight gain that avoids fetal stunting or overweight

Impaired fetal growth secondary to poor maternal nutrition or placental insufficiency can be associated with reduced brain development; growth retarded infants are at increased risk of hypoxic stress and hypoxic ischemic (HI) brain injury due to altered placental blood flow and sub-optimal fetal oxygenation, particularly at the time of delivery. Suboptimal nutrition also poses the risk of hypoglycemic brain injury immediately after birth; the impact of this form of brain injury can now be defined through neuroimaging [5]. At the opposite end of the spectrum, being large for gestational age, post mature, or the product of a multiple pregnancy poses unique challenges, and increases the risk of HI injury [2]. In addition, surviving infants born small or large for gestational age are at increased risk of developing adult-onset chronic diseases (e.g. hypertension, cardiovascular disease, stroke, type 2 diabetes, obesity); the current epidemic of non-communicable diseases has been shown to be linked to early stunting of growth and excessive infant weight gain [4].

Importantly many of the causes of brain damage are now avoidable or amenable to treatment. Neuroimaging protocols help to define both the timing and geographic location of injury, and document the evolution of neuronal changes through defined phases over time [6, 7]. In the acute phase, damage follows decreased cerebral blood flow and reduced oxygen and glucose delivery and resulting ischemia and acidosis. A period of latency follows with transient recovery of energy metabolism. Then an 'excito-oxidative' cascade leads to cerebral energy failure and progression to cell death [8–10]. In this phase, reduced adenosine triphosphate (ATP) production affects membrane integrity; intracellular accumulation of sodium and water follows, and brain cell injury is caused by neuronal depolarization, glutamate release, an influx of calcium, and release of toxic nitric oxide free radicals. The 'therapeutic window' offered by the 'latent phase' now allows interventions to ameliorate the effects of HI injury, and hypothermia initiated within 6 hours of age shows particular promise.

2. Predisposing factors for brain injury

Hypoxia is central to the genesis of much of the brain injury that occurs in the fetus. Compromised oxygen delivery is a particular risk during labor and delivery, but the fetus is at risk whenever brain ischemia occurs due to impaired cerebral blood flow (CBF). After ischemic injury, reperfusion can potentially cause additional injury or complicate recovery, as can any situations that compromise normal brain perfusion further, including disturbance of oxygen delivery and/or carbon dioxide transport, acid base status, or the supply of energy and metabolites required for normal brain function. Resuscitation of a newborn neurologically depressed by intrapartum asphyxia is such a situation, and ongoing brain injury will occur until effective cardiac output, cerebral perfusion and oxygen transport are restored.

Clinical effects of hypoxia include a disturbance of acid base status. An unrelieved hypoxic event in the fetus causes progressive acidosis which leads to systemic organ dysfunction, including cardiac depression, where compromised contractility and filling reduce cardiac output leading to a reduction in CBF and high risk of brain insult when cerebral hypoxia and ischemia occur. Importantly, cardiac functional impairment can precede depression of fetal heart rate. Hypoxic insults depress brain

function, so following intrapartum insults infants are neurologically abnormal at birth, often require resuscitation to initiate breathing, and cardiovascular support can be needed to stimulate heart function and provide adequate blood pressure and circulation. Tone and behavior usually remain abnormal on admission to the nursery; encephalopathy developing in the hours or days after birth is confirmation that a significant HI insult resulting in brain injury has occurred.

Hypoxic ischemic brain injury is estimated to occur in about 3 out of every 1000 births [8]. Diagnostic features include problems with level of consciousness, tone, respiratory drive, and coordination of sucking and swallowing, and seizure activity which is commonly refractory. In the longer term, the consequences of injury vary between death (15-20%) and complete recovery, with the spectrum of permanent brain injury ranging from mild motor and cognitive defects, to cerebral palsy and severe cognitive disabilities. The pattern and consequences of injury depend on the severity and duration of the insult. The neurovascular and anatomical maturity of the brain relative to the gestational age of the fetus is also a primary factor; co-related elements include the adequacy of metabolic reserves available to the fetus to compensate for oxidative stress, the presence or absence of infection, and pre-existing abnormalities in brain growth and development. Different regions of the fetal brain and individual cell lines have gestation specific vulnerability to damage.

Prematurity: The 10% of infants born prematurely are at particular risk for brain injury; their neurovascular anatomy has limited development making them vulnerable to fluctuations in brain blood flow and oxygen delivery. In those very immature, the brain lacks both the duplication of blood supply that develops as a fetus matures, and the ability to auto-regulate CBF in response to fluctuations in systemic blood pressure. Vascular complexes in areas such as the germinal matrix are vulnerable to bleeding when blood pressure fluctuates, and perturbations insufficient to cause damage in a more mature fetus may generate injury; bleeding is often related to asphyxial stress, and can result from complications of treatment entities very preterm infants require. Mechanisms underlying this form of injury include: variations in cerebral venous pressure, major cerebral vasodilatation or constriction, altered distribution of CBF, systemic fluctuations in circulating blood volume, and significant changes in either oxygen or carbon dioxide tension [11].

Periventricular leukomalacia (PVL) is predominately a condition affecting the preterm infant. The primary causal mechanism is HI injury, with ischemia being the major component. PVL acquired intrapartum is usually associated with abnormal neurological findings at birth, but may manifest as lower limb weakness evident in the first weeks of life. PVL can be aggravated by, or generated as a result of postnatal events. Neurobiologic research has shown that maturational dependent oligodendroglial precursor cells are a major target in PVL, and these are exquisitely vulnerable to damage by free radicals generated during ischemia and reperfusion. PVL is associated with intraventricular hemorrhage (IVH) in approximately 25% of cases. The pathogenesis of IVH is usually multifactorial, and related to: fluctuating CBF; increased cerebral venous pressure; decreased CBF followed by reperfusion; and disorders of coagulation, platelet function and capillary integrity [11].

The commonest clinical situation where pathogenic factors combine to generate sufficient ischemia to cause PVL is when a sick preterm infant requires mechanical ventilation, and problems occur during 'uncontrolled' intubation, with 'fighting the ventilator,' or when a pneumothorax (air leak) compresses the lung, which raises intrathoracic pressure and disrupts normal blood return to the heart; in turn, this reduces cardiac output and brain blood flow. Vascular factors are also relevant; blood transfusion or rapid IV volume replacement pose potential risk due to the pressure passive nature of the immature cerebral circulation; systemic variations in blood pressure, sequelae of sepsis, and the cerebral effects of hypocarbia can render

an infant symptomatic. Many infants with PVL have a normal neurologic outcome. Those with permanent sequelae exhibit a range of problems with varying degrees of severity; including intellectual and visual deficits, usually superimposed on spastic paresis involving the extremities, where the lower limbs are predominantly affected.

In late prematurity (34 weeks to 36 weeks plus 6 days gestation), the vulnerability of the brain to injury, and the pattern of damage commonly seen are different, due to increased structural and functional maturation; at 34 weeks of gestation the brain has 65% of its term volume compared to 13% at 28 weeks, and a fivefold increase in white matter volume occurs between 35 and 41 weeks of gestation.

Low birth weight (LBW) infants are those born <2500 g. and comprise infants born prematurely but appropriately grown for gestational age, and those who are small because of intrauterine growth retardation (IUGR). LBW is further divided into very low birth weight (<1500 g) and extremely low birth weight (<1000 g). Globally 14.6% of infants born are LBW (5-10% in industrialized countries); UNICEF data indicate that LBW infants have a disproportionate death rate and high intrapartum morbidity. Brain injury is caused by many factors, e.g. placental dysfunction and acute compromise of placental gas exchange, and risks in the newborn period due to the causal factors for their small size. Long-term, neurodevelopmental problems occur.

Extremely low birthweight (ELBW) infants are often born close to the limit of viability. Many who survive are at risk of brain injury and neurodevelopmental handicaps; however, advances in care have led to a substantial reduction in severe morbidity, with clear benefits evident for ELBW infants of higher gestation [3]. Consequently, gestational age is a factor that continues to drive interventions aimed at prolonging pregnancy. Where such treatment is an option and fetal wellbeing can be sustained, there are clear benefits for the fetus of longer gestation. Data from a national, prospective, population-based cohort study conducted in all maternity and neonatal units in France in 2011 indicate that survival to discharge, and survival without any severe adverse outcome are both gestation dependent (**Table 1**).

Small and large for gestational age (SGA/LGA) infants are those born below the 10th and above the 90th centiles respectively. Hypoxic composite neonatal morbidity is more common among SGA neonates and traumatic–composite neonatal morbidity more common with LGA. In symmetrically growth-retarded SGA infants, brain size and function are affected; long-term deficits in neural connectivity and cognitive problems can result. Fetal glucose is determined by maternal levels, but impaired glucose metabolism occurs with SGA where hepatic glycogen stores are low at birth, and in LGA associated with maternal gestational diabetes [2].

Placental pathology underlies many causes of compromised fetal growth and development and intrapartum hypoxia, e.g. decreased maturation of the terminal villi is associated with injury to the white matter/watershed areas and basal ganglia [12]; also, conditions that can cause fetal death (toxemia in pregnancy, twin to twin transfusion syndrome (TTTS), hemorrhage from placenta previa and placental abruption and fetal stroke) [13, 14]. Strokes occur between 14 weeks gestation and delivery. Etiology is often obscure; ischemic, thrombotic or hemorrhagic injury occurs; causes include maternal platelet abnormalities, trauma, TTTS, medication (warfarin and some antiepileptic drugs decrease vitamin K dependent coagulation

Gestation in weeks	23	24	25	26	27-31	32-34
Percentage of survivors	0%	11.6%	30%	47.5%	81.3%	96.8%

Table 1.
Gestation-related survival without grade 3/4 intraventricular hemorrhage, cystic periventricular leukomalacia, retinopathy of prematurity stage 3 or higher, severe bronchopulmonary dysplasia, or necrotizing enterocolitis stage 2-3 [3].

factors), parvovirus B19 and cytomegalovirus infections, and protein C deficiency [15, 16]. Diagnosis in utero can be made by ultrasound (US); magnetic resonance imaging (MRI) is the optimal imaging modality [16].

Twin to twin transfusion syndrome (TTTS) occurs in up to 1:4 monochorionic diamniotic twin pregnancies; nearly 100% have placental vascular anastomoses; most are hemodynamically balanced, but severe complications result when there is a chronic net transfusion imbalance between fetuses. Hemodynamically significant shunts classically manifest in the mid trimester; while subtle initially, cardiovascular effects do impact both recipient and donor twins and are an important factor contributing to morbidity and mortality [13, 17]; 70% of recipient twins show echocardiographic evidence of cardiac compromise [18]. Protocols for frequent US of at-risk twins are the mainstay of management; these monitor onset/progression of complications through defined stages of evolution (Quintero stages 1–5), quantify the adverse effects of the altered hemodynamics on each twin, and allow perinatal management interventions that have the potential to improve fetal morbidity and mortality. US provides assessment of amniotic fluid status, measurements of fetal structures, and fetal weight estimates which identify growth disparity, and are predictive of birth weight discordance [19]. As the transfusion of blood from one twin to the other increases, the donor twin becomes oliguric due to decreased renal perfusion, with virtual absence of amniotic fluid; this can be so marked it prevents fetal movement giving rise to the term 'stuck' twin. In contrast, the recipient develops polyhydramnios due to increased urine production. Without intervention to treat TTTS, increasing polyhydramnios will ultimately result in pre-term labor, due to the mechanical forces generated by overdistension of the uterus; overall, polyhydramnios is complicated by preterm labor in up to 26% of cases, and premature rupture of the membranes (PROM) in up to 19% of cases.

Ischemia is the principal mechanism underlying brain damage; lesions include white matter infarction, intra-ventricular hemorrhage, hydranencephaly, and porencephaly. In up to 58% of TTTS affected pregnancies combined US evidence is reported of antenatally acquired brain abnormalities and IVH, and periventricular echogenicity assumed to be perinatally acquired [20]. Fetal MRI can identify CNS injury; findings range from ischemic or hemorrhagic lesions in the brain to marked dilation of the cerebral venous sinuses secondary to central venous hypertension.

US can also evaluate flow in the umbilical vein (UV) and ductus venosus (DV). Normally, the UV blood flow velocity waveform has an even non-pulsating pattern, since the pulse waves caused by atrial contractions are not propagated backwards through the narrow ductus venosus. However, if the DV widens, the pulse waves propagate into the UV and result in a pulsating pattern. UV pulsations were first described in fetuses in imminent danger of asphyxia, then in those hydropic due to heart failure. In fetuses exposed to chronic hypoxia, UV pulsations predict poor outcome [21]. The presence of absent or reversed flow in the DV during atrial systole (defined as absent/reversed a-wave) is associated with poor perinatal outcomes because of compromise to mechanisms that normally preferentially supply the fetal brain with well oxygenated blood. The function of the DV is to shunt a portion of the oxygenated blood arriving from the placenta directly to the inferior vena cava, allowing oxygenated blood to bypass the liver. Consequently, DV flow plays a critical role in preferentially supplying oxygen to the fetal brain, in parallel with the other fetal shunts (foramen ovale and ductus arteriosus). And so, US evidence of an absent or reversed a-wave in the DV identifies those fetuses who are at the highest risk of hypoxic brain injury in utero [13, 22, 23].

The expectation of maternal treatment, even for severe TTTS, is for improvement, with probable resolution in utero [24], including regression of fetal cardiovascular pathology and improved myocardial performance. Recovery may take

longer in more severely affected pregnancies, but this is not the case in all series. Survival, particularly for the recipient twin, is likely to be compromised if treatment is delayed [25] hence the relevance of US surveillance and early diagnosis [17].

Maternal Illness during pregnancy: Some are specific to pregnancy such as gestational diabetes; others pre-exist; many have the potential to cause damage, or predispose the fetus to independent risks for neurological morbidity [2]. Some have well known associations with brain injury; rubella and the TORCH group of viruses are examples; TORCH viruses are also a potent cause of perinatal death and a particular burden in developing countries; some are amenable to treatment; early recognition, including maternal prenatal screening, is a key aspect in management [26]. Common upper respiratory tract infections and gastroenteritis, although often of concern to pregnant women, are not usually associated with brain injury [27].

Fetal inflammatory response syndrome (FIRS): Inflammatory mediators are known to precipitate premature rupture of the membranes (PROM) and preterm labor, inflame and cross the placenta, and have been linked to increased risk of fetal brain injury and cerebral palsy [28]. In FIRS, maternal systemic inflammation occurs with activation of the innate fetal immune system and elevation of fetal plasma cytokines. Cytokine production usually generates a normal immune response, but in the immature fetus and premature infant born after FIRS, the complex effects of cytokine activity have been linked to increased infant morbidity and mortality, perhaps because the balance of these agents is imperfectly controlled [11].

Many cytokines are vasoactive, so in the immature brain, focal variations in brain perfusion could result in local ischemia followed by reperfusion; such perturbations may cause cumulative injury to brain white matter due to the primitive neuro-vascular architecture, immature autoregulatory control mechanisms, and sensitivity of maturational dependent cells to free radical damage. The germinal matrix is also particularly vulnerable to variations in brain blood flow and blood pressure [11]; consequently, it has been hypothesized that periventricular hemorrhage would be more likely to occur in the preterm fetus exposed to FIRS.

The initial literature supported a role for inflammatory mediators in premature labor and delivery; linked maternal infection and pro-inflammatory mediators in the neonatal systemic circulation with increased risk of periventricular leukomalacia and/or spastic diplegia; emphasized the synergistic role of inflammation and hypoxia and ischemia when they occur together; and reported a higher incidence of HI brain damage where fetal exposure to maternal inflammation/infection occurred [2]. This literature also states: "For the premature fetus, once clinical chorioamnionitis occurs, rates of sepsis, pneumonia, respiratory distress syndrome and death are all increased by 2-4-fold and long-term neurologic injury is substantially more likely to occur" [29]. Strategies can be used to down-regulate the inflammatory response and treat mothers with signs and symptoms of infection; some antibiotic therapies reduce cytokine production; because of the independent association of elevated maternal temperature with worse fetal outcome, appropriate management to control fever is also cited as a treatment of potential benefit [30, 31].

Recent literature reappraises prior FIRS-related research. Isolated cytokine-mediated injury is not reported in term infants [11], and in the premature newborn, newer studies have found the relationship between chorioamnionitis and brain injury to be attenuated; this difference may result from heterogeneity of the studies, or possibly improved neonatal intensive care [32]. Current literature does conflict on whether or not histopathological chorioamnionitis is linked to an increased risk of white matter injury and intraventricular hemorrhage, or with abnormalities of brain development identifiable via MRI (e.g. variations in cortical thickness). But research continues to emphasize that postnatal complications from infections,

particularly when associated with hypotension in the premature newborn, are associated with an increased risk of white matter injury [33, 34].

Fetal and neonatal Infection significantly increases the risk of brain injury. Mechanisms promoting sepsis include PROM; the risk of fetal infection from membrane rupture beyond 18 hours increases (10-fold), as does the occurrence of perinatal asphyxia, maternal urinary tract infection and colonization with group B Streptococcus [35]. Maternal treatment and prophylactic antibiotics given in anticipation of sepsis to the infant at birth are essential, as by the time confirmatory tests (bacterial cultures) are positive, the risks of infection having disseminated into the blood stream (septicemia) or spread to the meninges (meningitis) are high. Hypotension secondary to sepsis can profoundly compromise brain perfusion and oxygen delivery, and dramatically increases morbidity; once present, it is often refractory to treatment as the underlying mechanisms are multifactorial, including the generation of cytokines, and release of toxic metabolites by bacteria.

Hypoglycemia: During transition to extrauterine life, fetal adaptation normally enables alternative fuels to be metabolized (lactate, ketone bodies, fatty acids) which ensures energy supply to vital organs when blood glucose concentration falls. But once born, this ability is down-regulated, especially by oral feeding [2], and transitional hypoglycemia can occur. While no single glucose value can define hypoglycemia, fully ensure an infant's safety or limit morbidity, management guidelines exist as hypoglycemia can have neurologic consequences [36–38], especially when accompanied by seizures, including: motor and/or psychodevelopmental delay, microcephaly, seizures, visual impairment, and spastic quadriplegia and hemiplegia.

Population data indicate that blood glucose levels as low as 2.0 mmol/L (or even 1.8 mmol/L at 1 hour of age) are not uncommon in healthy newborns. However, various syndromes and metabolic conditions cause or contribute to hypoglycemia. Importantly, HI injury can disrupt normal metabolic adaptation, as anaerobic glycolysis depletes hepatic glycogen and hyperinsulinism can also occur; there is a correlation between lower serum glucose levels and higher Sarnat stages in hypoxic ischemic encephalopathy (HIE).

For at-risk infants, outcome data support raising the intervention threshold from conventional levels. Current screening and management guidelines are that neonates with hypoglycemia persisting beyond the first 72 should be investigated further when levels remain ≤2.8 mmol/L, and ≥ 3.3 mmol/L should be the therapeutic glucose target level in symptomatic/at risk infants. Also, before discharge, those experiencing persistent hypoglycemia should have a 5-6 hour fast, while maintaining blood glucose levels ≥3.3 mmol/L, to ensure safety at home [39].

Differing patterns of damage now help to distinguish hypoglycemic from HI brain injury [5, 40, 41]; the combination on MRI of selective edema in the posterior white matter and pulvinar appears specific even in absence of hypoglycemic laboratory values. In neonates with concurrent hypoglycemia and HIE, injury is synergistic, and the imaging features of both HI injury and hypoglycemia may be detected [5].

Hyperglycemia: A blood glucose concentration > 125 mg/dL (6.9 mmol/L) is a common metabolic abnormality encountered in preterm and critically ill newborns [42]. Management varies; often iatrogenic, hyperglycemia can cause or aggravate brain damage, principally because of the hyperosmolar state that ensues [43].

Hyponatremia in the premature can cause sensorineural hearing loss, cerebral palsy, intracranial hemorrhage, and increase mortality following asphyxia [44, 45].

Hypernatremia/hyperbilirubinemia when extreme are neurotoxic. Inadequate fluid intake in immature infants and those primarily breast fed is contributory [46, 47]. Kernicterus selectively damages the globus pallidus and subthalamic nuclei [8, 48]; hazardous hyperbilirubinemia is often preventable; health care professional

compliance with best practices for screening, phototherapy and related treatment is required [49, 50].

Seizures: Major causes include brain malformation or structural injury, hypoxia, infection and reversible metabolic disorders. Clinical signs vary from subtle movement disorders to focal or generalized, brief or sustained convulsive activity. Abnormal movement often involves the eyes (blinking, staring, horizontal tonic deviation), mouth (lip smacking or sucking, tongue thrusting), and extremities ('bicycling', 'rowing' or jerking movement). Respiratory (apnea) and cardiac effects (tachycardia or bradycardia) occur, often with color change and significant oxygen desaturation. Focal clonic seizures may indicate brain damage due to arterial or venous infarction. Clinical signs suggesting seizures require confirmatory EEG. MRI can distinguish between seizures due to HI events and other causes. Preventable or reversible causes include hypoglycemia, hypocalcemia, hyponatremia, hypoxemia and acidosis. Seizures do not always imply poor neurodevelopmental outcome for affected infants. But the severity of seizures in human newborns with perinatal asphyxia is independently associated with brain injury, and not limited to structural damage detectable by MRI [51]. In term newborns, the predominant pattern of watershed and basal nuclei injury after hypoxic ischemic encephalopathy is a valuable predictor for later epilepsy; injury to the motor cortex, hippocampus and occipital lobe are also independent risk factors, and the severity of brain injury and recurrent neonatal seizures elevate risk [52]. Delayed treatment likely increases the probability of residual consequences, because of the stresses placed on the brain by the high oxygen and substrate requirements implicit when seizures are prolonged.

3. Hypoxic brain injury

As the physiologist Haldane said: "Hypoxia not only stops the machine it wrecks the machinery" [2]. A healthy fetus can respond to, and tolerate, the early effects of hypoxia, and the degree of acidosis that occurs initially in response to the associated retention of carbon dioxide. Acute hypoxia promotes adenosine release, which reduces fetal cerebral oxygen consumption via action on neuronal A1 receptors on the cerebral arteries, and initiates vasodilatation through activation of A2 receptors; release of nitric oxide and opioids and direct effects of hypoxia on the vascular endothelium also contribute [53]. As a result, while fetal vascular resistance can decrease up to 50%, the net effect is to maintain CBF with only minimal reduction in oxygen delivery; but normal or elevated mean arterial blood pressure is critical in parallel, and once hypotension ensues the brain suffers from the resulting ischemia.

With moderate HI stress and evolving acidosis, the fetus also has the physiologic ability to preferentially perfuse the deep structures of the brain that have higher metabolic rates (brainstem, cerebellum, basal ganglia). However, this compensatory redistribution of blood from the anterior to the posterior circulation results in the brain's cortical areas being less well perfused, and hence, if ongoing hypoxia remains unrecognized and unrelieved over the course of an hour or more, the end result is damage to cortical white matter, and the watershed areas of the cerebral hemispheres. In contrast to this partial prolonged pattern of injury, situations occur where the HI event is near total in nature and the effect profound. With such insults, acidosis develops relatively abruptly, and little or no compensatory redistribution of blood to the deep brain structures occurs, because there is no time for effective redistribution of CBF to maintain their perfusion. Hence it is the basal ganglia and thalami that are predominantly injured, and damage happens over a much shorter time frame [9, 54–56]. In the premature, mild to moderate HI injury results in periventricular leukomalacia and germinal matrix bleeds, and in full term

neonates parasagittal watershed infarcts are seen [55, 57]; severe injury in both term and preterm infants involves deep gray matter.

Distinction between partial/prolonged and near total/profound/patterns of injury is important from a diagnostic and prognostic standpoint, for understanding potential mechanisms for prevention, and over issues of causation in a medico-legal context. Modern neuroimaging is the definitive way to distinguish between them based on the selective geographic patterns of brain damage caused. Importantly however, mixed patterns of injury are also seen that involve both the cortex and deep structures [55, 57]. The mechanisms involved can be either superimposed insults involving periods of both partial/prolonged and near total/profound injury, or, situations where partial and prolonged injury is severe enough to extend to involve the deep brain nuclei, or vice versa, when a near total, profound event is extensive enough to also involve cortical damage [11, 58].

The time line of near-total HI events can be extrapolated from data obtained in animal studies, where fetal monkeys were exposed to complete (i.e. total) hypoxia and ischemia, generated by ligating the umbilical cord and preventing breathing. These animals could tolerate 10 minutes of HI insult without permanent effects if delivered and resuscitated immediately, but, where the HI event was continued beyond this 10-minute period for an additional 10 minutes, a progressive and cumulative increase in the level of neurological damage was then evident. Where the whole insult extended beyond 20 minutes, the fetal monkeys died, in spite of delivery and immediate resuscitation.

In applying these data to the human fetus, it is recognized that what occurs most often is a near total (profound) interruption of brain blood flow and oxygen delivery, rather than an event where hypoxia and ischemia are absolutely total in nature. Hence the time-line for tolerance of such events, and the period over which brain damage evolves, are accepted as being longer than in the landmark animal studies conducted by Myers [59–62]. For this reason, it is generally agreed that approximately 15 minutes, and possibly up to 20 minutes, of sudden profound asphyxia can be tolerated by the human fetus prior to brain damage beginning (in contrast to the 10 minutes seen in the animal model). Then, after this 'grace' period, damage to the brain begins to occur, and over a further period of 15 to 20 minutes the extent and severity of injury become progressively more profound over time. And beyond this time frame, a human fetus is usually born dead. It is important to recognize that the principal mechanism that causes fetal asphyxial brain injury is cerebral ischemia caused by the severe reduction in CBF that occurs as a result of hypoxic myocardial depression significantly reducing cardiac output (CO). The fetal heart has a fixed stroke volume, which means that CO, and the amount of blood supplied to the brain are a direct function of the rate of contraction; so, for example, with bradycardia where fetal heart rate slows to half normal, this equates to a 50% fall in CO, and a comparable reduction in CBF will result. CO also decreases where tachycardia accompanies hypoxic stress; at high heart rates poor contractility secondary to acidosis is then compounded by incomplete atrial filling in diastole.

The relationships between the geographic pattern of asphyxial brain injury and type of resulting disability have been defined [63], and the predictors of long-term morbidity delineated [64]. Near-total insults of moderate duration and degree which have the basal ganglia and thalamic pattern of damage, predominantly lead to athetoid or dystonic cerebral palsy, with intact or mildly impaired cognitive development. When severe, near-total insults damage the cerebral cortex in addition to the deep brain structures; and severe spastic quadriplegia results, with microcephaly, significant cognitive deficits and cortical visual impairment. The extent of injury is strongly associated with the intensity of resuscitation, the degree of encephalopathy, and severity of seizures [55, 65]. Prolonged partial insults of moderate degree with

injury confined to watershed regions cause variable degrees of cognitive deficit and epilepsy, and can be associated with spastic quadriplegia. But, when more severe or prolonged, injury causes extensive cortical brain involvement, or global brain injury; the end result is spastic quadriplegia, severe cognitive impairment, cortical visual impairment, and microcephaly. In addition, symptomatic brainstem involvement can be associated with severe patterns of injury, and lead to non-survival [66].

Hypoxic ischemic encephalopathy (HIE) is a clinically defined syndrome of disturbed neurological function in the earliest days of life, caused by intrapartum or late antepartum brain hypoxia and ischemia [67]. HIE evolves clinically following significant HI insult, and is a major predictor of neurodevelopmental disability. HIE develops in 1 to 8 per 1000 live births in developed countries, and up to 26 per 1000 worldwide [65, 67]; not all cases of neonatal encephalopathy are due to anoxia or HI injury [8, 58], but epidemiological studies confirm the association of HIE with pregnancy related risks, and intrapartum risk factors that predispose the fetus to hypoxia; 15-20% of affected infants die; in about 25% of survivors permanent neurologic deficits remain. Prospective studies employing MRI suggest that the majority of HIE occurs as a result of HI insult and brain injury at or near the time of birth [41]. Postnatal exacerbation of intrapartum acquired injury occurs relatively rarely (10%), but is a potentially preventable component in many instances [11, 67].

Hallmarks of neonatal encephalopathy are neurological depression, with altered level of consciousness and often respiratory depression, abnormal muscle tone and power, disturbances of cranial nerve function, and seizures. HI injury is strongly suggested in a neurologically depressed infant by associated acidosis, and further confirmed by concomitant multi-organ injury [58, 65, 68].

Acidosis has two components: respiratory - from retained carbon dioxide, and metabolic - from accumulation of fixed acids (lactic acid and β-hydroxybutyrate). While acidosis present at birth usually resolves in the first hours of life, HIE progresses with further depression of consciousness, abnormalities in tone and movement, and onset of seizures. Infants exhibit a range of behaviors and alterations of conscious level from lethargy and obtundation to irritability and a hyper-alert state. Similarly, disorders of tone range from a marked decrease to hyper-tonicity. Abnormal movements include tremors, jitteriness, mouthing and blinking, and 'bicycling' of the legs, through to frank seizures. Other manifestations include apnea, with bradycardia and impaired oxygen saturation, shrill cry, feeding difficulty (due to poor coordination of suck or altered peristalsis, and occasionally brain stem damage), absence of the Moro and/or gag reflexes, and exaggeration of deep tendon reflexes. Decerebrate or decorticate posturing may be seen. Sarnat et al. defined three levels of severity (mild, moderate and severe); these are linked to the probability that HIE will result in permanent neurological consequences [69].

The pathophysiology of HIE is now better understood and treatment with hypothermia has become the foundation of therapy [67]. All affected infants require supportive management that anticipates and limits the adverse effects on the brain of fluctuations in cerebral perfusion, metabolic instability, sepsis, suboptimal respiration, and any situation that increases oxygen and energy demands. This involves correction of hypotension, attention to glucose, fluid and electrolyte homeostasis, maintenance of $PaCO_2$ in the normal range, and treatment of seizures [58, 67]. Neuroimaging (US, CT, MRI) is best done at defined periods after injury [41, 57]; MRI in particular can then define the diagnosis, pattern, severity, timing and prognosis, and help rationalize hypothermia and other interventions, including the withdrawal of support. Several neuroprotective agents that can be combined with hypothermia have entered clinical trials; new biomarkers for HIE are being sought [70]. Affected survivors need follow up to manage their handicaps.

4. Multisystem involvement secondary to hypoxia

The effects of hypoxia extend beyond the brain [9, 11, 67, 68], associated injury to other organs principally occurs due to compensatory redistribution of blood during partial and prolonged insults, but can follow profound, near total episodes; 60-80% of affected neonates exhibit single or multiple organ injury [68].

The fetus often passes meconium (fetal bowel contents) in utero due to hypoxia; a combination of gut ischemia and reduced sphincter tone secondary to neurological depression is the likely mechanism, hence, the presence of meconium is a marker for probable HI. Following a recent event, meconium seen is usually thick and green; after a remote event, because mixing with amniotic fluid disperses and thins the meconium, the liquor is evenly discolored, and the fetal skin may be stained green.

In the neonate, multiple organs can show varying effects from hypoxia.

The lungs can be injured directly and indirectly; inhaled meconium, surfactant depletion, pulmonary hypertension and left ventricular failure can all result in impaired gas exchange and the need for assisted ventilation. The risks of brain injury increase where such effects are superimposed on the poorly compliant lungs of a preterm infant. A pneumothorax (air leak into the pleural space) causing lung compression and elevated intrathoracic pressure is less common with modern ventilation techniques, but when it occurs, major disturbances in cerebral perfusion pressure result that increase the risk of brain ischemia and hemorrhage.

The heart can suffer functional and structural damage; acidosis seriously impairs myocardial function, myocardial ischemia further compromises conduction and mechanical contractile efficiency; affected neonates often require fluid resuscitation at birth and inotropic agents (dobutamine/dopamine) to maintain their circulation. Abnormalities on ECG and echocardiogram, and elevated cardiac enzymes (creatine kinase–MB fraction/troponin T levels) reflect heart dysfunction and damage.

The kidneys: Absent or significantly reduced urine output in the 24 hours following HI is common, associated hematuria indicates renal tubular damage. Renal injury is the best systemic marker of potential brain injury when oliguria (urine output <1 ml/kg/h) is associated with an abnormal neurological exam [68]. Blood urea and serum creatinine rise progressively and peak in the days following injury. Inappropriate secretion of antidiuretic hormone (ADH) causes hyponatremia; hypoxia stimulates the carotid body chemoreceptors to secrete ADH which causes fluid retention, and a secondary fall in serum sodium concentration.

The liver: Elevated enzymes reflect hepatic cellular damage; lactate dehydrogenase (LDH) is the best hepatic predictor of HIE (sensitivity 100% and specificity 97%), and also of long-term outcome after HIE [71]; blood glucose concentration can fluctuate, with hypoglycemia being most common [72].

Bone marrow: Increased release of nucleated (immature) red blood cells (NRBC) and reduction in platelet numbers (thrombocytopenia) reflect hemopoietic effects. After HI, platelets numbers fall by 12 hours, with the nadir at 2-3 days [2], while NRBCs peak in the hours after birth and fall by 50% after 12 hours [73]; distinct patterns relate to timing of HI [74]. Hypoxic events likely induce exaggerated erythropoiesis as a compensatory response, with release of NRBCs into the fetal circulation. Elevated NRBCs are associated with intrapartum fetal distress and acidemia at birth secondary to hypoxia, with a direct correlation reported between decreasing UA pH and NRBC elevation in the term human fetus. Newborns with elevated NRBCs suffer a significant increase in both short-term morbidity and mortality and long-term disability [75]. NRBC counts are best given as an absolute number per unit volume rather than relative to 100 white blood cells as this avoids misleadingly low

values when wbc counts are high; published values indicate normal counts decrease with advancing gestation and increasing birth weight [73, 74]. A value >1000/mm³ (or > 10-20/100 wbc) in the first hours of life is considered elevated [73]; A prospective case-controlled study identified that a NRBC count of >13/100 leukocytes had a sensitivity of 81.3% and a specificity of 94.4% in predicting adverse outcomes [76]. In neonates subsequently cooled, those with absolute NRBC counts >1324/mm³ within 6 hours of birth had high risks of abnormal MRIs and adverse 2-year outcomes; the combination of NRBC count and other early markers, such as lactate levels and EEG, could increase the overall predictive ability [77]. The magnitude of increase in NRBCs is a function of the severity and duration of asphyxia, and a reliable index of perinatal brain damage [73–77].

Metabolic markers: Plasma lactate is an important marker for recent tissue hypoxia; lactate is a metabolite in aerobic metabolism, and measurements in arterial blood at 30 minutes of life show lactate to be as equally valuable as base deficit in assessing the severity of birth asphyxia; elevated concentrations >9 mmol/l are associated with moderate or severe encephalopathy and PVL (sensitivity 84% and specificity 67%) [78]. Low serum calcium and elevation of bilirubin can also occur.

Gastrointestinal tract: abnormal peristalsis underlies feeding intolerance after hypoxia, and the risk of necrotizing enterocolitis is increased [68]. Infants also feed poorly due to an impaired rooting reflex, reduced tone, diminished coordination and drowsiness; associated cranial nerve and brain stem lesions contribute.

5. Adjuncts to comprehensive care

Fetal ultrasound (US): Endovaginal ultrasonography has become the standard imaging measure in pregnancy. US uses pulsed high-frequency sound to produce images and employs terminology and standardized interpretations based on defined criteria to ensure safe maternal examination, and prevent inadvertent harm to early normal pregnancy [79]. US provides routine confirmation of gestational age/due date, detects fetal anomalies, oligo or polyhydramnios, and provides assessment of fetal growth parameters in early pregnancy [80]. Protocols also exist for the management of specific clinical scenarios that pose a risk for the fetus and require increased fetal surveillance; these allow for appropriate referral when complications are suspected, e.g. for intrauterine growth retardation, and monochorionic dichorionic twin gestation where there is a high risk of twin-to-twin transfusion syndrome developing [81].

Fetal scalp blood sampling: can assess the evolution of hypoxia and acidosis via blood gas measurement or lactate analysis, once the membranes have ruptured and the fetal head has descended into the birth canal during the later stages of labor.

Fetal heart rate monitoring (EFM): The physiologic perturbations in fetal oxygenation and hemodynamics that changes in fetal heart rate (FHR) reflect, provide the rationale for FHR measurement and EFM intrapartum [56]. With onset of hypoxia, physiological effects on the fetus usually generate detectable changes in fetal heart rate pattern, as the myocardium is sensitive to reduced oxygen tension, elevated carbon dioxide, and progressive evolution of acidosis. From a preventive standpoint the importance of EFM is that clinically relevant FHR changes are usually evident before the brain is affected sufficiently for permanent damage to begin.

Assessment at birth: Transition to extra-uterine life is physiologically complex. Where needed, resuscitation must mitigate any residual effects of compromised organ function or intrapartum events that have depressed or damaged the brain. A key element in reducing morbidity is the immediate availability of skilled personnel able to provide the well-established neonatal life support (NALS) priorities for resuscitation [68], assess the history, intrapartum events and clinical status of the

infant, and order the level of care and specific diagnostic and treatment entities required.

Apgar score: Named for Virginia Apgar, this is intended as an objective index to evaluate the condition of a newborn infant based on a rating of 0, 1 or 2 for each of the five components: color, heart rate, response to stimulation of the sole of the foot, muscle tone, and respiration. Scores are determined by observing/examining the newborn infant in real time at 1, 5 and 10 minutes of age. Scores principally gauge progress in response to resuscitation; persistently low scores equate with failure to respond, and imply the newborn has significant physiologic problems. Apgars were not meant to be an outcome parameter. Also, retrospectively estimated scores are problematic when they do not match contemporaneous event descriptors in the resuscitation record. Care with interpretation is also required where an infant is premature due to an associated degree of physical immaturity, and where active life support (e.g. assisted ventilation) is generating the improvements observed.

Umbilical cord blood gas analysis: Fetal oxygenation and acid base status can be assessed from paired blood samples collected from the umbilical vein (UV) and arteries (UA) at birth; this is an integral part of monitoring high-risk deliveries [82], but an understanding of fetal placental perfusion and how specific conditions affect values are necessary for accurate interpretation. Cord compression, for example, is associated with normal values when acute and complete, in spite of the infant being profoundly acidotic systemically, as they reflect fetal status when cord flow ceased. In contrast, partial restriction causes UA and UV values to progressively widen, and with impaired maternal placental perfusion UA/UV differences are small [82, 83].

Normally, oxygenated blood from the placenta flows through the UV and preferentially supplies the fetal brain and heart via shunts that bypass the liver; repeated uterine contractions during labor exert a significant, but manageable metabolic stress on the fetus. But when labor is precipitous, or contractions are abnormally frequent or prolonged, uterine artery blood flow becomes restricted, and inter-contraction restoration of placental perfusion is delayed as it is dependent on uterine relaxation; in this and similar scenarios maternal to fetal oxygen transfer via the UV can suffer sufficiently for HI injury to occur. Where blood return through the UA is also affected, normal removal of carbon dioxide from the fetus is reduced.

Acidosis occurs as a consequence of cellular hypoxia (inadequate oxygenation), tissue ischemia (inadequate blood flow) and retention of carbon dioxide; the unit of measurement, pH, is on a logarithmic scale, so small differences represent a major change in the degree of acidosis. Bicarbonate naturally buffers acid production; as reserves are depleted, base deficit increases. With resolution of acidosis, PCO_2 values are restored first, followed by bicarbonate and pH; base deficit remains abnormal longest. Normal cell metabolism only occurs when pH is held within a narrow range, beyond these limits, cells progressively lose their ability to sustain normal function and maintain their metabolic integrity, and organs begin to fail.

Blood gas data are compared to the reference range of the testing laboratory. Significant, recent HI stress usually manifests with low oxygen, elevated PCO_2, low pH, low bicarbonate and high base deficit, with UA values most affected. However, it is most relevant clinically to define pathological acidosis as the threshold at which the incidence of adverse events starts to correlate strongly [83]. Criteria to define an acute intrapartum event as sufficient to cause cerebral palsy include UA pH <7.00 and base deficit of >12; infants with a pH <7.0 who are not vigorous are at high risk of adverse outcome [84], and the threshold for moderate or severe newborn complications is defined as a UA base deficit of >12 [85]. With worsening acidosis progression of adverse sequelae rises sharply; in one reported series, HIE occurred in 12% of infants with cord pH <7.0, in 33% with pH <6.9, and in 80% with pH

<6.7; a pH <6.8 equated with the probability of neonatal death [86]. Persisting lactic acidosis is associated with severe encephalopathy [82]. Identifying those at risk is especially important now, since neuroprotection strategies are available.

Hematology: White blood cell (wbc) counts can be strongly indicative (but not always diagnostic) of the presence of infection. Elevated total wbc numbers, a high proportion of neutrophils (granulocytes), and elevated primitive (band) cells indicate that stimulation of the bone marrow by inflammatory cytokines has occurred; very low counts often indicate inability to mount an effective immune response. Elevation of band cells is the earliest change in response to inflammatory stimuli, although hypoxia can also result in an increase in band cell number [87].

Hemoglobin concentration and hematocrit are used to identify anemia and polycythemia where too few or too many red cells are circulating respectively. Both circumstances compromise oxygen delivery; anemia by limiting the amount of oxygen that can be transported, and polycythemia by reducing the ease with which blood flows, which also increases the risk of blood vessel occlusion (thrombosis), and is one of the mechanisms underlying stroke. Also, by following serial measurements from birth, situations can be identified where bleeding occurred while the fetus was in utero. After significant blood loss, the volume of the blood in the circulation is reduced, but the hemoglobin concentration remains the same initially, then, as physiological compensation for the blood lost occurs, fluid is drawn into the circulation to restore blood volume and, as a consequence, hemoglobin concentration and the number of red cells per unit of volume (hematocrit) fall.

Blood chemistry: Electrolyte and glucose measurements, in parallel with blood gas analysis of pH, oxygen and carbon dioxide tension, bicarbonate and base deficit, plasma lactate, serum calcium and liver transaminases are the mainstays of clinical monitoring in brain injured infants, particularly when multisystem involvement complicates the course of neonatal encephalopathy. A small but complex group of congenital metabolic abnormalities causing neonatal encephalopathy exist [58]; these require expert assessment, comprehensive investigation and management.

Neuroimaging: Modalities include ultrasound, computerized tomography and magnetic resonance imaging [55, 88]. US provided the initial method for imaging brain structures and is still clinically attractive because of the ability to study sick pre-term infants in the nursery. The advent of CT greatly advanced knowledge of brain development and injury. But MRI is now the imaging modality of choice, in spite of cost, due to the lack of ionizing radiation and its superior sensitivity and specificity in detecting brain abnormalities. CT remains relevant for infants too sick for MRI. MR image interpretation needs to be as sophisticated as the technology.

Magnetic resonance imaging (MRI) is now invaluable in assessing the neonatal brain following suspected perinatal injury. Imaging during the first week of life is prognostic and can aid management decisions. MR imaging is an excellent predictor of outcome following perinatal brain injury; characteristic lesions and patterns of changes are at their most obvious on conventional imaging between 1 and 2 weeks from birth [7]. Diffusion-weighted imaging (MRI sensitive to water diffusion) allows early identification of ischemic tissue; associated restricted diffusion on day 3 of life implies injury was acquired around the time of birth, and is not the late manifestation of remote in utero injury sustained during the third trimester [6]. However, DWI may underestimate the final extent of injury, particularly in basal ganglia and thalamic lesions. The outstanding contrast resolution of MRI, superimposed on the ability to image in any plane, means even subtle brain malformations are identified.

Like US and CT, MRI scans are best done at defined intervals after birth (3-5 and 10-14 days of life) for accurate diagnosis, timing and evolution of injury [55, 57].

Pathology identified includes structural developmental abnormalities, edema, hemorrhage, early ischemic damage, localization of the predominant injury to either cortical tissue or deep brain structures, the evolution and end stages of scarring, and, onset and progression of hydrocephalus or microcephaly. Importantly, intrapartum and late antepartum HI damage can be distinguished from congenital structural effects or lesions due to acquired causes that occurred well prior to birth, so MRI scans can identify damage caused to an otherwise normal and pristine brain.

MRI, magnetic resonance spectroscopy, and diffusion-weighted MRI have identified the patterns of brain injury that evolve after HI insults. Studies also define the severity of the insult and can indicate the age at which it probably occurred. Injury evolves over days, if not weeks before the final stage with scarring is evident. The anatomical regions of the brain affected define the mechanism of injury. Distinction can be made between an insult that involved a relatively short period of total or near total hypoxia/ischemia (profound hypotension), or one occurring over a more prolonged period where HI was partial in degree (moderate hypotension).

In near total insults, the most metabolically active brain structures are damaged; the lentiform nuclei, especially the posterior putamina, the ventrolateral thalami, the Rolandic cortex and the hippocampi are predominantly injured, while there is little or no involvement of the remainder of the cerebral cortex.

In contrast, in partial and prolonged hypoxia, cortical white matter integrity is compromised, and there is relative preservation of the basal ganglia and thalami. In severe cases the whole cortex may be involved, while with milder injury, the principal areas damaged are the interfaces between the perfusion zones of the anterior, middle and posterior cerebral arteries. An excellent schematic derived from a medicolegal database of MR images of term neonates with partial-prolonged HI injury illustrates the geography of the inter-arterial watershed zone [89].

While these are the two distinctive and predominant patterns of HI brain injury seen, in reality, the type, pattern, duration and variability in severity of HI are a continuum, so there is a spectrum of MRI findings, and mixed patterns of damage are seen, with changes of varying degree in both the basal ganglia thalami and cortical regions [55, 57]. Very severe injury from moderate or profound hypotension can also cause global brain involvement, and extend to include the brainstem [66].

MRI detectable changes take time to evolve; the first abnormality seen is diffusion restriction which peaks at about 72 hours [57]; brain edema, identified as T2 hyperintensity, reflects the progression of energy failure that follows brain cell damage, and precedes cell death due to the apoptosis necrosis continuum. Where there is significant involvement of the cortex, abnormal T1 hyperintensity is evident from about 1 week following the HI event; this can persist for several weeks. T1 hyperintensity due to basal ganglia damage is visualized over a similar time frame. The end result of injury is permanent scaring (gliosis), and compensatory enlargement of the ventricles (ventriculomegaly) [7, 55, 57].

Destructive lesions characterized by periventricular hyperintensity, focal defects in the germinal matrix, and areas of abnormal signal intensity occur in developing white matter. In encephalopathic term newborns, non-cystic white matter injury is a distinct and common pattern. A helpful sign in those >37 weeks gestation is loss of normal signal intensity in the posterior limb of the internal capsule. Hemorrhage is associated with hypointense areas; signal intensity depends on degree of evolution.

Periventricular leukomalacia can develop during fetal life and in the newborn period. Imaging predominantly identifies PVL in preterm infants, but importantly, lesions also occur in term and late preterm infants (those born between 34 weeks and 0 days and 36 weeks plus 6 days gestation) [90].

Fetal MR imaging is a technique that complements prenatal sonography as it has higher contrast resolution and allows direct visualization of the fetal brain, and

hence more readily identifies both cerebral malformations and destructive lesions, including agenesis of the corpus callosum, cerebellar dysplasia, germinal matrix hemorrhage, IVH, multicystic encephalomalacia, periventricular leukomalacia, periventricular nodular heterotopias, porencephaly, and sulcation anomalies. For post-natal studies, diffusion-weighted MR imaging and proton MR spectroscopy are the most sensitive modalities for diagnosis in the early hours following injury.

Future advances in MRI hardware and software will likely enable neuroimaging technologies to contribute more by further delineating the site(s), progression and extent of injury; this will aid evaluation of causation and timing, and advance care strategies able to reverse or mitigate the long-term effects of perinatal brain injury.

Electroencephalogram (EEG): Patterns of brain waves obtained allow the location and relative severity of various brain pathologies to be identified. Seizure activity occurring in the brain but not visible clinically is detected. Patterns of depression of cortical brain activity on EEG have been defined that are associated with varying stages and severity of HIE [69]. Serial measurements document the evolution of, and recovery from, abnormal brain function and the effect of therapy.

Placental pathology: Examination of the placenta is an integral part of investigation of fetal brain injury and neonatal encephalopathy [67]. Pathology provides key information related to the fetus, and causal mechanisms underlying intrapartum events [91] e.g. fetal distress, chorioamnionitis and hemorrhage; and to maternal conditions that affect placental function and fetal oxygenation e.g. hypertension and diabetes. Evidence of placental insufficiency links to fetal growth retardation and increased risk of fetal distress. Any significant disturbance of placental gas exchange and fetal perfusion poses risks of brain injury; examples include pre-eclamptic toxemia, hemorrhage from placenta previa, uterine tachysystole, cord compression and placental abruption [92–94]; abruption is the commonest identifiable antecedent factor for injury in preterm infants with HIE. Examination can also identify causal pathology in the absence of a 'sentinel event' [67] and in circumstances where the umbilical cord is vulnerable e.g. abnormal insertion, tearing, true knots, prolapse, occlusion, and entrapment, each of which causes recognized adverse consequences for fetal oxygenation. Decreased placental maturation is associated with increased risk of white matter/watershed injury with or without basal ganglia/thalami involvement, and chronic villitis with basal ganglia/thalami injury irrespective of white matter injury [93].

6. Prevention of brain injury

Prevention of brain damage requires knowledge of the etiologies underlying injury, awareness of the availability of preventive measures, and timely employment of them to address the underlying cause. In addition, situations that may aggravate existing or evolving brain injury need to be anticipated, recognized, and appropriate evidence-based care provided that is capable of improving outcome.

Maternal and paternal medical history and lifestyle: Maternal nutrition and trace element status, the health and age of both parents at conception, and other factors related to current developmental origins of health and disease (DOHaD) concepts are all relevant to prevention [4, 95]. The risk of fetal brain injury is decreased where mothers maintain a good diet, add folic acid and iron plus required prenatal supplements (vit. D, calcium), avoid smoking and the detrimental effects of alcohol and drugs, and exposure to TORCH infections is prevented. There are benefits to becoming a mother earlier rather than later in life, and from both parents having lifestyles that promote physical health and mental wellness especially at conception.

Antenatal care is central to optimizing the fetal environment, monitoring maternal health, detection of entities that require intervention or forward planning, and enabling pregnancy to progress to term. Care should ensure that fetal growth progresses normally, all indicated US and lab studies are done, necessary referrals are made, and parents prepared appropriately. Prevention of brain injury centers on labor and delivery, but relies on attention to multiple factors throughout pregnancy. The fetal brain probably benefits most from prevention of avoidable preterm delivery, and therapy such as antenatal steroid use to mature the fetal lung when prematurity is inevitable. Post maturity with the inherent risks of placental failure and increased fetal morbidity must be avoided, especially where at risk situations exist such as gestational diabetes. Prior cesarean section requires special planning and supervision, to avoid uterine complications that can jeopardize fetal wellbeing.

Monitoring during pregnancy: Confirmation by US of gestational age reduces premature delivery; monitoring of fetal growth parameters anticipates intrauterine growth retardation, and can identify placental anomalies that increase morbidity. Genetic screening can detect anomalies linked to brain defects; termination of pregnancy is a care option when a fetus is known to have a major anomaly. Surveillance for a broad range of maternal illnesses is possible with investigative protocols and preventive entities available to optimize maternal care and fetal health, and select appropriate timing, mode and location of labor/delivery.

Advance consultation with obstetric and neonatal referral centers should occur where necessary to obtain advice regarding priorities for care and delivery.

Transport with the fetus in utero should occur if care at a higher level is required to optimize the logistics of delivery and provide for a good neonatal outcome [2].

Intrapartum care: Guidelines exist in most jurisdictions based on the evidence base for best practice in obstetric management where the health of the mother and/or fetus becomes at risk. Monitoring of maternal and fetal wellbeing requires entities that provide for anticipation, detection and management of complications, particularly those linked to maternal emergencies and/or generate fetal distress; e.g. placental insufficiency, failure or abruption, hemorrhage, hypo or hypertension, uterine tachysystole or rupture, obstructed labor, or cord compromise. Importantly, a non-reassuring electronic fetal heart rate pattern, or changes in FHR reflecting alteration in fetal cardiac function, usually occurs prior to brain metabolism being affected sufficiently for neurological damage to begin. Hence, recognition of a 'non-reassuring' tracing, a 'sentinel event' involving fetal heart function, or a pattern known to be associated with pathology (e.g. cord compression) [84], allows prompt assessment, and instigation of interventions required to relieve compromised fetal oxygenation, expedite instrumental delivery, or do an emergency cesarean section.

Staff with the required skills must be available to comprehensively resuscitate any sick newborn, and promptly address residual morbidity after delivery. Skill with assisted ventilation is important, as prevention of detrimental hyperoxia and hypocarbia reduces brain injury risk in premature infants, and improves outcome in any sick neonate where hypoxia and ischemia have occurred [67]. After appropriate resuscitation, all the care entities required to minimize the possibility of a brain injury being sustained, or an existing intrapartum injury compounded, must be provided. Priorities to do this include: support of respiration and the circulation; provision of a neutral thermal environment, appropriate hydration and nutrition; prophylactic antibiotics and management of proven infections; hematological and biochemical surveillance; and neuroradiological monitoring. Good communication and support of the physical and mental wellbeing of both parents must be ensured.

Controlled hypothermia is indicated where HIE develops; the concept of cooling being beneficial stems from animal studies and the neuroprotective effects of hypothermia in children following near-drowning and during cardiac surgery. Interventions to minimize the effects of hypoxia and HIE postnatally continue to evolve; early studies of short periods of cooling had limited, contradictory results. Later studies were more promising; where cerebral hypothermia was initiated after HI insult, and before onset of secondary energy failure, newborns with moderate encephalopathy had better neurodevelopmental outcome compared to normothermic controls [96]. Neuroprotective hypothermia for neonatal encephalopathy has been the subject of systematic review [97]; it is currently the standard of care for moderate and severe HIE; improves survival without CP or other disability by 40%; and current protocols are considered near optimal. Therapy within 6 hours of age at 33–34°C, continued for 72 hours, decreases death or disability at 18 to 24 months of age and increases the number of normal survivors [8, 67, 97]. Defined obstetric antecedents indicative for cooling include umbilical cord prolapse, uterine rupture and placental abruption [98]. In cooled encephalopathic newborns, time to recovery of amplitude integrated EEG is a good predictor of outcome [8]; early MRI scans (3-6 days of life) robustly predict the predominant pattern and extent of injury, and late scans (10-14 days) long-term outcome, and the predictive value of MRI is not affected by hypothermia [99, 100].

In future, earlier initiation of cooling after resuscitation may prove beneficial; ongoing research aims to identify other neuroprotective approaches that can be used in parallel, and evaluate potentially beneficial therapeutic agents; ways that may help reduce the incidence of IVH during rewarming are also being explored.

7. Conclusion

Many causes of fetal and neonatal brain injury are now preventable. The consequences of cerebral hypoxia and ischemia remain considerable. Evidence-based care strategies during pregnancy and for premature and sick newborns infants are improving outcome.

Author details

Andrew Macnab[1,2]*

1 Department of Paediatrics, Faculty of Medicine, University of British Columbia, Vancouver, Canada

2 Stellenbosch Institute for Advanced Study, Wallenberg Research Institute at Stellenbosch University, South Africa

*Address all correspondence to: andrew.macnab @ubc.ca

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