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The Etiology and Evolution of Fetal Brain Injury

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1. Introduction

The nine months of intrauterine life are a continuum during which a series of situations and events can occur that result in abnormalities of normal brain growth or injury to the developing brain of the fetus. Genetic mutations and hereditary syndromes can predispose the fetus to intrauterine death, mortality in early life, and various degrees and combinations of brain injury and neurological deficits. Structural brain injury occurs due to a number of well defined and some relatively obscure causes. Premature delivery puts the fetus at risk of complications during birth and in the early days of life that can compromise the brain. Such infants have systems that are physiologically too immature to function normally, making them dependent on a range of care entities many of which are known to have risks associated with their use. The end result especially when prematurity is of extreme degree, is a significant incidence of cognitive and motor deficits. Maternal infection is increasingly recognized to precipitate premature labour and produce inflammatory by-products that cross the placenta and increase the vulnerability of the fetus to brain injury. (Gotsch et al, 2007; Kendall & Peebles 2005; Mercer 2004) Various pathologies related to the placenta also compromise the well being of the fetus. Impaired fetal growth secondary to placental insufficiency is associated with a reduction in the number of brain cells formed by the time the infant is born; growth retarded infants are at increased risk of hypoxic stress and hypoxic ischemic brain injury due to failure of placental blood flow, gas exchange and fetal oxygen delivery. Suboptimal nutrition also poses the risk of hypoglycaemic brain injury immediately after birth. Post mature infants are at risk from hypoglycaemia, hypoxic ischaemic injury and birth trauma. Infants conceived with in-vitro fertilization are at increased risk of neurological disability, especially cerebral palsy. (Stromberg et al 2002) Stroke is a significant cause of neurodevelopmental morbidity in newborn infants that can result in permanent sequelae and may be underreported. (Ozduman et al 2004) The overall incidence of cerebral palsy has not been reduced significantly in spite of advances in obstetric care, and CP remains a significant cause for motor deficits and cognitive disability that become evident in early life and result in permanent disability.
Hypoxia is central to the genesis of a significant proportion of the brain injury that occurs in the fetus. Compromised oxygen delivery is a particular risk factor during labour and delivery, but the fetus is at risk of brain injury whenever cerebral ischemia occurs as a consequence of impaired cerebral blood flow. After hypoxic ischemic injury, reperfusion of the brain and any situations that further compromise normal perfusion, oxygen and carbon dioxide transport, or the supply of metabolites required for normal brain function have the potential to complicate recovery, and can also contribute to additional brain injury. (Fellman & Raivio 1997, von Bell et al 1993) Major mechanisms linked to perinatal brain injury are hypoxic ischemic insults and haemorrhagic brain injury in term infants (those born beyond 37 weeks of gestation) and periventricular haemorrhage and white matter injury (leukomalacia) in preterm infants (those born before 37 weeks of gestation).

Hypoxic ischemic brain injury is estimated to occur in 0.5 – 0.75 per thousand deliveries. The pattern and consequences of injury depend on the severity and duration of the insult, the neurovascular and anatomical maturity of the brain which is primarily a factor related to the gestational age of the fetus, and co-related factors such as the presence or absence of infection, problems with fetal nutrition, or pre-existing abnormalities in brain growth and development. Ferriero (Ferriero 2004) has reviewed the gestation specific vulnerability of different regions of the fetal brain and individual cell lines to damage, and the central role of oxidative stress and excitotoxicity in fetal brain injury.

Infants born very prematurely are at particularly high risk for brain injury as brain development in such infants is so immature that they are vulnerable to fluctuations in brain blood flow and oxygen delivery that are insufficient to generate injury in a more mature fetus. Such fluctuations include variations in cerebral venous pressure, the degree of cerebral vasodilatation and constriction, and the distribution of cerebral blood flow, and also systemic alterations in circulating blood volume, or oxygen and carbon dioxide tension. The periventricular area of the immature preterm brain is particularly prone to injury in such ways. Haemorrhage in this area is a major cause of acute brain injury in premature infants, and the cystic changes that develop in consequence (periventricular leukomalacia – PVL) frequently result in permanent scarring. This form of periventricular haemorrhage can also be sufficiently extensive that it extends into the ventricles, where the presence of blood within the cerebrospinal fluid is irritant, and as a result often generates ventricular dilatation or causes obstructive hydrocephalus. (Volpe 2001a)

In larger premature infants and those born at term brain injury involving the cortex or basal ganglia predominates; (Okereafor et al 2008) watershed damage in the parasagittal areas of the brain results from moderate hypoxic ischaemic insults, and brain stem injury when injury is more profound. (Roland et al 1988) The regionalization of injury is dictated by the selective vulnerability of different areas of the brain which depends largely on differences in metabolic demand, compensatory mechanisms that occur in response to hypoxia, the maintenance of normal levels of substrate delivery (particularly oxygen and glucose), and the maturity and type of brain cells undergoing development at the time of injury.

The immediate clinical effects of hypoxia and ischemia result in an infant who is neurologically depressed at birth, requires resuscitation to initiate breathing and sometimes cardiovascular support to stimulate heart function and ensure adequate blood pressure and circulation. Tone and behaviour are abnormal and an encephalopathy develops in the hours
or days after birth where neurological abnormalities include problems with level of consciousness, tone, respiratory drive, and coordination of sucking and swallowing, and seizure activity usually occurs. In the longer term the consequences of hypoxic ischemic brain injury vary between death and complete recovery (Perlman & Shah 2001), with the spectrum of long term brain morbidity ranging from mild motor and cognitive defects to cerebral palsy and severe cognitive disabilities.

Importantly many of the causes of fetal brain injury are avoidable and some are amenable to treatment. The evolution of hypoxic ischaemic brain injury for example has two phases over time. Following the initial insult a ‘latent’ phase follows that is associated with a transient recovery of cerebral energy metabolism, then hours or sometimes days later a second phase occurs where cerebral energy failure and oedema within the brain cells initially injured compounds the degree of injury. (Gunn 2000) The interval between this biphasic response offers a therapeutic window during which interventions aimed at ameliorating the effects of hypoxia and ischemia are being explored.

2. Causal mechanisms for structural defects

Structural development: The structure of the fetal brain evolves throughout intra uterine life. Comprehensive reviews describe the initial proliferation of cells, generation of neurons in the cortical germinal zone, and process of normal brain growth and maturation. (Hatten 2002; Marin & Rubenstein 2003; Larroche et al 1997; Razic 2002) Normal growth involves a continuum that must be appreciated in order to fully understand the causes, evolution, and consequences of brain deficits associated with abnormalities in fetal brain development. Key influences that determine normal structure include genetic, embryonic, nutritional and environmental factors.

Genetic anomalies are the principal cause of fetal loss. (Heffner 2004) In such circumstances brain abnormalities at a macroscopic and microscopic level are commonly evident. Francis et al (Francis et al 2006) have reviewed the history and molecular genetic advances in cortical development disorders, and use microcephaly to explain the complex mechanisms underlying correct development of the human brain. Where a fetus with a genetic anomaly is born alive there may or may not be structural brain involvement. While many genetic mutations are random most are inherited, although some have variable expression. Environmental factors such as radiation or chemical exposure are uncommon but preventable causes, and parental age plays an important part. (Heffner 2004) Conception is less likely as females and males age, with the proportion of sub-optimal ova and unhealthy structurally abnormal sperm increasing exponentially with age, and there is the well recognized association between age and a number of genetic syndromes such as Trisomy 21 (Down syndrome). Infants conceived with the use of assisted reproductive technology are more likely than naturally conceived infants to have multiple major defects including chromosomal and musculoskeletal defects. (Hansen et al 2002) Some racial groups have a predisposition to specific genetic anomalies associated with structural brain abnormalities e.g. the Irish and Welsh to neural tube defects and hydrocephalus respectively.

Genetic counselling is central to diagnosis and prevention in situations where there is a family history of genetic abnormality with brain injury, birth of a prior infant with an anomaly, or predisposition to a genetic problem due to racial or age related factors. Information from autopsy is important after fetal loss, coupled with placental pathology after unexplained
stillbirth. An infant born with evidence of brain injury potentially due to a genetic cause requires chromosome studies, placental pathology, and family evaluation in addition to radiological and general and often specific laboratory studies. Prognosis varies; some genetic syndromes are invariably fatal while the spectrum for brain involvement, ability and life expectancy is broad in the remainder, hence the need for identifying the chromosomal anomaly or specific syndrome and making a definite diagnosis wherever possible.

**Embryonic development** progresses at a rapid pace from the moment first cell division occurs, and 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 it is brain growth that follows between this time and fetal maturity (40 weeks). There is always the potential for a variety of factors to negatively impact normal embryonic development, and in-vitro fertilization (IVF) has known associations with multiple pregnancy, infants of low birth weight, and a spectrum of anomalies. (Berg et al 1999, Stromberg et al 2002)

**Nutritional deficiencies** can negatively impact brain growth, as exemplified by the key role of periconceptual administration of folic acid in the prevention of defective neuropore closure. (Hagberg & Mallard 2000) This central role in reproductive health, normal neurological system structure, and brain function is underscored by the evolutionary adaptation of skin colour in humans to facilitate folate synthesis. When humankind’s African ancestors migrated to less sunny climes, a progressive reduction in skin pigmentation became essential in order for effective folate (and vitamin D) metabolism to occur, as exposure to sunlight and transmission of ultraviolet light through the skin is required for the effective production of both folate and vitamin D. (Jablonski 2006). Dietary intake is also relevant but optimal folate levels for normal fetal neural development are difficult to achieve, especially for sub-populations at particular risk of structural anomalies. Hence, for prevention, the majority of pregnant mothers can benefit from folic acid supplementation, as evidenced by the fall in neural tube defects in populations where food items are now supplemented. Rodent models also provide convincing evidence that iron deficiency alters metabolism and neurotransmission in major brain structures, such as the basal ganglia and hippocampus, and disrupts myelination brain wide. (Lotzoff & Georgieff 2006) While evidence for the same issues affecting the human fetus is less clear, even the possibility combined with the high worldwide incidence of iron deficiency in pregnancy makes iron supplementation logical to reduce the impact of this wholly preventable form of brain pathology.

**Environmental factors** relevant as a mechanism for brain damage range in severity due to the high toxicity of some agents, e.g. cocaine, the effect of dosage and cumulative exposure in others such as alcohol, and the frequency of fetal exposure to agents such as nicotine in mothers who smoke. Gestational age plays a role principally in that the fetal brain is most vulnerable during the early stages of structural development. The impact of environmental factors can be multi-factorial with exposure to multiple agents increasing the risk of brain damage, and in some situations a genetic predisposition to the toxic effect of individual agents is evident e.g. related to alcohol.

Perhaps the best known association is between fetal exposure to alcohol and the Fetal Abnormality Spectrum Disorder (FASD). Heavy prenatal alcohol exposure can have serious
and long-lasting effects on the developing fetal brain, that severely affect the physical and neurobehavioral development of a child. Autopsy and brain imaging studies indicate reductions and abnormalities in overall brain size and shape, specifically in structures such as the cerebellum, basal ganglia, and corpus callosum. A wide range of neuropsychological deficits have been found in children prenatally exposed to alcohol, including deficits in visuospatial functioning, verbal and nonverbal learning, attention, and executive functioning. These children also exhibit a variety of behavioral problems that can further affect their daily functioning. (Riley & McGee 2005).

The potential for adverse effects on the fetal brain from maternal drug use is exemplified by the effect of cocaine; use of the drug during pregnancy causes structural brain defects; increases the incidence of low birth weight with its attendant risks; and multiple functional deficits manifest once the child is born, some of which persist as learning difficulty into adult life. Sometimes infants exposed to cocaine in utero have ultrasound evidence of cyst formation in the frontal lobes of the brain, basal ganglia, posterior fossa, germinal matrix and septum pellucidum. These are particularly likely following drug use in the first trimester, and probably represent focal necrosis caused by complex vasoconstrictive effects of the cocaine. (Dow-Edwards 1991) This vulnerability of the fetal brain to damage in the first trimester is not unique to cocaine; many drugs and chemical agents cause structural anomalies as this is the time when key structures are being formed.

Maternal smoking increases the risk of an infant being of low birth weight (LBW) two fold; is responsible for 20% to 30% of all LBW infants; and causes such infants to weigh 150-250 g less on average than those born to non-smoking mothers. The adverse fetal effects of smoking are generated through several pathways. Placental function is impaired by vasoconstrictive cigarette smoke metabolites; these can reduce uterine blood flow by up to 38% depriving the fetus of both oxygen and nutrients. The episodic hypoxia and malnutrition that results underlie the intrauterine growth retardation that occurs in many infants born to smoking mothers. Nicotine is also a fetal neuroteratogen that targets nicotinic acetylcholine receptors in the fetal brain. Changes in cell proliferation and differentiation occur, synaptic activity develops abnormally, and cell loss and neuronal damage occurs. Even in mothers who do not smoke enough for their infants to be of low birth weight, the nicotine levels to which their fetus is exposed are high enough to produce deficits in fetal brain development (Law et al 2003)

Evaluation of structural brain damage: This is a process that combines relevant elements of the infant and maternal medical and family history, physical examination findings, and laboratory and radiological investigations, including: the infant’s condition at birth (requirements for resuscitation, APGAR score, and neurological status); general appearance (appropriateness of growth for gestational age, weight, head circumference, and length, and presence of associated defects); neurological status (especially tone, cry, ability to feed, and seizure activity); fetal sonography and MRI; post-natal ultrasound and neuroradiological studies (CT scan MRI); electroencephalogram; chromosome studies; and consultation with medical specialists such as a neonatologist, geneticist and neurologist.

3. Predisposing factors for fetal brain injury

Prematurity: Brain injury in the premature infant is an extremely important problem, in part because of the large absolute number of infants affected yearly. (Volpe 1997) Considerable
research documents that children born very prematurely (<32 weeks gestation) and or/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 behavioural and emotional problems. Also that the survival rate for extremely preterm infants (<26 weeks gestation or with a birth weight of <750 g) is approximately 50% but that 40% of survivors do not escape significant deficits. (Anderson & Doyle 2008) Modern neonatal care entities now enable 75-90% of preterm infants weighing < 1500g at birth to survive in Europe and the USA; however 5-10% of survivors exhibit cerebral palsy and many have cognitive, behavioural, attention-related or socialization deficits. (Halopainen & Lauren 2011)

The two principal brain lesions that underlie the neurological manifestations observed in premature infants are periventricular hemorrhagic infarction and periventricular leukomalacia. (Volpe 2001a) In the animal model relatively brief periods of hypoxaemic compromise appear to be more profound in the less mature brain in mid rather than late gestation, when they have significant effects on the fetal brain causing death of susceptible neuronal populations (cerebellum, hippocampus, and cortex) and cerebral white matter damage. (Rees & Inder 2005) Cerebellar injury is also increasingly recognized (Limperopoulos et al 2009)

Very premature infants are prone to these lesions because the structural anatomy and neurovascular immaturity of their brains predisposes them to injury from hypoxia (inadequate oxygenation) and ischemia (inadequate blood flow) which predispose them to cerebral haemorrhage. The immature brain lacks the duplication of blood supply that develops as a fetus matures and the ability to auto-regulate cerebral blood flow in response to changes in systemic blood pressure. Areas of the brain such as the germinal matrix have vascular complexes that are vulnerable to bleeding when blood pressure fluctuates. Such haemorrhage is common related to asphyxial stress and results in a pattern of injury unique to the preterm infant. In this context, prematurity is certainly the major causal factor of cerebral palsy. However, the literature also indicates that the odds of brain injury become much greater in the fetus in the presence of maternal fever, and from the effects of inflammation, or proven infection, than when the only risk factor is prematurity. (Rees & Inder 2005)

Premature and low birth weight infants are known to be at increased risk of brain injury as a consequence of intrauterine infection when microglial activation triggers excitotoxic, inflammatory and oxidative damage, (Malaeb & Dammann 2009) and of developing infections during the newborn period. Their postnatal vulnerability is because they are compromised in terms of how quickly and how effectively they can mount an immune response. This is in large part because bacterial colonization of the gut after birth is essential for digestive function, and for production of vitamin K, an essential component of the clotting mechanism without which haemorrhagic disease of the newborn can develop. This bleeding tendency can involve intracranial bleeds of sufficient severity to cause brain damage and even death. As an additional precaution, newborns are routinely given this vitamin prophylactically after birth. Risk factors for neonatal sepsis include prolonged rupture of membranes (beyond 18 hours the risk of infection increases 10 fold, and the occurrence of perinatal asphyxia adds additional risk); and maternal colonization with group B Streptococcus and urinary tract infection (Gerdes 2004). Prophylactic antibiotics are
used in anticipation of sepsis as by the time confirmatory tests (bacterial cultures) are positive the risks of increased morbidity or mortality rises. This is due in large part to the risk of dissemination of infection e.g. to the brain and meninges causing meningitis, or because of the greater levels of toxic metabolites released when the higher counts of bacteria present as a consequence of treatment being delayed are killed by therapy.

Brain injury in premature infants as a consequence of periventricular haemorrhagic infarction and periventricular leukomalacia may be preventable. Logical approaches would include measures to prevent germinal matrix-intraventricular hemorrhage, prevent or manage impairments of cerebrovascular autoregulation and cerebral blood flow, and the use of agents such as free radical scavengers to interrupt the cascade to oligodendroglial cell death. (Volpe 2001b). Importantly, the consequences of being born prematurely also predispose infants born following fetal brain injury to additional compounding stresses and insults in the newborn period; such events also pose a threat of increased morbidity and long term neurological compromise to those who have intact brains at birth. Hence the high overall risk of motor, cognitive, and educational defects in those that survive being born prematurely. (Rees & Inder 2005, Anderson & Doyle 2008)

**Low birth weight (LBW) infants** are those born weighing <2500 g. LBW infants comprise both those born prematurely but appropriately grown for gestational age and those who are small because of intraterine growth retardation. LBW infants accounts for 7.6% of all live born infants and 65% of deaths in the United States occur among LBW infants due to multiple risk factors related to the underlying cause of their small size. In most instances intrapartum morbidity is higher amongst this group, and many are also at risk during the newborn period. Brain injury in a fetus of LBW is potentially caused by many factors; where placental dysfunction is the underlying cause, acute problems may compromise placental gas exchange and precipitate fetal hypoxic ischemic stress.

**Small for gestational age (SGA) infants** are those with intrauterine growth retardation who when born are below the 10th centile for weight; where length and head circumference are also similarly compromised, such infants are known as symmetrically growth retarded and brain size and function are usually adversely affected. Long term deficits in neural connectivity are described (Rees & Inder 2005) and cognitive problems are common in surviving infants. SGA infants have no glycogen stores in their liver at birth and are hence prone to hypoglycaemia that can compound pre-existing fetal brain injury. In utero maternal blood glucose levels determine fetal levels, and, in addition, the fetal brain is able to metabolize lactate as an alternative energy source. However, this pathway is down regulated after birth once oral feeding begins. As a group, surviving SGA infants are at particular risk in adult life of developing cardiovascular disease, hypertension and stroke.

**Maternal Illness during pregnancy** poses a risk for fetal brain injury. Many are specific to pregnancy such a pre-eclamptic toxaemia, but others pre-exist prior to pregnancy and of themselves, or because of treatment they require, have the potential to cause damage, or predispose the fetus to situations such as prematurity or low birth weight that carry independent risks for neurological morbidity. Examples that pose clear risks for the fetal brain and neurological system are anticonvulsant medications and cancer therapies (Halopainen & Lauren 2011). But, while there is general recognition that any medication should be considered carefully in the context of pregnancy and wherever possible be discontinued, in some instances the wellbeing of the mother has to be weighed against the
potential for risk to the fetus. However, not infrequently drugs in common use that are initially identified as problematic sometimes only come to be recognized in their true context after some years of use and appropriately rigorous research and review.

A case in point relates to selective serotonin reuptake inhibitor (SSRI) use during pregnancy and the effects of these agents on the fetus and newborn infant. Serotonin is a neurotransmitter that appears very early in fetal life and has a broad role in brain morphogenesis. Studies to evaluate the neurotoxicity of SSRI’s identified a number of age-specific and site-specific effects in the fetal rat brain, especially related to the limbic system (Lattimore et al 2005). Subsequently a number of adverse effects were identified to occur in human newborns, and there was a clear association with low birth weight (Oberlander et al 2006), the need for special care in the newborn period, and an apparent increase in the incidence of prematurity (Lattimore et al 2005). This led to calls for SSRI use to be reconsidered in pregnancy, although there was debate as to whether the effects observed in the newborn were attributable to acute cessation of exposure (withdrawal) or a direct prenatal effect. However, this class of medications is widely prescribed to treat a number of psychiatric disorders, and is of particular value in severely depressed patients in pregnancy (Austin 2006). Hence, following studies of neonatal outcome and meta-analysis of existing research, the recommendation now is that the decision whether or not to discontinue SSRI use in pregnancy has to be made on a case by case basis. (Oberlander et al 2006; Lattimore et al 2005; Austin 2006)

Another challenge for caregivers and concern for pregnant mothers is that the literature indicates that something as common as maternal fever during intercurrent illness can pose problems. A maternal temperature of 38 °C or higher is an independent risk factor for significantly increased fetal morbidity, and the specific risk of brain damage resulting in Cerebral Palsy is increased many fold by maternal fever. (Gotsch et al 2007; Kendall & Peebles 2005; Barks & Silverstein 2002; Grether & Nelson 1997)

Some infections are well known to cause brain injury. Those known collectively as the TORCH group (toxoplasmosis, cytomegalovirus and herpes simplex) are examples. (Hagberg & Mallard 2000) Some viral infections are associated with stillbirth, and when infants are born alive many have systemic effects due to the infectious process. Parvovirus B19 infection is an example of an illness that has been associated with severe fetal complications; fetal involvement can result in vasculitis that causes pathological changes in the central nervous system which can include stroke. (De Haan et al 2006) Fetal outcome may be normal but anaemia, hydrops fetalis and stillbirth also occur. Approximately 30–50% of pregnant women are nonimmune. Fetal infection in the first trimester poses the greatest risk. Factor V Leiden mutation can lead to activated protein C resistance which increases the risk of thromboembolism, particularly in the presence of dehydration, asphyxia and infection. Maternal infections as varied as malaria and syphilis adversely affect the fetal brain, and rubella (German measles), varicella (chickenpox) and cytomegalovirus, and labour and delivery complicated by chorioamnionitis and FIRS (Garite 2001; Wu et al; 2003; Bashiri et al 2006) are associated with an increased risk of cerebral palsy and a range of illness specific central nervous system effects. However, upper respiratory tract infections and gastroenteritis, which are common and often a concern to pregnant women, are not. (O’Callaghan et al 2011).
3.1 Fetal inflammatory response syndrome (FIRS)

Inflammatory mediators are known to precipitate premature rupture of the membranes and preterm labour, inflame and cross the placenta, and increase the risk of fetal brain injury and cerebral palsy (O’Callaghan et al 2011). Recent literature uses the term Fetal Inflammatory Response Syndrome (FIRS). (Khwaja & Volpe 2008; Back & Rivkees 2004; Gotsch et al 2007; Bashiri et al 2006; Kendall & Peebles 2005) FIRS is characterized by systemic inflammation, activation of the innate fetal immune system, and elevation of fetal plasma cytokines. Cytokines are small, peptides or glycoproteins secreted de novo in response to inflammation/infection or other immune stimulus. Usually cytokine production is responsible for the generation of a normal immune response, but in the immature fetus or premature infant born after exposure to FIRS the complex effects of cytokine activity significantly increase infant morbidity and mortality, (Gotsch et al 2007; Bashiri et al 2006; Barks & Silverstein 2002) because the balance of these agents is imperfectly controlled.

Cytokines such as Interleukin -1, -3, and -6, and Tumour Necrosis Factor mediate and regulate immunity, inflammation, and haematopoiesis (blood cell production), and are central to the mechanism for elevation of temperature and stimulation of the bone marrow to produce white blood cells in response to infection. (Bashiri et al 2006; Kendall & Peebles 2005; Barks & Silverstein 2002) Importantly, many cytokines are also vasoactive products that increase the vulnerability of the premature fetal brain to hypoxic ischemic injury, and substantial evidence indicates that when a fetus is exposed to intramniotic inflammation there is an increased risk for direct brain injury that can cause short term morbidity and cerebral palsy. (Lee et al 2007)

In the presence of inflammatory cytokines, focal variations in fetal brain perfusion occur that result in local ischemia followed by reperfusion; these perturbations cause cumulative injury to the white matter due to the primitive neuro-vascular architecture, immature autoregulatory control mechanism, and sensitivity of maturational dependent cells to free radical damage in the immature brain (Volpe 2001b) The germinal matrix is particularly vulnerable to variations in brain blood flow and blood pressure; consequently, periventricular hemorrhage is all the more likely to occur in the preterm fetus exposed to FIRS; such haemorrhage may extend into the ventricular system to cause intraventricular hemorrhage. The literature emphasizes “the synergistic role of inflammation and hypoxia and ischemia when they occur together”, and the higher incidence of hypoxic ischemic brain damage that results in a fetus exposed to maternal inflammation/infection.

The literature also supports a role for inflammatory mediators in the mechanisms of preterm premature rupture of membranes (PPROM), premature labour and delivery, and links “maternal infection and pro-inflammatory mediators in the neonatal systemic circulation with an increased risk of PVL and/or spastic diplegia.” (Back 2004; Bashiri et al 2006; Barks & Silverstein 2002, Lee et al 2007; Grether 1997; Mercer 2004; Asrat 2001) Maternal cytokines are able to cross the placenta, enter the fetal circulation, cross the brain blood-brain barrier, and produce an inflammatory response in the white matter of the fetal brain which leads to brain damage. (Malaeb & Dammann 2009) Also, the incidence of fetal distress (Kilbride & Thibeault 2001) and hypoxic insults (Garite 2001) is higher following PPROM than in pregnancies with preterm labor and intact membranes. This is largely because of the increased risk of cord compression (Garite 2001; Mercer 2004; Kilbride & Thibeault 2001;
done at defined intervals after birth in order to evaluate the timing and evolution of brain injury. Pathology that can be identified includes structural developmental abnormalities, oedema (brain swelling), haemorrhage, early ischemic damage, localization of injury to cortical tissue or deep brain structures (basal ganglia and thalami), onset and evolution of scarring, onset and progression of hydrocephalus or microcephaly. Cerebral oedema following hypoxic ischaemic brain injury usually subsides in 48-72 hours, allowing recovery of brain stem function; (Perlman & Shah 2011) and intrapartum or late antepartum hypoxic ischaemic changes can be distinguished from structural brain damage due to congenital or acquired causes that occurred well prior to birth.

Advanced methods of neuroimaging are the subject of recent reviews; (Glenn & Barkovich 2006; Mathur et al 2010; Counsell et al 2010; Huang & Castillo 2008) MRI, magnetic resonance spectroscopy (MRS), and diffusion-weighted MRI have shown the patterns of brain injury that evolve after hypoxic ischaemic insults, that such patterns depend on the severity of the insult and the age at which it occurs, and that brain injury evolves over days, if not weeks. (Ferriero 2004) The anatomical regions of the brain affected by hypoxic ischemic injury define whether the insult occurred acutely and was near total in nature or occurred over a more prolonged period and was partial in degree. Deep brain structures have a high metabolic rate and hence are injured in acute profound hypoxia as significant ischemia develops before compensatory changes in cerebral perfusion can occur. In contrast, in partial and prolonged hypoxia, acidosis evolves that leads to preferential perfusion of deep brain structures; but ultimately, perfusion of the cerebral cortex is compromised and this area of the brain suffers hypoxic ischemic damage.

Fetal and post-natal MR imaging have redefined the diagnosis of congenital and acquired brain injury developing in utero and during the intra-partum period (Glenn & Barkovich 2006). 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, germinial matrix haemorrhage, intraventricular haemorrhage, multicystic encephalomalacia, periventricular leukomalacia, periventricular nodular heterotopias, poroncephaly, and sulcation anomalies (Filey et al 1991; Aubry et al 2003).

The most common abnormality observed is enlargement of the ventricles (ventriculomegaly), which may result from multiple developmental, obstructive and destructive causes; in the majority of cases there are associated anomalies within or beyond the central nervous system, which significantly increase the probability of the affected infant having developmental delay. Destructive lesions are characterized by periventricular hyperintensity, focal defects in the germinal matrix, or areas of abnormal signal intensity in the developing white matter. Haemorrhage is usually associated with hypointense areas, although signal intensity does vary depending on the stage of evolution.

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 and recent publications describe the major findings observed (Huang & Castillo 2008).

Electroencephalogram (EEG) recording monitors the electrical activity of the brain. Seizure activity occurring in the brain but not visible clinically may be detected by EEG. Patterns of...
brain waves are obtained that allow the location and relative severity of various brain pathologies to be identified. Patterns of depression of cortical brain activity on EEG have been defined (Table 2) associated with varying stages and severity of hypoxic ischemic encephalopathy (Sarnat and Sarnat 1976). Serial measurements are helpful to document the evolution and recovery of abnormal brain function and the effect of therapy.

**Blood counts:** The presence of abnormal findings in the white blood cell (WBC) count are strongly indicative (although not diagnostic) of the presence of bacterial infection due to sepsicaemia (bacteria multiplying in the blood stream). (Gerdes 2004) Very low counts indicate the inability of an infant to mount an effective immune response; elevated numbers of total WBC cells, a high proportion of neutrophils (granulocytes), and elevated numbers of primitive (band) cells indicate that stimulation of the bone marrow by inflammatory cytokines has occurred, and hence such changes evolve over time. Elevation of the band cell count is the earliest change seen in the peripheral blood count in response to an inflammatory stimulus, which is the most common cause of increased release of primitive (band) cells, although hypoxia can also result in an increase in band cell number.

Measures of haemoglobin concentration or the volume of red blood cells in the circulation are used to identify anaemia and polycythemia where too few or too many red cells are circulating respectively. Both circumstances compromise oxygen delivery; anaemia 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 haemoglobin concentration remains the same. As physiological compensation following haemorrhage occurs, fluid is drawn into the circulation to restore blood volume and, as a consequence, haemoglobin concentration and the number of red cells per unit of volume (hematocrit) fall.

**Blood chemistry:** The full range of biochemical abnormalities associated with brain injury is beyond the scope of this chapter. Congenital metabolic abnormalities constitute a small but complex group of conditions that require expert assessment, investigation and management. Blood glucose, and serum calcium, and electrolyte measurements, in parallel with blood gas analysis of pH, oxygen and carbon dioxide tension, bicarbonate and base deficit, are the mainstays of clinical monitoring in brain injured infants, particularly when multisystem involvement complicates the course of neonatal encephalopathy. Fetal measurement of some parameters is feasible; scalp blood sampling in particular has relevance in assessing the evolution of hypoxia and acidosis during the later stages of labour via blood gas measurement or lactate analysis, once the membranes have ruptured and the fetal head has descended into the birth canal. Lactate is a metabolite in aerobic metabolism and reflects tissue hypoxia. (Wiberg-Itzel et al 2008)

### 6. Prevention of fetal brain injury

Prevention of fetal brain damage requires knowledge of the aetiologies underlying injury, awareness of the availability of preventive measures, and the opportunity to employ them to address the underlying cause. In addition, situations that may aggravate existing or
evolving brain injury need to be recognized and care provided that is capable of improving outcome. Treatment of the effects of fetal brain injury often begins during the newborn period and some entities contribute to better outcome. However, the many therapies that have to continue during childhood to support infants born with brain damage and those that are entailed in providing for their care in adult life are beyond the scope of this chapter.

Maternal health and diet, parental age, and mode of conception are all relevant. (Hagberg & Mallard 2000) The risk of fetal brain injury is decreased where mothers maintain a good diet, add appropriate folic acid and iron supplements, and avoid smoking, the detrimental effects of alcohol, and exposure to TORCH infections. There are benefits to becoming a mother earlier rather than later in life and from lifestyles that promote physical health and mental wellness. In vitro-fertilization is associated with an increased risk of multiple pregnancy, preterm delivery and some specific structural defects. Good antenatal care is central to optimizing the fetal environment, detection of entities that require intervention or forward planning, and allowing pregnancy to progress to term. The fetal brain probably benefits most from prevention of avoidable preterm delivery, and therapy such as antenatal steroid use to mature the fetal lung (Hagberg & Mallard 2000) 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. Mothers who have had previous caesarean section require special planning and supervision to avoid uterine complications that can jeopardize fetal wellbeing.

Monitoring during pregnancy should screen for and detect major genetic anomalies, as termination of pregnancy is a care option for limiting the incidence of brain injury when a fetus is known to have a major anomaly. Confirmation of gestational age by monitoring fundal height and using confirmatory ultrasound also reduces the risk of prematurity. And allows monitoring of fetal growth parameters to anticipate and manage intrauterine growth retardation, and identify placental anomalies that carry a risk of increased morbidity. Surveillance for a broad range of maternal illnesses is also possible with preventive entities available to optimize fetal growth and health, and select appropriate timing, mode and location of labour and delivery.

Surveillance and monitoring of maternal and fetal wellbeing in labour requires entities that provide for anticipation, detection and management of fetal distress. Guidelines exist in most jurisdictions based on the evidence base for best practice in obstetric management where maternal wellbeing is compromised or the fetus becomes at risk. Where necessary, advance consultation with centres specializing in obstetric and newborn care should occur for advice regarding ongoing care of the mother and plans for labour and delivery. This may require transport of the mother with the fetus still in utero if care at a higher level is necessary to optimise the chances of healthy delivery and normal fetal outcome. (Jaimovitch & Vidyasagar 1993; Macnab 1994) An important consideration in this regard is that staff are available with the required skills to comprehensively resuscitate any sick newborn infant and promptly address residual morbidity from premature or complicated delivery; this is known to reduce the risks of brain injury following premature delivery, and in situations where hypoxia and ischemia or any other form of brain injury is considered a potential risk. It also follows that after birth and appropriate resuscitation newborn care entities must be available to minimize the risks of any fetal brain injury being compounded or new injury occurring in the newborn period. Measures to do this include support of respiration and
circulation, provision of a neutral thermal environment, hydration and nutrition, use of prophylactic antibiotics and management of proven infections, haematological and biochemical monitoring and neuroradiological studies, and appropriate discharge planning and follow up.

7. References


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“Brain Damage - Bridging Between Basic Research and Clinics” represents a collection of papers in an attempt to provide an up-to-date approach to the fascinating topic of brain damage in different pathological situations, combining the authors’ personal experiences with current knowledge in this field. In general, the necessary link between basic and clinical neurosciences is highlighted, as it is through this interaction that the theoretical understanding of the pathophysiological mechanisms can be successfully translated into better ways to diagnose, treat and prevent the catastrophic events that occur when the brain suffers from external or internal noxious events. The book spans different aspects of brain injury, starting from damage occurring in the fetal and child brain, followed by different neurodegenerative processes. Attention is also focused on the negative effects of drug addictions and sleep deprivation on the brain, as well as on the early assessment of brain injury for preventive strategies employing sensitive biomarkers.

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