# Stress and Developmental Programming of Health and Disease

## Beyond Phenomenology

*Lubo Zhang, Ph.D.*
*Lawrence D. Longo, M.D.*
*Editors*

Public Health in the 21st Century

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# Preface

Stress is a constant experience and threat throughout life. In his monumental volume *The physiology and pathology of exposure to Stress*, the McGill University endocrinologist, Hans Selye (1907-1982), observed that stress to the organism, in essentially any of its forms – dietary, environmental, disease, and others – could result in cellular, hormonal, and related damage, with the body mounting a response he termed the "General-Adaptation-Syndrome" (Selye, 1950). Writing years before many of the nuances of biochemical and molecular mechanisms were established, and before the phenomenon of epigenesis was appreciated, Selye envisioned an orchestrated brain to tissue system-wide biological defensive response to the challenge of stress of whatever origin. Subsequent investigation has clarified that while stress of relatively short duration is often followed by successful adaptation, that of longer duration and/or repeated insult many result in cell damage and death (Bale et al., 2010; McEwen, 2004).

In the present volume, we have attempted to bring together some of the latest thinking on the role of antenatal environmental stress to the pregnant mother and the developmental origins of health and diseases in the adult. Since the earliest days that David J. Barker (1937-2013), those before him, and others first articulated this Thesis/Hypothesis, epidemiologists have explored its many facets. As is well known, these include but not limited to cardiovascular diseases (hypertension, ischemic heart disease, cerebrovascular accident), metabolic syndrome/type 2 diabetes, schizophrenia and other neuropsychiatric diseases, and some cancers. It is a dizzying array of a multitude of serious disorders, the fundamental pathophysiology of which little is known. Developing the epidemiologic associations for these conditions to stress *in utero* often has not been easy, and at times, has been labeled as descriptive.

This depiction is unfortunate. For it is by establishing such relationships that one can postulate hypothesis as to the manner of origin and their fundamental mechanisms. Even so, as one journeys through the several hierarchical levels of organ, tissue, cell, subcellular, and molecular, too often we discover that we have only punted discovery of the fundamental mechanisms further down into the morass of complexity within the organism.

In the present collection of essays, each author has attempted to bring the latest, deepest thinking to bear on the subject. This includes providing background for rationale of the study, some details but more general principles of the methodologic aspects of study, findings of consequence, and their interpretation. Each of these Chapters has the goal of understanding, at a deeper level, the meaning of the investigation.

We trust that this offering may provide the reader with a more profound grasp of the issues involved, the complexity of the problem, and the diversity of challenges that lie ahead.

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Chapter 18

# Cranial Compression Ischemic Encephalopathy: Fetal Neurological Injury Related to the Mechanical Forces of Labor and Delivery

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## Abstract

Intrapartum events including asphyxia in term fetuses account for significant amounts of subsequent neurological handicap, including cerebral palsy (CP). The prevention of such handicap is a major justification for fetal surveillance during labor as well as for the increasing cesarean delivery rate. Despite the pervasive application of electronic fetal heart rate (FHR) monitoring for the detection of fetal asphyxia and the rising cesarean rate, there has been no diminution of the rates of CP, neonatal seizures or neonatal encephalopathy, despite a reduction in the frequency of stillbirth attributable to asphyxia

Fetal neurological injury during labor may result from mechanical forces associated with excessive uterine activity, prolonged labor, marked molding, malposition and difficult delivery, although such events currently are not commonly considered as an explanation for adverse neurological outcomes. In this review we trace the development of the understanding of the forces of labor as a mechanism of fetal head trauma and subsequent fetal neurological injury. In so doing, we illustrate the limitations of classical interpretations of fetal heart rate patterns and neuroradiological imaging used for the detection and timing of injury. Reliance upon these approaches has impeded our

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understanding of deleterious mechanical effects on fetal cerebral perfusion during labor. We propose the concept of cranial compression ischemic encephalopathy (CCIE) and present a strategy for the recognition and management of related, correctable obstetrical factors that predispose the fetus to hypoxic-ischemic injury.

**Keywords:** Asphyxia, cerebral palsy, cranial compression, encephalopathy, fetal neurological injury, hypoxia, neonatal seizure

# Introduction

Despite widely varying estimates of the relationship of perinatal asphyxial to subsequent fetal neurological injury, general consensus exists that intrapartum events at term account for a significant percentage of cases of cerebral palsy (CP) (Blair and Stanley, 1988, Hagberg et al., 2001). Prevention of neurological injury is a major justification for intrapartum fetal surveillance and the reliance on cesarean delivery (Himmelmann et al., 2011). Recent decades have seen a changing panorama in perinatal outcome statistics. While here have been dramatic reductions in intrapartum stillbirths and complications attributable to intrapartum asphyxia, there has been no diminution in the frequency of CP, neonatal seizures or neonatal encephalopathy in term infants (Foley et al., 2005, Perlman, 2006, Walsh et al., 2008). Indeed, the majority of babies with encephalopathy of perinatal origin are neither severely acidotic nor severely compromised at birth; their ischemic brain injuries may not even be identified during the neonatal period (Yeh et al., 2012). Furthermore, in addition to classical ischemic lesions detectable on neuroradiological examination, hemorrhagic lesions and ischemic stroke are now common neuroradiological diagnoses (Laugesaar et al., 2007, Takenouchi et al., 2012). The presence of non-classical ischemic lesions and the declining prevalence of asphyxia strongly suggest that mechanisms other than severe asphyxia have substantial influence on neurologic outcomes (Ferriero, 2004, McLean and Ferriero, 2004).

The idea that fetal neurological injury can result from mechanical forces of labor is centuries old (Amiel-Tison, 1988). In current practice, however, such forces are generally not considered an underlying mechanism for many of the adverse neurological outcomes in the perinatal period (Murray et al., 2009). This review traces the development of and roadblocks to understanding this relationship and illustrates the benefits and limitations of contemporary surveillance and diagnostic techniques in preventing the potentially correctable obstetrical factors that predispose the fetus to this type of injury.

The earliest reference to the interaction between the fetal head and the maternal pelvis was that of the Dutch obstetrician Hendrik van Deventer (1651-1724) who called attention to contracture of the pelvis as a factor in delayed or difficult labor, and suggested that molding of the fetal head could result in brain injury (Kriewall, 1960). In 1752, William Smellie (1697-1763) called attention to the dangers of trauma and excessive molding (Roberts et al., 2010, Smellie, 1752)

By the middle of the 19$^{th}$ century, the notion that the forces of labor and delivery can injure the brain received compelling support from William Little (1810-1894), a London orthopedist. Little described "abundant instances of deformities arising after birth from disorders of the nervous system: disorders of nutrition, affecting the muscular and osseous structures; disorders from malposition and violence" (Little, 1862). In those infants who

survived, he implicated difficult labors and mechanical injuries to the head and neck in later disorders of posture (Little, 1862). Unlike the previously held belief that the infant either survived the rigors of birth intact or died, Little espoused a "third option" for reproductive casualty, in that "many cases of deformity, [both] mental and physical, [were] traceable to potentially dangerous forces of labor and delivery including an increased intrauterine pressure attendant to contractions" (Little, 1862). For many years thereafter, the affliction we call cerebral palsy was referred to as "Little's disease" (Schifrin and Longo, 2000).

Despite obvious advancements in medical science and in clinical practice since Little's time, even up to the present day, nothing has mitigated the notion that excessive uterine activity and compressive forces on the fetal skull have the potential to injure the fetal brain during labor and delivery. In 1925, MH. Roberts found that more than 10% of infants suffer trauma in the perinatal period, and a small fraction of these show conspicuous neurologic deficits later (Roberts, 1925). In 1930 Irving estimated the incidence of trauma as the cause of perinatal death to be 2% (Irving, 1930). These results emphasizing the frequency of intracranial hemorrhage and cerebral damage in newborn infants "due to pressures on the fetal head." acknowledge that birth "is a very traumatic event" (Yates, 1959).

During the 1960s and 1970s the prevalence of perinatal death decreased precipitously, a gratifying trend, but one that might have conferred neurologic injury on more surviving children. D.G. Wilson Clyne in Scotland and Cyril B. Courville (1900-1968) and Nathan Malamud (1903-2000 ) in California published detailed studies on stillbirths, neonatal, and later deaths from their respective communities during that era (Clyne, 1964, Courville, 1963, Malamud, 1970). They confirmed that mechanical trauma as well as lack of oxygen to the fetal brain during labor and delivery carried serious consequences for survival and subsequent motor and developmental handicap (Clyne, 1964, Courville, 1963, Malamud, 1970). The postmortem data were weighted in the direction of severe grades of neurological injury and mental retardation (and death) and may not apply to the entire population of mental or physical subnormality related to birth. The role of birth trauma in lesser degrees of handicap was largely unknown at the time, although it was understood from the work of Little that neurological signs of birth injury occur across a broad spectrum of presentations (Penrose, 1963). Moreover, the valuable insights obtainable from magnetic resonance imaging (MRI), diagnostic ultrasound, computerized axial tomography, electronic fetal monitoring (EFM) and umbilical blood gas analysis were unavailable to these investigators. For progress to continue in this regard, it would be necessary to visualize the brain without the benefit of autopsy. In addition, improved understanding was needed of the dynamics of uterine contractions and cerebral blood flow, along with an understanding of the timing and mechanisms of mechanical brain injuries, in order to mount strategies for their prevention.

The theory of causation of perinatal brain injury that holds most sway today derives from the observations in experimental animals of William Windle (1898-1985), Ronald Myers and their colleagues in the 1950s-1970s (Ranck and Windle, 1959, 1961, Windle, 1940). They purported to show the role of oxygen deprivation in reproducing the neurological lesions of human CP (Myers, 1967, 1972, Selzer et al., 1972). In these models, progressive asphyxiation results in impaired cardiac output ultimately causing diminished cerebral blood flow (ischemia) (Perlman, 2004, Shalak and Perlman, 2004). The differing patterns of brain pathology were related to the severity and time course of the asphyxial insult (Myers, 1972, Selzer et al., 1972, Shalak and Perlman, 2004). From this point onward, the focus on perinatal asphyxia greatly overshadowed the importance of mechanical factors, which were

not studied in these experiments; indeed, they could not be studied. Unlike the human, the majority of experimental animals have smaller brains and skulls and less prominent faces and do not ordinarily undergo the mechanical rigors of human birth (including iatrogenic induction of labor oxytocin) (Lieberman, 2011). Further distracting attention from mechanical factors, these research efforts were conducted during the time when midforceps deliveries, complex obstetric maneuvers, and neglected labors as causes of obvious trauma were diminishing in favor of the rising use of cesarean delivery. Nevertheless, literature continued to reinforce the empirical relationship between mechanical forces of labor and fetal injury (Kriewall, 1960). Data from the Collaborative Perinatal Project, for example, implicated trauma specifically along with dysfunctional labor and midforceps delivery as strongly associated with neurologic damage (Clifford and Drorbaugh, 1970, Friedman and Acker, 1987, Friedman et al., 1984). These observations notwithstanding, the emphasis on the role of hypoxia and acidemia in brain injury has veiled recognition of the fact that permanent fetal brain injury associated with oxygen deprivation occurs as a consequence of ischemia, and not hypoxia per se (Paneth, 1986a, 1986b, 1993, Perlman, 2004). Indeed, in term infants who appear healthy, metabolic acidosis at birth is not associated with long-term developmental abnormalities (Hafstrom et al., 2012). Ischemia may well be the final common pathway for both severe hypoxia and the direct mechanical effects of excessive brain compression from forceps and vacuum, dysfunctional labor, and uterine hypercontractility.

## Pathophysiology of Intrapartum Cerebral Ischemia

There is a biologic basis to support the idea that cerebral ischemia during labor can occur without without being precipitated by severe, systemic fetal hypoxia and acidemia. To appreciate the role of mechanical factors it is necessary to understand the several effects of uterine contractions on uterine blood flow, fetal oxygenation, fetal cerebral blood flow and head molding. Uterine contractions can decrease oxygen availability to the placenta and fetus by reducing flow in the uterine artery branches that traverse the myometrium. The longer, stronger, and more frequent the contractions, the less oxygen is available to the fetus and the greater the risk of adverse outcome. The association of excessive uterine activity with neonatal depression and adverse neurological outcome is usually thought to be related to asphyxia from impaired blood flow (Bakker et al., 2007a, Hayes et al., 2013)

It is less well appreciated that the fetal intracranial pressure (ICP) maybe higher than the intrauterine pressure (IUP) and that descent of the fetal head raises the ICP further within the pliable portion of the fetal skull. (Lindgren, 1960, 1977, Schwarcz et al., 1969). Even normal strength contractions can moderate cerebral blood flow (Ueno, 1992). Fetal exposure to these forces, when excessive, may result in cerebral ischemia and injury even in the absence of systemic hypoxia or acidosis (Kelly, 1963, Lindgren, 1960, 1977, Schwarcz et al., 1969, Sorbe and Dahlgren, 1983). To maintain brain blood flow under conditions of elevated ICP the fetus must raise its blood pressure above the ICP (the differential pressure between the fetal blood pressure and the intracranial pressure is called the cerebral perfusion pressure, CPP). Figure 1 depicts schematically the relationships among intrauterine pressure (IUP), fetal intracranial pressure (ICP), mean arterial blood pressure (MAP) and cerebral perfusion pressure (CPP).

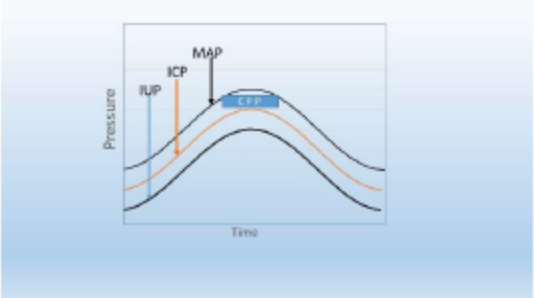


Figure 1. Schematic interrelationship of Intrauterine Pressure (IUP), Fetal Intracranial Pressure (ICP), and Mean Arterial Blood Pressure (MAP). The difference in pressure between the ICP and the MAP (MAP minus ICP) represents the cerebral perfusion pressure (CPP). In order to maintain CPP during a contraction, the fetal blood pressure must exceed the ICP.

When uterine contractions are of moderate intensity with an adequate time interval between them, the fetus compensates for the rise in ICP with a proportionate elevation of sympathetic tone, which raises arterial pressure so that CPP is maintained (the Cushing response) (Harris et al., 1989, 1992, 1998, Mann et al., 1972). As the amount of head compression is augmented from such factors as: increasing frequency and intensity of contractions, abnormal shape or resistance of the birth canal, cranial molding, maternal bearing-down efforts, rupture of the membranes, or dysfunctional labor, the fetus is required to mount more intense compensatory physiological responses (autoregulation and intracerebral shunting) in order to maintain cerebral perfusion (Harris et al., 1989, 1992, 1998).

At term, autoregulatory mechanisms can maintain a constant CBF over a broad range of perfusion pressures (Helou et al., 1994). Autoregulation, however, may be rendered inoperative by prolonged umbilical cord occlusion (Lotgering et al., 2003) impaired cerebral venous outflow, or extreme brain compression from excessive uterine forces, abetted by the effects of maternal bearing-down and molding (Volpe, 2008). Under these circumstances the ICP may become so high that it cannot be overcome by the limited capability of the fetus to elevate its blood pressure or of autoregulation to maintain flow, and normal brain perfusion would be curtailed, even in the face of pressures at which flow might otherwise be preserved (Fanaroff and Martin, 2002, Volpe, 2008). Also, compromised fetal autoregulation may lead to unchecked, pressure-passive blood flow and the potential for both hemorrhage and ischemic injury (Volpe, 2008). Ultimately, with sustained elevations of the ICP, even the most resilient fetus may be unable to maintain perfusion of the brain, resulting in critical reductions in CBF and the risk of ischemic injury (Volpe, 2001). Less severe restrictions of cerebral blood flow may result in redistribution to areas most vital to survival (basal ganglia and hippocampus at the expense of supratentorial white matter) (Volpe, 2008).

The fetus tolerates hypoxemia much more effectively than it does ischemia (Vannucci, 1993a, 1993b). In fact, it is very difficult to produce experimental fetal brain injury when perfusion is maintained, despite the presence of severe hypoxemia or acidemia (Volpe, 2008). With hypoxemia, brain blood flow and substrate availability are maintained [or even increased initially] despite low oxygen tensions (Bishai et al., 2003). However, with prolonged and severe oxygen deprivation, systemic acidosis develops along with reduced

cardiac output and diminished brain perfusion, potentially resulting in ischemia. In contrast, ischemia from cord or head compression promptly prevents oxygenated blood from even reaching the fetal brain, depriving it of oxygen as well as energy-yielding substrates (Longo, 1987, Lotgering et al., 2003). For this reason, head (or cord) compression-related ischemia may promote more rapid injury than, for example, contraction-related hypoxia. Ultimately, whether the mechanism of fetal neurological injury derives from prolonged hypoxia and acidemia or from mechanical factors, the final common pathway is ischemia of the brain. In the former ischemia derives from depressed cardiac output and cerebral hypotension; (Perlman, 2004) in the latter, the effect on blood flow is direct (Ghosh et al., 2011, Recker et al., 2009). Irrespective of the initiating mechanism, increased intracranial pressure from any cause can only aggravate the ischemia and increase the risk of injury (Perlman and Risser, 1993, Stewart et al., 2012, Volpe, 2012).

## Quantifying Intracranial Pressure

### *Theoretical Considerations*

To explain the manner in which forces exerted on the fetal head could generate increased intracranial pressure that, if sufficiently high, could cause constriction or collapse of cerebral arteries and diminish CPP, we take a reductionist approach, in which the fetal skull is modeled as a closed sphere. The cranial vault constitutes the pliable portion of the fetal skull and is represented by a hemisphere, the wall of which is movable. The other hemisphere, representing the skull base, is rigid. External forces generated by the uterus, cervix or pelvic bones applied to the pliable part of the skull will increase the intracranial pressure only if they possess components normal to the movable parietal plates. Tangential components of the forces will not contribute significantly to a rise in pressure. To isolate the normal components, the hemispheric model of the skull can, therefore, be further reduced to that of a simple mechanical system composed of a piston within a rigid cylinder closed on one end. The space delimited by the piston and the cylinder is filled with an incompressible fluid, like water. The rigid cylinder mimics the skull base and the movement of the piston the pliable cranial vault. The intracranial pressure ($P_{ICP}$) will therefore arise from mechanical forces that are applied perpendicular to the piston surface as the piston is forced into the cylinder.

Imagine the piston/cylinder model of the fetal skull placed into the uterine cavity. The intrauterine pressure, ($P_{IUP}$), applies forces that are normal to the piston. Mechanical equilibrium therefore requires that the intracranial pressure equals the IUP, that is $P_{ICP}=P_{IUP}$. When the cranial vault contacts the cervix, additional labor forces may develop on the skull. We denote by $f_C$ the surface density of the normal component of the force applied by the cervix, i.e., the head-to-cervix pressure ($P_{HC}$). Mechanical equilibrium of the uterus/skull/cervix system imposes the condition: $P_{ICP}=P_{IUP}+f_C=P_{IUP}+P_{HC}$. In this, we have assumed that the cervical force density is uniform. Of course the cervical force may not be uniform and may be applied only onto the region of the skull in contact with the cervix. In that case, one would need to address the mechanical equilibrium condition in the form of a surface integral equation. For the sake of simplicity we have not addressed this issue here, and consider only a uniform cervical force density.

Pu et al. investigated the effect of labor forces on the molding of the fetal skull and reported the application of $P_{HC}$ four to five times that of $P_{IUP}$ (Pu et al., 2011, 2013). With an

average $P_{IUP}$ of approximately 50 mmHg during the peak of a contraction, therefore, the head-to-cervix pressure would exceed 200 mmHg. The question that now arises is the extent to which an intracranial pressure of, say, 250 mmHg could cause collapse of cerebral arteries and subsequent reduction in perfusion of brain tissue. A sketch of an answer to this question can be drawn by considering the resistance to collapse of a tube under external pressure. The tube represents a cerebral artery within the skull (i.e. inside the chamber of our model cylinder/piston system).

An expression for the collapse strength of a tube under external pressure has been reported (Clinedinst, 1939, Holmquist and Nadai, 1939). There are two modes of collapse, namely elastic and plastic collapse. We limit our discussion here to elastic collapse, under normal conditions, as the walls of fetal arteries can be presumed to exhibit essentially elastic responses. Clinedist derived an expression for the elastic collapse pressure, $P_{EC}$, of a long tube with perfect roundness and no variation in its wall thickness:

$$P_{EC} = 2\frac{E}{1-\nu^2}\frac{1}{\frac{D}{t}\left(\frac{D}{t}-1\right)^2} \quad (1)$$

The factors that affect the collapse strength of tubes are the ratio of the outside diameter to the wall thickness (D/t), Young's modulus (E) and Poisson's ratio ($\nu$)[1] (Young's modulus is a measure of the stiffness of a material in tension. For a material subjected to tension in some direction, Poisson's ratio reflects the relative contraction of the material perpendicular to the applied tension). Under an external pressure that exceeds $P_{EC}$, the tube collapses and its cross section becomes oval and flattens thus inhibiting blood flow. In what follows we estimate $P_{EC}$ for a newborn carotid artery, a vessel for which nearly consistent sets of morphometric and elastic data are available. Less is known about the cerebral vessels, but the diameter of the middle cerebral artery (the vessel often used as a marker for brain blood flow in Doppler ultrasound studies) is about 75-80% that of the internal carotid (Gielecki et al., 2009). It can be reasonably assumed that our calculations for the internal carotid would apply as well to one of its primary branches, the middle cerebral artery.

The diameter of the newborn internal carotid artery ranges from approximately 1.2 to 1.9 mm (Sehirli et al., 2005). We therefore used a value of D=1.5 mm for our estimate. Ultrasound measurements of the wall thickness of the common carotid artery in normal term newborns give of an average value for t of 0.37 mm (Hondappanavar et al., 2013). These measurements give an approximate value of D/t of 4.

We have not been able to find data for Poisson's ratio of newborn arteries, but ultrasonic non-invasive methods have been used to measure *in vivo* Poisson's ratio of the human carotid artery in a normal young subject; (Hasegawa et al., 1997) based on those data, a value of $\nu$=0.46 will be used here. It is also important to note that the sensitivity of $P_{EC}$ on $\nu$ is limited and uncertainties on that elastic property will not impact significantly the estimated value of $P_{EC}$.

The collapse strength is finally given by:

$$P_{EC}=5.28\text{x}10^{-4}E \text{ (mmHg)} \quad (2)$$

where E is expressed in units of Pa. Reasonable values for Young's modulus in the carotid artery range from E=100 kPa to 900 kPa (13-117 mmHg) (Khamdaeng et al., 2012). This

range was measured in individuals aged 28±3.6 years. We may estimate the Young's modulus for newborn cranial arteries by downscaling the values. We therefore used a range of values between 100 and 400 kPa (13-52 mmHg) for our estimation of the collapse pressure. Within this assumption for the range of values of the elastic modulus, the collapse strength takes on values ranging from $P_{EC}$ ~50 mmHg to 200 mmHg. Resisting collapse would be the blood pressure within the artery. The condition for collapse of the artery is therefore attained when the difference between the intracranial pressure minus the systolic pressure ($P_{Sys}$) of the artery exceeds the collapse strength, that is, when $P_{ICP}$-$P_{Sys}$ > $P_{EC}$. A systolic pressure of about 50 mmHg would exist in a normal term fetus. Values for $P_{ICP}$-$P_{Sys}$ in excess of 200 mmHg may be sufficient to lead to artery collapse. It is only for values of Young's modulus exceeding 400 kPa that artery collapse may not occur for intracranial pressures of less than 200 mmHg. These conditions are illustrated in figure 2. In that figure, the solid line represents the elastic collapse pressure given by equation (2) as a function of Young's modulus of the artery wall. The pressure difference that may drive collapse, $P_{ICP}$-$P_{Sys}$=250-50 = 200 mmHg, is represented as the dashed horizontal line. The condition for collapse of the arterial wall is marked by the brace in figure 2.

These estimates indicate that forces exerted on the fetal head (such as IUP combined with head-to-cervix pressure) could generate increased intracranial pressures that in turn could cause elastic collapse of cerebral arteries, diminishing perfusion of brain tissue. Moreover, if the blood pressure within brain vessels were to be diminished, such as by severe hypoxia, sepsis, or certain drugs, the vessels would be even more susceptible to collapse.

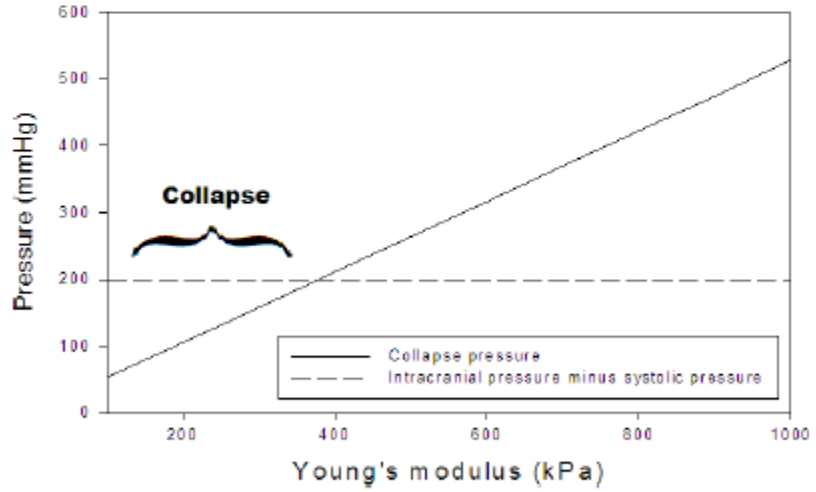


Figure 2. Graphical representation of the elastic collapse pressure, $P_{EC}$, (solid line) and of the intracranial pressure minus the systolic pressure, $P_{IC}$–$P_{Sys}$, (dashed line) as functions of Young's modulus of the cerebral arteries. Artery collapse will occur when $P_{ICP}$-$P_{Sys}$ > $P_{EC}$

## Experimental Observations

Considerable clinical and laboratory evidence supports the theoretical model described above. Beginning in the 1960s several research groups studied the physical effects of contractions on the fetal head (Buhimschi et al., 2002a, 2002b, 2004, Lindgren, 1960, 1966, 1977). Using pressure sensors introduced between the uterine wall and the fetal head, Schwarcz et al. showed that during a contraction pressures exerted on the biparietal diameter level of the fetal head were up to 2.5 times higher than the intra-amniotic pressure (Schwarcz et al., 1969) (Figure 3). The difference between intrauterine pressure (IUP) and pressures on the skull are due to the resistance offered by the cervix as well as by muscular and bony pelvic structures. Of importance, this gradient increased further with rupture of the membranes, maternal bearing-down efforts, progress in descent and head molding. (Buhimschi et al., 2002b, 2004, Furuya et al., 1981). Other experiments using intrauterine transducers are consistent with these observations (Amiel-Tison et al., 1988, Lindgren, 1960, 1966, 1972, 1977, Rempen, 1993b, Rempen and Kraus, 1991). Some have shown that the cervix-to-head pressure could be at least 3 to 4 times the IUP, depending on the state of the membranes. Pressures on the skull also may not be uniform, may be influenced by fetal position and station and may be multiplied during instrumental delivery (Rempen, 1993a). These experiments echoed the findings in those isolated cases in which simultaneous intrauterine and intracranial catheters were inserted into anomalous or dead fetuses (Mocsary et al., 1970, Schwarcz et al., 1969) (Figures 3 and 4). In each case, the pressures within the skull were always greater than the intrauterine pressure, even between contractions. Two-dimensional color Doppler flow technology in normal term human fetuses has demonstrated that the resistance index of the middle cerebral artery correlated positively with the intrauterine pressure, and was highest with descent of the fetal head (Ueno, 1992).

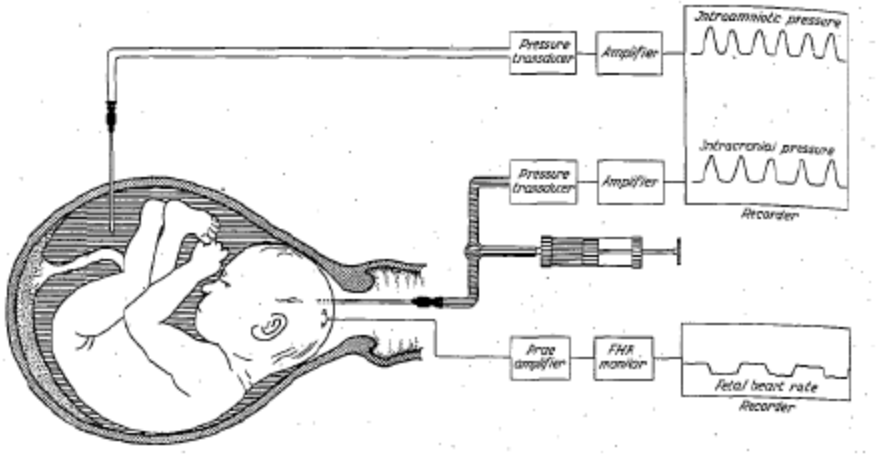


Figure 3. Illustration from Mocsary et al., revealing experimental set up in human (hydrocephalic) fetus. Measurements include intraamniotic pressure, fetal intracranial pressure and fetal heart rate pattern (Mocsary et al., 1970).

Experimental animal studies confirm that increased intracranial pressure can lead to brain ischemia and injury. In fetal lambs increased extracranial pressure caused vascular collapse and dramatically decreased blood flow to the brain (Mann et al., 1972, O'Brien et al., 1984). In one study increasing cerebral vascular resistance caused a 95% reduction in flow to the cerebral cortex, with less impairment to the brainstem and cerebellum (Mann et al., 1972, O'Brien et al., 1984). These studies make it clear that fetal head compression can cause substantial reduction in intracranial blood flow despite the absence of significant changes in systemic $PO_2$ and pH or in cardiac performance (O'Brien et al., 1984). When these laboratory studies are considered in conjunction with the theoretical model we have presented and the available human data, the evidence for the potential of forces of labor to produce brain ischemia is compelling.

## The Neuroradiological Topography of Injury

In the more than half century since the first experimental production of brain injury by perinatal asphyxia, different patterns of injury have been attributed to the severity and duration of the hypoxic–ischemic insult (Barkovich, 2006, de Vries and Groenendaal, 2010, Myers, 1967) (Table 1). Although most neuroradiological lesions represent infarction in the distribution of the arterial circulation, some cases of perinatal injury seem to occur from in utero sinus or periventricular venous infarction (Berfelo et al., 2010, Takanashi et al., 2003).

While the injuries associated with acute catastrophic events and obvious neonatal compromise tend to be basal ganglia and hippocampal lesions, the majority of neuroradiological patterns are associated with white matter injury and often a less dramatic neonatal course (Miller et al., 2005). Clinically, neonatal seizures in association with fetal compromise and birth asphyxia are associated with worse neurodevelopmental outcome, independent of the severity of hypoxic-ischemic brain injury (Glass et al., 2009). Of importance, a significant number of infants with obvious encephalopathy have no lesions discernible on neuroimaging (Miller et al., 2005, Okereafor et al., 2008).

Neuroradiological imaging has proved useful in delimiting the timing of an injury to the perinatal period and not to some earlier time in gestation. Cowan et al. found that more than 90% of newborns with encephalopathy had evidence of perinatally acquired ischemic lesions on an MRI performed within the first 2 weeks after birth, with a very low rate of established antenatal brain injury (Cowan et al., 2003, Martinez-Biarge et al., 2012, 2013). Their results strongly point to the immediate perinatal period as a common factor in the development of ischemic encephalopathy. Accordingly, the absence of severe umbilical acidosis at birth in association with a recent ischemic injury is not consistent with the notion that the injury developed prenatally. While neuroimaging techniques are helpful in the timing of an injury, they can only approximate a window in time rather than determine the moment when injury occurred. (Table 2).

**Table 1. Neuroradiological Findings in Perinatal Brain Injury**

| | Anatomic Features | Clinical Circumstances | Mechanism of injury | Neonatal Appearance | Follow-up Findings |
|---|---|---|---|---|---|
| **Selective Neuronal Necrosis**<br><br>**Other Names**:<br>Near-total acute asphyxia (TAA)<br>Acute profound asphyxia (APA)<br>Basal ganglia thalamic injury (BGT) | Involves central grey nuclei (ventrolateral thalami and posterior putamina) and perirolandic cortex bilaterally. Relative sparing of the cerebral hemispheres (though white matter may be involved). Involvement of the hippocampus and cerebellar nuclei not uncommon. | Short duration (minutes) event responsible. Considered "imaging signature" of acute, severe hypoxia-ischemia (often a sentinel event -such as placental abruption or cord prolapse.) Fetal bradycardia commonplace, often leading to death or delivery. Ischemic episode often brief, or else fetal demise/stillbirth may occur. | Typically, an abrupt impairment of perfusion (ischemia) to entire brain; central grey matter, perirolandic cortex, cerebellar and brainstem nuclei preferentially damaged due to higher baseline metabolic rate and high density of NMDA receptors. Cerebral cortex may be spared from injury. Brain edema may be trivial or absent. | Infant tends to be profoundly depressed at delivery and often meets criteria for "intrapartum asphyxia." Variable tone is common, neonatal seizures are frequently not seen. Organ involvement may be absent. | Infant usually severely disabled due to dyskinetic/extrapyramidal cerebral palsy (CP). Fluctuating tone as infant then involuntary movements are seen. Cognition may be relatively spared due to less cortical damage. |
| **White Matter/Cortical Injury**<br><br>**Other Names**:<br>Prolonged, partial asphyxia (PPA)<br>Watershed pattern.<br>Most common pattern seen. | Supratentorial, predominantly white matter, though some grey matter injury generally to the vascular watershed zones (anterior–middle and posterior–middle cerebral arteries) of the cerebral hemispheres. Deep cortical infarcts (ulegyria) may be seen when severe. The injury may be unilateral or bilateral, posterior and/or | Subacute event (many minutes to hours) is responsible. More prolonged fetal distress is evident. Hypoxia to fetus is the mechanism with greater preservation of perfusion; may be seen in setting of uterine hyperstimulation - mechanical forces of labor, uteroplacental insufficiency. | Prolonged, sublethal hypoxia, less ischemia - often > 1 hour. Due to duration of hypoxic event, greater acidosis often seen. Cerebral cortex and WM involved, brain edema common. Neonatal seizures often occur, may be severe. | Neonatal encephalopathy, often severe. Neurologic manifestations often meet criteria for "intrapartum asphyxia" and for neuroprotection. Organ involvement is common. Extensive damage to the cerebral cortex and white matter may occur, ultimately resulting in cystic encephalomalacia. | Infant often has suboptimal head growth (microcephaly), cognitive impairment, spastic quadriplegic CP feeding problems and communication deficits. |

**Table 1. (Continued)**

| | Anatomic Features | Clinical Circumstances | Mechanism of injury | Neonatal Appearance | Follow-up Findings |
|---|---|---|---|---|---|
| | anterior. Thalamus, basal ganglia and cerebellum / brainstem are typically spared. | | | | |
| **Perinatal stroke**<br><br>**Other Names**: Perinatal arterial ischemic stroke (PAIS) | Typically, ischemic brain injury in the distribution of a single major vessel supplying the brain - the left middle cerebral artery (MCA) most common vessel involved. May have multiple, single vessels involved. | More likely to occur around parturition than any other time in childhood. Associated with risk factors of late labor: trauma, perinatal asphyxia, prolonged rupture of membranes, FHR abnormalities, chorioamnionitis, dysfunctional labor, nulliparity, emergency cesarean section, higher birthweight. | Ischemic event - may have contribution from trauma, thrombophilic disorder, either genetic or acquired (inflammation), cardiac disease with embolus, congenital vascular anomaly, hyperviscosity. | May appear with little to no acute symptoms /signs ("normal newborn"). Severe neonatal depression is uncommon. May present with mild neonatal encephalopathy and/or seizures. Occasionally, neonatal hemiplegia may be evident. | Subsequent neurological deficits including cerebral palsy (often hemiplegic CP) and epilepsy occur in most survivors with varying effects on language, learning, vision (visual field cut), cognition and behavior that may continue to evolve over the several years of childhood. |
| **Cerebral Sinovenous Thrombosis (CSVT)**<br><br>**Other Names**: Sinus Thrombosis | Critical to distinguish arterial from venous cerebral infarct. Parietal, thalamic occipital infarcts more common w CSVT. Superior sag sinus (55%), lateral sinus (51%), Straight sinus (24%) most common. Cortical Venous engorgement, may have hemorrhage. | Mean gestational age of 39 weeks (range, 30 to 42 weeks; preterm uncommon). "Assisted or complicated delivery" common. In the neonate, systemic illness/risk factors often present (infection, surgery, hypoxia, trauma, dehydration, thrombophilia) | Often precipitated by alteration in venous flow from reduced volume, inflammation, vessel / venous injury, hyperviscosity, abnl. clotting, with multiple risks often present. Parenchymal infarcts in approx 40%. | Seizures, partial or generalized, most common presenting symptom, 25-35% w encephalopathy, 30 % w focal signs. Symptoms developed at a median postnatal age of 15 days (range, 0 to 28 days). Head CT may miss diagnosis, MRV, Angiogram or power Doppler highest yield. | At follow-up (median age, 19 months; range, 3 to 72 months), moderate to severe neurological sequelae were present in 38%, mortality 8%. Approximately 50% w "normal" outcome, but limited follow-up into school age. |

**Table 2. Summary of Imaging Neuroradiological Findings in Relation to the Timing of Birth Injury***

| Modality | Feature | Onset – From time of injury | Duration** |
|---|---|---|---|
| **Proton MRI spectroscopy** | Increased lactate. | First few hours | About 2 weeks |
| | Decreased N-acetyl aspartate | First few hours | Indefinitely |
| **Diffusion Weighted MRI (DWI)** | Reduced diffusion | 12 hours (onset) | About 10 days duration |
| **T1-weighted MRI** | Increased signal thalamus or basal ganglia | 2-3 days | Months, becoming more localized and globular |
| | Loss of signal post limb of internal capsule | <24 hours | |
| **T2-weighted MRI** | Increased signal in cortex or deep nuclei | 6-7 days | Months or indefinitely |
| | Decreased signal in deep grey nuclei | 3-4 days | Several days |
| **CT scan** | Decreased density thalami or basal ganglia | 18-24 hours | 5-7 days – may be permanent |
| | May not be visible | | |
| **Ultrasonography** | Increased echogenicity thalami or basal ganglia | Approximately 24 hours; may be earlier | Progresses over 2-3 days, persists 5-7 days |
| | Increased echogenicity in white matter | | |
| | Loss of clarity (due to edema) | | |

Recent reports present a changing pattern of perinatal brain injury in term infants born in 2004-2009 with "perinatal depression" (Takenouchi et al., 2012). Injuries included hypoxic-ischemic encephalopathy (HIE), intracranial hemorrhage, and focal cerebral infarction. Of interest, 13 of 33 infants studied by Tekenouchi et al. were initially admitted to the well-baby nursery because they were asymptomatic in the delivery room. The authors averred that "... most cases attributable to perinatal brain injury [other than HIE] are not identified according to any perinatal characteristics until the onset of [neonatal] signs, limiting opportunities for prevention" (Takenouchi et al., 2012). They also opined that such injuries antedated the onset of labor. Unfortunately, they did not attempt to correlate the non-HIE injuries with a detailed analysis of either antepartum or intrapartum problems or the condition of the fetus at the outset of labor (Takenouchi et al., 2012).

## The Nomenclature of Injury

The various terms that are applied to the appearance of the newborn and the lesions associated with neonatal encephalopathy and injury have not been consistent (Leviton, 2013, Volpe, 2012). HIE is widely used to refer to neonatal encephalopathy with evidence of hypoxia-ischemia during parturition. The term neonatal encephalopathy is commonly used to describe infants with an encephalopathy of any etiology, but often for those with the clinical and imaging characteristics of neonatal HIE (Volpe, 2012). Other terms, including acute near total asphyxia, partial prolonged asphyxia, birth trauma, birth injury, and perinatal asphyxia, have been used despite considerable variation in how they are defined (Table 1) (Gilbert et al., 2010, Shah and Perlman, 2009). Several years ago, the American College of Obstetricians and Gynecologists recommended that the term "perinatal asphyxia" be eliminated from the obstetrical lexicon (ACOG, 2004). Among the consequences of the confusing and sometimes contradictory descriptors of both the condition of the fetus at birth and the designation of perinatal brain injury is that it is difficult to be certain about both the prevalence and provenance of these illnesses. It stands to reason that we cannot fully understand or improve what we do not classify properly (Kodama et al., 2009). Changing the definition may cause dramatic changes in reporting statistics without changing the number of fetuses actually suffering from the problem (Dzakpasu et al., 2009, Kodama et al., 2009).

Volpe has pointed out that the terms perinatal trauma and birth injury have been given definitions so broad as to be confusing and nearly meaningless, and that the overlap between mechanical trauma and the occurrence of hypoxic-ischemic cerebral injury is important to recognize because perinatal mechanical insults may result in primarily hypoxic-ischemic cerebral injury" (Kodama et al., 2009, Volpe, 2001). Beyond the issues of nosology, there needs to be greater interdisciplinary cooperation in the study of the circumstances in which neonatal encephalopathies develop. Does the diagnosis of HIE, for example, require the presence of certain fetal heart rate patterns and/or a critical level of metabolic acidemia in the umbilical artery or severe signs and symptoms in the newborn? Do the neurological findings of HIE and near-normal umbilical blood gases exclude the events of labor as causative of injury? Does the presence of intracranial or extracranial hemorrhage and/or obvious skull trauma such as fracture, diffuse scalp swelling, marked molding and subgaleal hemorrhage mitigate the diagnosis of HIE irrespective of the umbilical artery pH? Does HIE with low Apgar scores and metabolic acidemia in the umbilical artery exclude mechanical factors? For the most part these and other issues remain unresolved with glaring differences in opinions among experts (ACOG, 2003a, Hayes et al., 2013, Shankaran et al., 2005).

Lee et al., have reminded us that "the clinical diagnosis of birth asphyxia is not specific for any single pathogenetic mechanism of brain injury" (Lee et al., 2005, Schifrin and Ater, 2006). To help clarify these manifold issues of nomenclature, we propose the concept of cranial compression ischemic encephalopathy (CCIE) and discuss below the various mechanical factors that may contribute to intrapartum fetal cerebral ischemia.

## Head Molding

Head molding during labor and delivery refers to changes in the fetal cranial bone relationships that occur in response to the compressive forces of uterine contractions and the

birth canal. Molding may contribute to progress in descent during labor and delivery by enabling the fetal head to accommodate to the geometry of the passage. The change in shape is possible because of the pliability of the bones and the loose connection they have with one another along the suture lines. This allows the cranial plates to override, thereby reducing the intracranial volume.

The response of normal fetal cranial bones to force is variable, and depends on a number of factors, including head position, labor character, gestational age, and pliability of the skull bones (Amiel-Tison et al., 1988). In general, the typical molded newborn head is elongated and cylindrical, reflecting misalignment among the bones of the cranial vault (parietal, frontal, and occipital bones) (Carlan et al., 1991, Sorbe and Dahlgren, 1983). Molding is a dynamic process that normally develops gradually during labor and begins to resolve after compressive forces are removed. The skull generally returns to a normal conformation within hours to days during the neonatal period. (Kriewall et al., 1977). It may not be recognized or described in the medical record and it is rarely quantitatively documented. While some molding is commonplace, "excessive molding" appears to be one of the mechanisms through which the forces of labor have the potential to impart traumatic physical damage to the fetal brain and surrounding tissues. Cranial compression of short duration, however, can produce substantially elevated intracranial pressure and cerebral ischemia without recognized head molding after birth.

Molding increases as labor progresses, especially when progress is slow and contractions are excessive. Overlap of the sagittal suture anticipates cephalopelvic disproportion (CPD) (Buchmann and Libhaber, 2008). The dislocation of the cranial bones can be large - up to 25 mm (Lindgren, 1977). In a study of 56 women with excessive uterine activity and slow progress, 16 (29%) of the infants died, all due to rupture of the tentorium cerebelli (Lindgren, 1977).

Using skull photographs obtained immediately after delivery and at three days of age of 319 vaginally delivered term babies, Sorbe and Dahlgren found that the mechanical forces of labor subjected the fetal head to considerable compression and molding and presumably, shearing forces. The region of the brain most affected and in greatest jeopardy of injury from these mechanical forces was not consistent, but depended upon the orientation of the head as it descended through the pelvis (Sorbe and Dahlgren, 1983). Not surprisingly, infants born after oxytocin stimulation of labor had significantly greater molding than those born after normal labor. Three days postpartum significant differences remained between the molding indices of the two groups. In comparing patients with prolonged labor in association with either "hypertonic" or "hypotonic" uterine contractions, they found that the amount of molding was related not to the duration of labor per se, but to the presence of frequent uterine contractions. Cerebral hemorrhage was 15 times more common as a cause of infant death in hypertonic inertia than in normal labor, and they concluded that intrapartum and neonatal death and injury can occur from mechanical trauma to the brain during birth (Sorbe and Dahlgren, 1983). Other investigations have also found an association between difficulty in labor and distortion of the fetal head (Aarnivala et al., 2014, Frymann, 1966)

Analysis of a non-linear model of the deformation of a complete fetal skull during the first stage of labor found that excessive molding could occur when labor is prolonged, when contractions are too forceful, when there is a malposition of the fetal head, or in association with "inept instrumental interference" (Lapeer and Prager, 2001). Excessive displacements of the skull bones may cause fractures, dural membrane injury, intracranial hypertension,

congestion of the Galenic venous system and direct injury of major intracranial vessels (Lapeer and Prager, 2001). More advanced dilatations were associated with significantly higher head-to-cervix pressures and higher degrees of molding with an increased risk of injury (Govaert et al., 1992b, Lapeer and Prager, 2001, McPherson and Kriewall, 1980a, 1980b).

In a classic article, Roberto Caldeyro-Barcia (1921-1996) underscored the potentially adverse effects of early amniotomy and prolonged rupture of the membranes (Caldeyro-Barcia, 1974). Compared to membrane rupture late in labor, early amniotomy increased the amount of cranial molding which, if exaggerated, may produce cardiac decelerations, lesions in the fetal brain, and subdural hemorrhage, frequently located near the sutures (Caldeyro-Barcia, 1974).

These studies establish a link between excessive cranial molding and intracranial injury during labor. While the definition of "excessive" molding is elusive, it is clearly more likely to occur in the context of abnormal labor progress, high levels of uterine activity and ruptured membranes. Molding of the fetal head deserves more attention as a cause or as a marker for potential mechanical injury and abnormalities of neonatal adaptation (Frymann, 1976, Frymann, 1966).

## Molding and Decreased Venous Return

Neuroradiological studies have shown that, in addition to the inverse relationship between cerebral arterial perfusion and intracranial pressure, there also is decreased venous return related specifically to both the resistance to flow and direct compression of the sagittal sinus (Barkovich, 2000a, Newton and Gooding, 1975, Towbin, 1998). While modest amounts of molding are considered commonplace and benign, such compression may increase cerebral venous pressure and precipitate intracerebral hemorrhage or cerebral venous thrombosis (Barkovich, 2000b, Berfelo et al., 2010, Newton and Gooding, 1975, Takanashi et al., 2003, Towbin, 1998). Hanigan and Tan and colleagues have called attention to the relationship of perinatal sinovenous thrombosis and sagittal sinus compression due to head molding during labor (Hanigan et al., 1985, 1990, Medlock and Hanigan, 1997, Tan et al., 2011).

## Maternal Bearing-Down Efforts

The resilient fetus is usually able to tolerate considerable amounts of even excessive uterine activity in the first stage of labor (Stewart et al., 2012). The effects of contractions on fetal blood pressure, oxygen availability and head molding, are greatly exaggerated later in the first stage of labor and especially during the second stage when expulsive efforts may increase the IUP by an average of 62% and the risk of adverse outcome (Asicioglu et al., 2014, Buhimschi et al., 2002a, 2002b). With the combination of frequent and prolonged uterine contractions with maternal bearing-down efforts, or fundal pressure or vacuum application, intrauterine pressures above 250 mm Hg may be seen, along with a marked reduction in placental and fetal cerebral perfusion (Dupuis and Simon, 2008, Furuya et al., 1981). Undoubtedly, at this pressure, not only has uterine blood flow ceased but fetal cerebral

blood flow has almost certainly ceased as well (Volpe, 2001). The maximum blood pressure response to head compression that the fetus can sustain has not been elucidated.

Considerable debate concerns the methodology, duration and impact of maternal pushing in the second stage of labor (Aldrich et al., 1995, Le Ray and Audibert, 2008, Petersen and Besuner, 1997, Schaal et al., 2008, Simpson, 2006). With coached Valsalva-based, maternal pushing, there may be several closely spaced, exaggerated peaks created by energetic pushing where the IUP may easily exceed, sometimes considerably, 100 mmHg. This dramatically increases the amplitude, duration and pattern of the IUP changes and potentially diminishes the relaxation time for recovery, thus imposing greater demands on the responsiveness of the fetal cardiovascular system (Lindgren, 1977). Alternatively, non-Valsalva pushing strategies with open glottis and slowly developing transient peak pressures not only appear to subject the fetus to less head compression, but also may improve Apgar scores and umbilical pH values at delivery (Yildirim and Beji, 2008).

Near infrared spectroscopy transducers in human subjects reveal a significant decrease in the calculated mean fetal cerebral oxygen saturation during pushing and a significant increase in the mean cerebral blood volume (Aldrich et al., 1995). While moderate pushing may not be detrimental if the fetus is healthy, the associated hemodynamic alterations may have important consequences if fetal oxygenation is already reduced prior to pushing, or if maternal effort is prolonged (Aldrich et al., 1995, Keeling, 1993, Svenningsen and Jensen, 1988).

Thus, during pushing, the pressures exerted on the fetal head are higher and more sustained than in the first stage of labor and the risks of significant ischemia and potential injury appear greatly increased, especially if decelerations are frequent and maternal pushing is relentless and unheeding of the responses of the fetus (Schifrin and Ater, 2006).

## Occiput Posterior Position

The occiput posterior [OP] position is a malposition often associated with FHR decelerations, prolonged labor, especially in the second stage, marked cranial molding, an increased risk of failed instrumental vaginal delivery, cesarean delivery, and oxytocin administration (Porreco et al., 2004). OP is an independent risk factor for subsequent CP and low mental scores in the offspring (Badawi et al., 1998, Senecal et al., 2005) and accounts for a disproportionate share of such injuries. (Ater et al., 2008). To what extent these long-term disabilities are the consequence of excessive or asymmetric forces exerted on a fetal head positioned inappropriately is unknown. Uterine activity with the fetus in OP position, however, appears equivalent to that in OA position (Buhimschi et al., 2003). Manual rotation of the head in the fetus in the OP position to a more favorable position can, in some circumstances, reduce the duration of the second stage and the frequency of operative delivery (Le Ray et al., 2007, Shaffer et al., 2006). The impact of successful rotation on the risk of fetal injury is unknown (Govaert et al., 1992c, Gurbuz et al., 2006, O'Grady et al., 2000, Pollina et al., 2001, Towner et al., 1999)

## Operative Vaginal Delivery

Operative vaginal delivery is a risk factor for mechanical, traumatic, and ischemic injury to the scalp and brain, including subgaleal hemorrhage (Govaert et al., 1992c, O'Grady et al., 2000). The risks increase if sequential instruments are used (Al-Kadri et al., 2003). While elective cesarean section appears to decrease the risk of neurological harm to the fetus, cesarean sections after the onset of labor, especially during the 2nd stage, appear to have higher risk of adverse outcome than does elective cesarean section (Asicioglu et al., 2014). Thus, a cesarean section performed too late in labor cannot be expected to prevent injury (Gurbuz et al., 2006, Towner et al., 1999). The ability to define the timing of injury and its antecedents are of crucial importance for determining both the timing of intervention and the institution of neuroprotective measures (Schifrin and Ater, 2006). More attention needs to be given to the circumstances of labor and the fetal condition prior to the application of vacuum or forceps.

## Excessive Uterine Activity

Several quantitative formulations for representing normal and excessive uterine activity have been proposed (Henry et al., 1979). This broad range of options has led inescapably to marked variations in practice patterns and nomenclature. Moreover, irrespective of the definition used, excessive uterine activity is often simply unrecognized or ignored (Kunz et al., 2013, Murray and Huelsmann, 2008). This is not surprising, in that the assessment of contractility is not simple, and, importantly, the relationship between contractility and progress in labor is not well understood; it is certainly not linear, as is commonly thought.

Tachysystole defined as a frequency of greater than 5 contractions in 10 minutes, averaged over 30 minutes, has been introduced as a simplistic measure of "excessive uterine activity" despite the acknowledgement that other parameters such as duration, rest interval between contractions and uterine tone may be important (Macones et al., 2008). Because the adverse effects of increased uterine activity on uterine and cerebral blood flows are proportional to the frequency, amplitude and duration of contractions, contraction frequency by itself seems an insufficient measure of the fetal effects of contractions. With a contraction frequency of 5 per 10 minutes with an average contraction duration of 60 seconds, the cumulative rest time is 5 minutes or 50%. If the average duration is 90 or 120 seconds, then the cumulative percentage rest times are 25% and 0% respectively. The latter would be unsustainable for the fetus. In addition, it is clear that the effects on fetal oxygenation of an excessive frequency of contractions appear long before 30 minutes have elapsed, especially in the second stage, and that optimal "rest time", requires at least 2 minutes between contractions, at least when decelerations are present. (Peebles et al., 1994, Simpson and James, 2008, Westgate et al., 1999, 2007). An elevated baseline tone associated with placental abruption is also a risk factor for adverse fetal outcome (Odendaal and Burchell, 1985). External monitors, however, do not permit assessment of intrauterine pressures or baseline uterine tone.

Our understanding of the role of excessive uterine activity in intrapartum fetal brain injury is based on the flawed notion, detailed above, that the only potential adversity caused by contractions, excessive or not, is hypoxemia. In recent decades, only scant attention has

been turned to the effects of the mechanical forces of labor and delivery on intracranial pressure, cerebral blood flow, fetal adaptive mechanisms, fetal head molding and descent. The prevailing monolithic view is that, as long as the FHR pattern does not show ominous, presumably hypoxemic, changes, contractile force cannot be "excessive" (ACOG, 2003b). Such an approach gives misguided acceptability to the notion that in an augmented labor it is permissible to increase oxytocin dose until the fetus manifests abnormal FHR patterns (Simpson and Knox, 2009, Tillett, 2011). During efforts to expedite delivery, this approach contributes to the dubious practice of encouraging aggressive maternal pushing to facilitate vaginal delivery in response to concerning FHR abnormalities in the second stage of labor. These attitudes account in part for the high prevalence of excessive uterine activity, the variability in response to its appearance depending on the presence or severity of associated FHR patterns, and in the widespread allegations of oxytocin abuse in medical and legal circles involving adverse neonatal outcomes (Berglund et al., 2008, Clark et al., 2009, Doyle et al., 2011, Simpson and James, 2008, Simpson and Knox, 2009).

In 1597 induced labors, Kunz et al. identified 661 instances of tachysystole (41%.). Fifty-four of 55 patients (98%) demonstrated one or more occurrences. More pertinently, we believe, they also found a diminished relaxation time (< 60 seconds rest between contractions) in 98% of women who received oxytocin for induction of labor (Kunz et al., 2013). Indeed, diminished relaxation time was nearly three times more sensitive for recognition of excessive uterine activity than was contraction frequency.

Inadequate relaxation time often accompanies tachysystole. It is strongly related to the adequacy of perfusion of the fetal brain between contractions. Bakker, et al. reported that reduced relaxation time between contractions was significantly correlated with fetal acidosis (umbilical artery pH <7.12), while contraction frequency greater than 5 per 10 minute period was not a sensitive measure for predicting acidosis (Bakker et al., 2007a). Uterine rest of more than 1 minute between moderate to strong contractions appears necessary to allow sufficient time for reperfusion and adequate oxygen delivery to the fetus (Bakker et al., 2007b, Johnson et al., 1994, McNamara and Johnson, 1995, Peebles et al., 1994, Simpson and James, 2008). These data affirm a positive relation between the patterns of uterine contractions and decreases in human fetal cerebral oxygen saturation, and suggest that contractions (of normal duration) should occur no more frequently than every 2 to 2.5 minutes. With shorter intervals, fetal cerebral oxygen saturation is likely to fall (Peebles et al., 1994).

Table 3 presents criteria for normal and excessive uterine activity using parameters readily discernable on the contraction monitor during labor. However defined, excessive uterine activity clearly is associated with diminished oxygenation of fetal blood and decreased umbilical artery pH at the time of delivery, abnormal FHR patterns, and even neonatal encephalopathy (Bakker and van Geijn, 2008, Bakker et al., 2007a, Graham, 2007, Hamilton et al., 2012, Hayes et al., 2013, Heuser et al., 2013, Simpson and James, 2008, Simpson and Knox, 2000, 2009). Of note, excessive uterine activity does not necessarily beget more rapid progress in the active phase of labor (Allman and Steer, 1993, Cohen et al., 1987, Ingemarsson et al., 1980, Steer, 1993). Indeed, there appears to be no relationship between the rate of progress after an arrest of labor and the frequency of oxytocin-induced contractions (Bidgood and Steer, 1987a, 1987b). Oppenheimer et al. have shown that optimal progress in labor is related to evenly spaced contractions of similar amplitude and duration rather than to their frequency (Oppenheimer et al., 2002).

## Fetal Heart Rate Patterns

While there is agreement that FHR monitoring has revolutionized our understanding of fetal cardiovascular responses to hypoxia during labor and reliably anticipates fetal acidemia (Spong, 2008, Steer, 2008), it has also been deemed to be of little value over auscultation of the FHR and to neither predict fetal neurological injury nor to improve perinatal outcome (Alfirevic et al., 2006, Costantine and Saade, 2012, Graham et al., 2008, MacDonald et al., 1985, MacLennan et al., 2005, Spong, 2008). Realizing the benefits of EFM is highly dependent on accurate interpretation of these patterns. International guidelines for its use have not been consistent in their recommendations and interpretation has been shown to be of a low standard in both clinical practice and in allegations of malpractice (Berglund et al., 2008, Hill et al., 2012, Steer, 2008).

Numerous studies have explored the neuroradiological findings in infants with presumed HIE, but any study of their correlation with obstetrical events is severely limited. For example, we have no comprehensive understanding of the relations among FHR patterns, uterine activity patterns, the course of labor and delivery, neonatal clinical presentation, serial neuroradiological findings and long-term neurological outcome. Various studies relating FHR patterns to early outcome may involve only the last few minutes of labor, but irrespective of the duration of sampling they frequently fail to document the timing of injury (if any) and whether on admission to labor the fetus was normal (Cahill et al., 2012, Graham et al., 2006, Spencer et al., 1997).

Controlled studies of excessive uterine activity have shown an increased risk of abnormal FHR tracings, fetal acidosis and low Apgar score, but have no long-term follow-up (Bakker et al., 2007a, Jackson et al., 2011). Studies of neonatal encephalopathy identified a high incidence of abnormal FHR patterns, but generally have not commented on the presence of specific FHR patterns or of excessive uterine activity. In various studies, abnormal FHR patterns including fetal tachycardia were commonplace in babies with encephalopathy (Hayes et al., 2013, Kazandi et al., 2003, Kodama et al., 2009, Murray et al., 2009, Phelan and Ahn, 1998). The majority of infants in these studies had low, but not severely depressed Apgar scores and only a minority of patients had low umbilical cord blood pH values. Further, abnormal heart rate patterns persisted for over 1 hour in about half the patients with neonatal encephalopathy and over 2 hours in one third (Murray et al., 2009). A preliminary study of a group of neonates who suffered neurological injury during labor in association with prolonged excessive uterine activity [>2 hours] and other mechanical factors showed significant evidence of cranial trauma [marked molding, bruising, etc.] at birth (Ater et al., 2008), On neuroradiological examination they showed diverse, supratentorial white matter lesions [both focal and non-focal] compatible with ischemia. Basal ganglia and thalamic injury were uncommon. Forty-six percent had intracranial hemorrhage. The majority of the newborns displayed neither umbilical artery acidemia nor other systemic evidence of intrapartum asphyxia. Invariably, FHR patterns were abnormal, but other than the conversion pattern (see below) in about half of these infants, the abnormalities were diverse.

These data are all consistent with the hypothesis that intrapartum brain injury and consequent neonatal encephalopathy can develop in association with abnormal FHR patterns, but without severe asphyxia or fetal acidosis. The ischemic and hemorrhagic injuries appearing during labor in such cases are likely the consequence of brain ischemia produced by mechanical compression or deformation of the head, and not primarily by systemic fetal

hypoxia or asphyxia (Ater et al., 2008). It becomes understandable that contemporary techniques of fetal surveillance including conventional electronic FHR monitoring, even abetted by detailed analysis of FECG complexes for asphyxia (STAN monitor), fetal pulse oximetry, and fetal blood gas analysis are unlikely to be helpful in this regard (Bloom et al., 2006, Dokus et al., 2013, Schifrin, 2003). Indeed, in one study, withdrawal of the STAN monitor was associated with an improvement in umbilical blood gases although the cesarean section rate increased (Dokus et al., 2013).

**Table 3. Uterine Activity Parameters**

| Parameter | Normal Range | Excessive (a) |
|---|---|---|
| Contraction Frequency | 2 – 4.5 / 10 min. | >5/10 min. (b) |
| Contraction Intensity [Amplitude] | 25 – 75 mmHg | Not defined |
| Contraction Duration | 60 – 90 sec. | >90 sec. |
| Resting Tone (IUPC) | 15 – 20 mmHg | >25 mmHg |
| Interval [peak-peak] | >2 – 4 min. | >2min |
| Interval [end-beginning] | 1 -2 min | < 1 min |
| Rest time (Duty cycle) (c) | <= 50 % | > 50% |
| Montevideo Units (Average amplitude above baseline x frequency / 10 minutes) | 200-250 MVU | >300 MVU |

(a) Must persist, alone or in combination, continuously for at least 20 minutes
(b) Called "tachysystole" (>5 contractions / 10 minutes - averaged over 30 minutes)
(c) The percentage of time that the uterus is at rest (not contracting).
IUPC = intrauterine pressure catheter

The contemporary classification of fetal heart rate identifies categories (I, II, III) of tracings according to their likelihood of associated fetal acidemia (Macones et al., 2008). Though the severity of acidemia increases with increasing severity of the patterns, they are in fact, poor predictors of either fetal acidemia or of subsequent cerebral palsy (Cahill et al., 2012, Dennis et al., 1989, Dijxhoorn et al., 1985, 1986, 1987, Ruth and Raivio, 1988, Schwarcz et al., 1969). Data from neonatal cooling studies strongly suggest that no single quantitative value of fetal arterial pH serves to define a point of hypoxia-induced damage applicable to all fetuses (Clark et al., 2013, Shankaran et al., 2005).

The current system of intrapartum fetal surveillance predicated on rapid intervention in the presence of acidemia or an acute clinical event is unlikely to diminish the risk of neurological injury. It has, however, reduced dramatically the risk of intrapartum fetal death attributable to intrapartum hypoxia at the same time increasing the cesarean section rate (Steer, 2009, Walsh et al., 2008). To obtain greater clinical benefit from EFM, it will be necessary to modify the precepts of EFM by using FHR and uterine contraction patterns not only for the detection of hypoxia (where it has high sensitivity, but low specificity) , but also to estimate directly whether or not the fetus is at risk of cranial compression ischemia or has already suffered neurological harm irrespective of its pH (Schifrin and Ater, 2006, Tranquilli et al., 2013).

Abundant data support the idea that, properly interpreted, FHR patterns are better predictors of neurological injury than is umbilical acidemia (Clapp et al., 1988, Dijxhoorn et

al., 1985, 1986, 1987). Experimental evidence from Ikeda et al., bears directly on this issue (Ikeda et al., 1998a, 1998b). In a study of fetal lambs severely asphyxiated by prolonged cord compression, they found that the severity of subsequent neurological injury was not related to the duration of the bradycardia or the severity of the drop in pH or base excess, but rather to the duration of the hypotension (with its potential for ischemia) and to the abnormal fetal heart rate pattern after the recovery from the deceleration. The latter is analogous to a pattern observed in human fetuses, which we have called the "conversion pattern" (Schifrin and Ater, 2006). The term refers to a sudden evolution of the behaviorally normal fetus with absent hypoxia to one with a pattern of absent variability and tachycardia (Asakura et al., 1994, Bennet et al., 2005, Clark et al., 2013, Schifrin and Ater, 2006, Shields and Schifrin, 1988).

Finally, authors have found abnormal FHR patterns, but absent acidemia, associated with oxytocin use, fetuses laboring in the OP position, and with intrauterine bacterial infection and subsequent CP (Porreco et al., 2004). Miller and Hankins and their colleagues have proposed that elective cesarean section offers significant benefits for the reduction of CP – a benefit of avoiding the rigors of labor –especially the 2nd stage of labor (Asicioglu et al., 2014, Hankins et al., 2006, Ingemarsson et al., 1980, Miller and Ferriero, 2013).

It is tempting to believe that above a certain ICP or compromise of fetal CBF decelerations occur, but the available evidence for such a pathognomonic sequence is conflicting and the reliability of FHR monitoring for detecting pathologic impairment of CBF is uncertain as are the parallels to be drawn from animal experiments. In the experiments with intracranial pressure catheters inserted into hydrocephalic fetuses (Figure 4), Mocsary et al. found recurrent decelerations with significant elevations of ICP. In some of these, the recovery of the deceleration was delayed beyond the end of the contraction (late deceleration). When the ICP was elevated significantly the fetus exhibited a sustained bradycardia that recovered to baseline only after the pressure was relieved (Mocsary et al., 1970). Caldeyro-Barcia and colleagues called attention to the high prevalence of early decelerations in patients with early rupture of the membranes and exaggerated molding, and to the appearance of these decelerations with high uterine pressures or pressure on the fetal skull (Figure 5) (Amiel-Tison et al., 1988, Caldeyro-Barcia, 1974, Schwarcz et al., 1969). In the study of Ueno cited above a high resistance index of the middle cerebral artery was negatively correlated with FHR. (Ueno, 1992). Early decelerations appeared in 67% of the cases with absent end-diastolic flow velocity, and in 100% of cases with reversed diastolic flow even in fetuses with normal outcomes. Nor are such decelerations present at modest elevations of pressure despite activation of the Cushing response (Harris et al., 1989, 1992). In the experiments of Mann and colleagues, the heart rate decreased in eleven experiments increased in twelve and remained unchanged in seven (Mann et al., 1972). There is also compelling evidence that head (or ocular) compression may cause variable decelerations, especially in the second stage of labor (Sholapurkar, 2012). It seems necessary to revise the concept that early decelerations are invariably benign or that variable decelerations only indicate umbilical cord compression and may be tolerated indefinitely (Amiel-Tison et al., 1988, Sholapurkar, 2012). Ultimately, even late decelerations, thought to represent fetal hypoxia, may represent delayed recovery from elevated intracranial pressure (Mocsary et al., 1970).

The objective of surveillance, therefore, must go beyond the search for hypoxia and take advantage of both the FHR and uterine contraction patterns and the factors related to progress in labor to minimize the frequency and duration of those factors that reveal or

suggest a potential adverse impact on the cerebral circulation – irrespective of their effect on fetal pH or fetal heart rate patterns. The absence of decelerations makes highly improbable the presence of significant hypoxia and acidemia, but does not eliminate the potential for excessive mechanical forces acting on the brain and diminishing cerebral blood flow.

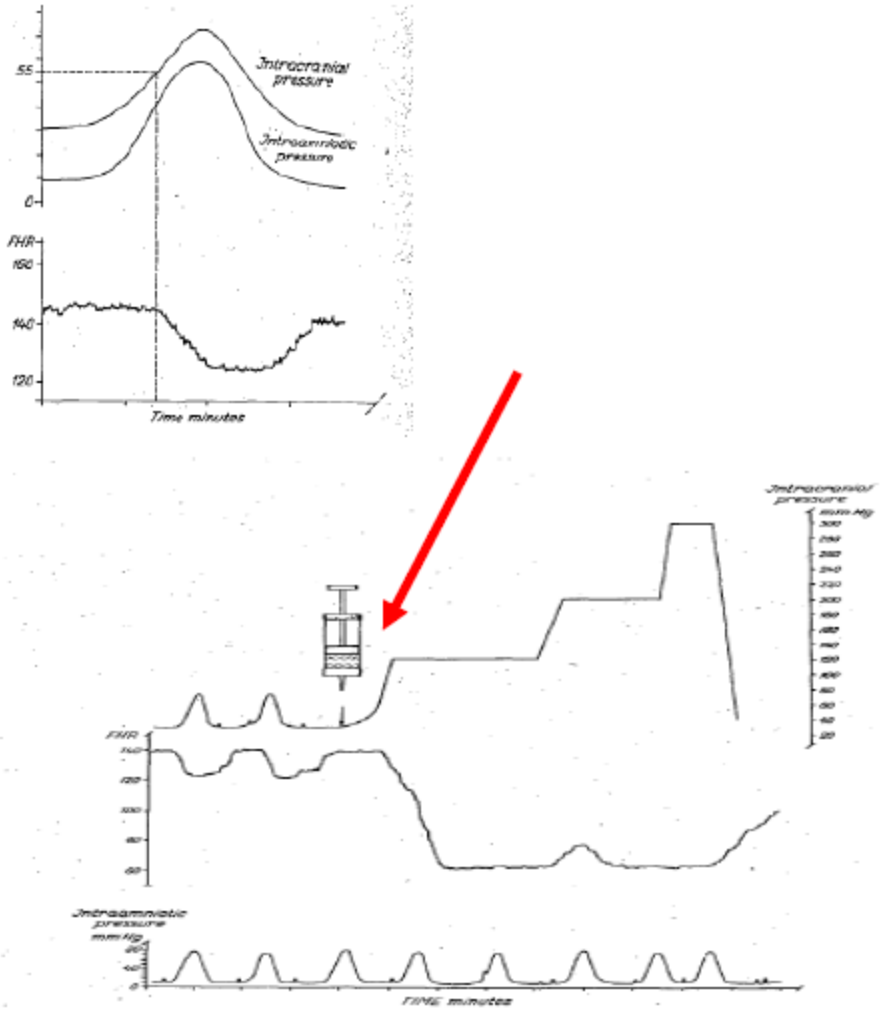


Figure 4. Relationship of fetal heart rate changes to spontaneous contractions and artificial increases in intracranial pressure (at arrow). Notice the appearance of fetal cardiac decelerations (beginning somewhat later in the contraction cycle - inset) and the appearance of prolonged decelerations when the intracranial pressure is artificially increased above 100 mmHg. Release of the pressure is accompanied by the return of the fetal heart rate (Mocsary et al., 1970).

FHR patterns do not represent the totality of intrapartum care, which must include a detailed evaluation of the course of labor and the position, molding and descent of the head, among other factors. Accordingly, efforts to reduce the risk of intrapartum injury to the fetus will require more appropriate recognition of the risks, proper classification of the role of mechanical factors [CCIE] and more suitable evaluation of the obstetrical antecedents of those identified as injured. Extensive evidence supports the concept that excessive fetal head compression during labor and delivery can result in reduced brain blood flow and consequent ischemic brain injury, even in the absence of superficial trauma, hemorrhage or acidemia (Clark et al., 2009, Geirsson, 1988, Govaert et al., 1992c, Keeling, 1981, Volpe, 2008, Welch and Strand, 1986). In the presence of hypoxia and hypotension from other causes excess head compression can further diminish cerebral perfusion and increase the risk of injury.

## Toward Reducing the Risk of Mechanical Injury

Evidence for the potential of head compression to cause injury is both clinical and experimental. Its significance has been overlooked, however, due in largest part to the widespread assumption that neonatal ischemic injuries are asphyxial, not mechanical, in origin. By consequence, there has been a dearth of research in this area (ACOG, 2003a, Volpe, 2012).

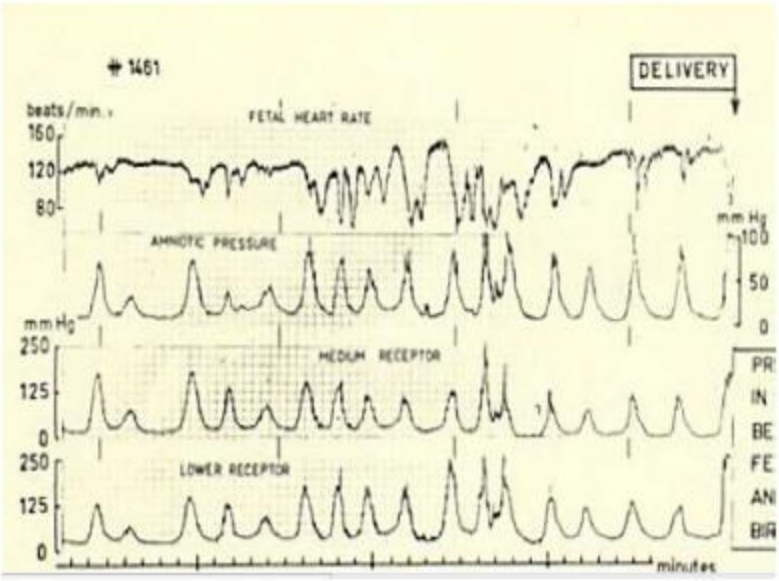


Figure 5. Relationship of intraamniotic pressure and external forces on the fetal head as measured by sensors between the fetal head and the birth canal and the response of the fetal heart rate. Notice that pressures exerted on the head during a contraction are consistently greater than the intrauterine pressure. Note also the association of decelerations with increasing pressures as the head approaches delivery (Schwarcz et al., 1969).

Many, probably most, newborns diagnosed with ischemic encephalopathy (absent an acute event) were not exposed to severe global asphyxia in utero. Their brain ischemia more likely represents a contribution of the effects of mechanical trauma in addition to the various pharmacological, infectious, hypoxemic factors during labor. Trauma could be caused by excessive uterine activity abetted by neglected dysfunctional labor in the presence of cephalopelvic disproportion, malposition, prolonged rupture of the membranes, molding of the fetal head, operative vaginal delivery or excessive maternal pushing in the second stage of labor. The overall contribution of these forces to ischemic brain injury during labor is difficult to establish, in no small measure because in modern obstetrics necessary details about these various factors are often unmeasured, unrecorded and not considered. To isolate the contribution of mechanical factors it will be necessary for epidemiologic studies to adjust for the role of potentially mitigating factors, including any prenatal, genetic, or hypoxemic contributors to injury. If inferences about the cause of the brain injury are to be accurate, studies of newborns with encephalopathy need to incorporate detailed obstetric data, including estimates of neurological integrity at the outset of labor and uterine activity measures. In so doing we will better understand the concept of CCIE and its contribution to neonatal morbidity. Injury related to CCIE may be far more common than generally appreciated.

With these historical perspectives and evolving pathophysiological concepts in mind we offer the following principles of fetal surveillance during labor. Assuming the well-being of the mother, the program is dependent upon a thoughtful analysis of the FHR pattern, the uterine activity pattern, and the course of labor.

Avoiding the need to rescue the fetus from serious adversity is a priority. Delivering a fetus under emergency circumstances, regardless of the outcome, is not a goal to which we should aspire. Emergency deliveries disrupt care of other patients and are more likely to beget complications in fetus and mother (Tolcher et al., 2014).

The avoidance of hypoxic, ischemic, and mechanical stresses is best realized by:

- The scrupulous avoidance of excessive uterine activity under any circumstances. (The definition of "excessive" must include the frequency duration and rest time between contractions or between expulsive efforts). A normal fetal heart rate tracing should never be considered reassuring if uterine activity is excessive - especially in late labor.
- With decelerations in the fetal heart rate, the fetus should be allowed to recover to its previously normal (and stable) baseline rate and variability if possible, before oxytocin or pushing is resumed. Failure to recover as defined requires the further application of conservative measures (cessation of pushing, lateral positioning, maternal oxygenation) and consideration of intervention as dictated by the expected course of labor (Clark et al., 2013).
- Close attention to the course of cervical dilatation and descent with prompt recognition and response to dysfunctional labor patterns. Decisions to use oxytocin should incorporate information about cephalopelvic relations (including pelvic architecture, station molding, position, attitude) as well as the FHR and contraction patterns.
- In the second stage of labor, maternal expulsive efforts are conducted only with, not between, contractions. If contractions are close together or decelerations are present,

encourage pushing only with every other or every third contraction, especially if epidural anesthesia is in place. Encourage pushing using the open glottis technique.

## Conclusion– Perspective

Fetal neurological injury during labor may derive from pharmacological, infectious, and hypoxemic factors and from mechanical trauma. Elucidating their individual contributions is difficult because of limited intrapartum and follow up data and a current perspective of injury slanted almost exclusively to identifying severe fetal hypoxia.

Mechanical forces resulting in fetal craniocerebral vascular insufficiency during labor may result in ischemic cerebral injury in the absence of obvious superficial trauma, hemorrhage or acidemia (Clark et al., 2009, Geirsson, 1988, Govaert et al., 1992a, Keeling, 1981, Volpe, 2001, Welch and Strand, 1986). In the presence of pre-existing hypoxia and/or hypotension, contractions, especially with pushing, can further diminish cerebral perfusion. Mechanical forces in the form of cranio-cerebral compression are an overlooked mechanism of injury. To isolate the contribution of mechanical factors it will be necessary to eliminate or minimize the role of potentially mitigating factors, including any prenatal, genetic, or hypoxemic cause of injury and perhaps, with newfound understanding, identify it specifically. We propose the concept of cranial compression ischemic encephalopathy (CCIE). Injury related to CCIE, may indeed be the more important link to intrapartum ischemic injury and its prevention than is the detection of hypoxia. The objective of enlightened obstetrical care is to avoid these adverse consequences. We must learn more about the ability of the fetal skull to protect the fetal brain.

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