Birth Trauma & Ischemic Stroke

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A wise man believes only in lies, trusts only in the absurd, and learns to expect the unexpected.
-- *Tales of the Unexpected* (British TV Anthology, c.1970s)

I. Introduction

One of many frequently-denied, heavily-defended, but undeniable complications of birth trauma is perinatal stroke. The incidence of perinatal stroke is increasing, and some common risk factors that are shared with HIE, such as prolonged inductions, prolonged second stages, malpositioning of the fetus, increased use and misuse of Pitocin, excessive uterine activity, alterations in the accepted labor curve, and the use or misuse of operative techniques like forceps and vacuum extraction probably play a role in that increase.

Perinatal stroke has been broadly defined as "an acute neurologic syndrome with chronic sequalae due to cerebral injury of vascular origin occurring between 20 weeks gestation and 28 days postnatal life."[1] Definitions are important. Strokes fall into several categories: arterial or venous, hemorrhagic, and ischemic. Hemorrhagic strokes occur when the vessel loses its integrity and bleeding occurs outside the vessel. Ischemic strokes happen when there is an interruption or reduction of the flow of oxygenated blood supply, oxygen, and other nutrients to an area of tissue below some critical level at which infarction occurs. Thus, the point at which infarction occurs is a matter of both degree and duration – that is, first, how much oxygen was in the blood before and at the time of infarct and at what rate it was it flowing, and, second, how long the reduction or interruption of flow lasted to push the metabolism past the critical level for infarction. To analyze these two factors, there are a couple of issues that require consideration: 1) the level of oxygen in the blood to begin with or, rather, the degree of hypoxia (hypoxia alone can cause or contribute to a stroke); and 2) the flow before and at the time of infarct.

In the human body, blood flow can be reduced or interrupted due to a number of factors. Simplistically, think of the artery as a hose. In a hose, flow can be interrupted in a number of ways:

a) the source can be turned down or off (reduction in cardiac output);
b) the hose can be kinked or blocked (vasospasm);
c) the outflow can be blocked or stopped up (cerebral venous return blocked) Note that the venous return is usually more susceptible to pressure causing reduction because of its makeup – lacking musculature in the vessels – and its location); or
d) the hose can be clogged (clot or embolus) Note that many things can trigger the clotting cascade in humans: interruption of the inflow of oxygenated blood (i.e., hypoxia), stasis, eddy currents, a tear in the intimal lining of a vessel either at the site of the infarct or upstream from

[1] Volpe, JJ. Neurology of the Newborn, 6th Edition (2018) at 564.

it, often in the carotids or, from a biologic plausibility standpoint, even from the placenta.

In the fetus particularly, it is important to consider the flow dynamics of fetal cerebral circulation where neither the metabolic needs nor the perfusion pressures are the same in all parts of the normal healthy fetal brain. In other words, there is marked variability in perfusion pressure and metabolic need in different parts of the fetal brain.

In a normal labor, the fetal head, once settled in the pelvis and after membranes are ruptured, is susceptible to decreases in blood flow due to increased intracranial pressure. Mother nature, however, has put in place significant safety mechanisms to protect the skull from the various pressures brought to bear on the head during labor and delivery. First, there is the relatively brief time at the peak of the contraction and in properly conducted labor there is sufficient time at rest between contractions to allow the reestablishment of cerebral (and uterine) blood flow. The most important compensatory response, however, is that of the fetal blood pressure which rises *pari passu* with the contraction to maintain blood flow in the face of the increased intracranial pressure. Normally, this is all that is required and explains the safety of normally conducted labor. Should this pressor response be threatened, e.g., by too frequent contractions and excessive pushing, additional resources to protect cerebral blood flow are mobilized. These include the Cushing response, autoregulation and diminution of metabolic demands of the brain, and, to some extent, a reduction in the amount of cortical cerebrospinal fluid. When these compensations prove insufficient, the fetus may compensate by diverting blood away from higher centers of the brain and preferentially perfusing the brainstem and those centers necessary for survival. These safety mechanisms, like all safety mechanisms, can be overcome. Once they fail, the risk of ischemic injury to the fetal brain increases tremendously.

As indicated, definitions are important. Defendants will invariably claim that a cerebral stroke (typically in the Middle Cerebral Artery or MCA) is, by definition, caused by a clot. They will further claim that such a clot must have come from the placenta or either from the placenta or the heart. They will adamantly claim that obstetrical factors could not cause injury to the fetal brain and that, even if they could, it would result in a global injury and not in a discrete focal injury such as a stroke. Inevitably, defendants will file *Daubert* and other motions to disqualify legitimate experts from providing a science-based explanation for what happened to your client. Therefore, a thorough understanding of the biology of what happens to the fetal brain during labor is imperative when prosecuting your claim.

In this paper, we will discuss the various definitions of stroke that have been used, the incidence, and outcomes from this injury. We will then discuss hypoxia and trauma (compression) as factors causing or contributing to cerebral strokes.

II. Definitions

A. Perinatal Stroke, Generally

Perinatal Stroke is generally categorized into three types: arterial ischemic stroke, cerebral venous thrombosis, and primary intracerebral hemorrhage. It is considered a common cause of acute neonatal encephalopathy, with arterial ischemic stroke subtype being the most common (80% versus 20% for hemorrhagic or cerebral sinovenous thrombosis).[2]

B. Perinatal Ischemic Stroke

Perinatal ischemic stroke has also been defined as a "sudden, focal infarction of brain tissue on neuroimaging or autopsy".[3] At a perinatal stroke workshop conducted by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke, perinatal ischemic stroke was defined as "group of heterogenous conditions in which there is a focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolization, between 20 weeks of fetal life through twenty-eighth postnatal day confirmed by neuroimaging or neuropathologic studies."[4] It should be noted that such "strokes" are often bilateral and associated with other forms of hypoxic ischemic encephalopathy even though the term "stroke" often connotes a single lesion.

Perinatal ischemic strokes are further classified based on the timing of the injury, the clinical presentation, and the blood vessel affected into one of the following syndromes: 1) Symptomatic neonatal arterial ischemic stroke; 2) Symptomatic neonatal cerebral sinovenous thrombosis; 3) Presumed perinatal ischemic stroke; and 4) Periventricular venous

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[2] *Id.*

[3] Swaiman, Kenneth F. Swaiman's Pediatric Neurology: Principles and Practice. Edinburgh: Elsevier Saunders, 2018.

[4] Raju TN, Nelson KB, Ferriero D, Lynch JK. Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurologic Disorders and Stroke. NICHD-NINDS Perinatal Stroke Workshop Participants. Pediatrics 2007;120:609-16.

infarction.[5] Of these, perinatal arterial ischemic strokes are the most common, accounting for 80% of strokes being reported, and are the most frequently studied.

1) Symptomatic neonatal arterial ischemic stroke;

Neonatal arterial ischemic stroke (NAIS) present clinically in the neonatal period, usually with seizures, and can be defined by either "documented partial or complete occlusion of the vessel in relation to a focal brain lesion" or "documented lesion pattern with imaging that can only be explained by occlusion of a specific brain vessel."[6]

2) Symptomatic neonatal cerebral sinovenous thrombosis;

Neonatal cerebral sinovenous thrombosis (CSVT) has been defined "as the presence of a thrombus in a cranial venous sinus, a large deep brain vein or a smaller cortical or deep vein, with partial or complete occlusion."[7]

3) Presumed perinatal ischemic stroke;

Presumed perinatal ischemic stroke (PPIS) is diagnosed when an infant or young child "presents clinically with evidence from any imaging technique suggestive of long-standing stroke without previous fetal or neonatal clinical symptoms."[8]

4) Periventricular venous infarction.

Periventricular venous infarction (PVI) is part of the spectrum of germinal matrix and intraventricular hemorrhage, thought to be caused by obstruction of the medullary and terminal veins by the associated intraventricular hemorrhage.[9]

III. Incidence

In the NEACP in 2003, ACOG reported a 1-in-4,000 incidence of cerebral infarction with more than 50% of those infants developing CP, most commonly of the hemiplegic type. However, more recently, it has been noted that the highest risk of stroke occurs in the perinatal periods, affecting 1 in every 1,600 to 4,000 births.[1] In 2014, ACOG reported the incidence of symptomatic neonatal arterial ischemic stroke as 1 in 3,000 and "likely underestimated".[10] Also, incidence rates of 1.3 to 1.8 per 100,000 children have been reported for childhood arterial ischemic stroke.[11] Mackay postulated that "[i]ncreasing incidence rates reflect more sensitive diagnostic tests, particularly magnetic resonance imaging and increased survival in previously lethal pediatric diseases predisposing to stroke, such as congenital heart disease, sickle cell disease, and childhood malignancies."[12] As discussed below, prolonged inductions, prolonged second stages, malpositioning of the fetus, increased use and misuse of Pitocin, excessive uterine activity, alterations in the accepted labor curve, and the use or misuse of operative techniques like forceps and vacuum extraction probably play a role in the increasing incidence. These risk factors are shared with HIE.

IV. Outcomes

Perinatal strokes of all types can cause cerebral palsy, especially hemiplegic cerebral palsy, and other life-long motor function disabilities, as well as vision impairment, cognitive impairment, speech and language disabilities, developmental delays, behavioral issues, and seizures. The severity of injury and resulting level of disability varies widely.[2, 13] Childhood strokes overall are among the top ten causes of death in children, with a reported mortality of 5% to 10%.[5]

Term neonates with perinatal arterial ischemic stroke usually present with seizures after having been considered healthy at birth with normal APGAR and cord PH values.[14] A significant majority of children suffering perinatal arterial ischemic stroke will suffer long-term sequelae, often in the form of motor disability or cerebral palsy, cognitive impairment,

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[5] *Id.*

[6] Govaert P, Ramenghi L, Taal R, de Vries L, Deverber G. Diagnosis of perinatal stroke I: definitions, differential diagnosis and registration. Acta Paediatr. 2009:98(19):1556.

[7] *Id.*

[8] *Id.*

[9] Ichord, R. Stroke in the newborn: Classification, manifestations, and diagnosis. UpToDate, 2017.

[10] American College of Obstetricians and Gynecologists, American Academy of Pediatrics. Neonatal encephalopathy and neurologic outcome, Second Edition. American College of Obstetricians and Gynecologists, 2014.

[11] M. Mackay, et al., Arterial ischemic stroke risk factors: the International Pediatric Stroke Study. Ann. Neurol. 69, 130-140.

[12] *Id.*

[13] Ichord, R. Stroke in the newborn: Management and prognosis. UpToDate, 2017.

[14] Dudink J, Mercuri E, Al-Nakib L, et al. Evolution of unilateral perinatal arterial ischemic stroke on conventional and diffusion-weighted MR imaging. AJNR Am J Neuroradiol. 2009;30(5):998–1004 citing Sreenan C, Bhargava R, Robertson CM. Cerebral infarction in the term newborn: clinical presentation and long-term outcome. *J Pediatr* 2000;137:351–55 and Mercuri E, Rutherford M, Cowan F, et al. Early prognostic indicators of outcome in infants with neonatal cerebral infarction: a clinical, electroencephalogram, and magnetic resonance imaging study. *Pediatrics* 1999;103:39–46.

developmental disability or behavioral or emotional problems. Only 19% to 41% of infants suffering perinatal ischemic stroke recover to "normal" development.[15] In one study, 46 children with perinatal ischemic stroke were followed for up to 164 months, and only 33% were found to be neurodevelopmentally normal.[16] Of the 67% of children with neurodevelopmental abnormalities, cerebral palsy occurred in 71%, and cognitive impairment occurred in 61%.[17] Another study followed 36 patients for 12 months and showed abnormal outcomes in 81%, including cerebral palsy in 58%, epilepsy in 39%, language delay in 25% and behavioral abnormalities in 22%.[18]

Perinatal ischemic stroke commonly results in motor disability, usually with hemiparesis, especially when the stroke involves the entirety of the "vascular territory of the middle cerebral artery." It accounts for up to 30% of hemiplegic cerebral palsy cases in term births.[19] Cognitive impairment is seen in up to 25% of children with unilateral perinatal arterial stroke present. The risk of poor cognitive outcome is increased with bilateral involvement.[20] Furthermore, there are studies that indicate that cognitive deficits from stroke increase with time. One such study showed no intellectual deficits from published norms on tested preschool age children, but statistically significant deficits in nonverbal reasoning, working memory, and processing speed on those same children when tested at school age.[21] As to behavioral disability, one study seems to indicate that survivors of unilateral stroke showed no clinically significant increase in behavioral or emotional problems.[22] Another significant injury from perinatal ischemic stroke is epilepsy, which has been shown in 10% to 40% of children presenting with acute stroke and 19% to 67% percent of children with delayed presentation and infant hemiplegia.[23]

V. Etiology – Hypoxia and Trauma

Neonatal arterial ischemic stroke (NAIS) can be caused by embolism from distant sites or by situ thrombus formation. Vessels are occluded in all these lesion types. This occlusion can be due to thrombosis or embolism. Occlusion can, however, also be caused by hypoxia, direct trauma, compression, spasm, or obliteration by an inflammatory response.[8,24] Here, we will focus on hypoxia and trauma.

First, we must consider some basics of fetal cerebral circulation and physiology. The fetal brain receives its blood supply primarily from the carotid and vertebral/basilar arteries. The carotids supply the cerebral arteries. The basilar arteries supply the brain stem and posterior aspects of the brain. Venous return is predominately through venous sinuses. There are two related biologic parameters for cerebral circulation: cerebral perfusion pressure and cerebral blood flow. Cerebral perfusion pressure refers to cardiac output less

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15 Nelson KB, Lynch JK. Stroke in newborn infants. *Lancet Neurol* 2004;3(3):150; Sreenan C, Bhargava R, Robertson CM. Cerebral infarction in the term newborn: clinical presentation and long-term outcome. *J Pediatr* 2000;137:351–55; deVerber GA, MacGregor D, Curtis R, Maynak S. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. *J Child Neurol* 2000;15(5):316; Lee J, et al. Predictors of outcome in perinatal arterial stroke: a population-based study. *Ann Neurol* 2005;58(2):303; Chabrier S, Peyric E. et al. Multimodal Outcome at 7 Years of Age after Neonatal Arterial Ischemic Stroke. *J Pediatr.* 2016 May;172-156-161. e3.

16 Wusthoff CJ et al. Risk of later seizure after perinatal arterial ischemic stroke: a prospective cohort study. *Pediatrics* 2011 Jun;127(6):e1550-7.

17 *Id.*

18 Lee J, et al. Predictors of outcome in perinatal arterial stroke: a population-based study. *Ann Neurol* 2005;58(2):303.

19 Ichord R, Stroke in the newborn: Management and prognosis. UpToDate, 2017

20 *Id.*

21 Westmacott R, MacGregor D, Askalan R, deVerber G. Late emergence of cognitive deficits after unilateral neonatal stroke. Stroke 2009;40:2012-9

22 Ichord R, Stroke in the newborn: Management and prognosis. UpToDate, 2017 citing Trauner DA, Nass R, Ballantyne A. Behavioral profiles of children and adolescents after pre- or perinatal unilateral brain damage. Brain 2001;124(Pt 5):995.

23 *Id* citing Lee et al. Predictors of outcome in perinatal arterial stroke: a population-based study. Ann Neurol. 2005;58(2):303; Golomb MR et al. Perinatal stroke and the risk of developing childhood epilepsy. J Pediatr. 2007)ct;151(4):409-13, 413 e1-2; Wusthoff et al. Risk of later seizure after perinatal arterial ischemic stroke: a prospective cohort study. Pediatrics, 2011 Jun; 127(6):e1550-7; Billinghurst LL et al. Incidence and predictors of epilepsy after pediatric arterial ischemic stroke. Neurology 2017; 88(7):630.

24 Remillard GM, Ethier R, Andermann F. Temporal lobe epilepsy and perinatal occlusion of the posterior cerebral artery. A syndrome analogous to infantile hemiplegia and a demonstrable etiology in some patients with temporal lobe epilepsy. Neurology 1974; 24: 1001–9.

resistance. This equates generally to fetal mean arterial pressure minus intracranial pressure. Cerebral blood flow refers to the actual blood flowing throughout various parts of the brain. Importantly, cerebral hemodynamics in a healthy fetus is autoregulated. Autoregulation of cerebral blood flow refers to the maintenance of a constant cerebral blood flow over a broad range of perfusion pressures, if the system is intact.[25] Autoregulation is, accordingly, a safety measure to protect perfusion, but it is not absolute. The margin for safety is small at the lower end of the autoregulatory curve and points to vulnerability to ischemic brain injury with modest hypotension.[26]

Autoregulation stimulates changes in the vascular diameter, induced by the deformation of endothelial cells and the generation of endothelial derived signals that act on vascular smooth muscle. Nitrous oxide, calcium, and potassium are important in these vascular responses. Additionally, there are chemoreceptors and baroreceptors as a part of the autonomic nervous system that can affect autoregulation. Hypoxia, increased carbon dioxide, and other factors can disable the autoregulation protection, resulting in a pressure passive vascular supply at risk for ischemic injury. Additionally, there is a coupling of cerebral function, metabolism, and blood flow, wherein certain areas of the brain have higher metabolic needs as a result of their function. Those areas are afforded higher energy supplies. The coupling is mediated by regulation of cerebral blood flow by a number of vasoactive factors. For example, greater neuronal metabolic activity can decrease local pH, thus increasing substrate supply.[25]

Additionally, one must look at other factors that affect the vascular supply of oxygen to the fetal brain. As Volpe writes:

> "Potentially deleterious effects of labor and delivery were laid in considerable part to the easily deformed, particularly compliant skull of the premature infant. Such deformations could lead to such cerebral hemodynamic disturbances as increases in venous pressure and perhaps an impairment of cerebrovascular autoregulation (see Chapter 13). Prolonged labor and breach delivery potentially could lead to such hemodynamic effects (see Chapter 24). The relation of cerebral white matter injury to such clinical markers as fetal metabolic acidosis (see earlier) supports the notion that labor and delivery are important periods for management to prevent hypoxic – ischemic insults or the development of cerebral vascular auto regulatory dysfunction that might lead to hypoxia – ischemia subsequently."[27]

Volpe writes that there are a number of major causes of perinatal arterial ischemic stroke, including vasculopathy, vasospasm, vascular distortion, trauma, dissection, and perinatal asphyxia, among others.[28] The pathogenesis of a perinatal arterial stroke is very often multi-factorial.[29]

1. Hypoxia as cause

Hypoxia-ischemia can play a role in the genesis of perinatal focal arterial stroke in the newborn with or without evidence of non-focal hypoxic-ischemic brain injury.[30] In a retrospective study of 62 term newborns with acute arterial stroke on neuroimaging during the first week of life, Michoulas et al. found that there were multiple risk factors in common for both hypoxic-ischemic encephalopathy and perinatal arterial ischemic stroke. In fact, 42% of the term newborns with stroke had evidence of additional non-focal hypoxic-ischemic brain injury, and those infants had more clinical risk factors/markers for hypoxia-ischemia compared to those who had stroke alone. Michoulas noted that:

> "These observations raise the possibility that even when hypoxic-ischemic insult is of insufficient magnitude to result in additional neuroimaging abnormalities, it may still be a risk factor for focal stroke, perhaps by causing alterations of blood flow, similar to those described in animal models."

Other studies have suggested that intrapartum events including hypoxia and ischemia may play a more significant role in the pathogenesis of arterial ischemic stroke than previously recognized.[31] Martinez-Biarge et al. compared infants with neonatal arterial ischemic stroke ("NAIS") with those born with HIE and found that all the intrapartum factors associated with NAIS were also highly prevalent in infants with HIE:

> "…NAIS was preceded by the same intrapartum antecedents as HIE, and the presence of these factors (low Apgar scores, low pH values, major resuscitation at birth) was independently associated with both NAIS and HIE ... Some intrapartum

[25] Volpe, *supra* at *330*.
[26] Id at 332.
[27] Id at 442.
[28] Id at 567.
[29] Id at 572.
[30] Michoulas, et. Al., "The Role of Hypoxic-Ischemia in Term Newborns with Arterial Stroke, Pediatric Neurology 2011 44(4).
[31] Martinez-Biarge, et al., "Risk Factors for Neonatal Arterial Ischemic Stroke: The Importance of the Intrapartum Period," Journal of Pediatrics, 173, June 2016.

> factors may play a role in the pathogenesis of NAIS in a similar way as in HIE. It is possible that, depending on previous predisposing factors, including genetic factors, and/or the severity of the hypoxic-ischemic insult, some infants will develop HIE, whereas others will have a focal lesion. A milder insult, not enough to cause HIE, might be the final trigger for an ischemic stroke in a predisposed infant."

As noted above, in his textbook *Neurology of the Newborn*, Volpe discusses how "the potential overlap between mechanical trauma and the occurrence of hypoxic-ischemic cerebral injury is important to recognize, because perinatal mechanical insults may result also in hypoxic ischemic cerebral injury, perhaps secondary to disturbances of the placental or cerebral blood flow."[32] Other medical literature likewise indicates an association between hypoxic-asphyxial events and perinatal stroke: Ment et al., 1984[33] ("The common cause of cerebral infarction in our series was perinatal asphyxia."); Sheth et. al., 1995[34] ("Multiple cystic lesions in brain parenchyma supplied by the anterior cerebral circulation is a recognized pattern of cerebral injury associated with hypoxic-ischemic encephalopathy in the term infant." This may be related to the rich sympathetic innervation of the anterior cerebral vessels.); Kirton et al. 2011[35] (In a large international study of arterial ischemic stroke in newborns, 8% of infants also had birth asphyxia.).

2. Trauma/Compression as Cause

The effect of trauma or compression of the fetal head has been well-studied and well-researched but is a lightning rod in the medical legal context. Volpe discusses trauma and its similarity to HIE-type injury in his textbook, *Neurology of the Newborn*:

> "The terms 'perinatal trauma' and 'birth injury' have been given definitions so broad as to be confusing and nearly meaningless. Indeed, a commonly used definition of birth injury is considered to be any condition that affects the fetus adversely during labor and delivery. In this discussion, however, perinatal trauma refers to those adverse effects on the fetus during labor or delivery and in the neonatal period that, as noted earlier, appear to be caused primarily by mechanical factors. Thus, specifically excluded are the disturbances of labor and delivery that lead principally to hypoxic ischemic brain injury, (see Chapter 17 to 20). (Nevertheless, the potential overlap between mechanical trauma and the occurrence of hypoxic-ischemic cerebral injury is important to recognize because perinatal mechanical insults may result also in hypoxic ischemic injury, perhaps secondary to disturbances of the placental or cerebral blood flow. The precise mechanistic relationships remain largely unknown.)"[33]

The damaging effects of compression during delivery have been recognized for many decades. For example, in 1963, Kelly said:

> "Compression of the fetal skull may produce brain damage by one of three mechanisms: The increased pressure is transmitted inside the calvarium, where it may overcome the intravascular blood pressure, resulting in arrest of the cerebral circulation. The ensuing development of anoxia and asphyxia may damage not only the brain cells, but also the blood vessel walls, making them liable to rupture when exposed to hypertension."[36]

An increase in intracranial pressure and relative decrease in cerebral perfusion can be caused by contractions.[37] Once a threshold is reached, ischemic damage begins to occur to the fetal brain. If compression or trauma resulting in pressure on the fetal head continues beyond the threshold, ischemic damage will continue. As Dr. Volpe has previously stated:

> "Determination of intracranial pressure is of particular importance in neonatal neurologic disorders, since marked alterations of this pressure have major implications for diagnosis and management. Intracranial pressure alterations per se may lead to deleterious consequences via two basic mechanisms, disturbances of CBF (cerebral blood flow) and shifts of neural structures within the cranium. With the former consequence, cerebral perfusion pressure is related to the mean arterial pressure minus the intracranial pressure. Therefore, when intracranial pressure increases cerebral perfusion pressure decreases; if intracranial pressure increases markedly, cerebral perfusion pressure

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[32] Volpe, Neurology of the Newborn, 6th Edition (2018) at p.1093.

[33] Ment, et al., "Perinatal cerebral infarction" Annals of Neurology, 16(5) Nov. 1984

[34] Sheth, et al., Differential involvement of the brain in neonatal asphyxia: A pathogenic explanation, Journal of Child Neurology, 10(6) Nov. 1995.

[35] Kirton, et al., "Symptomatic Neonatal Arterial Ischemic Stroke: The International Pediatric Stroke Study," December 2011, Pediatrics, 128(6).

[36] Kelly, VJ. Compression of the fetal brain. Am. J. Obst. & Gynec: 85:687-694.

[37] Lindgren, LM, The Influence of Pressure upon the Fetal Head During Labor Acta Obstet. Gynecol Scand., 56: 305 (1977).

> declines below the low limit of autoregulation and CBF ... may be impaired severely. Indeed, recent evidence suggests that because normal arterial pressure in the newborn, especially the premature newborn, is relatively low, cerebral perfusion pressure already may be dangerously close to the downslope of the autoregulation curve."[38]

Cerebral perfusion must be substantially impaired before such loss of autoregulation occurs. As Faranoff and Martin's textbook explains:

> "The ischemic threshold below which prenatal brain damage occurs in the setting of normal systemic oxygenation is probably quite low, on the order of one third or less of even normal CBF ..., an ischemic threshold that reliably produces brain damage in adult animals. One reason for the resistance of the perinatal brain to cerebral ischemia in absence of the concurrent hypoxemia relates to the CBF autoregulatory plateau, which is shifted to the left relative to the adult brain. Numerous studies in fetal and newborn animals have shown that the mean arterial pressure must be reduced by at least 60% of control before the reduction of CBF occurs at normoxia."[39]

In 1972, Mann et al. reported in fetal sheep that cerebral oxygen consumption decreased markedly as cerebral blood flow was significantly impaired by the increase in intracerebral pressure and vascular resistance.[40] In Chapter 10 of the text *Fetal and Neonatal Pathology*, Keeling explained:

> "The normal fetus may be subjected to abnormal stresses during labor in several circumstances. It may be stressed because labor is prolonged. Excessive uterine contractions, either naturally occurring or because of the use of oxytocic drugs, may adversely affect the fetus. Increased pressure to the fetal head may occur because the abnormal shape or resistance of the birth canal impedes fetal passage. This problem may be aggravated by maternal bearing down efforts which can impair uterine circulation by interference with both the arterial perfusion and venous drainage ... the fetus which is abnormal as a result of intrauterine growth retardation, infection, malformation, or injury may be unable to withstand the amount of physical stress engendered by a normal labor".[41]

In addition to compression of the cerebral pressures from uterine contractions, pressure on the fetal skull, brain, and blood vessels occur as a result of vacuum extraction and/or the application of forceps. The use of forceps and vacuum extraction to facilitate delivery of an infant's head is known to be associated with injury to the fetal skull, brain and associated blood vessels. According to *Swaiman's Pediatric Neurology*, "[d]elivery via vacuum extraction has been linked to many types of nervous system trauma ... Extracranial complications of vacuum extraction include caput succedaneum, cephalohematoma, subgaleal hematoma, and skull fracture." Additionally, the author notes that "vacuum extraction has been associated with every type of intracranial hemorrhage, although the most commonly observed types of bleeds are extracranial hemorrhages. Subdural hematomas of the posterior fossa are of particular concern, because expansion of the hemorrhage can cause brainstem compression and may require surgical evacuation. Dural tears, tentorial laceration, and venous sinus rupture have been reported as a consequence of vacuum extraction, as have focal ischemic strokes."[42]

Mechanical birth trauma has been recognized as a direct cause of intracranial arterial injury leading to ischemic or hemorrhagic stroke in the newborn. Although ACOG and the AAP contend that "there is no existing evidence supporting the biological plausibility that *controlled, external mechanical manipulations (whatever this means)* [emphasis added] could lead to clot formation in deep arterial structures resulting in arterial ischemic stroke," ACOG cites many of the case reports linking ischemic stroke and trauma in its Neonatal Encephalopathy and Neurologic Outcomes publication.[43] There are, in fact, multiple articles and case reports, several of them cited in the NEANO

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[38] *See* Volpe, Neurology of the Newborn, 5th Edition (2008) at p.175. It should be noted that Volpe filed an affidavit in *Ward v. Bronson Health Care Group, Inc.*, Case No. 12-0448-NH (Kalamazoo Circuit Court) in which he disclaims the possibility that uterine hyperstimulation can create sufficient intracranial pressure to decrease cerebral perfusion and result in hypoxic-ischemic injury. In the most recent version of his textbook (6th Ed.), the cited discussion appears to be omitted.

[39] Faranoff AA, Martin FJ. Neonatal-Perinatal Medicine, Diseases of the Fetus and Infant, 7th Ed. 2002.

[40] Mann et al., "The effect of Head Compression on Fetal Heart Rate, Brain Metabolism and Function," Obstet. Gynecol., 39(5) 721:1972.

[41] Keeling J. Fetal and Neonatal Pathology (2nd ed.) Springer Verlag, London 1993 at p.239.

[42] Harbert M., Pardo, A. Neonatal Nervous System Trauma. Swaiman's Pediatric Neurology 6th Edition (2018).

[43] The American College of Obstetricians and Gynecologists, American Academy of Pediatrics. Neonatal Encephalopathy and Neurologic Outcome (Second Edition) at p. 128-9.

publication, that link arterial ischemic stroke to operative vaginal delivery and that provide at least some evidence in support of a causative link:

Kumar M, Avdic S, Paes B. Contralateral cerebral infarction following vacuum extraction. *Am J Perinatol* 2004;21:15-7

A 2004 case report by Kumar et. al described a cerebral infarction that was contralateral to the side of the vacuum application in a term infant.[44] While the authors cautioned that all relevant causes of infarction should be excluded before implicating a vacuum-assisted delivery as the underlying pathogenesis, they concluded that – in the absence of an identifiable cause – an infarction may be considered due to the skull being subjected to abnormal forces during birth. This was the second reported case of cerebral infarction contralateral to the site of vacuum application. In the first, researchers had found that the mechanical forces caused stretching of the middle and posterior cerebral arteries, which led to skull fracture, ischemia, and cerebral infarction.[45]

Lequin MH, Peeters EA, Holscher HC, et al. Arterial infarction caused by carotid artery dissection in the neonate. *Eur J Paediatr Neurol.* 2004;42:412-13

A 2004 case report detailed a case of arterial stroke following a traumatic delivery involving forceps and vacuum extraction.[46] A postmortem exam confirmed a diagnosis of intracerebral infarction due to dissection with thrombosis in the internal carotid arteries. The authors summarized that, although rare, arterial brain infarction can be caused by birth trauma in the following ways: direct trauma to an intracranial vessel, compression and vasospasm, vasospasm due to subarachnoid blood, stretch injuries of the arteries supplying blood to the brain (associated with vacuum and forceps handling), spontaneous dissection of cervicocephalic arteries due to minor trauma, and compression of the posterior circulation due to uncal herniation of the swollen brain. The authors postulated that the incidence of dissection is most likely underestimated due to a lack of specificity of clinical signs.

Roessmann U, Miller RT. Thrombosis of the middle cerebral artery associated with birth trauma. *Neurology* 1980;30:889-892

In 1980, researchers presented a case of middle cerebral artery occlusion resulting from birth trauma.[47] The subject baby was born following a labor assisted with Pitocin, a high forceps delivery attempt, and an emergency cesarean section. An autopsy proved that the forces exerted on the baby's head and neck by the attempted high forceps delivery damaged the inner layers of the right middle cerebral artery, which led to thrombosis and infarction. The authors noted that this was the first case in which birth trauma was "definitely implicated as the cause of middle cerebral artery thrombosis." They explained that "[t]he most likely mechanism underlying the thrombus formation involved the changes observed in the arterial wall. Absence of intima and tearing of the internal elastic lamina were probably caused by stretching of the artery during the attempted high forceps delivery. This roughened surface then served as a point of attachment of the platelets and subsequent thrombus formation."

Ng YY, Su PH, Chen JY, Lee IC. Do vacuum-assisted deliveries cause intracranial vessel injuries? *J Child Neurol* 2010;25:222-6

A case report published in 2009 presented two cases of intracranial vessel infarction after vacuum-assisted deliveries.[48] The cases showed left middle cerebral artery infarct and venous thrombosis associated with vacuum-assisted deliveries. The pathogenic mechanisms cited as contributing to mechanical traumatic deliveries include ruptured diploic or emissary vessels, lacerations of the middle meningeal artery that results in a stretch injury of the vertebral artery and its branches, occlusion of the posterior cerebral after uncal herniation due to intracranial hypertension, and a stretch or spasm injury of the middle cerebral artery or its branches. The authors found that the combined pressures of prolonged uterine contractions, the application of forceps, and intermittent vacuum extraction must be considered additive on the fetal skull, brain, and blood flow, as the pressures may lead to impairment of blood flow to the brain. The authors suggested that HIE should have been a differential diagnosis in both cases, but – even though some of the signs and symptoms of traditional HIE were absent in both cases – they opined that "[i]t would be helpful if obstetricians and pediatric neurologists were more aware of the association between vacuum-assisted extractions and intracranial vessel injuries," before

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[44] *Id.*

[45] Choy CM, Tam WH, Ng PC. Skull fracture and contralateral cerebral infarction after ventouse extraction. Br J Obstet Gynaecol 2001;108:1298-1299.

[46] Lequin MH, Peeters EA, Holscher HC, et al. Arterial infarction caused by carotid artery dissection in the neonate. *Eur J Paediatr Neurol.* 2004;42:412-13.

[47] Roessmann U, Miller RT. Thrombosis of the middle cerebral artery associated with birth trauma. Neurology 1980;30:889-892

[48] Ng YY, Su PH, Chen JY, Lee IC. Do vacuum-assisted deliveries cause intracranial vessel injuries? *J Child* Neurol 2010;25:222-6.

going on to encourage detailed neurological examination and brain ultrasonography after every vacuum-assisted delivery.

Lee J, Croen LA, Backstrand KH, Yoshida CK, Henning LH, Lindan C, Ferriero DM, Fullerton HJ, Barkovich A, Wu YW. Maternal and Infant Characteristic Associated With Perinatal Arterial Stroke in the Infant *JAMA*. 2005;293:723-29

In a case-control study nested within the cohort of all infants born from 1997 through 2002, researchers found that intrapartum complications, including vacuum assistance, were more common in infants with PAS than in control infants.[49] Researchers reported that "although fetal distress and low Apgar scores often lead to a clinical diagnosis of birth asphyxia, these complications do not always reflect a global hypoxic-ischemic event, as implied by the term *birth asphyxia*." In this study, all 6 infants with PAS who were diagnosed with birth asphyxia had a focal arterial infarction, not the more typical neuroimaging findings of hypoxic-ischemic brain injury, such as deep gray-matter or arterial-watershed injury. The researchers concluded that "the clinical diagnosis of birth asphyxia is not specific for any single pathogenic mechanism of brain injury."

VI. Conclusions and Practical Considerations

Birth trauma is a known cause of perinatal arterial ischemic stroke with or without concurrent hypoxia. While the causes of ischemic stroke can be multi-factorial, the literature cited earlier strongly suggests that trauma must be within any reasonable differential diagnosis.

When evaluating a perinatal ischemic stroke case, look for evidence of trauma in the newborn, including fracture, caput, molding, bruising, or the like. Also, carefully examine the neuroimaging studies. Often, scout images may reveal the existence and location of trauma. Look for other evidence of the sources of trauma, like failure to progress, prolonged second stage of labor, failure to descend, hyperstimulation, malposition or asynclitic presentation, instrumented operative vaginal delivery or attempted delivery, or evidence of fundal pressure. Remember that perinatal ischemic stroke is often multi-factorial.

When a fetus is hypoxic, the hypoxia, together with carbon dioxide in the fetal blood, take out cerebral autoregulation and dilate cerebral vasculature, making them pressure passive. This leaves little protection for the brain tissues against prolonged uterine hyperstimulation, prolonged second stage of labor, malposition or asynclitism, or an attempted operative vaginal delivery producing an increased risk for ischemia. Accordingly, when initially reviewing the records, look at the cord- and subsequent blood-gases. Look not only at the pH, but also for decreased PO2 and increased PCO2. All of these factors can cause or contribute to an ischemic reduction in oxygen delivery severe enough to cause ischemic injury, especially when combined with trauma or compression.

Also, beware of other causes or built-in defenses. Look carefully at the clotting factors on blood work and at the coagulation studies. These typically include Factor V Leiden, MTHFR, homosystein, protein C, and protein S. These factors can significantly increase the fetus's risk of clotting and stroke. The presence of such factors does not rule out negligence as a proximate cause of the stroke. However, it does give the defense a potentially powerful argument that the normal physiology of labor, together with one of these clotting defects, caused the stroke. Finally, rule out maternal history of cocaine use, as maternal cocaine use has been linked to vasospasms that could cause a perinatal ischemic stroke.

Considering the extensive lifelong suffering, damage, and extraordinary expense that ischemic strokes can cause, it is vital that preventable-trauma cases, though difficult, should be thoroughly evaluated and seriously pursued.

[49] Lee J, Croen LA, Backstrand KH, Yoshida CK, Henning LH, Lindan C, Ferriero DM, Fullerton HJ, Barkovich A, Wu YW. Maternal and Infant Characteristic Associated With Perinatal Arterial Stroke in the Infant *JAMA*. 2005;293:723-29.

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