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Introduction

In March 2014, the American College of Obstetrics and Gynecologists (ACOG) published *Neonatal Encephalopathy and Neurological Outcome* (2nd Ed.). The American Academy of Pediatrics (AAP) is cited as an issuing body. The first edition was published in January, 2003 and was entitled *Neonatal Encephalopathy and Cerebral Palsy* (1st Ed.). ACOG Technical Bulletin 163 (1992) was the first of the trilogy of ACOG consensus statements addressing the issue of causation of cerebral palsy by peripartum hypoxia ischemia ("ACOG 163").

ACOG 163, Chapter 8 of the 1st Ed., and Chapter 13 of the 2nd Ed. have all been attempts by ACOG to assist defendants in medical malpractice cases with consensus opinions of what criteria or markers are necessary in order to conclude that hypoxic-ischemic encephalopathy (HIE) was the cause of a patient's cerebral palsy. The consensus statements are designed to support medical expert testimony that, because an infant did not meet certain criteria or have a sufficient number of markers from a "constellation of markers", his or her cerebral palsy was unlikely to have been caused by hypoxia-ischemia.

In order to determine whether any of the trilogy of ACOG publications should be permitted to be referred to in the Courtroom, either on direct or cross examination of any expert, it is helpful to understand both that the criteria and markers are arbitrary, and that the methodology used to establish the consensus statements is flawed.

In the 1st Ed., the Task Force determined that there were four "Essential Criteria (must meet all four)" and "five other criteria that collectively suggest an intrapartum timing" in order to define an "Acute Intrapartum Hypoxic Event Sufficient to cause Cerebral Palsy". This phrase, repeated in each document, has never been defined and the "essential criteria" offered in one guise or another have no epidemiological support in the literature either at the time of the original publication or since. While the titles such as "essential criteria" have been abandoned

in the 2nd Ed., gatherings of risk factors continue to appear.

In the 2nd Ed., the Task Force acknowledged its "sober recognition" that knowledge gaps still preclude a definitive test or set of markers (obstetrical, neonatal, neuroradiological) that accurately (meaning "unfailingly" to a p level of >05) identifies, with high sensitivity and specificity, an infant in whom neonatal encephalopathy (NE) is attributable to an ***acute*** intrapartum event.[1]

In its determination to maintain the original "criteria" even while necessarily retreating from the 1st Ed. list, the 2nd Ed. Task Force "determined that a broader perspective may be more fruitful". Thus, in the 2nd Ed. we find that the "criteria" are now referred to as a "constellation of markers" or "elements in item categories" or simply a "list". The 2nd Ed. Task Force does acknowledge that the information in the 2" Ed. "should not be viewed as a body of rigid rules".

The model of "acute intrapartum hypoxic event sufficient to cause cerebral palsy" is a neologism created by ACOG. There is no such definable break point, either in terms of cord pH or base deficit, or even the condition of the infant at birth. Further, the model of injury that forms the basis of the discussions and the distractions is NOT the most common cause of reproductive compromise during labor. The model discussed relates to progressive, systemic hypoxia/acidemia leading up to the time of birth. Indeed, the majority of infants injured during birth are neither asphyxiated nor severely compromised at birth and their major handicap may only be appreciated long after birth.

There is simply no evidence to support the Task Force's assumption that developmental disabilities result only from "severe" intrapartum hypoxia-ischemia followed by severe disorders of neonatal adaptation or encephalopathy in the neonatal period (i.e. NE). Developmental disorders may emerge even following mild hypoxic exposure without the development of encephalopathy (Perna & Cooper, 2012 and Odd, D.E., *et al,* 2009).

The limitations of the 2d Ed Task Force's approach to its list of "markers" of neonatal encephalopathy purportedly attributable to an acute intrapartum event is outlined below.

1. There is no evidence to support the Task Force's assumption that developmental disabilities resulting only from intrapartum hypoxia-ischemia must be preceded by disorders of neonatal adaptation or encephalopathy in the neonatal period (i.e., NE).

The large scale study by Odd, D.E., et al. (2009) compared three groups of children born at 36 weeks or greater. 815 infants were resuscitated at birth yet were asymptomatic for NE, while 58 infants were resuscitated and showed evidence of NE. The control group of 10,609 infants were not resuscitated and did not have NE. The authors established an association between infants resuscitated at birth and impaired cognitive functioning at eight years of age; this group had substantially increased risk of low full-scale IQ score, even without symptoms of NE. The authors conclude that, "... mild perinatal physiological compromise might be sufficient to cause subtle neuronal synaptic damage, and thereby affect cognition in childhood and potentially in adulthood. By comparison, substantial perinatal compromise presents with NE and large cognitive deficits. ... The results of this study are consistent with prolonged partial hypoxia."

Perna & Cooper (2012) studied the long-term cognitive sequelae and behavioral consequences of "brief or transient hypoxia and cyanosis" as opposed to serious hypoxic-ischemic episodes (i.e., minor perinatal hypoxia without development of NE). The authors found that "all children in the study who

[1] Neonatal encephalopathy (NE) is a heterogeneous syndrome characterized by central nervous system dysfunction in the newborn. NE does not imply a specific underlying pathophysiology. Hypoxic-ischemic encephalopathy (HIE) is a subset of NE. It indicates brain injury in the peripartum period associated with severe hypoxia and metabolic acidosis (asphyxia). In his 5th Edition (and several prior editions), Volpe uses the term neonatal neurological syndrome (NNS). Although NNS and NE may be used interchangeably, Volpe, Sarnat, and others have stressed clinical observations, while the Task Force now uses two arbitrary "markers" (Apgar score and pH value) along with an abnormal MRI / MRS (rarely performed in the NICU), and confirmation of other organ damage.

suffered transient cyanosis eventually, during toddler years, had developed disorders in speech and/or motor functioning and then were diagnosed with ADHD in elementary school".

2. Recent research does not support the Task Force assumption that chronic antenatal factors are chiefly responsible for NE.

The 2nd Ed. Task Force acknowledges that MRI studies have defined most cerebral injuries seen in term born infants as having acute (perinatal), rather than antenatal, origin. Nevertheless, the 2nd Ed. Task Force chooses to rely on the 1998 Badawi study to take the position that epidemiologic studies have suggested that 70% of causation is related to chronic antenatal factors. But Badawi did not clearly define NE, included children whose conditions almost certainly had antenatal or genetic origins, and ultimately had no reliable way of assigning with any precision the timing of injury which in the study rested with the pH and the Apgar score.

In contrast to the Task Force's characterization of epidemiological studies pointing to antenatal etiology, the findings from a recent large scale demographic study by Martinez-Biarge, et al. (2013) point to the crucial role of intrapartum causality in the development of neonatal encephalopathy. The methodological strength of this study included improved selection criteria as well as corroboration of hypoxic-ischemic injury by MRI evidence.

In the study by Martinez-Biarge (2013), 405 infants > 35 weeks gestation was compared with 239 neurologically normal infants. The authors reported:

> Antepartum factors may predispose some women to adverse intrapartum episodes but their presence alone is not sufficient to cause HIE in their infants. ... Our results do not support the hypothesis that neonatal HIE starts antenatally, but point to the intrapartum period as the necessary factor for its development. ... Other studies, using a stricter definition of encephalopathy that automatically excludes most conditions with an antenatal or genetic origin (unlike Badawi), have found that intrapartum events are the main or a contributing factor in the causal setting of HIE.

Similarly, the studies of Cowan, et al., clearly underscore the paucity of modern evidence for any significant contribution of prenatal factors in the etiology of infant neurological handicap. In a study of 71,189 births at two Swedish hospitals from 1994 to 2003, Jonsson and colleagues found the incidence of moderate and severe NE (Sarnat grades 2 -3) to be 1.1 for 1,000 infants; of those, moderate to severe NE was considered to be due to asphyxia in 60% of cases, of which 54% occurred during labor. Curiously, the Task Force does not even consider the results of the Martinez-Biarge 2013 study, choosing instead to rely on the criticized methodology of Badawi (1998).

3. The Executive Summary by the Task Force on NE provides neither guidance nor research evidence to establish the number or type of diagnostic criteria that should be met to attain an acceptable degree of diagnostic accuracy.

While the 2nd Ed. Task Force did not use four "essential" and five "criteria that collectively suggest an intrapartum timing", as was done in the 1st Ed., the 2nd Ed. Task Force attempted to:

> ... compile a constellation of markers concerning neonatal status, contributing events, and developmental outcome to determine if they are consistent with acute hypoxia-ischemia and may not be explained by other etiologies. Thus, when more of the elements from each of the item categories are met, it becomes increasingly more likely that the peripartum or intrapartum hypoxia-ischemia played a role in the pathogenesis of neonatal encephalopathy. (2nd Ed., Executive Summary, p. xxii and Chapter 13, p. 208)

The quote above provides the overall diagnostic framework recommended by the 2nd Ed. Task Force to determine whether "acute hypoxia-ischemia" was an etiological factor in a case with "confirmed" NE. Within this framework of "comprehensive multidimensional assessment", a "constellation of markers concerning neonatal status, contributing events, and developmental outcome" was presented as "elements" in a "list" that an individual case (infant) with NE either does or does not meet. The 2nd Ed. Task Force stated that the likelihood that intrapartum hypoxia-ischemia caused or contributed to the infant's

disturbed neurological function (encephalopathy) increases when the infant meets "more of the elements" in the list. The "list" is comprised of two categories.

The first category:

"Neonatal Signs Consistent with an Acute Peripartum or Intrapartum Event"

A. Apgar Score of Less Than 5 at 5 Minutes and 10 minutes:
B. Fetal Umbilical Artery Acidemia:
C. Neuroimaging Evidence of Acute Brain Injury Seen on Brain MRI or MRS Consistent with Hypoxia-ischemia
D. Presence of Multisystem Organ Failure Consistent With Hypoxic-Ischemic Encephalopathy).

The second category:

"Type and Timing of Contributing Factors That Are Consistent With an Acute Peripartum or Intrapartum Event"

A. Sentinel Hypoxic or Ischemic Event Occurring Immediately Before or During Labor and Delivery;
B. Fetal Heart Rate Monitor Patterns Consistent With an Acute Peripartum or Intrapartum Event:
C. Timing and Type of Brain Injury Patterns Based on Imaging Studies Consistent With an Etiology of an Acute Peripartum or Intrapartum Event; and
D. No Evidence of Other Proximal or Distal Factors That Could Be Contributing Factors).[2]

Notably, the diagnostic framework suggested in the 2nd Ed. is not accompanied by a clear procedure to make an actual diagnosis of HIE. There is no proposed number of "markers" or "elements" (out of the total listed) that a given case with NE should meet in order to attribute this neurological condition with confidence and accuracy to intrapartum hypoxia-ischemia. In other words, in the 2nd Ed., the Task Force does not recommend a minimal number of elements (a threshold of criteria met) for making an accurate diagnosis of HIE with high or at least an acceptable degree of sensitivity and specificity. Lastly, the 2nd Ed. Task Force did not even provide recommendations regarding the relative importance of the multiple criteria that are listed for making a diagnosis.

Within the framework provided by the 2nd Ed. Task Force, the likelihood of hypoxia-ischemia being a causal factor in the etiology of NE is to determined by the number of "elements" that are met by an infant. However, it is misleading to infer that a diagnosis of HIE is increasingly more accurate as an infant meets additional listed "elements": Accuracy of a diagnostic procedure requires both high diagnostic sensitivity (correct identification of "true" cases whose neonatal encephalopathy is attributed to intrapartum hypoxia-ischemia) and high diagnostic specificity (correct rejection of "false" cases whose neonatal encephalopathy is not due to intrapartum hypoxia-ischemia). Yet the 2nd Ed. Task Force Report does not provide empirical research evidence that meeting a greater number of the proposed "elements" yields greater diagnostic sensitivity and specificity. Without evidence for its sensitivity and specificity, the diagnostic framework proposed by the 2nd Ed. Task Force may be characterized as lacking empirical validation. Alternatively, one may view it as merely an exhaustive list entailing all the items that may have relevance, *albeit* to an unknown degree, for the diagnosis of a particular case.

In this context it should be noted that an earlier version of ACOG diagnostic criteria, ACOG 163 (1992), was found by Korst, et al. (1999) to lack diagnostic validity. Only 21% of the study participants, all of whom experienced HIE after "delivery from a catastrophic event," satisfied all 4 criteria required at the time for attribution of brain injury to intra-partum hypoxia-ischemia (*see* Korst, et al. (1999); Phalen, et al. (1998)). The combined results from these investigations showed that the preponderance of cases with substantiated HIE did not meet the diagnostic criteria of ACOG 163, thereby demonstrating the reduced accuracy (and particularly sensitivity) of the older ACOG diagnostic framework. The findings from the Korst (1999) study only highlight the need for research data about the accuracy, sensitivity, and specificity of the diagnostic framework as outlined by the 2nd Ed. Task Force Report.

[2] Item C., "Neuroimaging Evidence of Brain Injuries Consistent with Hypoxia-ischemia" is, for some reason, in both categories.

4. Individual criteria listed as components of the "comprehensive multidimensional assessment" have been shown to have questionable diagnostic validity.

Korst, et al. (1999) criticized the assumption or premise on which the previous diagnostic framework (and to a large extent the current one) is based; that is, that criteria that had been individually criticized and found to be lacking, somehow in aggregate could yield an accurate identification of infants who had been exposed to a significant intra-partum hypoxic event. As stated by Korst:

> Individually, each of these criteria has been criticized (citations), yet each of the authors of the intrapartum asphyxia criteria (ACOG 163) emphasize that these criteria taken together should more accurately identify those neonates injured during the birth process. As before in a heterogeneous population ACOG Technical Bulletin 163 was not found to be valid in an acute intrapartum asphyxia model. (Korst, et al. (1999), p. 105.)

Three of the four individual markers listed by the 2nd Ed. Task Force have not been found to be valid for identification of HIE in previous research by Korst and others. They are:

> A. Apgar Score of Less Than 5 at 5 Minutes and 10 minutes:
> B. Fetal Umbilical Artery Acidemia; and
> D. Presence of Multisystem Organ Failure Consistent With Hypoxic-Ischemic Encephalopathy).

For instance, in the study by Wayock, et al. (2014), about 36% of the children who had undergone whole-body hypothermia for hypoxic-ischemic encephalopathy had had Apgar scores > 5 at 5 minutes. This rate reveals that in infants with HIE, the likelihood of obtaining a score of five and above is by no means small. Similarly, 22.45% of the sample, a rather substantial minority of the children who had undergone therapeutic hypothermia for moderate and severe HIE, had cord pH values > 7.00.

Korst (1999) found that 44% of their infants with neonatal encephalopathy had cord pH > 7.00, while Jonsson, et al. (2014) reported on the association of metabolic acidemia and neonatal encephalopathy. Of 80 neonates with neonatal encephalopathy 48 (60%) did not reveal metabolic acidemia, while of 30 neonates with seizures alone, none had metabolic acidemia." Jonsson, et al. (2014). Again, a rate of 40% without metabolic acidemia is, by no means, small. In the study by Phelan, et al. (1998) singleton infants with HIE and permanent neurologic injury, 36% of the infants had no evidence of multisystem organ failure. In Korst (1999) the percentage of infants with HIE and no evidence of multisystem organ failure was 30%.

In sum, results from various investigations of infants with HIE show a relatively high rate of failure to meet individual markers set forth by the 2d Ed. Task Force for the attribution of NE to an intrapartum/peripartum hypoxic-ischemic event.

5. Extra emphasis is placed on the "markers" of "Neuroimaging Evidence of Acute Brain Injury seen on brain MRI or MRS consistent with Hypoxia-Ischemia" which is repeated in two categories in the list.

A positive or abnormal MRI/MRS can certainly be helpful in determining the existence and extent of brain damage in the newborn. The problem with listing an abnormal MRI/MRS as a "marker" is that MRIs are rarely done in the NICU, as acknowledged by the authors of Chapter 10 of the 2nd Ed. The authors of Chapter 10 note that many infants cannot be safely transported from the NICU to radiology. The authors note that few centers have experience in routinely imaging critically ill infants. They further note the risk of injury to the hearing of the newborn. They also note that the infants must remain still during the MRI and that sedation, which is often required, has risks, and is often not effective. The authors of Chapter 10 also point out that 20% of children with cerebral palsy do not have detectable abnormalities on MRI. Given the concern and limitations noted by their own authors in Chapter 10, it is curious why the 2nd Ed. Task Force listed neuroimaging as a "double marker".

Methodology of the 2nd Ed. Task Force Report

The 2nd Ed. Report is based on 1500 references that were "collectively reviewed" by 17 Task Force members and 88 consultants for the stated purpose of updating the 1st Ed.. There are 13 chapters, and Chapter 13 provides recommended "markers" for assessment of an acute peripartum or intrapartum hypoxic event sufficient to cause HIE. The 2nd Ed. Task Force Report does not provide a division of labor between the 17 Task Force members; the specific contribution of the many consultants is also not elucidated. The 2nd Ed. Task Force Report is neither a study nor meta-analysis. It is a consensus document. The reviews of the pertinent topics are not systematic, and the contents of the sections and chapters are almost certainly influenced by the experience, judgment, and opinions of the particular authors involved.

A systematic review of the literature (meta-analysis) is essential for providing the scientific basis (empirical evidence) for the diagnostic criteria (markers, elements, and lists) provided in Chapter 13. There is no systematic review in the 2nd Ed. Task Force Report. For instance, the process by which the 2nd Ed. Task Force arrived at its two Apgar score cutoffs (i.e., Apgar score < 5 at 5 and 10 minutes that are said to be "consistent with acute intrapartum event", and "if Apgar score > 7 at 5 minutes, it is unlikely that there was peripartum HIE") is not explained beyond the fact that they were the "consensus". The cut-offs are also contradicted by the literature cited by the 2nd Ed. Task Force, which shows a significant increase in cerebral palsy risk even in term infants with Apgar scores of 4-6 and 7-8. (Lie, et al., (2010); Table 2).

Further, there is no explanation of how the "Apgar score of <5" was chosen. Why not 7? -- or 3? Were the 2nd Ed. Task Force members and authors polled? Were they given a choice of Apgar scores of 3, 4, 5, 6 or 7? Were they asked to select an Apgar number, after which the 2nd Ed. Task Force calculated an average to form the consensus? We would have been critical of any of these methodologies, but without further disclosure by the 2nd Ed. Task force, we can simply state that there is no known methodology.

A similar methodology deficiency is illustrated in the 2nd Ed. Task Force rationale for pH < 7.0 as the specific value that "increases the probability that NE, if present, had an intrapartum component" (Chapter 13, p. 209). This pH value is presumably based on the literature reviewed in Chapter 6 of the 2nd Ed. report. The authors of Chapter 6 relied primarily on a meta-analysis by Malin, et al., BMJ 340 (2010), and an observational study by Yeh, et al., BJOG 119 (2012). Malin, et al. (2010) found a "graded increase of risk of perinatal mortality and morbidity with increasingly acidemic status at birth". Findings of mortality and morbidity were significant at < 7.20 but increased when pH measured < 7.0. Yeh, et al. (2012) report that "The threshold pH for adverse neurological outcomes is 7.10, and that the ideal cord pH is 7.26 - 7.30."The authors of Chapter 6 concluded that "Less severe levels of acidosis measured by pH > 7.0 also may be predictive of neonatal morbidity" and added that, "[c]onversely, reports exist of well-documented intrapartum events leading to severe or moderately severe neonatal encephalopathy with umbilical artery pH > 7.0 or base deficit < 12 mmol/L." (2nd Ed, Chapter 6, p. 97). The literature cited by the authors of Chapter 6 thus does not support a pH < 7.0 cut-off. Rather, the literature supports the notion of "a graded increase in risk" with a decrease in pH, or, conversely, a graded decrease in risk with increasing pH up to 7.3. The "consensus" of the authors of Chapter 13, however it was arrived at, is simply not supported by the research and findings of the authors of Chapter 6 of the 2nd Ed..

Conclusion

Like ACOG Technical Bulletin 163 (1992) and Chapter 8 of the 1st Ed. (2003), Chapter 13 of the 2nd Ed. Task Force Report has been written to help defendants in medical malpractice litigation. The "Constellation of Markers" devised by the 2nd Ed. Task Force is of absolutely no use to the obstetrical staff monitoring labor and delivery or to the clinicians in the newborn nursery.

We can anticipate a defense expert attempting to testify, "I have reviewed the 2nd Ed. Task Force Report's 'Constellation of Markers' and the newborn records, and this child did not have one of those markers. Therefore, I can state to near mathematical certainty that hypoxia-ischemia did not cause this child's cerebral palsy."

We submit that no Court should permit reference to ACOG's 2nd Ed. Task Force report, and certainly

not to the "Constellation of Markers". The 17-member 2nd Ed. Task Force met three times over a two year period and then "deliberated to achieve consensus on the recommendations included in this report". By definition, consensus is "an opinion held by all or most". This report is not the result of a controlled trial, or of a cohort or case controlled analytical study, or of a meta-analysis. There is not even a reported methodology of how the 2nd Ed. Task Force arrived at its consensus.

Plaintiffs counsel would be well advised to file a Motion *in Limine* before trial and, in those jurisdictions where experts are not deposed, request a *voir dire* of any defense expert witness who intends to make reference to any of the trilogy of ACOG publications. Finally, we note that the 2nd Ed. Task Force report relates only to risk for cerebral palsy. The epidemiology of developmental disabilities and mental retardation resulting from HIE which was not severe enough to cause cerebral palsy, has been developing steadily over the past five years, but this subject is not addressed in the 2nd Ed. Task Force report.

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