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## Neonatal Encephalopathy and Neurologic Outcome, Second Edition

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### Neonatal Encephalopathy and Neurologic Outcome, Second Edition

Report of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy

Neonatal Encephalopathy and Neurologic Outcome, Second Edition, was developed by the Task Force on Neonatal Encephalopathy: Mary E. D'Alton, MD, Chair, Gary D.V. Hankins, MD, Vice Chair, Richard L. Berkowitz, MD, Jessica Bienstock, MD, MPH, Alessandro Ghidini, MD, Jay Goldsmith, MD, Rosemary Higgins, MD, Thomas R. Moore, MD, Renato Natale, MD, Karin B. Nelson, MD, Lu-Ann Papile, MD, Donald Peebles, MD, Roberto Jose Romero, MD, Diana Schendel, PhD, Catherine Yvonne Spong, MD, Richard N. Waldman, MD, Yvonne Wu, MD, MPH, and the American College of Obstetricians and Gynecologists' staff: Gerald F. Joseph Jr, MD, Debra Hawks, MPH, Alyssa Politzer, MA, Chuck Emig, MA, and Kelly Thomas.

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#### **EXECUTIVE SUMMARY**

In the first edition of this report, the Task Force on Neonatal Encephalopathy and Cerebral Palsy outlined criteria deemed essential to establish a causal link between intrapartum hypoxic events and cerebral palsy. It is now known that there are multiple potential causal pathways that lead to cerebral palsy in term infants (see Fig 1), and the signs and symptoms of neonatal encephalopathy may range from mild to severe, depending on the nature and timing of the brain injury. Thus, for the current edition, the Task Force on Neonatal Encephalopathy determined that a broader perspective may be more fruitful. This conclusion reflects the sober recognition that knowledge gaps still preclude a definitive test or set of markers that accurately identifies, with high sensitivity and specificity, an infant in whom neonatal encephalopathy is attributable to an acute intrapartum event. The information necessary for assessment of likelihood can be derived from a comprehensive evaluation of all potential contributing factors in cases of neonatal encephalopathy. This is the broader perspective championed in the current report. If a comprehensive etiologic evaluation is not possible, the term hypoxic-ischemic encephalopathy should best be replaced by neonatal encephalopathy because neither hypoxia nor ischemia can be assumed to have been the unique initiating causal mechanism. The title of this report has been changed from Neonatal Encephalopathy and Cerebral Palsy: Defining the Pathogenesis and Pathophysiology to Neonatal Encephalopathy and Neurologic Outcome to indicate that an array of developmental outcomes may arise after neonatal encephalopathy in addition to cerebral palsy.

To determine the likelihood that an acute hypoxic—ischemia event that occurred within close temporal proximity to labor and delivery contributed to neonatal encephalopathy, it is recommended that a comprehensive multidimensional assessment be performed of neonatal status and all potential contributing factors, including maternal medical history, obstetric antecedents, intrapartum factors (including fetal heart rate monitoring results and issues relating to the delivery itself), and placental pathology. A description of the items to be included in the assessment follows.

	А	В	С	D	Е	
Conception		$\pm$ DRF	$\pm$ DRF	± DRF	± DRF	
Antepartum		$\pm$ DRF	PRF ↓ ★	PRF ↓ ★	± DRF	<ul> <li>Time of irreversible brain damage or anomaly</li> </ul>
Intrapartum	PRF ↓ ★ ↓	PRF ↓↓ ★ ↓		PRF ↓ ★ ↓	± DRF	
Neonatal	NE	NE	± NE	NE	$PRF \rightarrow \ast \rightarrow NE$	
Childhood	СР	СР	СР	CP	СР	

#### FIGURE 1

Prenatal and perinatal causal pathways to cerebral palsy in term infants. Distal risk factors exert a pathogenic effect on fetal brain development starting at a time that is remote from the onset of irreversible brain injury. Examples include genetic abnormalities, environmental and sociodemographic factors, and some placental abnormalities. Proximal risk factors exert pathogenic effects on fetal brain development at a time that closely predates or coincides with the onset of irreversible brain injury. Examples include abruptio placentae, chorioamnionitis, and twin-twin transfusion. There are multiple potential causal pathways that lead to cerebral palsy in term infants, and the signs and symptoms of neonatal encephalopathy may range from mild to severe, depending on the nature and timing of the brain injury. **A**. Intrapartum brain injury that is due to a proximal risk factors that predispose the fetus to brain injury and cerebral palsy. **B**. Intrapartum brain injury may be the result of both distal and proximal risk factors. When brain injury or anomaly may occur in the antepartum period as a result of distal and proximal risk factors. When brain injury may occur at multiple points during gestation. **E**. Proximal risk factor and brain injury may occur in the neonatal period following predisposing distal risk factors. Abbreviations: DRF, distal risk factor; PRF, proximal risk factor.

#### **I. CASE DEFINITION**

Neonatal encephalopathy is a clinically defined syndrome of disturbed neurologic function in the earliest days of life in an infant born at or beyond 35 weeks of gestation, manifested by a subnormal level of consciousness or seizures, and often accompanied by difficulty with initiating and maintaining respiration and depression of tone and reflexes. This expanded clinical definition must be put into use based on measures that can be reliably and accurately implemented by trained staff. The first mandatory step in an assessment of neonatal encephalopathy is to confirm whether a specific infant meets the case definition.

In confirmed cases of neonatal encephalopathy, the following assessment will determine the likelihood that an acute peripartum or intrapartum event was a contributor. This list is

based on the premise that neonatal encephalopathy that is due to acute hypoxia-ischemia will be accompanied by abnormal neonatal signs and be associated with contributing events in close temporal proximity to labor and delivery. The goal of the assessment is 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 peripartum or intrapartum hypoxia ischemia played a role in the pathogenesis of neonatal encephalopathy.

#### II. NEONATAL SIGNS CONSISTENT WITH AN ACUTE PERIPARTUM OR INTRAPARTUM EVENT

- A. Apgar Score of Less Than 5 at 5 Minutes and 10 Minutes
  - Low Apgar scores at 5 minutes and 10 minutes clearly confer an increased relative risk of cerebral palsy. The degree of Apgar abnormality at 5 minutes and 10 minutes correlates with the risk

of cerebral palsy. However, most infants with low Apgar scores will not develop cerebral palsy.

- There are many potential causes for low Apgar scores. If the Apgar score at 5 minutes is greater than or equal to 7, it is unlikely that peripartum hypoxia—ischemia played a major role in causing neonatal encephalopathy.
- B. Fetal Umbilical Artery Acidemia
  - Fetal umbilical artery pH less than 7.0, or base deficit greater than or equal to 12 mmol/L, or both, increases the probability that neonatal encephalopathy, if present, had an intrapartum hypoxic component; lesser degrees of acidemia decrease that likelihood.
  - 2. If the cord arterial gas pH levels are above 7.20, it is unlikely that intrapartum hypoxia played a role in causing neonatal encephalopathy.
  - Although the aforementioned thresholds are commonly accepted as indicative of pathologic

fetal acidemia, there is a continuum of increasing risk of neonatal encephalopathy with worsening acidemia. It is important to remember that even in the presence of significant acidemia, most newborns will be neurologically normal. The presence of metabolic acidemia does not define the timing of the onset of a hypoxic-ischemic event.

- C. Neuroimaging Evidence of Acute Brain Injury Seen on Brain MRI or Magnetic Resonance Spectroscopy Consistent With Hypoxia–Ischemia
  - MRI is the neuroimaging modality that best defines the nature and extent of cerebral injury in neonatal encephalopathy. Cranial ultrasonography and computed tomography lack sensitivity for the evaluation of the nature and extent of brain injury in the term encephalopathic infant.
  - 2. Distinct patterns of neuroimaging abnormalities are recognized in hypoxic-ischemic cerebral injury in the infant born at or beyond 35 weeks of gestation and have prognostic value for predicting later neurodevelopmental impairments. If the results of the MRI or magnetic resonance spectroscopy, obtained after the first 24 hours of life, are interpreted by a trained neuroradiologist and no areas of injury are noted, then it is unlikely that significant peripartum or intrapartum hypoxic-ischemic brain injury was a significant factor in neonatal encephalopathy. It is important to note that the full extent of injury may not be evident on MRI until after the first week of life.
  - Early MRI obtained between 24 hours and 96 hours of life may be more sensitive for the delineation of the timing of perinatal cerebral injury, whereas an MRI

undertaken optimally at 10 days of life (with an acceptable window between 7 days and 21 days of life) will best delineate the full extent of cerebral injury.

- Despite the advances in neuroimaging, the ability to precisely time the occurrence (estimating within days rather than hours or minutes) of a hypoxic-ischemic event is still limited.
- D. Presence of Multisystem Organ Failure Consistent With Hypoxic–Ischemic Encephalopathy
  - Multisystem organ failure can include renal injury, hepatic injury, hematologic abnormalities, cardiac dysfunction, metabolic derangements, and gastrointestinal injury, or a combination of these.
  - Although the presence of organ dysfunction increases the risk of hypoxic—ischemic encephalopathy in the setting of neonatal encephalopathy, the severity of brain injury seen on neuroimaging does not always correlate with the degree of injury to other organ systems.

#### III. TYPE AND TIMING OF CONTRIBUTING FACTORS THAT ARE CONSISTENT WITH AN ACUTE PERIPARTUM OR INTRAPARTUM EVENT

- A. A Sentinel Hypoxic or Ischemic Event Occurring Immediately Before or During Labor and Delivery
  - 1. A ruptured uterus
  - 2. Severe abruptio placentae
  - 3. Umbilical cord prolapse
  - Amniotic fluid embolus with coincident severe and prolonged maternal hypotension and hypoxemia
  - 5. Maternal cardiovascular collapse
  - 6. Fetal exsanguination from either vasa previa or massive fetomaternal hemorrhage

- B. Fetal Heart Rate Monitor Patterns Consistent With an Acute Peripartum or Intrapartum Event
  - A Category I or Category II fetal heart rate tracing when associated with Apgar scores of 7 or higher at 5 minutes, normal umbilical cord arterial blood (± 1 SD), or both is not consistent with an acute hypoxicischemic event.
  - There is a great distinction to be made between a patient who initially presents with an abnormal fetal heart rate pattern and one who develops an abnormal fetal heart rate pattern during labor.
    - a. A category II fetal heart rate pattern lasting 60 minutes or more that was identified on initial presentation with persistently minimal or absent variability and lacking accelerations, even in the absence of decelerations, is suggestive of a previously compromised or injured fetus. If fetal well-being cannot be established by appropriate response to scalp stimulation or biophysical testing, the patient should be evaluated for the method and timing of delivery. An emergency cesarean delivery may not benefit a fetus with previous severe compromise.
    - b. The patient who presents with a Category I fetal heart rate pattern that converts to Category III as defined by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development guidelines is suggestive of a hypoxicischemic event.
    - Additional fetal heart rate patterns that develop after a Category I fetal heart rate pattern

on presentation, which may suggest intrapartum timing of a hypoxic-ischemic event, include tachycardia with recurrent decelerations and persistent minimal variability with recurrent decelerations.

- C. Timing and Type of Brain Injury Patterns Based on Imaging Studies Consistent With an Etiology of an Acute Peripartum or Intrapartum Event
  - 1. Cranial ultrasonography lacks sensitivity for the common forms of brain injury in the encephalopathic newborn. However, if echodensity or echogenicity is detected on cranial ultrasonography, as it may be the only neuroimaging modality able to be obtained in a very unstable infant, it is observable 48 hours or longer after an ischemic cerebral injury. Computed tomography lacks sensitivity for brain injury in the newborn and will often not reveal abnormalities in the first 24-48 hours after an injury.
  - 2. MRI and magnetic resonance spectroscopy are the most sensitive neuroimaging modalities to assist with the timing of cerebral injury. MRI—combining conventional, diffusion, and spectroscopy between 24 hours and 96 hours of life provides the most useful guide on the potential timing of a cerebral insult.
  - 3. Diffusion abnormalities are most prominent between 24 hours and 96 hours of life. With conventional qualitative MRI, cerebral abnormalities will become most evident after 7 days from a cerebral injury. Two MRI or magnetic resonance spectroscopy scans the first between 24 hours and 96 hours of life with emphasis on the evaluation of diffusion and spectroscopic abnormalities to assist in clinical man-

agement and evaluation of the timing of cerebral injury, and a second at day 10 of life or later—will assist with full delineation of the nature and extent of cerebral injury.

- 4. There are several well-defined patterns of brain injury and their evolution on MRI that are typical of hypoxic–ischemic cerebral injury in the newborn, including deep nuclear gray matter or watershed cortical injury. If a different pattern of brain injury or evolution of injury exists on MRI, then alternative diagnoses should be actively pursued (eg, metabolic and genetic investigations).
- 5. Certain patterns of brain injury seen on MRI—such as focal arterial infarction, venous infarction, isolated intraparenchymal or intraventricular hemorrhage, porencephaly, or atypical patterns of metabolic encephalopathies suggest that peripartum hypoxiaischemia did not play a role in causing neonatal encephalopathy.
- 6. Accurate interpretation of neuroimaging is important, and ongoing education in the interpretation and reporting of neonatal neuroimaging is encouraged. If there is limited expertise in neonatal neuroradiology and inconsistencies in the clinical profile of the infant, an expert opinion should be sought for the interpretation of the neuroimaging.
- 7. In the presence of cerebral injury that is diagnostically consistent with a hypoxic-ischemic pattern of injury, neuroimaging cannot determine the etiology of the hypoxia-ischemia, such as placental insufficiency or interruption of umbilical cord blood flow.

D. No Evidence of Other Proximal or Distal Factors That Could Be Contributing Factors

In the presence of other significant risk factors—such as abnormal fetal growth, maternal infection, fetomaternal hemorrhage, neonatal sepsis, and chronic placental lesions—an acute intrapartum event as the sole underlying pathogenesis of neonatal encephalopathy becomes much less likely.

#### IV. DEVELOPMENTAL OUTCOME IS SPASTIC QUADRIPLEGIA OR DYSKINETIC CEREBRAL PALSY

- A. Other subtypes of cerebral palsy are less likely to be associated with acute intrapartum hypoxic—ischemic events.
- B. Other developmental abnormalities may occur, but they are not specific to acute intrapartum hypoxic-ischemic encephalopathy and may arise from a variety of other causes.

#### NEUROIMAGING ADVANCES OVER THE PAST DECADE

With the wider use of MRI, the recognition of different patterns of injury has become established. Two main patterns often are distinguished on MRI: 1) the basal–ganglia–thalamus pattern and 2) the watershed or border zone predominant pattern. In the interpretation of the literature on MRI in neonatal encephalopathy, there are two major weaknesses: 1) the exact timing of the insult is generally not known and, more importantly, 2) there are little to no data on the neuropathological correlate of the MRI pattern.

MRI studies have defined that the vast majority of cases of cerebral injury that are seen in term-born infants with neonatal encephalopathy are acute. In comparison, epidemiologic studies have suggested that 70% of causation is related to chronic antenatal factors. This apparent contradiction reflects the fact that the MRI studies relate imaging findings in the first 2-3 weeks of life and demonstrate a subacute pattern. These studies cannot, however, delineate if the injury occurred during labor or within the days before labor and delivery. There are few studies that have imaged infants in the first day of life to assist in the timing of ischemic cerebral injury. MRI can provide mutual information from diffusion-weighted imaging, conventional imaging, and magnetic resonance spectroscopy, which can inform timing. Information regarding the likely timing is best obtained with early imaging (first 24-96 hours of life) with further follow-up imaging to define the full nature of the abnormalities, optimally at 10 days of life (but with an acceptable window between 7 days and 21 days of life, depending on the logistics of acquiring MRI in the clinical setting).

It is now accepted that identifying the predominant pattern of brain injury is an important predictor of neurodevelopmental outcome for a term newborn with encephalopathy. It is important to note that most studies that relate patterns of injury to neurodevelopmental outcome undertook imaging after day 7 of life. Conventional images provide a robust measure of the nature and severity of injury when performed after 1 week from the initial insult, which correlates well with neurodevelopmental outcome. Conventional MRI in the first 24-96 hours of life may underestimate the total extent of the injury but is better in timing.

In summary, although MRI studies suggest that the period around the time of birth accounts for more than 75% of the causative period, studies have not systematically investigated the extent to which injury may have occurred during the 24 hours before delivery. Therefore, studies of early (first 48 hours of life) and serial (eg, day 1, 4, 10 of life) MRI in termborn encephalopathic infants are needed and will assist in determining the evolution of imaging findings. These studies should include careful evaluation of the placenta.

#### **OTHER ADVANCES**

Greater awareness of the importance of placental attributes and genetic susceptibility to neonatal encephalopathy has emerged, although both areas of investigation are still fairly new. The implementation of hypothermia for the treatment of neonatal encephalopathy is a milestone in neonatal medicine and represents the culmination of research spanning decades that has proved the potential for neural rescue after "perinatal asphyxia." The recognition that this therapy improves early childhood outcomes has accelerated the pace of investigations to find other brain-oriented treatments. The fact that greater than 40% of neonates undergoing hypothermia treatment still develop adverse neurologic outcomes underscores the need to further understand the underlying processes in neonatal encephalopathy. Understanding the underlying processes, ideally, will yield more effective clinical criteria for matching each patient with tailored treatment options. The current emphasis in this document is on identification of the optimal criteria for the identification of cases in which there is a hypoxic or ischemic contribution to neonatal encephalopathy of recent onset, which inevitably will be much less stringent than defining essential criteria.

#### **PATIENT SAFETY**

A new and important addition to this report is a review of patient safety efforts directed at preventing neonatal encephalopathy. Enhancing patient safety requires changing the culture of health care delivery from one that names and blames to one that is dedicated to reducing medical errors through a constructive, nonthreatening, and professional process. A template is provided for performing a root cause analysis as part of this process. Furthermore, because many obstetricians and pediatricians who practice in small hospitals will not be expected to encounter many cases of neonatal encephalopathy, an obstetric and neonatal data collection tool is provided to serve as a guide for obtaining necessary information to learn from these cases.

#### **CONCLUSIONS**

In the decade since this report was first published, considerable advances have been made in the knowledge and understanding of the processes contributing to neonatal encephalopathy and long-term neurodevelopmental outcome, including the landmark introduction of neonatal hypothermia as a therapeutic intervention. Although full understanding is still elusive, the recommended multi-dimensional assessment process for neonatal encephalopathy described in this Executive Summary and in Chapter 13 reflects the current state of scientific knowledge and acknowledges limitations definitively distinguishing hypoxic-ischemic encephalopathy from other forms of neonatal encephalopathy with the array of clinical tools currently available. The multidimensional aspect of the assessment process is key to recognizing that no single strategy to identify hypoxic-ischemic encephalopathy is infallible and will achieve 100% certainty of the cause of neonatal encephalopathy in all cases. Promoting a multidimensional perspective should stimulate the laboratory, clinical, and epidemiologic research needed to fill the knowledge gaps and better guide treatment and long-term prognosis of neonatal encephalopathy, assist families in care and support of their affected children, and improve clinical practice.

The task force recognizes that this report will require updating as the

scientific database and knowledge on this topic expands. Several important areas of research are recommended, which are detailed in the text of the full document. Those engaged in research are encouraged to pursue these areas and others to exert influence to the degree possible to propel this to a high priority for funding and study.

Finally, the task force acknowledges the many consultants and support staff who made this project possible. In addition, co-publication of this report with the American Academy of Pediatrics, the input from the Centers for Disease Control and Prevention\* and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the endorsement from the following organizations has resulted in a highly peer-reviewed and scientifically rigorous document:

- American College of Nurse-Midwives
- American Gynecologic and Obstetrical Society
- American Society for Reproductive Medicine
- Association of Women's Health, Obstetric and Neonatal Nurses

- Australian Collaborative Cerebral Palsy Research Group
- Child Neurology Society
- Japan Society of Obstetrics and Gynecology
- March of Dimes Foundation
- Royal Australian and New Zealand College of Obstetricians and Gynaecologists
- <sup>T</sup>Royal College of Obstetricians and Gynaecologists
- Society for Maternal-Fetal Medicine
- Society of Obstetricians and Gynaecologists of Canada

<sup>†</sup>The Royal College of Obstetricians and Gynaecologists has reviewed and approved the task force report and provided its official designation of "support" in lieu of endorsement.

The information in Neonatal Encephalopathy and Neurologic Outcome, Second Edition, should not be

\*The findings and conclusions in this task force report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

viewed as a body of rigid rules. The guidelines are general and intended to be adapted to many different situations, taking into account the needs and resources particular to the locality, the institution, or the type of practice. Variations and innovations that improve the quality of patient care are to be encouraged rather than restricted. The purpose of these guidelines will be well served if they provide a firm basis on which local norms may be built.

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