Neonatal Encephalopathy and Neurologic Outcome

SECOND EDITION

(Reaffirmed 2019)
Neonatal Encephalopathy and Neurologic Outcome, Second Edition, was developed under the direction of the Task Force on Neonatal Encephalopathy. The information in Neonatal Encephalopathy and Neurologic Outcome, Second Edition, should not be 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 served if they provide a firm basis on which local norms may be built.

Studies were reviewed and evaluated for quality according to the method outline by the U.S. Preventive Services Task Force:

I. Evidence obtained from at least one properly designed randomized controlled trial.
II-1. Evidence obtained from well-designed controlled trials without randomization.
II-2. Evidence obtained from well-designed cohort or case-controlled analytic studies, preferably from more than one center or research group.
II-3. Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
III. Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

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The following organizations have reviewed and endorsed this report:

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- American Gynecological 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
- *Royal College of Obstetricians and Gynaecologists
- Society for Maternal-Fetal Medicine
- Society of Obstetricians and Gynaecologists of Canada

*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.
In 2000, Dr. Frank Miller, then president of the American College of Obstetricians and Gynecologists (the College), initiated the Task Force on Neonatal Encephalopathy and Cerebral Palsy. At that time, Dr. Miller issued the following mission statement:

“To create a multidisciplinary task force to review and consider the current state of scientific knowledge about the mechanisms and timing of possible etiologic events which may result in neonatal encephalopathy. The purpose of such review will be to produce a consensus statement, report or monograph for Fellows of the College which will succinctly summarize the neuroscience of neonatal encephalopathy and provide a framework for explaining to patients and the general public, in understandable language, medicine’s ability and capacity (and limitations) to detect, treat or in any way affect the pathophysiologic mechanisms which result in neonatal encephalopathy.”

The American College of Obstetricians and Gynecologists collaborated with the American Academy of Pediatrics and published the final report in 2003. The task force acknowledged that the publication was a work in progress and would require updating.

Dr. Richard Waldman became president of the College in 2010. This revision of the 2003 report was one of his presidential initiatives. The charge was simple and straightforward: “to update the document to the current state of scientific and clinical knowledge relating to neonatal encephalopathy and neurologic outcomes.” This charge was accomplished over 2 years.

Methods

The second Task Force on Neonatal Encephalopathy was convened in 2010 and comprised several physicians with expertise in different aspects of this issue, along with liaison members from the American Academy of Pediatrics, the Centers for Disease Control and Prevention, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Beginning in 2010, the task force met three times over the span of 2 years. At the first meeting, members outlined the subject matter to be covered, identified clinicians and scientists with particular expertise in the field, and agreed to edit solicited written contributions based on an extensive review of the literature from those individuals. At subsequent meetings, the task force reviewed and edited the draft manuscripts and deliberated to achieve consensus on the recommendations included in this report. Throughout the process, primary source documents were cited to the fullest extent possible.

Significantly more consultants were used in creating this document than in the report of the first task force, including an increased number of international contributors. There were 17 task force members and 88 consultants who collectively reviewed approximately 1,500 references as part of an extensive undertaking to review the evidence and present new findings and recommendations to update the first report. Furthermore, the report in 2003 refined criteria from the International Cerebral Palsy Task Force that published a consensus statement in The British Medical Journal in 1999. Because the International Cerebral Palsy Task Force report has not been updated since 1999, it is our hope that this document will have global value.
Once the initial draft was completed, the following organizations endorsed the current report:

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- American Gynecological 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
- Royal College of Obstetricians and Gynaecologists
- Society for Maternal-Fetal Medicine
- Society of Obstetricians and Gynaecologists of Canada

Those federal agencies that had endorsed the first edition—the Centers for Disease Control and Prevention† and the Eunice Kennedy Shriver National Institute of Child Health and Human Development—have had a change in policy that preclude endorsement of this edition, but both agencies had representation on the current task force. The American Academy of Pediatrics was a major contributor throughout the project and is a coauthor of this report.

**Task Force Goals**

The task force identified five specific goals:

1. To continue to broaden the understanding of neonatal encephalopathy by summarizing the best available primary-source scientific data and expertise of highly qualified individuals who have been major contributors to the field.

2. To develop recommendations for evaluation of a newborn with encephalopathy to assist the clinician in defining both the cause and timing of that disorder.

3. To identify areas in which further research is needed and to incorporate those recommendations in each chapter.

4. To continue to raise awareness of the need for standardization of terminology and precision in its use, which is imperative for the interpretation of meaningful research on neonatal encephalopathy and its neurologic outcome.

5. To review the criteria for determining the presence of hypoxic insult during the intrapartum period outlined in the first report and make recommendations for change if needed based on new insights obtained over the past decade.

**Changes in the Current Document**

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.

The focus of the current edition is on moderate and severe neonatal encephalopathy in infants born at or beyond 35 weeks of gestation. Several new chapters have been added and all of the previous chapters have been significantly updated.

Chapter 1 provides a definition of neonatal encephalopathy in the infant born at or beyond 35 weeks of gestation, and a diagram to demonstrate the different causal pathways to cerebral palsy. The task force prefers the general term *neonatal encephalopathy* to *hypoxic–ischemic encephalopathy*, which is a cause-specific subset of neonatal encephalopathy, and highlights the continued absence of precise terminology in the literature since the publication of the 2003 document. In particular, there is great disparity in the literature in the usage of the term “asphyxia.” The task force defines *asphyxia* as marked impairment of gas exchange leading, if prolonged, to progressive hypoxemia, hypercapnia, and significant metabolic acidosis. The term asphyxia, which describes a process of varying severity and duration rather than an end point, should not be applied to birth events unless specific evidence of markedly impaired intrapartum or immediate postnatal gas exchange can be linked to neurologic illness in the neonate. Throughout the report, the terms “asphyxia” and “birth asphyxia” and their variations appear in quotes when used in reference to a particular study to emphasize the wide variation in study definitions of asphyxia. (For more information, please see Chapter 1.) Chapter 1 also discusses two very different perspectives on risk: 1) timing of adverse events and 2) neurodevelopmental outcome in neonatal encephalopathy based on epidemiologic evidence, which was relied on heavily in the previous document versus data from neuroimaging studies that have been published since 2003.
Chapter 2 is a new contribution that reviews basic science studies specific to hypoxic–ischemic encephalopathy. These demonstrate that maintenance of cerebral perfusion is an essential prerequisite for long-term neuronal survival and that some neural cells are particularly vulnerable to primary energy failure. The neurotoxic cascade of molecular events that result in secondary brain injury is described in detail. The cofactors of bacterial infection, inflammation, and chronic fetal substrate deprivation that have been shown in animal studies to alter the fetal response to ischemia or make the fetal brain more vulnerable to hypoxia–ischemia are discussed.

Chapter 4 is a new contribution on placental pathology and umbilical cord abnormalities, which highlights the fact that clinical correlation with those entities has been difficult because the placenta often has been discarded when neonatal encephalopathy is identified. The information presented underscores the need for population-based studies that include detailed pathologic correlation of the placenta and other antenatal and perinatal risk factors with neuroimaging studies and possible genetic markers of neonatal encephalopathy.

Chapter 6 addresses the issue of standardization of the terminology used in intrapartum monitoring. Also discussed is the association of various electronic fetal heart patterns with fetal and neonatal acidemia.

Chapter 8 is a new contribution that discusses focal ischemic fetal and neonatal strokes. Magnetic resonance imaging (MRI) is the neuroimaging investigation of choice in all perinatal stroke syndromes, and despite a lengthy list of putative associations, evidence for a true causative factor cannot be found in most cases of perinatal stroke. Perinatal strokes are the predominant cause of hemiplegic cerebral palsy, and many children affected have additional abnormalities.

Because of the significant advances in neuroimaging over the past decade, several experts were asked to collaborate on Chapter 10, and Dr. Terri Inder provided the lead on this very substantial effort. Magnetic resonance imaging has been found to be the neuroimaging modality that will best define the nature and extent of cerebral injury in neonatal encephalopathy. Early MRI performed 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.

Chapter 11 is a new contribution on the subject of neonatal interventions. 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 following "perinatal asphyxia." The recognition that this therapy improves early childhood outcomes has accelerated the pace of investigations to find other brain-oriented treatments, which also are described in the chapter.

Chapter 12 is a new contribution from several obstetricians, including maternal–fetal medicine specialists, and neonatologists reviewing patient safety efforts directed at preventing neonatal encephalopathy. Discussed strategies include root cause analysis, communication, team training, and simulation exercises. 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.

In the first edition of this report, the task force outlined essential criteria necessary to establish a causal link between intrapartum hypoxic events and the subsequent development of cerebral palsy. Chapter 13 reflects the broader perspective championed by the current task force and includes a proposed comprehensive multidimensional assessment tool of neonatal status to determine the likelihood that an acute hypoxic–ischemic event that occurred within close temporal proximity to labor and delivery contributed to neonatal encephalopathy.

In 2003, the task force identified the following four essential criteria required to define an acute intrapartum hypoxia event as being sufficient to cause cerebral palsy: 1) evidence of a metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH less than 7.0 and base deficit 12 mmol/L or greater), 2) early onset of neonatal encephalopathy, 3) cerebral palsy of spastic quadriplegic or dyskinetic type, and 4) exclusion of other identifiable etiologies. These criteria were useful for several reasons. It was important to recognize that neither spastic diplegic nor hemiplegic cerebral palsy is likely to have its origin in birth hypoxia. It also was useful to stress that moderate degrees of acidemia and low Apgar scores are relatively common in infants with normal subsequent neurologic outcomes. Nevertheless, one of the goals of
the current guideline was to review these criteria for possible revision and to assess their utility in light of new knowledge. Despite the many advances highlighted in the new and updated chapters in this document, new epidemiologic data on neonatal encephalopathy and hypoxic–ischemic encephalopathy have been very limited since the publication of the report in 2003. There have been no population-based studies of the incidence of neonatal encephalopathy or hypoxic–ischemic encephalopathy with updates from more recent birth cohorts since the mid 1990s, and very few reports on risk factors based on studies with larger sample sizes than the Western Australia study published in the late 1990s. Despite standardizing fetal heart rate interpretation systems, we still lack reliable assessment tools of fetal and neonatal status, which are both sensitive and specific to an intrapartum insult that correlates with long-term outcome. The critical hypoxic or ischemic threshold for neuronal necrosis in the developing brain remains unknown. Clinical and epidemiologic studies of risk factors often appear discordant. The timing of contributory events and developmental outcome is unclear. Confusion persists in the terminology relating to neonatal encephalopathy and hypoxic–ischemic encephalopathy used in the scientific literature. Laboratory studies of etiology continue to focus almost exclusively on the hypoxia–ischemia pathway. All of these factors underscore existing knowledge gaps.

For the current edition, the task force concluded that a broader perspective might be more fruitful. We simply do not have a definitive test or set of markers that reliably identify an infant in whom neonatal encephalopathy is attributable to an acute intrapartum event. Nevertheless, the task force felt there was strong justification for undertaking steps to assess the probability that an acute hypoxic–ischemic event that occurred within close temporal proximity to labor and delivery was solely responsible for or significantly contributed to an episode of neonatal encephalopathy. The Executive Summary and Chapter 13 outline the information necessary for making this assessment, which can be derived from a comprehensive evaluation of all the potential contributing factors to any case of neonatal encephalopathy, including the maternal medical history, obstetric antecedents, intrapartum factors (including fetal heart rate monitoring patterns), and placental pathology. Subsequent analysis of all that information will produce a number of benefits that extend far beyond the provision of a single probability estimate.

About This Document

The task force acknowledges that like its predecessor, this publication is a work in progress. It incorporates concepts as they are currently understood, and we hope that it will serve as another building block that leads toward a complete understanding of neonatal encephalopathy.

This second edition would not have been possible without the commitment of all of the task force members who spent countless hours writing portions of this document and reviewing the work of consultants and other members of the group. In addition, the College staff—led by the capable Debra Hawks and her team of Chuck Emig, Anna Hegge, Mary Hyde, Karina Ngaiza, Nancy O’Reilly, Alyssa Politzer, Jean Riedlinger, Pamela Van Hine, Sarah Son, Sarah Tedrow-Azizi, Kelly Thomas, and Margaret Villalonga—was continuously available to assist the task force with numerous communications and innumerable conference calls throughout the project.

Dr. Gerald F. Joseph Jr served as the College’s primary liaison physician for the task force, and Dr. Hal C. Lawrence, Dr. Richard N. Waldman, and Dr. James N. Martin Jr also attended our meetings. I am thankful to all four physicians for giving the task force their complete support and total academic freedom.

Finally, I am personally grateful to Dr. Richard Waldman for making the update of this document one of his presidential initiatives and for his unwavering support and confidence throughout the process since its inception. It has been my privilege and honor to work with an extraordinary group of task force members, national and international consultants, the American Academy of Pediatrics, and the College in the preparation of this report.

Mary E. D’Alton, MD, FACOG
Chair, Task Force on Neonatal Encephalopathy
Executive Summary

n 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. E-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

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* Time of irreversible brain damage or anomaly

FIG. E-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 factor may lead to neonatal encephalopathy and subsequent cerebral palsy. B. Intrapartum brain injury may be the result of both distal and proximal risk factors that predispose the fetus to brain injury and cerebral palsy. C. Brain injury or anomaly may occur in the antepartum period as a result of distal and proximal risk factors. When brain injury or anomaly occurs at a time that is remote from the delivery process, neonatal encephalopathy may or may not be seen after birth. D. 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.
encephalopathy is attributable to an acute intrapar- tum 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.

In order 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.

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

1. 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.
2. 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

1. 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–ischemia played a role in causing neonatal encephalopathy.
3. 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 Magnetic Resonance Imaging or Magnetic Resonance Spectroscopy Consistent With Hypoxia–Ischemia

1. Magnetic resonance imaging (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.

3. 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.

4. 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 Hypoxia–Ischemic Encephalopathy

1. Multisystem organ failure can include renal injury, hepatic injury, hematologic abnormalities, cardiac dysfunction, metabolic derangements, and gastrointestinal injury, or a combination of these.

2. 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
4. 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

1. 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 standard deviation), or both is not consistent with an acute hypoxic–ischemic event.

2. 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 cesar-
ean 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 hypoxic–ischemic event.

c. 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. Magnetic resonance imaging and magnetic resonance spectroscopy are the most sensitive neuroimaging modalities to assist with the timing of cerebral injury. Magnetic resonance imaging—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 management 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 hypoxia–ischemia 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.

Magnetic resonance imaging 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. Magnetic resonance imaging 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 term-born 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, nonterrorizing, 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 multidimensional 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 Gynecological 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
- Royal College of Obstetricians and Gynaecologists†
- Society for Maternal-Fetal Medicine
- Society of Obstetricians and Gynaecologists of Canada

*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.
†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.
Background

In this chapter, and throughout the guideline, evidence is drawn from a spectrum of study types (ie, laboratory, clinical, and population-based epidemiologic studies), and it is important to be aware of the differences in their roles in the understanding of neonatal encephalopathy and its sequelae. At one end of the study-type spectrum are laboratory studies using nonhuman experimental surrogates to model different pathophysiologic pathways leading to brain injury under carefully controlled conditions. These types of studies are invaluable tools for drawing scientific inferences regarding biologic processes that may inform the design of human studies, including clinical interventions. What laboratory studies cannot provide, however, is the proportion and characteristics of human neonates in the general population in whom encephalopathy can be attributed to the specific processes observed in the controlled experiment. At the opposite end of the study-type spectrum are population-based epidemiologic studies that are designed to determine the prevalence and risk factors for neonatal encephalopathy and the characteristics of affected infants at the population level. Because it is rarely possible to study an entire population, it is important to ensure by study design and implementation that infants in an epidemiologic study are representative of the underlying population to generalize the observed findings to all infants. The detail of information that can be gathered on individual infants in a population-based study, however, may be limited by the expense of data gathering in large numbers. In between the laboratory and population-based studies are clinical studies designed to improve care and outcome of individual patients. Because clinical studies are typically smaller in size than population-based studies, great depth of information gathering is often feasible. However, because study participants are drawn from the clinical setting, the study sample may not be representative of the underlying population of all affected neonates, depending on the determinants of clinical referral and admission in a particular facility. Thus, findings from clinical studies may be generalizable to specific patient populations, but what is not known is the degree to which the evidence is generalizable to the overall population. In summary, laboratory studies provide a focused but very narrow and, by design, simplified view of brain-injury processes. Clinical studies provide a depth of data that are informative of specific patient populations but may not be representative of all affected infants. Population-based epidemiologic studies are most valuable for providing unbiased estimates of prevalence and identification of risk factors for neonatal encephalopathy and its sequelae (the broad view) against which interpretation of clinical and laboratory evidence (the deep, narrower views) can be calibrated.

Neonatal Encephalopathy and Cerebral Palsy

The terms central to this guideline, neonatal encephalopathy and cerebral palsy, describe two neurologic symptom complexes. There are no specific diagnostic tests for either entity, and both terms are used when a number of agreed-upon criteria are met. Signs of neonatal encephalopathy appear in the first hours or days of life and cerebral palsy in the first 5 years of life. Neonatal encephalopathy occurs in infants born at or beyond 35 weeks of gestation. Cerebral palsy can
occur in infants born at any gestational age, but more than 60% of all cases of cerebral palsy occur in infants born at or near term (1, 2). Neonatal encephalopathy lies on a number of causal pathways to cerebral palsy and other neurodisabilities, yet many infants who experience mild or moderate degrees of neonatal encephalopathy will later be free of adverse outcomes (2–4). For those infants born at term, cerebral palsy can be preceded by neonatal encephalopathy or follow a seemingly asymptomatic neonatal course (5–7).

Health factors that influence the risk of neonatal encephalopathy and cerebral palsy include maternal disease, multiple pregnancy, gestational age at delivery, malformations within or outside the nervous system, congenital infections, intrapartum hypoxic–ischemic events, metabolic problems, and stroke (8–12). The causal pathways to neonatal encephalopathy and cerebral palsy are typically complex; more like a web of interacting factors than a strictly linear causal chain. In addition to health factors, low socioeconomic status and, in some studies, male sex also appear to influence the risk of neonatal encephalopathy and cerebral palsy (8–11, 13). An increased risk has been reported for cerebral palsy among males across all gestational ages for unclear reasons (14–16), although in the setting of newborn brain injury hormonal factors and sex differences in cell death pathways may play a role (17). Socioeconomic status has been measured and analyzed in a variety of ways (eg, parental education or occupation, insurance status, access to prenatal care, and neighborhood income), which make it difficult to compare results directly across studies. Furthermore, the mechanisms by which low socioeconomic status (and its link to health factors) affects the risk of neonatal encephalopathy or cerebral palsy are not understood (8, 18–20). Because prognosis and treatment will differ depending on underlying etiology, as well prevention strategies in the future, it is important to gain as thorough as possible an understanding of the etiological factors in neonatal encephalopathy.

Conclusions

- Health factors that influence the risk of neonatal encephalopathy and cerebral palsy include maternal disease, multiple pregnancy, gestational age at delivery, malformations within or outside the nervous system, intrapartum growth restriction, congenital infections, intrapartum hypoxic–ischemic events, metabolic problems, and stroke.

Historical Understanding of Neonatal Encephalopathy and Relation With Cerebral Palsy

Until relatively recently, it was assumed that all newborns compromised at term (and neonatal encephalopathy in particular) was the result of “birth asphyxia” (see Table 1-1 for definitions of physiologic terms). Further, it was assumed that cerebral palsy was also largely asphyxial in origin. The theory was that a poor neonatal condition and subsequent adverse motor outcome had origins in adverse intrapartum events, acting through the common causal pathway of hypoxia sufficient to overwhelm the fetus's compensatory mechanisms and cause cerebral ischemia. The basic problem with this premise (which was indeed accurate for some infants) was an accompanying assumption that everything that had clinical signs similar to those in neonatal encephalopathy must have the same cause. Thus, poor neonatal condition and signs of early neurologic dysfunction in a term infant were called hypoxic–ischemic encephalopathy (HIE), postasphyxial encephalopathy, “birth asphyxia,” and “perinatal asphyxia” (21–25).

If sufficiently prolonged, asphyxia (disruption of exchange of oxygen and carbon dioxide between the fetal and maternal circulation) can lead to cerebral hypoxia–ischemia (as a result of severe hypoxemia and reduced cerebral blood flow from reduced cardiac function), which can overwhelm the fetus's compensatory mechanisms and cause neonatal encephalopathy and cerebral palsy, especially spastic or dyserkinetic quadriplegia. The problem, however, in attributing neonatal encephalopathy and cerebral palsy to asphyxia lies in how to recognize a sufficient degree of asphyxia to cause these outcomes and how to rule out other causes. Delivery of oxygen to the fetus during birth is seldom measured directly; the surrogates of inadequate oxygen delivery—low

*Throughout the report, the terms “asphyxia” and “birth asphyxia” and their variations appear in quotes when used in reference to a particular study to emphasize the wide variation in study definitions of asphyxia. See recommended asphyxia definition in Table 1-1 and discussion of asphyxia terminology later in the chapter.
### TABLE 1-1. Definitions and Implications of Physiologic Terms Relevant to Hypoxic–Ischemic Encephalopathy

<table>
<thead>
<tr>
<th>Physiologic Term</th>
<th>Definition and Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia</td>
<td>Reduced amount of oxygen delivered to tissues; unlikely to cause encephalopathy or brain injury in the fetus or newborn infant</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>Reduced oxygen concentration in blood; associated with hypoxia but unlikely to cause brain injury if cerebral blood flow is adequate</td>
</tr>
<tr>
<td>Hypoxemia–ischemia</td>
<td>Reduced amount of oxygen and inadequate volume of blood delivered to tissues; can cause brain injury if delivery of oxygen and glucose falls below critical levels</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Low pH because of increase in lactic acid in the blood that reflects the severity of asphyxia and hypoxia–ischemia</td>
</tr>
<tr>
<td>Respiratory acidosis</td>
<td>Low pH because of increased carbon dioxide in blood; may protect the brain because of cerebral vasodilation and increased cerebral blood flow</td>
</tr>
<tr>
<td>Mixed acidosis</td>
<td>Low pH that reflects both increased carbon dioxide and lactic acid</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>Marked impairment of gas exchange leading, if prolonged, to progressive hypoxemia, hypercapnia, and significant metabolic acidosis. The term asphyxia, which describes a process of varying severity and duration rather than an end point, should not be applied to birth events unless specific evidence of markedly impaired intrapartum or immediate postnatal gas exchange can be linked to neurologic illness in the neonate.</td>
</tr>
</tbody>
</table>

Umbilical cord pH and high base deficit—may have other causes; and fetuses vary in the degree of asphyxia they can withstand (26). The clinical signs taken as indicators of asphyxial birth—including meconium release, prolonged bradycardia, abnormalities of fetal heart rate patterns, low Apgar scores, and neonatal seizures—all have other potential causes, several of which are more common than HIE. Furthermore, in some instances, these signs may be early manifestations or steps in a sequence of events, rather than causes, of brain injury. Placental inflammation and other chronic placental lesions have been associated with these clinical signs that are not asphyxial at initiation (27, 28). The use of a nonspecific marker (eg, Apgar score) for perinatal hypoxia–ischemia overestimates the number of individuals who are exposed to perinatal hypoxia–ischemia; the risk of neurologic damage from perinatal hypoxia–ischemia also will be biased because components of risk from other causes may be associated with the same marker. Figure 1-1 schematically illustrates the complexity of cerebral palsy causal pathways composed of multiple potential cerebral palsy risk factors and their diverse timing through gestation and the perinatal period, all of which may challenge the ability to determine a specific pathway leading to an individual case of cerebral palsy.

Although HIE composes a cause-specific subset of all neonatal encephalopathy, neonatal encephalopathy often is mislabeled HIE, sometimes based on historical assumptions and sometimes on very slender evidence of clinical markers that are not specific to asphyxia (29). One of the four goals of the original task force was “To raise awareness of the need for standardization of terminology and precision in its use, which is imperative to allow meaningful research on neonatal encephalopathy and cerebral palsy.” However, in the ensuing years, opinion papers, reviews, and original research continue to be published with neonatal encephalopathy and HIE—and also intrapartum hypoxia–ischemia, intrapartum asphyxia, postasphyxial encephalopathy, “birth asphyxia,” and birth hypoxic encephalopathy—used interchangeably and with varying inclusion and exclusion criteria (29). The effects of terminological confusion is evident in a recent review of the literature on cerebral palsy attributable to “birth asphyxia” that concluded that use of nonspecific clinical signs in the study definitions of asphyxia, different study definitions of cerebral palsy, and confusion of proximal effects with causes led to wide disparities in reported results (30). The problem with terminology is evident also when searching PubMed on this topic. Neonatal encephalopathy is not a medical subject heading; however, a search on PubMed for hypoxic–ischemic encephalopathy will find the medical subject heading “Hypoxia–Ischemia, Brain” with 61 subsequent entry terms, none of which include “neonatal encephalopathy.”

**Definitions**

*Neonatal Encephalopathy*  
Neonatal encephalopathy is the term recommended to describe neurologic dysfunction in the earliest days
of life in an infant born at or beyond 35 weeks of gestation (29, 31, 32) (see Box 14); the clinical signs that define neonatal encephalopathy are not specific with respect to its cause and can be difficult to recognize reliably and consistently in newborns. Definitions of neonatal encephalopathy vary widely in the literature and no two studies define neonatal encephalopathy in the same way. Some researchers require stringent criteria, such as two or more symptoms of encephalopathy that last more than 24 hours (8), whereas others require no more than a low 5-minute Apgar score (33).

Because neonatal encephalopathy is defined by a constellation of symptoms and no definitive diagnostic tests are available, implementing the definition in the clinical setting is challenging. The clinical features of neonatal encephalopathy can be difficult to recognize reliably and consistently in newborns, thereby prompting the need for standard criteria to be applied systematically across all infants to ensure consistent classification across all examiners. Given the immature nervous system in preterm infants, it is difficult and often impossible to diagnose encephalopathy in infants born before 35 weeks of gestation. This document focuses on neonatal encephalopathy and outcome in infants born at or beyond 35 weeks of gestation. Evidence that relates to preterm infants delivered before 35 weeks of gestation is provided in separate subsections.

Using the term neonatal encephalopathy rather than HIE or “birth asphyxia” is important for families, clinicians, and researchers because it permits identification of affected infants on the basis of clinically observable data and imposes no assumptions about etiology of the disorder (34). Consequently, by using this term, the true burden of neonatal encephalopathy in the population can be estimated because there is no biased preselection of infants based on a presumed cause or exposure. The full range of possible etiologic factors leading to neonatal encephalopathy also can be investigated so that the most appropriate treatment strategy can be identified and the full contribution of neonatal encephalopathy to long-term neurologic dysfunction can be assessed. Ultimately, it is important to identify the earliest instigating factors in each causal pathway to neonatal encephalopathy because for primary preventive strategies to be successful, intervention must occur as early as possible in the causal pathway before any pathological damage takes place.

FIG. 1-1. **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 factor may lead to neonatal encephalopathy and subsequent cerebral palsy. B. Intrapartum brain injury may be the result of both distal and proximal risk factors that predispose the fetus to brain injury and cerebral palsy. C. Brain injury or anomaly may occur in the antepartum period as a result of distal and proximal risk factors. When brain injury or anomaly occurs at a time that is remote from the delivery process, neonatal encephalopathy may or may not be seen after birth. D. 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. (Note: Fig. 1-1 also appears in Chapter 13 as Fig. 13-1.)
Three clinical categories of neonatal encephalopathy (Stage I, Stage II, and Stage III) based on severity and duration of symptoms—including abnormal response to handling, consciousness, tone and reflexes, and the presence of seizures (25)—are well accepted. These categories have proved useful as predictors of survival and risk of neurodevelopmental disabilities, including cerebral palsy (3, 35, 36). One systematic review (36) stated that no infants with mild neonatal encephalopathy and definite “asphyxia” developed cerebral palsy, which encourages research to focus on those with moderate and severe neonatal encephalopathy. However, it is important to note that mild neonatal encephalopathy (without signs of intrapartum events or asphyxia) may be part of other pathways to cerebral palsy (and other neurodevelopmental problems) and should not be overlooked. In a population-based case–control study of term infants with cerebral palsy, 10% of cases had two or more signs of neonatal encephalopathy that were not considered sufficiently severe to warrant admission to a neonatal intensive care unit (NICU) or neonatal special care unit (7). Prospective studies monitoring infants with neonatal encephalopathy may not be identifying all those with mild neonatal encephalopathy, especially if they are not being admitted to an NICU or neonatal special care unit.

Cerebral Palsy
Cerebral palsy describes a group of conditions involving motor disability of early onset that, despite a wide range of possible abilities and disabilities, satisfy the following criteria:

- The presence of a motor disorder (spasticity, dyskinesia, ataxia, mixed motor abnormalities, and hypotonia)
- The result of a cerebral abnormality
- Origination early in development
- Condition not progressive or degenerative (37) (but lifelong with no known cure)

Associated impairments—including vision, hearing, cognition, speech, epilepsy, and behavioral disorders—often accompany the motor impairment (38). The more severe the motor impairment, the more likely that a number of associated impairments will add to the complexity of the disorder. Severity of cerebral palsy is frequently classified by gross motor function using the Gross Motor Function Classification System, which ranges from level I to level V (39). A 5-year-old with level I gross motor function will be able to walk, run, jump, and climb stairs, but speed, balance, and coordination will be limited. A 5-year-old with level III gross motor function will use a hand-held mobility device in most indoor settings and will need wheeled mobility when traveling longer distances. A 5-year-old with level V gross motor function will have no independent mobility and will be limited in ability to maintain antigravity head and trunk postures. The Gross Motor Function Classification System seems to be stable into adulthood, and very few individuals will improve in level after the age of 10 years (39).

The risk of cerebral palsy increases substantially as gestational age of delivery decreases, with very preterm birth (less than 32 weeks of gestation) being the strongest risk factor for cerebral palsy (6). Because of their high risk, researchers have appropriately focused on reducing neonatal mortality and morbidity in very preterm births (40–42). Subsequently, trends across the developed world have shown that rates for both death and cerebral palsy for very preterm infants have been steadily decreasing since the mid 1990s (1, 2, 16), likely because of improvements in perinatal care. However, decreases in rates of cerebral palsy in the youngest gestational age groups have made little effect on overall birth prevalence of cerebral palsy (2–2.5/1,000 live births) because very preterm births make up only 2% of all births.

Conversely, late-preterm and term infants are individually at relatively low risk of cerebral palsy compared with very preterm infants (43); however, they
make up at least 60% of all cases of cerebral palsy (1, 2). This is mostly because of the fact that term and late-preterm infants constitute approximately 98% of all births. Unlike the rates of very preterm and extremely preterm infants with cerebral palsy, which have seen changes in birth prevalence, the rates of term infants with cerebral palsy have remained remarkably stable. The rate of 1.4–1.8 per 1,000 live births is consistent around the developed world and over time (1, 2, 44).

The risk of cerebral palsy in late-preterm and term infants varies by race and ethnicity. Compared with white infants, African American infants have an increased risk of cerebral palsy that is largely attributed to their increased rate of low birth weight. Among infants born at term, African American infants exhibit a significantly increased risk of spastic or dyskinetic cerebral palsy for unclear reasons. In contrast, Asian American infants have a reduced cerebral palsy risk at all gestational ages (10, 19, 45). Exploring race-ethnicity disparities in term cerebral palsy prevalence may contribute to the understanding of the etiologic mechanisms underlying term cerebral palsy and the link with neonatal encephalopathy.

Conclusions

• Neonatal encephalopathy and cerebral palsy are neurologic complexes defined by constellations of multiple symptoms rather than specific diagnostic tests.
• Perinatal hypoxia–ischemia can cause neonatal encephalopathy and neurologic injury leading to cerebral palsy, especially spastic or dyskinetic quadriplegia, but it is only one of many potential causes of these conditions.
• Clinical signs taken as indicators of asphyxial birth may reflect a step in a sequence of events in more than one causal pathway leading to neonatal encephalopathy and cerebral palsy.
• The use of a nonspecific marker (eg, Apgar score) for perinatal hypoxia–ischemia overestimates the number of individuals who are exposed to perinatal hypoxia–ischemia; the risk of neurologic damage from perinatal hypoxia–ischemia also will be biased because components of risk from other causes may be associated with the same marker.
• Hypoxic–ischemic encephalopathy composes a cause-specific subset of all neonatal encephalopathy, yet the terms HIE, neonatal encephalopathy, and many similar terms are used interchangeably in the literature, reflecting the need for standardization and precision in use of terminology.
• The clinical signs that define neonatal encephalopathy are not specific with respect to its cause and can be difficult to recognize reliably and consistently in newborns.
• It is important to identify the earliest instigating factors in neonatal encephalopathy because for primary preventive strategies to be successful, intervention must occur as early as possible in the causal pathway before any pathological damage takes place.
• Term and late-preterm infants make up at least 60% of all cases of cerebral palsy and term cerebral palsy rates have remained remarkably stable around the developed world and over time.

Neonatal Encephalopathy Epidemiology

Incidence
An epidemiologic review estimated that the incidence of neonatal encephalopathy in developed countries is 3 per 1,000 live births (95% confidence interval [CI], 2.7–3.3) (29). This rate is based on the only population-based studies reporting incidence. However, there are only two such studies, both are based on birth years 1993–1995 (8, 9, 46), and there are no data that can be examined for trend analyses. Three population studies estimated the incidence of the subset of neonatal encephalopathy, HIE (8, 47, 48). The review authors combined the data and estimated the incidence of HIE to be 1.5 per 1,000 live births (95% CI, 1.3–1.7). The latest birth year for either neonatal encephalopathy or HIE estimates was 1996, so there is a clear need for updated population data. When hospital-based estimates are included, the rates are much higher for neonatal encephalopathy (up to 6/1,000 live births) and HIE (up to 8/1,000 live births), but these estimates are subject to referral bias of both cases born elsewhere and admitted to the target hospital after delivery and complicated pregnancies (29).

The review authors noted one further problem. No two groups of investigators used the same definition of neonatal encephalopathy or its subset HIE, a problem contributing to the confusion in terminology already discussed in this chapter. As a result, it is unlikely that cases identified among different studies are equivalent in terms of their etiologic profile or their neonatal course. However, the estimates may demonstrate the effects on incidence rates of the degree of inclusiveness or exclusiveness among criteria for defining
neonatal encephalopathy, with lower rates typically reported from studies in which the criteria were more exclusive. Thus, the best recent estimates of the incidence of neonatal encephalopathy come from large, population-based studies that used restrictive (exclusive) criteria to define HIE (incidence estimate of 1.5/1,000 live births [95% CI, 1.3–1.7]) and broad (inclusive) criteria to define neonatal encephalopathy (incidence estimate of 3/1,000 live births [95% CI, 2.7–3.3]).

**Risk Factors**

Historically, the incorrect assumption that virtually all cases of neonatal encephalopathy resulted from intrapartum hypoxemia has impeded the search for other causes, especially causes arising before the onset of labor. This assumption often narrowly dictated the selection criteria for study participants (eg, only infants presumed to be exposed to intrapartum hypoxemia), thus creating small, select samples not representative of all infants affected by neonatal encephalopathy. Typically, the studies also did not include a group of unaffected infants for comparison, so it was impossible to determine whether the perinatal characteristics of the study infants (if such data were even reported) differed in any way from a comparable group of normal infants. As a result, the data generated from these studies cannot give a complete picture of the factors contributing to neonatal encephalopathy.

To address these issues, investigators designed a case–control study of all term infants (37 weeks of gestation or greater or birth weight 2,500 g or greater if gestational age was unknown) born in Perth, Western Australia, from June 1993 to September 1995, in whom moderate or severe neonatal encephalopathy was diagnosed in the first week of life (8, 9). The study broadly defined neonatal encephalopathy based only on features of abnormal consciousness, tone and reflexes, feeding, respiration, or seizures and did not assume an intrapartum etiology. A sample of controls was randomly selected from term infants without neonatal encephalopathy in the same study population. Preconceptional, antepartum, intrapartum, newborn, and neonatal variables were all obtained by a combination of prospective questionnaire and retrospective review and abstraction of the mothers’ and infants’ medical records.

Since this large population-based study there have been a number of studies that have verified or refuted these findings, but only two groups had more infants with neonatal encephalopathy than the Western Australian study. Investigators in Washington State (13, 18), conducted a data-linkage study of the population for birth years 1994–2002. They investigated maternal socioeconomic status (18), intrapartum fever, and chorioamnionitis (13) and their relationship with neonatal encephalopathy. One thousand sixty infants with neonatal encephalopathy were identified, but 11% of the population was not able to have their data linked. Investigators in the United Kingdom and the Netherlands aimed to identify the timing of injury associated with neonatal encephalopathy and seizures and studied 351 infants (49). However, they were not (reported to be) consecutive, were not population based (infants were born in two large cities in different countries rather than from a regional base population), and there was no control group to adequately identify risk factors; infants with neonatal encephalopathy were compared with infants with seizures who did not meet criteria for neonatal encephalopathy rather than to a representative sample of population controls. All three studies (Western Australia, Washington State, and the United Kingdom and the Netherlands) had different inclusion criteria and definitions of neonatal encephalopathy, and neither of the later studies (Washington State or Europe) are equivalent in quality for the purposes of identifying risk factors for neonatal encephalopathy. However, they are more recent and offer different perspectives in two different continents. The rest of this section looks at the Western Australian data in detail, but for comparative purposes, findings from the Washington State and European groups have been tabulated.

A multivariate analysis of 164 cases and 400 controls evaluated the role of preconceptional, antepartum, and intrapartum factors in neonatal encephalopathy (8, 9) (Table 1-2, Table 1-3, and Table 1-4). The strongest antepartum risk factor for neonatal encephalopathy was fetal growth restriction (low centile birth weight; Table 1-3). There are, however, many different causes of fetal growth restriction, and each may differ in its capacity to cause or predispose a fetus to neonatal encephalopathy. The risk of neonatal encephalopathy also increased with each advancing week of gestation after 39 weeks (Table 1-3). Several sociodemographic characteristics were significant risk factors for neonatal encephalopathy (Table 1-2). Elective cesarean delivery before labor, primarily because of cesarean deliveries in previous pregnancies, was associated with a significantly reduced risk of neonatal encephalopathy (adjusted odds ratio [OR], 0.17; 95% CI, 0.05–0.56). This finding has been repeated in more recent studies of women with prior cesarean deliveries who undergo elective repeat operation when
### TABLE 1-2. Preconception Sociodemographic and Maternal Medical Conditions That Are Independent Risk Factors for Newborn Encephalopathy

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Reference Group</th>
<th>Unadjusted Odds Ratio</th>
<th>Adjusted* Odds Ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>1†</td>
<td>1†</td>
<td></td>
</tr>
<tr>
<td>20–24</td>
<td>2.37</td>
<td>4.21 (1.10–17.50)</td>
<td></td>
</tr>
<tr>
<td>25–29</td>
<td>1.85</td>
<td>5.91 (1.42–24.54)</td>
<td></td>
</tr>
<tr>
<td>30–34</td>
<td>1.31</td>
<td>6.71 (1.53–29.44)</td>
<td></td>
</tr>
<tr>
<td>≥35</td>
<td>1.46</td>
<td>6.01 (1.28–28.15)</td>
<td></td>
</tr>
<tr>
<td>Blume US (2007‡, 2008§)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>1.2 (1–1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–24</td>
<td>1†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cowan UK (2003³)</td>
<td></td>
<td></td>
<td>Significantly younger maternal age distribution (chi-square test)³</td>
</tr>
<tr>
<td><strong>Maternal employment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professional</td>
<td>1†</td>
<td>1†</td>
<td></td>
</tr>
<tr>
<td>Unskilled manual</td>
<td>2.35</td>
<td>3.84 (1.43–10.28)</td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>3.57</td>
<td>2.48 (1.14–5.39)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>4.47</td>
<td>3.60 (1.10–11.80)</td>
<td></td>
</tr>
<tr>
<td>Blume US (2007‡, 2008§)</td>
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<td></td>
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</tr>
<tr>
<td>Cowan UK (2003³)</td>
<td></td>
<td></td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Health insurance</strong></td>
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</tr>
<tr>
<td>Private</td>
<td>1†</td>
<td>1†</td>
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</tr>
<tr>
<td>Public</td>
<td>2.2</td>
<td>3.46 (1.25–9.59)</td>
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</tr>
<tr>
<td>Blume US (2007‡, 2008§)</td>
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<td></td>
</tr>
<tr>
<td>Cowan UK (2003³)</td>
<td></td>
<td></td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Family history of seizures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1†</td>
<td>1†</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.10</td>
<td>2.55 (1.31–4.94)</td>
<td></td>
</tr>
<tr>
<td>Blume US (2007‡, 2008§)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cowan UK (2003³)</td>
<td></td>
<td></td>
<td>Significantly higher frequency (Fisher's exact test)³</td>
</tr>
<tr>
<td><strong>Family history of neurologic disorder</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1†</td>
<td>1†</td>
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<tr>
<td>Yes</td>
<td>2.6</td>
<td>2.73 (1.16–6.41)</td>
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<td>Blume US (2007‡, 2008§)</td>
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<td></td>
</tr>
<tr>
<td>Cowan UK (2003³)</td>
<td></td>
<td></td>
<td>Significantly higher frequency (Fisher's exact test)³</td>
</tr>
<tr>
<td><strong>Infertility treatment</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1†</td>
<td>1†</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.23</td>
<td>4.43 (1.12–17.60)</td>
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<tr>
<td>Blume US (2007‡, 2008§)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cowan UK (2003³)</td>
<td></td>
<td></td>
<td>No significant difference in frequency (Fisher's exact test)³</td>
</tr>
</tbody>
</table>


*Adjusted for effects of all other variables in table as well as for parity, maternal race, maternal hypertension, maternal height, maternal thyroid disease, preeclampsia, bleeding, viral illness, alcohol consumption, gestational age, centile birth weight, infant’s sex, appearance of placenta, late or no antenatal care, hospital of delivery, and plurality.

† Baseline comparison group.


¶ Cowan et al grouped cases by calculated timing of injury on magnetic resonance imaging; this finding was in the nonacute origin (26%) (Cowan 2003).

# Adjusted for maternal age, parity, race/ethnicity, marital status, preeclampsia, and birth year.

** Recurrent, nonfebrile seizures.

†† Excludes seizures.
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Reference Group</th>
<th>Unadjusted Odds Ratio</th>
<th>Adjusted Odds Ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal thyroid disease</td>
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<td></td>
</tr>
<tr>
<td></td>
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<td>1†</td>
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<tr>
<td></td>
<td>Yes</td>
<td>5.9</td>
<td>9.70 (1.97–47.91)</td>
</tr>
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<tr>
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<tr>
<td></td>
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<td>Severe</td>
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<td>2.1 (1.6–2.5)</td>
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<tr>
<td></td>
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<td>No</td>
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<td>Yes</td>
<td>2.32</td>
<td>3.57 (1.30–9.85)</td>
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<tr>
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<td>Lower frequency, but not significant (Fisher’s exact test) ¶</td>
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<td>Cowan UK (2003³)</td>
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<tr>
<td></td>
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<td>38</td>
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<td>1.18 (0.90–1.56)</td>
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<td>42</td>
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<td>Agree with J curve</td>
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<tr>
<td>Cowan UK (2003³)</td>
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<td></td>
<td>Agree with J curve</td>
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<tr>
<td>Centile birth weight**</td>
<td>&gt;90th</td>
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<td>3rd–9th</td>
<td>1.63</td>
<td>4.37 (1.43–13.38)</td>
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<td>&lt;3rd</td>
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<td>38.23 (9.44–154.79)</td>
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<tr>
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<td>Nonsignificant trend for higher frequency of lower centile birth weights (chi-square test) ¶</td>
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<td>Appearance of placenta</td>
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<td>Abnormal</td>
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<td>Late or no antenatal care</td>
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<td>1†</td>
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<td></td>
<td>Yes</td>
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<td>5.45 (0.47–62.98)</td>
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(continued)
Independent Risk Factors for Newborn Encephalopathy compared with those undergoing trial of labor (50, 51). Significant associations between neonatal encephalopathy and maternal seizures, maternal thyroid disease, bleeding in pregnancy, congenital anomalies, abnormal appearance of the placenta, and markers of prenatal and perinatal infection also have been associated with cerebral palsy, supporting the idea of multiple causal pathways that lead to neonatal encephalopathy and cerebral palsy (8) (Table 1-2, Table 1-3, and Table 1-4). Of greatest significance, however, was that 70% of cases of neonatal encephalopathy were likely the result of events arising before the onset of labor. Infants with neonatal encephalopathy experienced a more adverse antepartum course than controls. In the presence of other significant risk factors (such as abnormal fetal growth, maternal infection, fetomaternal hemorrhage, neonatal sepsis, and chronic placental lesions) intrapartum hypoxia as the sole underlying pathogenesis of neonatal encephalopathy becomes less likely.

An estimate of the maximal possible contribution of intrapartum hypoxia to neonatal encephalopathy was made using the following criteria (that is nonspecific with high false-positive predictive values) to indicate intrapartum hypoxia: an abnormal intrapartum cardiotocogram or abnormal fetal heart rate on auscultation or fresh meconium in labor plus a 1-minute Apgar score less than 3 and a 5-minute Apgar score less than 7. Nineteen percent of case infants (n=31/164) and 0.5% of controls (n=2/400) met these criteria. An additional 10% (16 case infants) did not meet these criteria (or the Apgar score was not recorded) but had significant intrapartum events that may have been associated with hypoxia (eg, breech presentation or head entrapment), providing a total of 47 case infants (29% of all cases) with any possible evidence of intrapartum hypoxia (9) (Table 1-3). Even using such inexact markers for intrapartum fetal hypoxia, the following notable conclusions were reached regarding all 164 cases of neonatal encephalopathy:

• 69% (n=113) had only antepartum risk factors
• 25% (n=40) had antepartum risk factors and evidence for intrapartum hypoxia
• 4% (n=7) had evidence of intrapartum hypoxia in the absence of preconceptional or antepartum factors that also might have contributed to neonatal encephalopathy
• 2% (n=4) had no recognized risk factors for neonatal encephalopathy

Conversely, the United Kingdom investigators investigators did not aim to identify risk factors but did aim to identify timing of the injury responsible for neonatal encephalopathy by magnetic resonance imaging (MRI) (49). They identified that approximately 80% of their infants had an injury only in the perinatal period (although MRI could have occurred up to 10 days after birth). The apparent discrepancies between the two studies may be partly answered by looking at serious outcomes. In the Western Australian study, 22% died or developed cerebral palsy, whereas 43% died or developed cerebral palsy in the United Kingdom and Netherlands study. It seems the definitions of neonatal encephalopathy used and the patients selected were different. Additionally, because the United Kingdom and Netherlands study focused on timing of injury as opposed to timing of risk factors as in the Western Australian study, in some cases the brain damage might have occurred at or near delivery in a fetus rendered vulnerable by antenatal or genetic risk factors; in the future, prenatal MRIs may shed light on this possibility. What is clear is that the

**Birth weight adjusted for gestation, parity, maternal height, and infant’s sex.
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Reference Group</th>
<th>Unadjusted Odds Ratio</th>
<th>Adjusted* Odds Ratio (95% confidence interval)</th>
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<tr>
<td>Occipitoposterior position</td>
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<td></td>
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<tr>
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<td>No</td>
<td>1†</td>
<td></td>
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<tr>
<td></td>
<td>Yes</td>
<td>2.97</td>
<td>4.29 (1.74–10.54)</td>
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<tr>
<td>Maternal pyrexia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blume US (2007*, 2008*)</td>
<td>No</td>
<td>1†</td>
<td></td>
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<tr>
<td></td>
<td>Yes</td>
<td>5.34</td>
<td>3.82 (1.44–10.12)</td>
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<tr>
<td>Acute intrapartum event*</td>
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<td>1†</td>
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<tr>
<td></td>
<td>Yes</td>
<td>6.80</td>
<td>4.44 (1.30–15.22)</td>
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<td>Mode of delivery</td>
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<tr>
<td>Spontaneous</td>
<td>1†</td>
<td></td>
<td></td>
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<tr>
<td>Instrumental, vaginal</td>
<td>2.23</td>
<td>2.34 (1.16–4.70)</td>
<td></td>
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<td>Emergency cesarean</td>
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<td>2.17 (1.01–4.64)</td>
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<td>Elective cesarean</td>
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<td>0.17 (0.05–0.56)</td>
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<td>1†</td>
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<tr>
<td></td>
<td>Yes</td>
<td>4.40**</td>
<td>3.08 (1.16–8.17)</td>
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</table>


*Adjusted for effects of all other variables in the table as well as for maternal age, parity, employment status, health insurance status, race, family history of epilepsy and other neurological disease, infertility treatment, hypertension, height, thyroid disease, preeclampsia, moderate or severe bleeding, viral illness, alcohol consumption, gestational age, centile birth weight, infant sex, appearance of placenta, late or no antenatal care, hospital of delivery, plurality, membrane rupture to delivery interval greater than 12 hours, blood pressure abnormalities, nuchal cord, umbilical cord prolapse, onset of labor, shoulder dystocia, and epidural anesthesia.

† Baseline comparison group.


¶Adjusted for year of birth, parity, education, and obstruction of labor. This study identified chorioamnionitis as the most important finding (odds ratio, 5.4 [3.6–8.0]), adjusted as for maternal pyrexia.

# Hemorrhage, maternal convulsions, rupture of uterus, snapped umbilical cord, and birth of neonate before arrival at obstetric facility.

**Not significant increased risk at \( P < 0.05 \).
pathways to serious adverse outcomes, of which neonatal encephalopathy is a component, are not well understood.

As illustrated in Figure 1-1, the antepartum and intrapartum factors associated with neonatal encephalopathy may act independently of each other, or the antepartum factors may initiate a sequence of events followed by specific intrapartum responses. Alternatively, the imprecise and indirect markers for intrapartum hypoxia currently available may in some cases be the first clinical manifestations of a preexisting injury that has already caused an encephalopathy. It is important to remember that the understanding of cerebral palsy pathogenesis is incomplete. The first sign of neurologic abnormality often does not become evident until the intrapartum or postpartum periods; this is true for all five pathways. Therefore, the clinical tools are limited in their ability to discern specific causal pathways in individual cases of cerebral palsy. To elucidate the different causal pathways to neonatal encephalopathy and cerebral palsy, it is important that a reliable and readily available assessment of fetal status be possible and that more specific markers of the intrapartum insult be developed.

Information from placental examination may provide further information about processes active during the course of pregnancy. These data, coupled with early and sequential imaging studies, may provide valuable windows into the processes underlying neonatal encephalopathy and their timing.

Conclusions

- The best recent incidence estimates from large population-based studies in developed countries indicate that neonatal encephalopathy occurs in 3 per 1,000 live births and HIE, a cause-specific subset of neonatal encephalopathy, occurs in 1.5 per 1,000 live births.
- There are no data that can be examined for trend analyses of the incidence of neonatal encephalopathy in developed countries, but the best recent estimates come from large, population-based studies that use restrictive (exclusive) criteria to define hypoxic–ischemic encephalopathy and broad (inclusive) criteria to define neonatal encephalopathy.
- In the presence of other significant risk factors, such as abnormal fetal growth, maternal infection, fetomaternal hemorrhage, neonatal sepsis, and chronic placental lesions, intrapartum hypoxia as the sole underlying pathogenesis of neonatal encephalopathy becomes less likely.
- The antepartum and intrapartum factors associated with neonatal encephalopathy may act independently of each other, or the antepartum factors may initiate a sequence of events followed by specific intrapartum responses. Alternatively, the imprecise and indirect markers for intrapartum hypoxia currently available may in some cases be the first clinical manifestations of a preexisting injury that has already caused an encephalopathy.
- To elucidate the different causal pathways to neonatal encephalopathy and cerebral palsy, it is important that a reliable and readily available assessment of fetal status be possible and that more specific markers of the intrapartum insult be developed.
- Information from placental examination may provide further information about processes active during the course of pregnancy.
- Data from an assessment of fetal status and a placental examination, coupled with early and sequential imaging studies, may provide valuable windows into the processes underlying neonatal encephalopathy and their timing.

Long-Term Neurologic Outcome

From epidemiologic evidence, the absence of neonatal encephalopathy in an infant who later manifests cerebral palsy indicates that the cerebral palsy was not caused by perinatal hypoxia–ischemia. Thus, the pathway from intrapartum hypoxic–ischemic injury to subsequent cerebral palsy must certainly progress through neonatal encephalopathy. Broad questions regarding the outcome of neonatal encephalopathy, however, are as follows: What proportion of children with neonatal encephalopathy develops long-term neurodevelopmental problems, and what types of problems might the affected children have? Conversely, what proportion of children with long-term neurologic problems had evidence of encephalopathy as neonates?

Neurodevelopmental Follow-up of Neonatal Encephalopathy

Studies have attempted to answer the question regarding developmental outcome of neonatal encephalopathy by applying a broad array of measures, including imaging studies to identify specific types and timing of brain injury and psychometric assessment of specific areas of functioning of encephalopathic children at different ages. In a developmental follow-up of participants of the Western Australian neonatal...
encephalopathy study (previously introduced in this chapter in “Risk Factors”) during their second year of life, investigators observed that 23% of children with neonatal encephalopathy were significantly developmentally delayed (Griffiths General Quotient score less than 2 standard deviations below control mean) and had significant 1.5–2.5 months developmental age deficits in specific areas of functioning (ie, locomotor, personal social, speech and hearing, eye and hand, and performance); children with severe neonatal encephalopathy or neonatal encephalopathy with seizures had a poorer outcome than children with moderate neonatal encephalopathy or neonatal encephalopathy without seizures (35). Even after excluding children with cerebral palsy or other conditions that contribute to developmental deficit, 9% of the Western Australian neonatal encephalopathy cases were significantly developmentally delayed (35).

In the population-based Avon Longitudinal Study of Parents and Children, cognitive testing at age 8 years revealed risks of IQ less than 80 that were significantly increased risks (threefold to sevenfold) of children with low 5-minute Apgar scores (less than 2) and neonatal encephalopathy symptoms had significantly increased risks (threefold to sevenfold) of minor motor problems, epilepsy, school assistance, poor reading and mathematics skills, and behavior problems compared with children with low Apgar scores and no neonatal encephalopathy symptoms or children with higher 5-minute Apgar scores. Children with low 5-minute Apgar scores who were asymptomatic had no significantly increased risks of poor outcomes compared with children with higher Apgar scores (55). Despite the significant elevated risks of various minor disabilities, however, another study noted that the prevalence of a combined low Apgar score and neonatal encephalopathy symptoms, as measured in the study, was very low in the birth population and, therefore, could only account for a very small proportion of all cohort children affected by a poor outcome.

An unexpected developmental finding in the Western Australian participants (subsequent to the Western Australian neonatal encephalopathy follow-up study) was a higher-than-expected prevalence of autism spectrum disorder (ASD) in the neonatal encephalopathy cases (5%, 12 of 239 in cases versus 0.9%, 5 of 563 in controls) (4); the prevalence of ASD among the controls is consistent with current population-based prevalence estimates of ASD (56). Although the numbers of affected children were small and insufficient for multivariate analysis of risk factors, the association of ASD with neonatal encephalopathy certainly warrants further investigation. In another follow-up of the Western Australian neonatal encephalopathy study participants that focused on cerebral palsy at age 5 years as the outcome, 13% of neonatal encephalopathy cases were diagnosed with cerebral palsy (3). The researchers noted that this was comparable with cerebral palsy rates of 12–14% reported in three previous follow-up studies of HIE in developed countries (46, 48, 57). A systematic review and meta-analysis of studies reporting developmental outcome in the subset of infants with neonatal encephalopathy after “asphyxia” produced a metaestimate of 47% of exposed infants having an adverse outcome (defined as death, cerebral palsy, or motor and cognitive impairment more than 2 standard deviations below the norm): 0% with mild neonatal encephalopathy, 32% with moderate neonatal encephalopathy, and nearly 100% with severe neonatal encephalopathy (36).

Hearing loss, vision impairment, or epilepsy also have been reported in children with neonatal encephalopathy or HIE (57–63), and there are reports of possible neonatal encephalopathy or HIE (eg, “perinatal–neonatal distress”) as risk factors in children with these disabilities (64, 65). These outcomes,
However, are not specific to acute intrapartum HIE and may arise from a variety of other causes. They often co-occur with cerebral palsy after neonatal encephalopathy (66, 67). Although the prevalence of co-occurring deafness or blindness was reported to be no different in children with cerebral palsy and with or without neonatal encephalopathy in the Western Australian neonatal encephalopathy follow-up study, the occurrence of epilepsy, however, was higher in children with cerebral palsy after neonatal encephalopathy than with cerebral palsy and no neonatal encephalopathy (3). Overall, firm conclusions cannot be drawn as to the prevalence of hearing loss, vision impairment, or epilepsy in children with neonatal encephalopathy or HIE or the proportions of all individuals with one of these specific outcomes that experienced neonatal encephalopathy or HIE. In part, the difficulty lies in the relatively low prevalence of these conditions (and the resulting small numbers of affected individuals reported in individual clinic-based studies) and methodological differences across studies, such as varying definitions or inclusion criteria for neonatal encephalopathy and HIE and the relevant outcomes.

It generally is reported that death or developmental impairment is confined to infants with moderate or severe neonatal encephalopathy, but the outcome profile of neonatal encephalopathy may differ between high-income and low-income countries. A population-based neonatal encephalopathy study in Nepal found that 17% of infants with mild neonatal encephalopathy died and 71% of infants with moderate neonatal encephalopathy died or had major impairment at 1 year of age compared with no increased risk of death or impairment in mild neonatal encephalopathy and a 15–25% risk of death or severe impairment in infants with moderate neonatal encephalopathy reported in reviews of data from high-income countries (68).

Apart from the adverse outcomes of death or severe impairment in neonatal encephalopathy, an ongoing debate in the literature concerns whether low cognitive performance, other neurobehavioral problems in specific functional domains (eg, memory, perceptual-motor ability, executive function, attention), learning difficulties, or poor school performance arise independently of cerebral palsy or functional motor impairment in children with a history of neonatal encephalopathy after “asphyxia” (57, 61, 62, 67, 69, 70). Because of the availability in recent years of MRI and other imaging techniques, developmental outcome data have been augmented in some studies of neonatal encephalopathy and HIE with corresponding imaging data on types of neurologic injury and their timing.

The focus of Chapter 10 of this report is the role of neuroimaging in neonatal encephalopathy. In brief, evaluation of clinical samples of infants referred for MRI scans have identified two general patterns of injury after presumed HIE: 1) a watershed-distribution pattern that involves the white matter, particularly in the vascular watershed, plus cortical gray matter when severe, and 2) a basal ganglia-thalamus predominant pattern involving deep gray nuclei, hippocampi, and perirlandic cortex, with additional cortical involvement when severe (70, 71). Magnetic resonance imaging scans on neonates who develop seizures but no other symptoms of encephalopathy show a different pattern of injury (eg, focal infarctions or hemorrhagic lesions or lesions that are due to non-hypoxic medical conditions or syndromes [49]; [for a detailed discussion, see Chapter 8, “Focal Ischemic Stroke”], which underscores the diversity of conditions underlying the clinical presentation of different encephalopathic symptom patterns. The basal ganglia-thalamus predominant injury pattern has been associated with greater likelihood of severe developmental outcome (eg, death, quadriplegic cerebral palsy, and intellectual disability), whereas the watershed distribution pattern has been associated with a more mixed and often less severe outcome, with cognitive deficits occurring in some cases in the absence of functional motor impairment (71–73). Moderate or severe basal ganglia lesions and severe white matter changes also have been associated with abnormal visual function, whereas infants with normal MRI, minimal basal ganglia lesions, and minimal or moderate white matter involvement tended to have normal vision (74). Studies that have investigated risk factors for these different patterns of injury detected on MRI for infants with presumed HIE have identified few antenatal or perinatal factors specific to pattern of injury (49, 71), which lead one investigator to conclude that either they did not measure the relevant antenatal risk factors or better antenatal markers need to be identified (71). Magnetic resonance imaging studies also indicate that most lesions in such series of infants who meet the criteria for HIE (as opposed to neonatal encephalopathy) are acquired perinatally rather than from antenatal injury (49, 71). The age at which imaging was performed, however, should be considered in the interpretation of these data.

In summary, two very different pictures of risk and neurodevelopmental outcome in neonatal encephalopathy have been reported. Population-based epidemiologic data indicate the importance of antenatal...
antecedents in neonatal encephalopathy and the small proportion of total neonatal encephalopathy that is due to acute intrapartum hypoxia–ischemia. In contrast, data from clinic-based samples of infants with signs of encephalopathy and referred for MRI indicate that acute brain injury is predominantly associated with “asphyxia,” there are no apparent contributing antenatal risk factors, and developmental outcomes may include neurodevelopmental abnormalities in the absence of cerebral palsy. The apparent disparity between these two bodies of data has led some researchers to suggest that the conclusions in the first publication of this report may need to be modified to accommodate these new data (73, 75). To reconcile these different bodies of published data, however, a fundamental question must be addressed: Do the samples of children in these different types of studies represent the same underlying population at risk of neonatal encephalopathy? The objective answer is that they may not. Researchers have acknowledged that study design and participant recruitment differences may contribute to discrepant findings between population-based epidemiologic studies with a preponderance of antenatal factors in neonatal encephalopathy and clinical MRI studies with a preponderance of perinatally acquired brain injury in neonatal encephalopathy (with asphyxia origins) (71). Along similar lines, in the aforementioned systematic review of the outcome of postasphyxial neonatal encephalopathy, of the more than 3,000 publications since 1966 identified for the review, only 13 met the review criteria for defining postasphyxial neonatal encephalopathy (modified from the consensus statement from the International Cerebral Palsy Task Force) and there was significant heterogeneity, even among the 13 included studies (36). The authors concluded that researchers have used very loose and disparate criteria for postasphyxial neonatal encephalopathy, thus making study samples heterogeneous and across-study comparison difficult.

To fully reconcile the between-study data differences in neonatal encephalopathy, the HIE subset, and their developmental aftermath, a large population-based study of neonatal encephalopathy is required that includes collection of detailed antenatal and perinatal risk factor data, placental pathology, MRI, genetic markers, and long-term developmental follow-up. In addition, careful analytic consideration needs to be made of important factors that influence cognitive and other developmental outcomes, such as parental socioeconomic status, which may confound associations between developmental outcome and perinatal risks (76, 77). This approach provides the optimal means of addressing the apparent disparities between the epidemiologic and clinical evidence, including shedding light on the hypothesis that for some infants the causal pathway leading to neonatal encephalopathy is initiated before labor (thereby predisposing the vulnerable fetus to injury from peripartum factors) whereas in the absence of the antenatal risks, the fetus might sustain the same peripartum factors unharmed. The latter hypothesis underscores the potential challenge to identifying effective intervention strategies and time points for intervention if the etiologic course of neonatal encephalopathy spans multiple events that individually may not be sensitive markers of risk (eg, as illustrated in Fig. 1-1).

Conclusions

• From epidemiologic evidence, the absence of neonatal encephalopathy in an infant who later manifests cerebral palsy indicates that the cerebral palsy was not caused by perinatal hypoxia–ischemia. Thus, the pathway from intrapartum hypoxic–ischemic injury to subsequent cerebral palsy must certainly progress through neonatal encephalopathy.

• Two very different pictures of risk and neurodevelopmental outcome in neonatal encephalopathy have been reported. Population-based epidemiologic data indicate the importance of antenatal antecedents in neonatal encephalopathy and the small proportion of total neonatal encephalopathy that is due to acute intrapartum hypoxia–ischemia. In contrast, data from clinic-based samples of infants with signs of encephalopathy and referred for MRI indicate that acute brain injury is predominantly associated with “asphyxia,” there are no apparent contributing antenatal risk factors, and developmental outcomes may include neuro-developmental abnormalities in the absence of cerebral palsy.

• To fully reconcile the between-study data differences in neonatal encephalopathy, the HIE subset, and their developmental aftermath, a large population-based study of neonatal encephalopathy is required that includes collection of detailed antenatal and perinatal risk factor data, placental pathology, MRI, genetic markers, and long-term developmental follow-up.

Neonatal Encephalopathy in Cerebral Palsy

Considering the contribution of neonatal encephalopathy or its subset HIE to cerebral palsy in term infants,
Researchers linked the population-based Western Australian neonatal encephalopathy study participants at age 5 years with the population-based Western Australian cerebral palsy registry of similar birth dates and observed that 24% of term infants with cerebral palsy had neonatal encephalopathy; the proportion of term infants with cerebral palsy and HIE was not reported (3). Compared with children with term cerebral palsy and no neonatal encephalopathy, children with cerebral palsy and neonatal encephalopathy were significantly more likely to have spastic quadriplegia or dyskinetic cerebral palsy subtypes and less likely to have other spastic or nonspastic subtypes; they were also significantly more likely to have severe cerebral palsy, intellectual disability, epilepsy, or to die by age 5 years. The proportions of term-born children with cerebral palsy and neonatal encephalopathy, distribution of cerebral palsy subtypes, and risk of associated developmental problems, such as intellectual disability was noted to be comparable to a previous population-based study of term cerebral palsy, despite the more restrictive selection criteria for neonatal encephalopathy that were employed in that study (66).

The advent of more widely available MRI and other imaging techniques also has augmented our understanding of the contribution of neonatal encephalopathy in cerebral palsy compared with data from earlier studies relying only on clinical data. In a series of two case–control studies of term and late-preterm infants with cerebral palsy in members of Northern California Kaiser Permanente (10, 45), a large managed-care organization that serves approximately 30% of the regional population, 72–83% of cases of cerebral palsy had MRI data, and only a minority of children had imaging abnormalities associated with HIE (only 12% in the larger second study based on 377 children with near-term cerebral palsy). Further, in the first study of the series that investigated the role of clinical chorioamnionitis in late-preterm infants with cerebral palsy, chorioamnionitis was associated with a 17-fold increased risk of imaging abnormalities associated with HIE. This suggests an infectious link with events leading to HIE, perhaps predisposing exposed infants to asphyxial injury during labor and delivery. The same apparent discrepancy was noted between prenatal and perinatal risk factors, such as chorioamnionitis, implicated in neonatal encephalopathy and cerebral palsy in population-based studies versus the predominance of acute brain injury in neonatal encephalopathy based on study samples drawn from tertiary care centers (10). The authors concluded that both prenatal and perinatal factors are likely to be important in the pathogenesis of cerebral palsy, and in some cases presence of prenatal factors may predispose infants to acute brain injury during labor and delivery.

The possibility that clinic-based studies may not be fully representative of cerebral palsy or neonatal encephalopathy is highlighted by a study that investigated neonatal risk factors among low-risk, term infants with cerebral palsy (7). In this study, the largest population-based study of term infants with cerebral palsy to date, 67% of these infants were never admitted to an NICU or special care unit (NICU group). Although children in the no-NICU group were more likely to have cerebral palsy of mild or moderate severity than the NICU group, because they were more numerous, the no-NICU group accounted for fully 54% of all children with severe cerebral palsy. Furthermore, four of the six identified neonatal predictors of cerebral palsy in the no-NICU group were reminiscent of neonatal encephalopathy (ie, abnormal temperature regulation and tone, abnormal consciousness, and need for resuscitation). Thus, although many studies report that mild neonatal encephalopathy is not a risk of cerebral palsy, this study suggests that the full spectrum of mild neonatal encephalopathy and its associated risks may be underascertained (7), thereby underestimating the contribution of mild neonatal encephalopathy to cerebral palsy.

Even though the relative risk of cerebral palsy, and especially spastic quadriplegia, associated with commonly used clinical markers of asphyxia (such as a low 5-minute Apgar score, adverse neonatal signs, and seizures) is typically high and statistically significant (78–82), a minority of children with cerebral palsy—less than 10%—actually have these indicators (79, 83). Analysis of the National Collaborative Perinatal Project data attributed 9% of the cases of cerebral palsy to possible asphyxia (84). This result has been replicated in MRI studies in a large regional sample in which only 12% of children (who were born as term or late-preterm infants with cerebral palsy) had brain injury associated with HIE (10). One systematic review estimated that 14.5% of term infants with cerebral palsy was associated with HIE, based on data from five studies, including the National Collaborative Perinatal Project (85). The calculated fraction of spastic cerebral palsy attributable to asphyxia or potential asphyxial events, according to two large population-based studies, was 6–17% for infants of normal birth weight (greater than 2,500 g) (79, 80). In children with spastic quadriplegic cerebral palsy, potential asphyxiating events...
appear to attribute a larger proportion of cases, ranging from 14% (81) to 43% (79) of patients. Other factors apart from intrapartum HIE that potentially contribute to spastic quadriplegia include placental infarction (86, 87).

The attributable (or etiologic) fraction represents the proportion of cases in a target population that are attributable to a specific exposure (e.g., intrapartum events); it also represents how much of the burden of a specific disease in a population could be eliminated if certain causal factors were eliminated from the group under study (assuming distributions of other risk factors in the population remain unchanged). Attributable fraction is a composite value based on both the prevalence and relative risk associated with a specific risk factor (88). Because it is a composite value, a risk factor that has a large relative risk for disease but is of low prevalence in the population will have a low attributable fraction (89). This is the case when the markers typically used for perinatal asphyxia in cerebral palsy are examined.

Conclusions

- In an MRI study of a large managed-care population of children (who were born as term or late-preterm infants) with cerebral palsy, only 12% had imaging abnormalities associated with HIE. Further, clinical chorioamnionitis markedly increased the risk of imaging abnormalities associated with HIE suggesting an infectious exposure possibly predisposing infants to HIE.

- Mild neonatal encephalopathy and its associated risks may be underascertained, thereby underestimating the contribution of mild neonatal encephalopathy to cerebral palsy.

Research Recommendations

- To elucidate the different causal pathways to neonatal encephalopathy and cerebral palsy, it is important that a reliable and readily available assessment of fetal status be possible and that more specific markers of an intrapartum insult be developed.

- Because the most recent population-based studies of neonatal encephalopathy and HIE incidence were based on birth cohorts from the early to mid 1990s, updated population-based estimates of incidence based on more recent births are greatly needed.

- To fully reconcile the between-study data differences in neonatal encephalopathy, the HIE subset, and their developmental aftermath, a large population-based study of neonatal encephalopathy is required that includes collection of detailed antenatal and perinatal risk factor data, placental pathology, MRI, genetic markers, and long-term developmental follow-up. In addition, careful analytic consideration needs to be made of important factors influencing cognitive and other developmental outcomes, such as parental socioeconomic status, which may confound associations between developmental outcome and perinatal risks.

- An array of developmental outcomes may arise following neonatal encephalopathy. Apart from the cerebral palsy outcome that has received most research attention, more work is needed to better understand the proportions of children with neonatal encephalopathy or HIE that develop these other outcomes (with or without cerebral palsy) or the etiologic contribution of neonatal encephalopathy or HIE to the total pool of affected children with a given outcome.

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CHAPTER 2

Fetal Physiology and Cell Biology

Much of the understanding of the processes that lead to brain injury in the term infant derives from experimental studies in fetal or neonatal animals. The ability to accurately control contributory factors, such as severity of hypoxic-ischemic insult, gestation, temperature, exposure to infection, and fetal growth restriction—combined with the wide range of neuroscientific techniques available to measure outcomes—make such experiments a rich source of data describing mechanism and potential therapy. Given the history of the understanding of neonatal encephalopathy and hypoxic-ischemic encephalopathy (HIE) and their relations to cerebral palsy, it is not surprising perhaps that HIE (a specific type of neonatal encephalopathy) and cerebral palsy have been most commonly studied in vitro and in vivo. Consequently, this chapter focuses on the understanding of the cellular mechanisms of HIE because this is the pathway to neonatal encephalopathy that has been best studied. This chapter reviews the HIE-specific studies to demonstrate the following:

• A failure of cerebral perfusion leads to adenosine triphosphate (ATP) depletion (primary energy failure).
• Adenosine triphosphate depletion triggers a neurotoxic cascade of molecular events resulting in delayed “secondary” energy failure.
• Cofactors make the fetal brain more vulnerable to hypoxia–ischemia.
• The term fetus compensates to mitigate the damaging effects of hypoxia–ischemia. Effective neural rescue or protection strategies target these early molecular events.

Fetal Cardiovascular and Metabolic Defenses Against Hypoxia

It is striking that although normal labor is associated with a decrease in fetal oxygenation, the incidence of moderate or severe encephalopathy after birth is low at less than 4 per 1,000 live births (1, 2). This is in part because the healthy term fetus is able to mount a series of compensatory mechanisms that protect the brain from hypoxia-related damage.

Adult and Fetal Strategies

Ex utero, the atmospheric supply of oxygen is abundant. Therefore, in the adult, a reduction in oxygen supply to the tissues is met with an increase in ventilation to increase the level of oxygenation in pulmonary blood. This plentiful supply of atmospheric oxygen allows the adult cardiovascular system to increase perfusion even to peripheral circulations, maintaining oxygenation, during periods of systemic hypoxia (3, 4). In utero, the supply of oxygenated fetal blood is dependent on the placenta. In contrast to pulmonary ventilator processes, mechanisms within the placenta to increase the input and output of oxygenated blood are limited. However, a number of adaptations unique to life in utero permit the supply of oxygen to the fetus to exceed its metabolic needs, equipping the fetus with a considerable margin of safety for oxygenation under basal conditions during development. For instance, the fetus is able to bind greater concentrations of oxygen in its hemoglobin, to have an increased basal blood flow to most tissues, and to relinquish this bound oxygen to the fetal tissues at lower oxygen tensions (5). In addition, shunts in the fetal circulation and preferential streaming ensure an adequate supply of oxygenated blood to tissues most...
at risk of damage during reductions in oxygenation (6). Finally, the fetus has a greater capacity than the adult to limit oxygen-consuming processes (7). Consequently, the fetal defense strategies during episodes of acute hypoxia concentrate on increasing the efficiency of some of these adaptations, thereby either consuming even less oxygen, extracting even more oxygen from hemoglobin, or making better use of this finite supply of oxygenated blood.

Fetal Cardiovascular Responses
The initial cardiovascular responses to acute hypoxia in the fetus include bradycardia, increased blood pressure, and increased cerebral blood flow (8). The pattern and magnitude of these changes depend on the stage of gestation at which the challenge occurs and the maturity of the mechanisms that mediate them. In the past, the fetal cardiovascular responses to acute hypoxia have been studied in the late-gestation ovine fetus (ie, past 120 days out of a 145–150-day term for most ovine breeds). However, a few studies have concentrated on the fetal cardiovascular responses to an episode of oxygen deprivation earlier in the gestation (9) and as the fetus approaches term, just before birth (10). In the late-gestation ovine fetus, acute hypoxia leads to transient bradycardia, an increase in arterial blood pressure, and a redistribution of the cardiac output (11). The bradycardic response is described in clinical obstetric practice as decelerations in heart rate and has been shown in the human fetus during acute hypoxia secondary to relative placental insufficiency during uterine contractions in the actual processes of labor and delivery (12). Fetal bradycardia retards the speed of cardiac blood flow, which could enhance myocardial oxygen extraction if needed (13, 14). Second, it prolongs end-diastolic filling time, which increases ventricular end-diastolic volume. An increase in ventricular end-diastolic volume promotes a greater force of ventricular contraction through the Frank-Starling mechanism and increases stroke volume (15, 16). During acute hypoxia, fetal cardiac output is therefore maintained despite a pronounced decrease in heart rate.

The circulatory redistribution occurs as a result of differential changes in vascular tone in peripheral and essential vascular beds. Circulations perfusing the kidneys, gut, and striated muscle, for example, undergo vasoconstriction. Conversely, the cerebral, adrenal, and myocardial circulations undergo active vasodilatation (17). In this way, blood flow follows the path of least resistance because it is shunted away from peripheral vascular beds toward essential circulations, such as those perfusing the brain (the so-called brain-sparing response). This innate brain-sparing effect has been conserved across all species studied to date, including the ovine, nonhuman primate, and human fetus (11, 18, 19). With initial arterial hypoxemia, fetal cerebral vascular resistance can decrease by at least 50% to maintain cerebral blood flow with a minimal decrease in oxygen delivery in an experimental model (20, 21). Critical to this state is a normal or elevated mean arterial blood pressure. Parallel measurement of continuous changes in carotid and femoral blood flow using transonic flow probes implanted long-term in the late gestation fetus submitted to acute hypoxia provides an important index of the brain sparing effect in vivo in real time (Fig. 2-1) (22). In human obstetric practice, the redistribution of the fetal cardiac output during fetal hypoxia is represented by decreases in indices of resistance, an increase in the blood velocity in the common carotid or middle cerebral arteries, and reductions in blood velocities to the umbilical artery and descending aorta (which result from increased resistance in those circulations) (23–25).

The physiology underlying the cardiac and vascular responses in the fetus during acute hypoxia involves neural, endocrine, and local mechanisms. The fetal bradycardia and peripheral vasoconstriction are triggered by the same carotid chemoreflex. Bilateral transection of the carotid sinus nerves prevents bradycardia and markedly delays the increase in femoral vascular resistance (22, 26). After transient bradycardia, the heart rate returns to control levels secondary to β-adrenergic stimulation opposing vagal outflow as fetal treatment with atenolol prolongs the fetal bradycardic response to hypoxia (27). Once triggered by the carotid chemoreflex, the peripheral vasoconstriction is mediated by enhanced sympathetic outflow and increased stimulation of α₁-adrenergic receptors in peripheral circulations (22, 28). Peripheral vascular resistance is kept high during hypoxia by an increased release of powerful vasoconstrictor agents into the fetal circulation, such as catecholamines, neuropeptide Y, and vasopressin (29–32). In addition, the endothelium acts as a hypoxic sensor and effector system that releases vasoactive agents to act locally on the vascular smooth muscle, such as nitric oxide and endothelin (33, 34). Fetal exposure to acute hypoxia during fetal nitric oxide synthase blockade leads to a significant enhancement of the femoral constrictor response (35), suggesting that hypoxia-induced increases in nitric oxide oppose and diminish the peripheral constrictor neural and endocrine influences on the fetal peripheral circulation (35).
More recently, it has become evident that the cellular oxidant milieu is also an important modulator of vascular resistance (36). Vascular endothelial cells generate reactive oxygen species, such as the superoxide anion (37). Superoxide readily combines with nitric oxide, limiting its bioavailability (38). Hence, under physiologic conditions, manipulation of the vascular nitric oxide to superoxide anion ratio is also an important determinant of vascular tone. Accordingly, studies have shown that fetal treatment with antioxidants enhance basal umbilical blood flow (39) and depresses the fetal peripheral vasoconstrictor response to acute hypoxia (40, 41) by increasing the bioavailability of nitric oxide.

**Fetal Metabolic Responses**

Fetal cerebral metabolic responses to acute hypoxia include reducing energy consumption and maximizing substrate delivery to ensure that supply and demand are balanced and ATP levels stay stable. A number of studies in the ovine fetus have shown that overall oxygen consumption can be maintained for up to 24 hours despite a 40–50% reduction in oxygen delivery to the placenta (42, 43). This is achieved by increasing umbilical blood flow so that oxygen delivery to the fetus is not so severely reduced, as well as by increasing the percentage of oxygen extracted. However, although whole body oxygen consumption is not affected until oxygen delivery is reduced by more than 50%, there are regional differences in oxygen delivery and, therefore, oxygen consumption that are consequent on the changes in regional blood flow. Therefore, peripheral vasoconstriction (by imposing a further reduction in oxygen delivery to the organs, such as the skeletal muscles and gut, at a time when arterial PO₂ is already reduced) produces a reduction in oxidative metabolism because oxygen delivery and consumption are so tightly linked in the fetus. One study showed that oxygen use by fetal skeletal muscles (studied in vitro) decreases linearly as PO₂ is decreased over a range that is substantially higher than that at which aerobic metabolism fails in the adult (44). The same principle has been demonstrated in the fetal intestines (45) and in the hind limbs (46), where abrupt decreases in oxygen consumption occur when oxygen delivery decreases below critical threshold values, and anaerobic metabolism and lactate production ensue (47). Adenosine, a breakdown product of high-energy phosphates during hypoxia, inhibits fetal breathing and eye and body movements, triggers bradycardia and peripheral vasoconstriction, depresses excitatory neurotransmission, and causes neuronal hyperpolarization, all of which will reduce fetal oxygen consumption (48–50).
Hypoxia also triggers an increase in the circulating concentrations of glucose and lactate (51, 52). Fetal hyperglycemia during acute hypoxia results from a decrease in glucose uptake and use by peripheral tissues (53) and an increase in hepatic glucose production (54). Fetal lactic acidemia results from anaerobic metabolism of glucose in hypoxic fetal tissues, particularly in the skeletal muscles where blood flow and oxygen delivery are markedly decreased. Increased sympathetic outflow also inhibits insulin release from the fetal pancreas, thereby decreasing glucose uptake and use by the fetal tissues (53). As the hypoxic challenge progresses, catecholamines mobilize and release glucose from glycogen stores in the fetal liver (55). Combined with increasing cerebral blood flow, these factors ensure that neural tissue is adequately supplied with glucose to maximize ATP production. In addition, in contrast to the older infant, the fetal brain also can use alternate energy substrates, such as lactate and ketone bodies, for energy production (56, 57). The relative resistance of the fetal and neonatal myocardium to hypoxia–ischemia also contributes to the resistance of the fetal brain to hypoxic–ischemic injury (58, 59).

Conclusions

• The healthy term fetus is able to mount a series of compensatory mechanisms that protect the brain from hypoxia-related damage.

• The initial cardiovascular responses to acute hypoxia in the fetus include bradycardia, increased blood pressure, and increased cerebral blood flow.

• Fetal cerebral metabolic responses to acute hypoxia include reducing energy consumption and maximizing substrate delivery.

Primary Hypoxic–Ischemic Insult

Fetal Hypoxia–Ischemia

It is clear that the fetal brain at term is protected against the deleterious effects of acute hypoxia by hemodynamic and metabolic compensatory mechanisms. If, however, hypoxia is of sufficient length or severity, compensatory mechanisms will be overwhelmed, resulting in severe cerebral hypoxia–ischemia, triggering a cascade of molecular events (see “Mode of Cell Death”) leading to neuronal death after a delay of hours to days (60). Myers’s pioneering studies examined the threshold values for oxygen deficiency leading to brain pathology in term fetal monkeys (61). He reported that the oxygen content of blood in the abdominal aorta can decrease through a wide range before any changes are observed in vital signs or central nervous system function. The least oxygen-deprived monkeys had a Po2, 28–30 mm Hg, yet fetal vital signs started to change at Po2, 15–16 mm Hg. Fetal oxygenation could remain in this range for prolonged periods (beyond 1–2 hours) without producing brain injury or other abnormalities. However, evidence of brain damage occurred regularly when Po2 decreased below 11–12 mm Hg for more than 10–15 minutes (61). In a study of the fetal cerebral consequences of maternal uterine artery occlusion, a strong correlation was reported between hypotension and the severity of neuronal loss, assessed histologically (62). No association was seen with fetal oxygenation. Therefore, maintenance of cerebral perfusion is an essential prerequisite for long-term neuronal survival.

The critical ischemic threshold for neuronal necrosis in the developing brain remains unclear. In adults, cerebral blood flow thresholds, below which functional disturbances (electroencephalographic slowing) occur, have been identified. If cerebral blood flow reaches an even lower threshold, ion pump failure occurs (63–65). However, cerebral blood flow values in both preterm and term infants below those that are associated with ion pump failure in adults are associated with subsequent normal neurologic development (66).

Mode of Cell Death

Neuronal death can occur by programmed cell death (apoptosis) if cellular energy remains available or by necrosis if energy stores are exhausted (67, 68). During apoptosis, nuclear DNA condenses and becomes fragmented, leading to shrinkage and death of cells, whereas necrosis is associated with destruction of cell membranes and an inflammatory response. Neurons in the developing brain are more likely to die by apoptosis than those in the adult brain, and histopathology often reveals a continuum of forms that are intermediate between these two types of cell death (69). This age-dependent difference in cell death is probably related to the fact that the immature brain contains more neurons than it will need for later development, and apoptotic programs are enhanced at this age to delete them.

Cellular Vulnerability

The distribution and extent of cell death reflects a number of factors.

Metabolic Rate

Myers reported that the ranking of brain structures in order of susceptibility to injury correlated with their
regional cerebral blood flow of blood per unit of time, which is a direct reflection of their metabolic rate (70). Positron emission tomography in normal infants shows high metabolic rates for glucose in the sensorimotor cortex, thalamus, cerebellum, and brain stem (71). If ATP production is limited by depletion of metabolic substrates, such as oxygen and glucose, these areas of the brain with the highest energy requirements will be most affected.

Cerebral Perfusion
Neural cells are particularly vulnerable to primary energy failure if they have a high metabolic rate or lie at a watershed between vascular beds. In addition, there appears to be a hierarchy whereby blood flow to deep brain structures is preserved for longer than to superficial structures, such as the cortex.

Developmental Factors
There are developmental factors that influence the vulnerability of certain cells, such as the link between neuronal vulnerability and the development of excitatory amino acid receptors. Glutamate, the principle excitatory amino acid in the brain, is released in large quantities during hypoxia–ischemia and acts via a variety of receptor subtypes to allow accumulation of toxic intracellular calcium concentrations (72). Pharmacological blockade of these channels, in particular the N-methyl-D-aspartate (NMDA) receptor, is neuroprotective in experimental models of hypoxic–ischemic brain injury (73–75). Studies of the ontogeny of glutamate receptors in the ovine central nervous system show higher levels of NMDA receptors at 135 days of gestation relative to 80 days or the adult (76). In addition, binding is higher in the areas particularly prone to hypoxic injury, namely the cortex and basal ganglia.

Insult Severity and Outcome
As a consequence, different populations of cells are more or less affected by different types of hypoxic–ischemic insult. In the human, such insults range from the almost complete cord occlusion (which can occur after umbilical cord prolapse or the severe, continuous prolonged hypoxemia resulting from abruptio placenta) to the intermittent hypoxic episodes related to uterine contractions. Animal studies have not mimicked these precisely but provide important insights into the nature of “primary” energy failure (77).

Complete occlusion of the umbilical cord for 10 minutes results in a decrease in cerebral blood flow and arterial pressure in the ovine fetus (78) and has been shown to result in loss of hippocampal neurons (79). An even more severe acute insult is produced by clamping the umbilical cord and slipping a thin, saline-filled, rubber sac over the heads of rhesus monkey fetuses at surgical delivery. Envelopment of the fetal head prevents the onset of air breathing for a specified period, after which resuscitation is performed (70). The first evidence of brain damage in survivors occurred at 10 minutes of total “asphyxia,” whereas fetuses “asphyxiated” for longer than 25 minutes died from myocardial injury in the early hours after the insult in the intensive care unit. In this model, arterial Po2 decreased precipitously to 6 mm Hg and pH decreased to 6.8 with a base deficit of approximately 18 mEq/L. The pattern of injury observed—with damage to thalamus, brain stem, spinal cord, and relative sparing of the cerebral cortex—is similar to that seen in term infants exposed to acute severe insults (80, 81).

Researchers also used partial placental ablation or maternal aortic constriction extended over several hours in term rhesus monkeys to produce less severe hypoxia–ischemia (70, 82). In contrast to the deep gray matter injury observed with acute severe hypoxia–ischemia, this insult produced extensive cortical or more limited cortical watershed damage. This is similar to the damage observed after 30 minutes of uterine artery occlusion or repeated (every 2.5 minutes) 1-minute umbilical cord occlusions in sheep (62, 83). Similar predominantly cortical lesions often are seen in term human infants exposed to hypoxia–ischemia that is less severe but more prolonged (84). Researchers have summarized the strengths and weaknesses of nonhuman primate models of brain injury at different gestational ages and concluded that they have remarkably high similarity to human brain injuries (77).

Molecular Mechanisms of Hypoxic–Ischemic Brain Injury
In experimental studies, cerebral hypoxia–ischemia of sufficient severity to deplete tissue energy reserves (primary insult) often is followed by transient but complete restoration of glucose use, ATP, and phosphocreatine upon reperfusion (85–87). Thereafter, a secondary decrease of high-energy phosphates occurs in parallel with a decrease in tissue glucose metabolism and development of cell injury (85–87). Similarly, infants with neonatal encephalopathy after severe intrapartum asphyxia show characteristic

* Throughou the report, the terms “asphyxia” and “birth asphyxia” and their variations appear in quotes when used in reference to a particular study to emphasize the wide variation in study definitions of asphyxia. See recommended asphyxia definition in Table 1–1 and discussion of asphyxia terminology later in the chapter.
abnormalities in cerebral energy metabolism, which is frequently normal soon after birth but shows a progressive decline in phosphocreatine and inorganic phosphate some hours later (88). Infants displaying this phenomenon develop severe neurodevelopmental impairment or die, and there is a close relationship between the magnitude of the late decrease in phosphocreatine and inorganic phosphate and the severity of neurodevelopmental impairment 4 years later (89).

Most of the cerebral injury after hypoxia–ischemia evolves over time, after rather than during the insult. There are many examples of successful posttreatment after hypoxia–ischemia in animals (90), suggesting a therapeutic window after hypoxia–ischemia before the secondary phase of tissue deterioration. Hypothermia after hypoxia–ischemia reduces secondary energy failure and brain injury in experimental studies (91) and was later proved effective as a neuroprotective treatment in newborns with neonatal encephalopathy after severe “asphyxia” (92). Because of these advances, there is now a renewed interest in the mechanisms of injury operating during the delayed phase after the insult.

Mechanisms of Secondary Brain Injury
The deficit in high-energy phosphates induced by hypoxia–ischemia leads to a primary failure to maintain transmembrane ionic gradients, release of neuroactive compounds into the extracellular compartments, accumulation of intracellular calcium, and the activation of a series of mechanisms that if sustained will lead to immediate cell death. If the individual is resuscitated, these acute alterations are completely or partly reversed, but the complex process has been started in which multiple interrelated factors may produce secondary brain injury. The precise mechanisms of damage are only partly understood, but excitatory amino acids, mitochondrial impairment and apoptotic mechanism, reactive oxygen species, and the immunoinflammatory system are key factors in the process of secondary brain injury.

Excitatory Amino Acids
Glutamate and aspartate are the main excitatory transmitters in the brain, but they also are known to exert toxic effects (excitotoxicity) in the central nervous system. The NMDA receptor and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and kainate receptor are expressed on neurons and oligodendrogial precursors in gray and white matter (73, 93, 94), and the developing brain is highly susceptible to excitotoxicity (74). There is considerable evidence for a role of excitatory amino acids in the process leading to hypoxic–ischemic brain injury. Excess activation of neuronal NMDA or AMPA receptors leads to neuronal cell death (74, 95). Excess activation of oligodendroglia AMPA receptors leads to cell death, and NMDA receptor activation in these cells impairs recovery (73, 94). Activation of microglial NMDA receptors leads to microglial activation and release of factors potentially toxic for neighboring neural cells (96). Extracellular concentrations of excitatory amino acids, and to some extent glycine (which enhances NMDA receptor activation), increase extracellularly during neonatal hypoxia–ischemia in fetal ovine (72) and are followed by a secondary increase during reflow. Excitatory amino acids also increase markedly in the cerebrospinal fluid of newborns with neonatal encephalopathy after intrapartum asphyxia, and the levels are associated with the degree of encephalopathy and short-term outcome (97). Blocking NMDA and AMPA receptors before or after hypoxia–ischemia reduces subsequent neuronal and oligodendrogial damage (73–75). The mechanism of excitotoxicity in response to hypoxia–ischemia probably involves perturbation of calcium homeostasis, which triggers reactive oxygen species production with subsequent mitochondrial impairment.

Mitochondria and Apoptotic Mechanisms
Apoptosis or programmed cell death was initially recognized for its role in development. In some brain regions, half of the neurons die by apoptosis during normal brain development. Therefore, it is entirely appropriate that many apoptosis-related factors are upregulated in the immature brain, such as caspase-3, Apaf-1, Bcl-2, and Bax (98–100). Multiple apoptotic pathways converge on caspase-3, so this protease is critical in the execution of neuronal apoptosis during brain development and after acute injury (99). Caspase-3 appears to be particularly important in the brain because mice devoid of caspase-3 through genetic targeting displayed a hyperplastic, disorganized brain, whereas other organs appeared normal (99). Thus, because of on-going apoptotic processes during brain development, the apoptotic biochemical machinery is highly upregulated, which may confer heightened vulnerability.

Studies suggest that mitochondria regulate apoptotic cell death through their capacity to undergo mitochondrial membrane permeabilization and release of proapoptotic proteins (100). Cytochrome C and other apoptogenic proteins, such as apoptosis-inducing factor, are released from the mitochondrial intermembrane space. Bax, Bad, Bid, and other members of the Bcl-2 family are involved in the regulation of mitochondrial release of proapoptotic proteins. Cytochrome C interacts with Apaf-1, ADP, and
procaspase-9 to form the heptameric apoptosome, leading to the activation of caspase-9, which in turn cleaves and activates procaspase-3 (100). Apoptosis-inducing factor, on the other hand, promotes apoptosis in a caspase-independent manner (100). In addition, the downstream activation of executioner caspases like caspase-3 can be triggered through Fas receptor-mediated activation of caspase-8 without the involvement of mitochondria, the so-called extrinsic pathway.

Apoptosis is found in the brains of infants who die after intrauterine insults or perinatal hypoxia–ischemia (101). Caspase-3 is markedly activated after hypoxia–ischemia in the immature brain (102), and cells with the cleaved active form of caspase-3 colocalize with markers of DNA fragmentation in injured brain regions. Caspase inhibitors (102), down-regulation of apoptosis-inducing factor (103), or transgenic overexpression of X-linked inhibitor of apoptosis (104) provide a considerable degree of neuroprotection in the immature brain. There are data to suggest that the extrinsic pathway is activated in response to hypoxia–ischemia, and Fas receptor deficiency seems to confer some degree of protection in neonatal hypoxia–ischemia (105), but most data suggest that the mitochondrial pathway is most important (100).

**Reactive Oxygen Species**

Reactive oxygen species are molecules that contain one or more unpaired electrons (106), which make the free radicals highly reactive and able to disrupt the molecular structure of lipids and proteins with devastating consequences for cellular function (106). There are several pathways whereby reactive oxygen species are produced in the brain. The superoxide radical is produced by the following four elements: 1) electron leakage from the electron transport chain in mitochondria; 2) oxidation of hypoxanthine to xanthine and urate by xanthine oxidase; 3) degradation of free fatty acids by phospholipase A2 into arachidonic acid and subsequent oxidation of arachidonic acid by cyclooxygenase and lipoxygenase; and 4) nicotinamide adenine dinucleotide phosphate oxidase activity in macrophages, neutrophils, and microglia. The superoxide radical can react with Fe2+ ions and form hydroxyl radicals, which react with almost every molecule and exert toxic effects on DNA and proteins, and initiate lipid peroxidation, which disrupts membrane function (106). There are several defense systems in the brain to reduce the formation of oxygen free radicals and several pathways for their inactivation. The superoxide radical adduct is dismutated by superoxide dismutase into hydrogen peroxide, which is converted to water and oxygen by either the catalase enzyme or the glutathione peroxidase enzyme. Compounds like vitamin E (α-tocopherol) act as lipidsoluble scavengers, which inhibit lipid peroxidation. Chelation of transition metals, such as iron, is another endogenous protective mechanism against excessive formation of reactive oxygen species.

There is evidence for increased hypoxanthine levels, reactive oxygen species formation, and lipid peroxidation during reperfusion after hypoxia–ischemia in many species (107). Treatment with lipid peroxidation inhibitors, xanthine oxidase blockers, reactive oxygen species scavengers, antioxidants, and nitric oxide inhibitors reduce injury in some experimental studies (107–110).

**Inflammation**

Noninfectious exposure to hypoxia–ischemia (111) induces inflammation in the immature brain. Immunoinflammatory cells—predominantly microglia and macrophages but also neutrophils, lymphocytes, natural killer cells, mast cells, and astroglia—are activated (112, 113). The cellular changes are accompanied by altered expression of Toll-like receptors, cytokines, chemokines, and reactive oxygen species (111, 114). Microglia and macrophages may contribute to secondary brain injury through the production of proinflammatory cytokines, proteases, complement factors, and excitotoxic amino acids (115). In addition, microglial cells can induce oxidative injury through the production of reactive oxygen species and nitric oxide.

The early proinflammatory phase seems to aggravate injury after hypoxia–ischemia as inhibition of platelet-activating factor, the proinflammatory cytokines interleukin (IL)-1 and IL-18, caspase-1 (activating IL-1 and IL-18), and the complement C1q all worsen hypoxic–ischemic injury (116–118). The effect of inflammation is, however, highly context and time dependent. Hence, activation of microglia and macrophages and components of the complement system also can exert beneficial effects (119, 120), probably through production of trophic factors that affect regenerative responses.

**Factors That Increase Vulnerability to Hypoxia**

Although human studies make it clear that an isolated severe hypoxic–ischemic insult can lead directly to fetal brain injury, they also suggest that this is a rare event and that many cases of encephalopathy are associated with preceding or coexisting factors (1). Experimental studies suggest possible mechanisms whereby the severity of primary cerebral energy depletion resulting from a hypoxic–ischemic insult, as well as the secondary response to it, can be exacerbated. Although data from human studies demonstrate the
importance of the placenta in these mechanisms (see also Chapter 4, The Role of Placental Pathology in Neonatal Encephalopathy and Cerebral Palsy), data from experimental studies are scarce.

**Infection and Inflammation**

In experimental animal studies, fetal exposure to bacterial infection or proinflammatory molecules alters the subsequent cerebral response to hypoxia. Endotoxin (lipopolysaccharide) has been shown to sensitize and dramatically increase the lesion size in the immature rat brain after hypoxic–ischemic injury. Similar effects are seen in the neonatal mouse when exposed to *Escherichia coli* endotoxin 4 hours before hypoxia–ischemia. This effect is seen when endotoxin is administered systemically (121–123) or intracerebrally (124). Although the exact mechanism of this interaction is unclear, it does not seem to result from an attenuated metabolic response (125) but is mediated through microglia, Toll-like receptor 4 (126), and the tumor necrosis factor-α cluster of genes (127).

Animal studies describe clearly the direct correlation between increasing brain temperature and susceptibility to a variety of neurotoxic factors. Hypothermia can be neuroprotective after hypoxia–ischemia in neonatal animals (128), whereas hyperthermia increases brain injury after ischemia in adult rats (129). Maternal pyrexia, resulting from both microbial infection as well as noninfective causes, such as epidural anesthesia, therefore, could augment the deleterious effects of hypoxia on the fetal brain, possibly by increasing the cerebral metabolic rate and demand for oxygen.

**Previous Hypoxia and Substrate Deprivation**

The observed association between fetal growth restriction and neonatal encephalopathy could result from a diminished fetal cardiovascular and metabolic capacity to respond to episodes of acute hypoxia. Data show that previous fetal exposure to a period of adverse intrauterine conditions, such as that induced by partial measured compression of the umbilical cord, elevates nitric oxide activity and results in a markedly diminished cardiovascular defense response to subsequent acute hypoxia (55). In addition, lactate production by hind-limb muscle was decreased, despite a fall in oxygen delivery, suggesting that preexposure to chronic hypoxia impairs the normal anaerobic fetal response (130). Similarly, growth restriction markedly attenuated the increase in cerebral lactate levels, measured by magnetic resonance spectroscopy in chick embryos during acute hypoxia, compared with controls (131). The data imply that preexposure to adverse antenatal conditions may render the fetus more susceptible to the acute hypoxia that can accompany relatively uncomplicated labor and delivery. These data are compatible with those from postnatal studies in which hypoglycemia can cause or exacerbate hypoxia-related brain injury (see also “Hypoglycemia” in Chapter 7). It is important to note that similar studies suggest that alterations in experimental design can lead to the opposite effect, whereby preexposure to endotoxin or fetal growth restriction can actually protect against subsequent hypoxia–ischemia. This complexity needs to be appreciated when interpreting the possible sequence of events that lead to human encephalopathy.

**Conclusions**

- Maintenance of cerebral perfusion is an essential prerequisite for long-term neuronal survival.
- Neural cells are particularly vulnerable to primary energy failure if they have a high metabolic rate or lie at a watershed between vascular beds.
- Most of the cerebral injury after hypoxia–ischemia evolves over time, after rather than during the insult.
- Excitatory amino acids, mitochondrial impairment and apoptotic mechanism, reactive oxygen species, and the immunoinflammatory system are key factors in the process of secondary brain injury.
- In experimental animal studies, fetal exposure to bacterial infection or proinflammatory molecules alters the subsequent cerebral response to hypoxia.

**Induced Hypothermic Neuronal Rescue**

Animal studies have shown that hypothermia affects most cell death pathways, including pathways leading to excitotoxicity, apoptosis, inflammation, and free radical production. Hypothermia has effects in the acute, subacute, and chronic phases after hypoxia–ischemia; no single factor can explain the neuroprotection associated with hypothermia (132).

Magnetic resonance spectroscopy has been used to study the evolution of brain energy metabolism during and after a transient hypoxic–ischemic insult in the piglet (85). A biphasic pattern of energy disturbance is associated with hypoxia–ischemia: During the hypoxic–ischemic insult itself (primary energy failure) there is typically a decrease in ATP and high-energy phosphates, such as phosphocreatine, as well as an increase in brain lactate (85, 133). Some cells die mainly by necrosis during this phase; the magnitude of this loss will depend on the duration
and severity of the hypoxia–ischemia. During reperfusion there is an apparent recovery of oxidative phosphorylation back to near baseline levels; to be effective, therapies, such as hypothermia, need to be started during this phase known as the “therapeutic window.” Cerebral oxidative metabolism may then secondarily deteriorate 6–15 hours later (secondary energy failure) (88). This phase is marked by the onset of seizures, secondary cytotoxic edema, accumulation of cytokines, and mitochondrial failure. Hypothermia has been shown to ameliorate the secondary decrease in brain energy metabolism (91). The more severe the hypoxia–ischemia, the shorter the therapeutic window; importantly, hypothermia extends the therapeutic window when other pharmacological therapies may be effective (134).

**Acute Effects of Hypothermia on Metabolism, Blood Flow, and Excitotoxicity**

Reductions in temperature decrease brain oxygen consumption and glucose metabolism by approximately 5% per 1°C (135). Hypothermia preserves ATP and other high-energy phosphates, such as phosphocreatine (88), thus reducing lactate production from anaerobic brain metabolism (133). The effect of hypothermia on cerebral blood flow depends on the severity and time from the injury. During the index injury, hypoxia–ischemia blood flow is reduced. When blood flow is restored at resuscitation, reperfusion occurs and there generally is an overshoot of flow (hyperemia) followed by a gradual decrease over some hours to a period of hypoperfusion associated with suppressed oxygen metabolism and increased tissue oxygen levels (136). In fetal ovine studies, delayed hypothermia was associated with an extension of the phase of secondary hypoperfusion (137). This prolonged hypoperfusion was associated with improved neural outcome.

The increase in oxygen levels during reperfusion is associated with a transient burst of oxygen free radicals, which lead to peroxidation of cell membrane lipids. A reduction in oxygen metabolism during this phase with hypothermia can suppress the oxygen free radical burst and lipid peroxidation (138). Therapeutic hypothermia also has been shown to prevent the accumulation and release of excitatory amino acids, such as glutamate (139, 140). The reduction in excitatory amino acids may be due to ATP preservation with cooling (because ATP is needed to preserve ion gradients). Hypothermia also may limit the effects of excitotoxicity by limiting calcium influx through AMPA channels. The glutamate receptor 2 subunit of the AMPA receptor limits calcium influx in the uninjured brain; its downregulation with hypoxia–ischemia leads to the excess influx of calcium. Hypothermia attenuates ischemia-induced downregulation of glutamate receptor 2 (141).

These early upstream mechanisms do not fully explain the protective effects of hypothermia, however. The fact that cooling is protective, even if started hours after hypoxia–ischemia, suggests that hypothermia has major effects on the subacute and chronic phases of the injury as well as the acute phase (132). However, it is critical that hypothermia is started early in the latent phase before the start of the secondary deterioration (seizures or secondary energy failure) for it to be effective (142). Animal studies also have shown that if there is a delay in the start of hypothermia for some hours after hypoxia–ischemia, cooling needs to be continued for at least 48–72 hours for full benefit to be achieved (143).

**Subacute and Chronic Effects of Hypothermia on Cell Death and Survival Pathways, Reactive Oxygen Species, and Inflammation**

Hypothermia affects both the intrinsic and extrinsic pathways that lead to apoptosis. The intrinsic pathway stems from within the cell at the level of the mitochondria (144), whereas the extrinsic pathway is triggered via a cell surface receptor (145). Whether cooling has an effect on neuronal survival depends on the injury severity. Models of moderate injury lead to predominantly apoptotic cell death, whereas more severe insults lead to predominantly necrotic death; however, there is a continuum of cell death with intermediate forms of cell death (69).

Cooling can interfere with the intrinsic pathway by changing the expression of Bcl-2 family members (reductions in the proapoptotic BAX protein and increases in the antiapoptotic Bcl-2 protein), reducing cytochrome c release, and decreasing caspase-3 activation (146). In the extrinsic apoptotic pathway, the most widely studied apoptosis-inducing receptor and ligand is Fas and FasL. Hypothermia suppresses the expression of the Fas protein and FasL, protein in models that show hypothermic neuroprotection (147). Hypothermia also has been shown to suppress the apoptosis-inducing factor translocation (a caspase-independent pathway that involves direct cell killing through the release of the apoptosis-inducing factor) (148).

Hypothermia influences certain neurotrophic proteins that control synaptic function and plasticity and sustain neuronal cell survival, morphology, and differentiation. Brain-derived neurotrophic factor (149), glial-derived neurotrophic factor (150), and
neurotrophin (151) are increased in models of neuro-protection after hypoxia–ischemia. Hypothermia also promotes activation of Akt, a protein kinase that has roles in glucose metabolism, cell proliferation, apoptosis, transcription, and cell migration (152).

Hypothermia generally suppresses the inflammation that comes after hypoxia–ischemia. Hypothermia has been shown to lower the numbers of neutrophils and activated microglia in the injured brain and reduce levels of many inflammatory mediators, including reactive oxygen species (153), adhesion molecules, and the proinflammatory cytokines (such as interleukin-1β, TNF-α, and IL-6). However, antiinflammatory cytokines, such as IL-10 and TGF-β, are also reduced by hypothermia (154), indicating that hypothermia does not have a purely antiinflammatory effect. Hypothermia also suppresses the activation of NF-κB, a transcription factor that can activate many inflammation-related genes (155) and the mitogen-activated protein kinase pathway (156), an enzyme system that regulates inflammation.

Hypothermia has important protective effects on the blood–brain barrier (157) and reduces brain edema formation by suppressing aquaporin 4 expression (158). Hypothermia also may support regenerative and reparative processes by enhancing synapse formation and reorganization (132). Hypothermia thus favorably modulates nearly every metabolic, molecular, and cellular event in cell death in the acute, subacute, and chronic phases after hypoxia–ischemia. Hypothermia has its place as a routine treatment for moderate to severe neonatal encephalopathy in an intensive care setting. (See also “Cooling for Neuroprotection” in Chapter 11.)

**Other Potential Neuroprotective Medications**

Despite the robust neuroprotective effects in animal studies of hypothermia in the laboratory, in the clinic, hypothermia offers just an 11% reduction in risk of death or disability in infants with moderate to severe neonatal encephalopathy (92). The use of hypothermia with other neuroprotective medications is being studied by many research groups because there may be additive or synergistic neuroprotection with such combinations (159, 160). Few studies have examined possible interactions of medications with hypothermia and whether combination therapies may augment neuroprotection. There are many questions (such as the following five) that need consideration with adjunct cooling therapies: 1) How easily can the medication be given?; 2) What is the optimal dose?; 3) What are the adverse effects, and are these exacerbated with cooling?; 4) Are there any neurotoxic effects?; and 5) What is the overall benefit of the combination, and does it outweigh any adverse effects? One study assessed 13 possible neuroprotective medications according to the aforementioned criteria (161). The six highest-scored medications were (ranked in order) melatonin, erythropoietin, N-acetyl cysteine, erythropoietin mimetics, allopurinol, and xenon. Phase II clinical trials are under way for xenon-augmented cooling, and phase I combination trials are underway for erythropoietin and are planned for melatonin. Such neuroprotective medications target multiple points in the neurotoxic cascade with some (for example, erythropoietin) showing potential effects by regeneration and repair.

**Conclusions**

- The more severe the hypoxia–ischemia, the shorter the therapeutic window; hypothermia extends the therapeutic window when other pharmacological therapies may be effective.
- It is critical that hypothermia is started early in the latent phase before the start of the secondary deterioration (seizures or secondary energy failure) for it to be effective.
- Hypothermia favorably modulates nearly every metabolic, molecular, and cellular event in cell death in the acute, subacute, and chronic phases after hypoxia–ischemia.

**Research Recommendations**

- Experiments should be designed to assess interactions between hypoxia and factors identified from human epidemiological studies as being relevant to hypoxic–ischemic encephalopathy (eg, pyrexia, infection, and growth restriction).
- High-throughput, carefully designed proof-of-principle experiments should be performed, often in rodents, to identify new therapeutic targets and perform initial interventions.
- Clinically relevant experimental studies should be used to develop neuroprotective interventions to the stage of clinical phase I trials.

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A number of maternal conditions have been linked with neonatal encephalopathy, including bleeding during pregnancy, trauma, coagulation and autoimmune disorders, infection, thyroid disorders, and epilepsy. Additional maternal conditions are addressed in Chapter 5, “Fetal Considerations and Assessment.” It is controversial whether other maternal risk factors, such as advanced maternal age and obesity, are associated with an increased risk of neonatal encephalopathy and cerebral palsy. Several large population-based studies have documented an association between infertility treatments and cerebral palsy. In most of these studies, the association was explained by preterm delivery or multiple births, or a combination of these two factors. Both moderate to heavy maternal alcohol consumption and cocaine consumption may affect neurologic development. The effects of other illegal substances have not been clearly defined. This chapter focuses on whether, and to what degree, certain maternal conditions may affect fetal and neonatal neurologic development.

Maternal Bleeding in Pregnancy

Although maternal hemorrhagic shock caused by placenta previa or abruptio placentae can result in impaired oxygen delivery to the fetus, third-trimester bleeding is rarely associated with neonatal hypoxic-ischemic encephalopathy (HIE). A significant association has been reported between neuronal necrosis, white-matter gliosis or necrosis, and pathologically diagnosed abruptio placentae (1). Confounding this association is the common coexistence of abruptio placentae with inflammatory lesions, such as chorioamnionitis and funisitis, which are themselves linked to neonatal brain injury (2). Early research demonstrated an association between maternal bleeding in pregnancy and cerebral palsy, but most of those studies were flawed by their failure to adjust for confounding variables, such as the effect of low birth weight. Review of the studies that have controlled for fetal growth restriction suggests an association, if present, is modest and limited to term pregnancies. In a case-control study of antecedents to HIE among Western Australian women and their term infants (89 cases, 89 matched controls), antepartum vaginal bleeding was associated with neonatal encephalopathy (18% versus 4%, odds ratio [OR], 5.0; 95% confidence interval [CI], 1.5–17.3) (3). However, this association was not adjusted for infection, hypoxia, congenital anomalies, or other underlying maternal or pregnancy-related conditions that may have contributed to the bleeding. In another case-control study (164 cases, 412 randomly selected controls) conducted by the same group, a significant association between moderate-to-severe antepartum vaginal bleeding and newborn encephalopathy was noted (6.7% versus 3.0%, adjusted OR, 3.57; 95% CI, 1.30–9.85) (4).

Studies also suggest a link between other placental abnormalities associated with bleeding and cerebral palsy. A prospective U.S. study observed 42,704 women who gave birth to infants weighing more than 2,500 g and found placenta previa to be a risk factor for cerebral palsy with 1.9% of such pregnancies affected (P<.05), (relative risk of 6) (5). However, the number of affected infants born to women with placenta previa was small (n=3). Although abruptio placentae carried an increased risk of fetal death in the first year of life, the risk of cerebral palsy in the survivors was not increased. This study also did not
control for maternal or pregnancy factors that may have contributed to placenta previa or abruptio placentae. A case–control study of 46 infants who weighed more than 2,500 g with unexplained spastic cerebral palsy and 378 randomly selected controls from the California Birth Defects Monitoring Program failed to demonstrate an association between either abruptio placentae (OR, 4.3; 95% CI, 0.65–39) or placenta previa (OR, 2.8; 95% CI, 0.52–25) and an increased risk of cerebral palsy (6). However, a subgroup analysis found abruptio placentae (OR, 11.0; 95% CI, 1.6–103) and placenta previa (OR, 7.4; 95% CI, 1.3–66) to be associated with increased risks of the cerebral palsy subtype, spastic quadriplegia. This study evaluated placenta previa and abruptio placentae as univariate risk factors.

The only published paper to evaluate the relationship between third-trimester maternal bleeding and HIE in preterm infants was a Danish case–control study (7). In this study, neither placenta previa (OR, 0.26; 95% CI, 0.1–1.1) nor abruptio placentae (OR, 0.97; 95% CI, 0.61–1.55) was a significant predictor of cerebral palsy. Calculated risks for neonates who develop cerebral palsy after delivery from women with placenta previa or abruptio placentae are problematic and likely represent unstable estimates. Moreover, abruptio placentae does not necessarily arise de novo but most often in association with underlying disease states, such as hypertension, coagulopathy, substance abuse, uterine overdistention, or infection. Intervention during labor cannot reverse these underlying causes of bleeding or other antecedent events that may have caused damage to the fetus.

Conclusions

• Third-trimester placental bleeding is often associated with a chronic and long-standing underlying condition that may have resulted in fetal injury antedating clinical bleeding.
• Third-trimester bleeding is rarely associated with neonatal HIE.

Maternal Trauma During Pregnancy

Traumatic brain injury (TBI) is common and significant, resulting in 50,000 deaths and 1.5 million new cases in the United States each year (8). When the trauma occurs ex utero, attribution of the sequelae of TBI to the inciting event is relatively straightforward because of the observed changes in functionality subsequent to the injury. Traumatic brain injury results from rapid deceleration of the skull with the brain striking the inner portion of the skull, intracranial bleeding that is due to cerebral hypoxia or traumatic disruption of blood vessels within the brain or the surrounding structures (eg, meninges). In utero, the fetal skull and its contents are cushioned by maternal soft tissues and amniotic fluid, which results in a significant decrease in direct energy transmission as well as a dampening effect on decelerative forces (9). As a result, adverse neurologic sequelae secondary to fetal trauma during pregnancy are infrequently reported and appear to be rare events.

Without in utero imaging evidence (ie, within 1 week of trauma) (10), direct attribution of fetal trauma during pregnancy as a causative event of childhood neurologic sequelae is difficult. Because routine fetal brain imaging after trauma during pregnancy is not standard management (11), the incidence of imaging evidence of fetal TBI is unknown. However, an important population-based study does provide some evidence of the magnitude of the effect of trauma during pregnancy on the subsequent development of cerebral palsy. Relying on a long-standing cerebral palsy registry in Australia, the incidence of cerebral palsy was measured over a 10-year period in children of women who were hospitalized for trauma during pregnancy and compared with children of women who were not hospitalized for trauma during pregnancy. A total of 286,745 newborns were monitored over 10 years and a total of 770 pregnant women were hospitalized for trauma during pregnancy. Among this trauma group, there were only two childhood cases of cerebral palsy, whereas there were 527 cases of cerebral palsy among the 285,974 women who were not hospitalized for trauma. There was no statistically significant difference in the incidence of cerebral palsy between the two groups (relative risk 1.4; 95% CI, 0.34–5.77) (12).

Large population-based studies like that in Australia are reassuring, validating that the in utero location of the fetus largely protects the skull and its contents from injury and that childhood neurologic sequelae after trauma in pregnancy are rare. Moreover, these results call into serious question the scientific validity of reports that attribute childhood neurologic sequelae to in utero trauma months or years after the event occurred. In one of such reports, 10 cases of cerebral palsy were allegedly a result of in utero trauma, diagnosed by postnatal magnetic resonance imaging that showed “lesions consistent with prenatal insult at the time of the trauma” (13). Because the many causes of cerebral palsy have multiple contributory causes or are due to underlying placenta pathologic processes (placental pathology
was not reported in this case series), ascribing causation to a traumatic event during pregnancy months after the event occurred should be considered carefully. More research needs to be done to improve our understanding about the relationship between maternal trauma during pregnancy and the subsequent development of neurologic sequelae.

Conclusions

• Fetal trauma during pregnancy appears to be quite rare and typically is due to severe and direct abdominal trauma.

• Ascribing causation of fetal trauma in pregnancy with subsequent adverse ex utero neurologic sequelae is most accurate if fetal brain imaging in close proximity to the trauma demonstrates findings consistent with fetal TBI.

• Because fetal TBI appears to be so rare, fetal brain imaging following the traumatic event is not routinely recommended.

Coagulation Abnormalities and Autoimmune Disorders

Fetal and Maternal Thrombosis and Coagulopathy

Case–control and small retrospective cohort reports proliferated in the 1990s and early 2000s demonstrating a putative relationship between inherited thrombophilias and various thrombotic placental lesions, stillbirth, organ thrombosis, and early neonatal death (14). Moreover, fetal placental vessels had been found to show obvious thrombi in most cases of well-documented cerebral palsy (15). However, more recent studies have cast doubt on the relationship between these thrombophilias and specific placental pathology. For example, Ariel and colleagues examined placentas from 64 pregnancies complicated by preeclampsia, abruptio placenta, or intrauterine growth restriction; 15 had maternal thrombophilic mutations and 19 had fetal mutations (16). The authors found no statistical difference in the prevalence of thrombotic lesions of the fetal circulation between newborns or mothers with and without thrombophilia. Experts have noted that the case for inherited thrombophilias causing placental-mediated complications does not meet Hill’s criteria to establish causality (17). In 2010, the American College of Obstetricians and Gynecologists (the College) concluded that the possible association between inherited thrombophilias and uteroplacental thrombosis, which leads to adverse pregnancy outcome, such as stillbirth (fetal death), preeclampsia, and fetal growth restriction, was controversial and derives from small case–control and cohort studies of heterogeneous populations (18). Existing analyses do not exclude the possibility that placental pathology may result from an additive or synergistic relationship between inherited thrombophilias and other clinical occurrences, such as infection, linked to adverse pregnancy outcomes.

Neuroimaging findings of focal cerebral infarctions presumed to be due to perinatal ischemic stroke are common in children with congenital hemiplegic cerebral palsy (19, 20). A systematic review and meta-analysis found that thrombophilias are risk factors for arterial ischemic stroke in neonates and children (21). In a meta-analysis of the six studies that involved only perinatal stroke, factor V Leiden (OR, 3.56; 95% CI, 2.29, 5.53) and prothrombin gene mutation (OR, 2.02; 95% CI, 1.02, 3.99) were both associated with an increased risk of perinatal ischemic stroke. The relationship between genetic thrombophilias and perinatal stroke are further reviewed in Chapter 8.

Experts note that fetal mutations inherited from either parent might predispose to thromboses in the fetoplacental circulation, which, in turn, might gain access to the central nervous system (CNS) via the patent foramen ovale, resulting in CNS damage before birth. In one study, investigators analyzed analytes of dried blood samples on filter paper that were obtained from 31 children with spastic cerebral palsy of unknown cause and 65 control children (22). Twenty of the 31 children with cerebral palsy had one or more coagulation abnormalities, and several demonstrated multiple coagulation abnormalities. However, studies that have studied the association between maternal and fetal thrombophilias and cerebral palsy have produced inconsistent results (23, 24).

Autoimmune Disorders

Antiphospholipid syndrome is an acquired condition associated with thrombosis and adverse pregnancy outcomes, including placental insufficiency in affected individuals (25). Several lines of evidence suggest that the associated autoantibodies, lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein I are causative in nature (26). The immunoglobulin G isotype of these autoantibodies crosses the placenta and can be found in the umbilical cord blood of infants born of women with antiphospholipid syndrome. A comprehensive review published in 2007 examined 16 infants with perinatal stroke. In addition to antiphospholipid antibodies in 9 out of the 14 evaluable children, risk factors included preeclampsia, intrauterine growth
restriction or “perinatal asphyxia,”* sepsis, arterial or venous catheter placement, and inherited thrombophilia. However, antiphospholipid antibodies were the only risk factor found in four full-term infants who suffered from stroke (27). In addition to a potential coagulopathic role in the fetus or neonate, antiphospholipid antibodies are associated with placental insufficiency, severe preeclampsia, fetal growth restriction, and the need for preterm birth (28); all features associated with perinatal hypoxia and cerebral palsy. Investigators have found that anti-DNA antibodies, found in patients with systemic lupus erythematosus, cross-react with NR2a and NR2b (subunits of the N-methyl-D-aspartate [NMDA] receptor) that are found in neurons throughout the brain (29). The authors posit that these findings suggest that lupus antibodies may cross-react with NMDA receptors to mediate nonthrombotic and nonvasculitic abnormalities of the CNS. In a murine model, this cross-reactivity induces neuronal cell death when injected directly into the hippocampus. Subsequent studies show that experimental disruption of the blood–brain barrier allows antibody-mediated neuronal cell destruction in adult murine models (30). The premature fetus lacks a fully formed blood-brain barrier, and fetuses from dams with high titers of the pertinent cross-reacting antibody have abnormalities of brain cortex (31). Investigators hypothesize that anti-DNA antibodies that cross-react with neuronal membrane receptors may mediate brain dysfunction. As yet, though, studies in humans are lacking.

Conclusions

• Some studies have found that placental vascular lesions, including those likely to be thrombotic, are associated with inherited thrombophilias of the mother or fetus or neonate, but causality has not been established.

• Factor V Leiden and prothrombin mutations may be associated with a modest increase in risk of perinatal stroke. The relationship between maternal and fetal thrombophilias and cerebral palsy remains unclear.

• Large, properly designed studies are required to determine if thrombophilias are significant and independent causes of cerebral palsy.

• Case reports suggest a possible relationship between antiphospholipid antibodies and fetal or neonatal stroke, although the occurrence seems infrequent.

• Some autoantibodies associated with systemic lupus erythematosus cross-react with neuronal membrane receptors. The implication of this for the fetus–neonate is uncertain at present.

**Maternal Infection**

During pregnancy the diagnosis of fetal infection or a fetal inflammatory response to maternal infection is difficult to ascertain, and diagnosis by cordocentesis or amniocentesis is uncommon. Antenatal intrauterine infection is a risk factor for neonatal encephalopathy and neurologic disability. The prevalence of bacterial, viral, and protozoan infections during pregnancy that can cross the placenta and have a neurotropic effect on the developing fetus may be underestimated. Human immunodeficiency virus (HIV); toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus infections; syphilis; varicella zoster; and lymphocytic choriomeningitis virus have all been documented to cause neurologic sequelae, including cerebral palsy (32). In a case–control study using stored neonatal blood spots, cytomegalovirus and Epstein-Barr virus DNA was detected in five (1.5%) and three (0.9%) of the 339 cases of cerebral palsy, respectively, but not in any of the 594 controls (P=.006 and .048, respectively) (33). In a large case–control study, self-reported maternal infection of any kind during pregnancy was associated with cerebral palsy (OR, 1.55; CI, 1.26–1.91) (34). In that study, however, common upper respiratory tract and gastrointestinal infections, retrospectively reported by mothers were not associated with cerebral palsy. Bacterial urinary tract infections at any time during pregnancy have been separately reported as being associated with cerebral palsy outcomes (OR, 3.9; CI, 1.7–8.9) (35). (See also “Chorioamnionitis” in Chapter 4 and “Chorioamnionitis and Intrapartum Fever” in Chapter 6.)

**Biological Pathways**

Several biological pathways may lead from infection to neurologic disability. Plausible mechanisms include a direct effect of neurotropic organisms on the fetal brain or indirect effects mediated by the immune system (eg, release of inflammatory mediators) or cardiovascular system (eg, causing hypotension). (See also the section on “Infection and Inflammation,” Chapter 2.)

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* Throughout the report, the terms “asphyxia” and “birth asphyxia” and their variations appear in quotes when used in reference to a particular study to emphasize the wide variation in study definitions of asphyxia. See Chapter 1 for recommended asphyxia definition (in Table 1–1) and discussion of asphyxia terminology.
Candidate gene studies of cytokine polymorphisms have not associated these mutations with cerebral palsy after adjustment for multiple analyses (23, 24). However, infection during pregnancy may act as an environmental trigger in those who are genetically susceptible. This field needs more research and larger studies, but a link between the antiinflammatory cytokine interleukin-4, perinatal viral exposure, and subsequent quadriplegic cerebral palsy has been described in preterm infants (OR, 4.25; CI, 1.21–14.95) (36).

Advances in second-generation genomic sequencing allow examination for copy-number variants in cerebral palsy families. These genetic variants have been associated with other developmental neurologic disorders, such as autism, epilepsy, schizophrenia, and intellectual disability (37). (See also Chapter 9 “Role of Genetics.”)

Conclusion

- Antenatal intrauterine infection is a risk factor for neonatal encephalopathy and neurologic disability. The prevalence of bacterial, viral, and protozoan infections during pregnancy that can cross the placenta and have a neurotropic effect on the developing fetus may be underestimated.

Maternal Thyroid Disorder

Normal brain development requires thyroid hormone at many points during fetal life and later (38, 39). Thyroid hormone is also involved in such basic reproductive processes as fertilization and implantation. For example, remodeling of maternal spiral arteries, a key process in implantation, was more often abnormal in placentas of hypothyroid women (40), perhaps related to the role of thyroid hormone in trophoblast invasiveness (41). Defective placentation, in turn, is associated with a range of reproductive complications that includes preeclampsia, preterm birth, fetal growth restriction, and placental infarction (40, 42), which are risk factors for adverse neurologic outcome in the infant. Maternal thyroid disorders also are associated with increased rates of preeclampsia, preterm delivery, and “fetal distress” in labor (43, 44). Thus, there are both direct and indirect pathways by which thyroid status can influence neurologic outcome in the child.

Maternal thyroid disorders in pregnancy are relatively common. Overt hypothyroidism is present early in the second trimester in 0.5–2.3% of pregnancies (45, 46) and overt hyperthyroidism in approximately 0.3% (45). In women undergoing treatment for hypothyroidism, the dose often must be modified (commonly increased) during pregnancy to optimize outcome (47).

Subclinical thyroid disorders, with aberrant values of thyroid-stimulating hormone (TSH) or thyroxine (T4) but without clinical features of thyroid disease, are about twice as common as clinically evident thyroid disease (48). Subclinical hypothyroidism appears not to be associated with a consistent pattern of pregnancy or birth complications (49). There has been no demonstration to date that therapeutic intervention improves outcome in infants born to women with subclinical thyroid disease.

The need of the fetus for thyroid hormone begins early in gestation, before the fetal thyroid is present or autonomously functional. Transplacental delivery of maternal thyroid hormone to the fetus is key early and, if the fetal thyroid is hypofunctional, remains important throughout pregnancy (50). Thus, maternal thyroid status and selective transport mechanisms in the placenta are critically important in fetal brain development.

Maternal Thyroid Disease and Neonatal Encephalopathy

In a small retrospective case–control study, maternal hypothyroidism was not statistically significantly associated with neonatal encephalopathy, with an odds ratio of 3.8 (51). Three controlled population-based studies have observed maternal thyroid disorder (hypothyroidism or hyperthyroidism), defined by clinical diagnosis (3, 4) or low maternal TSH (52), to be associated with increased risk of neonatal encephalopathy. In the largest study of precursors of neonatal encephalopathy, maternal thyroid disorder was associated with an almost 10-fold increase in risk of neonatal encephalopathy (adjusted [OR], 9.7; 95% CI, 1.97–47.7) (4). In this prospective study, mothers of infants with neonatal encephalopathy had fewer thyroid function tests in pregnancy than mothers of control infants, more often remained on the same dose of medication throughout pregnancy, and more often experienced other complications of pregnancy (53).

Maternal Thyroid Disorder and Cerebral Palsy

In areas of endemic cretinism, maternal thyroid disorder due to iodine deficiency results in a syndrome that

*The term “fetal distress” is imprecise and nonspecific. Although still used in the literature, its continued use as an antepartum or intrapartum diagnosis is discouraged. It is recommended that the term “fetal distress” be replaced with “unreassuring fetal status,” followed by a further description of findings.
includes congenital diplegic motor disability (54). In a prospective study of North American births, mothers of children with cerebral palsy were more often hypothyroid or receiving thyroid hormone treatment during pregnancy than mothers of children without cerebral palsy (55), a difference that persisted on multivariate analysis (56).

In blood eluted from newborn blood spots, triiodothyronine levels were markedly higher in term and late-preterm children with cerebral palsy who also had high levels of interferons, compared with children with cerebral palsy but unremarkable interferon levels and compared with normal controls (22). Thyroid-stimulating hormone levels were high in children with low triiodothyronine levels, indicating functionality of the hypothalamic–pituitary axis.

Researchers of one study concluded that although a “number of lines of evidence point to a possible role of thyroid hormone, the full contribution of [thyroid disorders] to the risk of [cerebral palsy] remains to be elucidated” (57). Maternal thyroid disease was not examined as a risk factor for cerebral palsy in term infants in studies published between 2000 and 2010 (58).

**Thyroid Autoantibodies in the Absence of Clinical Thyroid Disease or Aberrant Thyroid Hormone Levels**

In areas of iodine sufficiency, the most common cause of maternal thyroid disorder is autoimmune disease. Autoimmune thyroid disease is the most common autoimmune disorder in women of reproductive age; 10–18% of women have antithyroid peroxidase antibodies early in pregnancy (59, 60), and 50–60% of women with increased TSH or low normal T4 levels have evidence of antithyroid antibodies, antithyroid peroxidase, or antithyroglobulin antibodies. High parity is associated with an increased risk of high levels of antithyroid peroxidase antibodies (61).

Ten percent of neonates have antithyroid antibodies. It has not been investigated whether these are related to maternal antibodies (although that is likely a priori). Guidelines exist for treatment of thyroid disorders in symptomatic women (47) but not for subclinical states, whether or not they are antibody positive.

**Other Neurologic Outcomes**

The full syndrome of neonatal hypothyroidism that is due to maternal iodine deficiency includes mental retardation, high-tone hearing loss, and motor disorder. Studies since the 1970s have described impaired intellectual development in children born to women with non–iodine-deficient hypothyroidism during pregnancy (62). Later studies confirmed this finding, demonstrating a significantly lower IQ level in children of women with a high thyroid-stimulating hormone level when compared with control children of women who were euthyroid (63). Additional studies, a Dutch study (64) and a study from China (65), reported decreased neurologic development at 2 years of age in children born to women with subclinical hypothyroidism during pregnancy compared with children of women who were euthyroid. There may be more specific cognitive impairments associated with maternal hypothyroidism. A low free T4 level (without an increased level of thyroid-stimulating hormone) has been associated with psychomotor deficit in infancy (66) and at the age of 2–3 years (67), as well as with delays in the development of expressive language (68).

Other studies have shown a decrement of orientation (69), vision abnormalities (70), and behavioral changes (71) in children born to women with hypothyroidism in pregnancy. Defects in memory, visual attention, and processing have been described in the children of women with untreated low free T4 levels during pregnancy (72). However, a randomized trial concluded that antenatal screening and maternal treatment for hypothyroidism did not result in improved cognitive function in children at 3 years of age (73).

Current guidelines do not recommend routine antenatal screening for hypothyroidism in pregnancy (47). A randomized trial to assess the effect of screening and treatment on IQ at 5 years of age in the children of women with elevated thyroid-stimulating hormone or reduced free T4 levels in blood samples provided between 8 weeks and 20 weeks of gestation is ongoing (74).

**Conclusions**

- Maternal thyroid disease, clinical or subclinical, is common in pregnancy and in developed countries is chiefly autoimmune.
- Maternal thyroid disease is a risk factor for neonatal encephalopathy and for lower cognitive performance in the child.
- The role of maternal thyroid status in cerebral palsy remains uncertain.
- Current guidelines do not recommend routine antenatal screening for hypothyroidism in pregnancy.

**Maternal Epilepsy**

Epilepsy is defined by the presence of recurrent, unprovoked, nonfebrile seizures, and treatment is
typically a daily regimen of one or more antiepileptic drugs. Most women with epilepsy have well-controlled seizures and expect to participate fully in their life experiences, including childbearing. The guiding principle in treating women with epilepsy is that generalized tonic–clonic (convulsive) seizures pose an immediate risk to the woman and could possibly be of danger to the developing fetus. However, antiepileptic drugs have teratogenic potential and also pose a risk to the neurocognitive development of the fetus. In a study of infants exposed to antiepileptic drugs in utero (n=316), in which the largest control group of women with epilepsy were not taking antiepileptic drugs (n=98), there was no increased risk of teratogenesis among epileptic controls who were not taking antiepileptic drugs compared with women without epilepsy (n=508) (75). Similarly, two meta-analyses of this issue have found no evidence for a significant risk of major malformations among epileptic women who were taking no drugs (n=182 [76] and n=400 [77]). After adjusting for publication bias in the meta-analysis of Fried, the OR for congenital malformations among the offspring of epileptic women not taking antiepileptic drugs was 0.99 (95% CI, 0.49–2.01). It always can be argued that this reflects the fact that only women with very mild epilepsy are left untreated and that it is the offspring of women with more severe epilepsy that are at greatest risk of malformations due to the epilepsy per se. There will never be a definitive resolution of this dispute because women with frequent convulsive seizures could not ethically be left untreated in significant numbers for study. However, there is growing evidence that both frequent tonic-clonic seizures during pregnancy and fetal exposure to antiepileptic drugs, especially valproic acid, are associated with cognitive impairment in offspring (78, 79).

**Potential Fetal Effects of Maternal Epilepsy**

Impaired cognitive development in the offspring of women with epilepsy could be due to the underlying genetics of the disease or the effects of poorly controlled maternal epilepsy. Individuals with epilepsy have a risk of sudden, unexpected death during a seizure, with the risk increasing with duration of exposure to epilepsy and severity of epilepsy as judged by generalized convulsive (tonic-clonic seizures) versus partial complex seizures and frequency of seizures. Although it is rare for these sudden-death events to be witnessed, near-miss events and circumstances surrounding the unwitnessed events do seem to indicate that they are associated with convulsive seizures. The mechanisms thought to be potentially responsible for death include central respiratory arrest, laryngospasm, suffocation as a result of prone position during sleep, hypercarbia, hypoxemia, acidosis, pulmonary edema, cardiac arrhythmia, and postictal generalized electroencephalography suppression (cerebral shutdown) (80). A severe but non-lethal event of this nature could theoretically cause neurologic injury to a fetus in utero at the time of the event, but the occurrence of these events is so rare that it precludes any serious attempt to establish a formal association.

**Potential Fetal Effects of Antiepileptic Drug Therapy**

Data regarding fetal effects of antiepileptic drugs, such as valproic acid and carbamazepine, are derived primarily from studies of women with seizures. The association between first-trimester valproic acid exposure and neural tube defects is well documented (81). Antiepileptic drug polytherapy regimens containing valproic acid appear to increase the risks of congenital malformations (82). Varying degrees of cognitive impairment, including developmental delay, may be reported with fetal exposure to valproic acid (83–87). As first reported in 1991 and confirmed in a meta-analysis in 2002, carbamazepine is teratogenic, associated with a 0.5% incidence of CNS malformations, including hydrocephalus, lumbosacral meningo-myelocele, and spina bifida (76, 88). As compared with valproic acid, carbamazepine, phenytoin, and lamotrigine monotherapies were not associated with neurocognitive impairment at 3 years of age (87).

A retrospective cohort study of offspring of epileptic women in the United Kingdom included 83 children with no fetal antiepileptic drug exposure, 121 with exposure to antiepileptic drug monotherapy, and 52 with exposure to antiepileptic drug polytherapy (78). It found that fetal exposure to valproate monotherapy, antiepileptic drug polytherapy, and five or more generalized tonic-clonic seizures in pregnancy were significantly associated with a lower verbal IQ despite adjusting for other confounding factors, which provides some evidence that fetal exposure to multiple convulsive seizures is harmful. A Cochrane meta-analysis concluded: “In general, [antiepileptic drug] polytherapy exposure is associated with some poorer outcomes in neuropsychological or developmental testing, though the outcomes in terms of significant developmental delay or schooling problems are not well studied” (78).

**Neonatal Encephalopathy and Cerebral Palsy**

There are no studies of women with epilepsy that specifically assess neonatal encephalopathy or cerebral...
palsy in their offspring. A case–control study was conducted of 164 cases of moderate to severe neonatal encephalopathy and 400 control term (greater than 37 weeks of gestation) infants born in metropolitan Perth, Western Australia, between June 1993 and September 1995 (4). The authors’ definition of encephalopathy included a number of criteria occurring during the first week of life, including simply seizures. Of the 164 cases, 109 had seizures with or without other criteria, such as abnormal consciousness, difficulty maintaining respiration, difficulty feeding, and others. Ten times as many cases as controls (23.3% versus 2.3%) had birth defects, which were not defined, and 12.8% of cases and 1.2% of controls were growth restricted at less than the third percentile (adjusted OR, 38.2; 95% CI, 9.4–154). There were no criteria that required that the encephalopathy was the result of a hypoxemic or ischemic insult (eg, measured hypoxemia or acidosis, or renal or hepatic dysfunction). Ninety-two percent of the cases and 99% of the controls had no “acute intrapartum events” recorded, and only 29 cases had umbilical cord pH values measured, of which 5 were below 7.0. Antepartum risk factors for neonatal encephalopathy included a family history of seizures (adjusted OR, 2.55; 95% CI, 1.31–4.94) and a family history of neurologic disorders (adjusted OR, 2.73; 95% CI, 1.16–6.41). These associations may result from hereditary factors associated with neurologic and seizure disorders, which in turn are associated with a clinical presentation of neonatal encephalopathy, as defined in this study. Associations with other antepartum factors or conditions had modest effect sizes, or wide confidence intervals indicating low-frequency events, or were not modifiable risk factors. Analysis of intrapartum events noted that only 13 of the 164 cases were deemed to have an acute intrapartum event, and only 2 of these events were listed as maternal convulsions (89). Whether the convulsions occurred in the setting of eclampsia, with other acute neurologic events, or in women with underlying epilepsy was not clarified.

In 1986, investigators used a stepwise multiple logistic regression analysis of data from the National Collaborative Perinatal Project to identify risk factors for cerebral palsy among 189 case children with cerebral palsy as compared with more than 45,000 control children (56). Twenty-three percent of the case children with cerebral palsy had experienced at least one nonfebrile seizure by 7 years of age, and 2.7% of the case children had a mother with seizures as compared with 0.4% of the control children. There was a modest association between maternal seizures and risk of cerebral palsy in the offspring. There was a much stronger association with neonatal seizures: 12.2% among children with cerebral palsy as compared with 0.3% among control children.

Conclusions

• It is unclear whether poor neurodevelopmental outcomes in the offspring of women with epilepsy are due to the underlying pathology of the disease, teratogenic effects of AED treatment, or a combination of both.

• The mechanism behind the association between maternal epilepsy, the occurrence of maternal seizures, and neonatal encephalopathy in the offspring is unclear and could be due to shared genetic causes of anatomic or metabolic abnormalities.

• There are no data to support an association between maternal epilepsy or the use of AEDs in the mother with the development of cerebral palsy in the offspring.

Environmental Factors and Alcohol and Drug Exposure

Environmental Factors

Heavy Metal Exposure

There are numerous studies evaluating the relationship between environmental chemical exposure and neurologic development. However, there do not appear to be any studies that specifically evaluate the relationship between environmental chemical exposure and neonatal encephalopathy or cerebral palsy, with the exception of data on methylmercury. It is plausible that chemicals that can affect neurologic development could contribute to these conditions. The developing human brain is more susceptible to environmental chemical exposure than that of adults (90). Further, pregnant women are exposed to numerous environmental chemicals because thousands are registered for use in the marketplace; studies of a subset of these chemicals find that pregnant women have many measurable environmental chemicals in their body, most which can be transferred to the fetus (91).

One of the best-known prenatal environmental toxins, methylmercury, has been shown to cause damage to the developing brain, with more subtle neurologic effects found at levels of possible exposure to pregnant women in the U.S. population (92). The primary source of this environmental toxin is thought to be maternal consumption of varieties of fish and seafood that are the most likely to be contaminated with harmful levels of methylmercury (93). More severe effects—including cerebral atrophy, cerebral
palsy, mental retardation, spasticity, seizures, and blindness—have all been reported to be associated with exposure to high concentrations of organic methylmercury during pregnancy (94). However, no increased adverse pregnancy effects were found in two reports of occupational metallic mercury exposure among dental workers (95, 96).

Lead is known to affect the developing brain. It increases the risks of learning problems, such as reduced intelligence and cognitive performance. Its behavioral effects include attention-deficit/hyperactivity disorder and antisocial behaviors (97–99). Several studies have found a relationship between prenatal exposure to lead and cognitive and behavioral effects in young infants and children (100–103). If maternal lead exposure is associated with cerebral palsy, the level and degree of lead exposure resulting in such damage is unknown because this outcome has not been specifically studied.

Environmental Chemicals
Numerous studies support a relationship between environmental chemical exposure and effects on neurodevelopment (90). Although data are often lacking because of limited requirements to test chemicals that are in the marketplace, approximately 200 chemicals have been found to be neurotoxic in adults and, thus, may pose a risk to the developing brain. Some more well-studied developmental neurotoxicants include polychlorinated biphenyls (PCBs), polybrominated bisphenol diethers, some pesticides, and manganese (90, 104). Population exposure levels to PCBs are decreasing worldwide because they are no longer used or produced in most countries; however, PCBs are persistent in the environment and accumulate in the food chain. Human studies have suggested that prenatal and postnatal exposure to PCBs through breast milk are at least associated with developmental delays (105). Prenatal occupational exposure to solvents have been associated with major malformations, including CNS defects (106–111).

Ionizing Radiation
In utero exposure to ionizing radiation above a threshold dose and during sensitive periods of fetal development has been associated with adverse neurodevelopmental effects, although the outcomes of neonatal encephalopathy and cerebral palsy have not been studied (112). Studies of offspring of women exposed to high doses of radiation through the atomic bombs in Hiroshima and Nagasaki as well as the Chernobyl disaster have shown evidence of brain injury, microcephaly, lowered IQ, and mental retardation (113–118).

Alcohol and Drug Exposure
Intrauterine exposure to alcohol and certain drugs may cause congenital anomalies or fetal growth restriction, increase the risk of preterm birth, produce signs of withdrawal or toxicity in the neonate, or impair normal neurodevelopment. The 2010 National Survey on Drug Use and Health: Summary of National Findings reported current illicit drug use was 4.4% and alcohol use was 10.8%, with 3.7% binge drinking and 1% heavy drinking, among surveyed pregnant women aged 15–44 years in the 2-year period from 2009 to 2010 (119). The reported rates of illicit drug use most likely underestimate the true rate because the percentage of pregnant women who report recent use of illicit drugs on screening interviews can be substantially lower than the rates determined by drug screening using biological samples.

Alcohol
Prenatal alcohol exposure is associated with an increased risk of fetal alcohol syndrome (FAS), a pattern of structural, growth, and neurodevelopmental abnormalities that is predominately characterized by cognitive and behavioral deficits in affected children (120). The full-blown syndrome is one end of a spectrum of prenatal alcohol-related effects known as fetal alcohol spectrum disorders (FASD). The full spectrum includes children who have no alcohol-related structural or growth abnormalities but exhibit alcohol-related neurodevelopmental disorders (121).

Based on national survey data collected between 1991 and 2005, more than 50% of women of childbearing age in the United States reported consuming alcohol, and approximately 12% reported drinking in a binge pattern. Because more than 50% of pregnancies in the United States are unplanned, the high prevalence of drinking in nonpregnant women leads to the common occurrence of inadvertent exposure to alcohol before pregnancy recognition (122). During pregnancy, 12% of women reported any drinking and 2% reported drinking in a binge pattern (121). Of particular concern, despite widespread public health education, is that reported rates of alcohol consumption among women of childbearing age and among pregnant women have remained largely unchanged over 14 years of national survey data (121).

Traditional surveillance methods are limited in ability to monitor for the incidence of the FAS. The national incidence of the FAS is estimated to be 1–3 per 1,000 live births. Based on one study, the incidence of FASD is estimated to be at least 9.1 per 1,000 (nearly 1 in 100 births) (123). Knowledge of the true incidence of FASD is limited because no
large-scale national incidence studies have yet been completed (124).

Fetal alcohol spectrum disorders are characterized by a pattern of neurodevelopmental outcomes. The extent of alcohol-related structural effects is correlated with the degree of neurobehavioral impairment, but clearly prenatal exposure to moderate to heavy amounts of alcohol can induce neurobehavioral deficits in the absence of some or all of the physical features of FAS. The emerging neurobehavioral profile associated with prenatal alcohol exposure includes impaired intellectual ability (reduced IQ) and deficits in executive functioning, visual attention, verbal and nonverbal learning, motor function, social skills, and adaptive functioning (125). These problems persist into adolescence and adulthood. Prenatal alcohol exposure also is associated with a high incidence of secondary disabilities, including school disruption, mental illness, substance abuse, trouble with the law, and incarceration (126).

Prenatal alcohol exposure has been convincingly related to abnormal neurobehavioral outcomes, even below exposure levels required to induce the complete syndrome. It is less clear whether there is a direct relationship between prenatal alcohol exposure and cerebral palsy, and the topic remains controversial (127). However, a database linkage study from Western Australia reported a threefold increased risk of cerebral palsy in nonaboriginal children whose mothers had an alcohol-related diagnosis (128).

**Illicit Drugs**

The effects of maternal cocaine exposure on fetal neurologic development are less clear than the effects of alcohol on the developing fetus. However, there have been numerous reports of maternal cocaine use and fetal brain damage (129–134). Two reports of maternal cocaine exposure and adverse fetal effects suggest maternal cocaine abuse is associated with a decrease in newborn head circumference (135, 136). Reports regarding long-term effects or more subtle effects of maternal cocaine abuse on language development, cognitive performance, attention, and behavioral regulation have been conflicting (137–140). No definite relationship exists between cerebral palsy and cocaine unless associated with a coexistent obstetric problem (eg, abruptio placentae).

The effect of other illicit substances, such as methamphetamine and marijuana, on fetal neurologic development has not been clearly defined. Pregnant women who abuse methamphetamines have the same increased risk of abruptio placentae, preterm birth, “fetal distress,” and intrauterine growth restriction as those who use cocaine. There are several reports of long-term adverse effects of fetal methamphetamine exposure on cognitive skills, physical dexterity, and behavior (141, 142).

**Selective Serotonin Reuptake Inhibitors**

Selective serotonin reuptake inhibitors (SSRIs) are the most frequently used drugs to treat depression in the general population and in pregnant women (143). Third-trimester use of SSRIs has been associated with a constellation of neonatal signs, including continuous crying, irritability, jitteriness or restlessness, hypertonia or rigidity, and seizures that are thought to represent drug toxicity rather than withdrawal (144, 145). The vast majority of published reports of adverse neurodevelopmental outcomes following SSRI exposure during pregnancy have not demonstrated any evidence of long-term effects.

**Assessing Fetal Exposure to Alcohol and Chemicals**

Maternal blood or urine can be assessed for the presence of environmental and recreational chemicals that may cause fetal brain damage. However, these tests will detect only very recent exposure, and maternal report of these types of prenatal exposure may be unreliable. In contrast, assessing meconium or neonatal or maternal hair may detect exposure occurring earlier during pregnancy because these chemicals (or biomarkers of exposure to these chemicals) accumulate in meconium starting in the 13th week of gestation and in neonatal hair during the third trimester of pregnancy. Maternal hair grows on average 1 cm per month; hence, sectioning of hair can define gestational exposure. These tests are currently in use clinically to detect drugs of abuse (eg, cocaine and methamphetamine) and risky exposure to alcohol (by measuring fatty-acid ethyl esters or other markers of exposure) and mercury, but have not been instituted as a standard of care of public health practice for newborn screening (146).

**Conclusions**

- Moderate to heavy maternal alcohol use may result in neurologic dysfunction, behavioral abnormalities, and cognitive dysfunction.
- There is no known relationship between alcohol consumption and cerebral palsy.
- No definite relationship exists between cerebral palsy and cocaine unless associated with a coexistent obstetric problem (eg, abruptio placentae).
- Maternal cocaine use may affect fetal neurologic development.
Infertility Treatment

The latest population-based data in the United States indicate that just more than 1% of infants born annually were conceived with assisted reproductive technology (ART) (147). Additionally, an estimated 5% of U.S. births are conceived using non-ART ovulation treatments (used in conjunction with either timed intercourse or assisted insemination) (148).

Neonatal Encephalopathy

In their population-based case–control study of births in Western Australia, researchers (4) reported an adjusted OR of 4.43 (95% CI, 1.12–17.60) for the association between neonatal encephalopathy and infertility treatment. Data on infertility treatment, like other medical history information, were ascertained via maternal questionnaire. Specific types of treatment were not provided, and the total number of women who reported infertility treatment was fairly low for both cases (n=8 of 164, 4.9%) and controls (n=9 of 400, 2.2%). Still, the association was relatively strong, statistically significant, and independent of numerous other preconception and antepartum lifestyle and medical risk factors.

Cerebral Palsy

In a systematic review and meta-analysis, five population-based studies inclusive of a total of more than 19,000 pregnancies conceived via ART were identified that assessed the association between ART and cerebral palsy (149). All were conducted in Scandinavian countries, which are very similar in demographic factors, socioeconomic status, and ethnicity, and which all have free access to health care (including fertility treatment). Such uniformity might limit extrapolation of the findings to populations of different ethnic profiles, demography, and health care systems. All studies reported significant positive associations. The summary OR based on three of the five studies without overlapping study populations was 2.18 (95% CI, 1.71–2.77). However, a disproportionate number of children conceived via ART were multiple births, preterm births, or both. A significant association between ART and cerebral palsy was found in the meta-analysis when it specifically examined the association among singleton births (OR, 1.82; 95% CI, 1.31–2.52) (149). In secondary analyses that controlled for preterm delivery, two of the three studies reported that the ART and cerebral palsy association was no longer evident, whereas in the third study, despite a 22% reduction in the OR, the association remained significant (OR, 2.9; 95% CI, 1.4–6.0) (150).

Results from a more recent assessment of births in Denmark were fairly similar to most studies included in the systematic review. Before adjustment for either preterm delivery or multiple births, ART was associated significantly with cerebral palsy (OR, 2.00; 95% CI, 1.51–2.65). After adjustment for preterm delivery, multiple births, or both, ORs were reduced to near 1.0 and were no longer significant (151). Similarly, an updated assessment of births in Sweden found that during the most recent years evaluated—2004–2007 birth cohorts—the twinning rate associated with ART in Sweden had decreased to less than 10%; concurrently, the OR for the association between ART and cerebral palsy for children from these birth cohorts was reduced to 1.0 (152). Finally, a case–control study in Australia reported no difference in the frequency of ART conceptions resulting in the birth of singleton children with and without cerebral palsy (153).

In sum, most of the studies examining cerebral palsy as an outcome have suggested that the main route through which infertility treatment affects cerebral palsy is disorders related to preterm delivery rather than neonatal encephalopathy. However, one study that documented a fairly sizable association after adjustment for preterm delivery and two studies that documented associations after restriction to singletons indicated that this is not a settled issue, and further research is needed. Although the use of single-embryo transfer has increased markedly in many countries, including the United States, it is still only used in a minority of U.S. ART treatments (12% in 2008) (147).

Caveats

In the published studies, infertility treatments were ascertained using various methods (eg, maternal questionnaire, medical record review, and linkage with population-based treatment registries), and in some studies the type or types of infertility treatments women used to conceive the index child are not specified. Positive reported associations must be interpreted in the context that it is not possible to disentangle infertility treatments used from the underlying disorder or disorders that necessitated those treatments. Two studies offer limited and conflicting data on outcomes relevant to this review. An analysis of the children included in the National Collaborative Perinatal Project, a prospective study of pregnancies in the 1960s, documented that a maternal history of prior infertility (ascertained at the first prenatal visit) was not predictive of a cerebral palsy diagnosis when offspring were 7 years of age (55).
Researchers have reported a strong association between subfertility without ART and cerebral palsy (adjusted OR, 2.9; \( P = .086 \)); the OR lost statistical significance after prematurity was added to the model \( (P = .371) \), which suggests that subfertility may lead to cerebral palsy through prematurity \((153)\). Another study noted an increased risk of cerebral palsy in children born after ovulation induction alone, after adjusting for sex, maternal age, educational level, smoking, and parity \( (OR, 1.47; 95\% CI, 1.09–1.97) \) \((151)\). Similarly, in one cohort study, the significant association between in vitro fertilization and risk of cerebral palsy disappeared after adjusting for time to pregnancy, a proxy for subfertility \((154)\). Studies inherently limited to women who conceived spontaneously after experiencing infertility may not be representative of the total population of women who conceive using an infertility treatment.

Conclusions

- Several large, population-based studies have documented an association between infertility treatments and cerebral palsy. In most, the association was explained by preterm delivery, multiple birth, or both.
- In all of the studies examined, it was not possible to disentangle completely the infertility treatment from the underlying infertility disorder.

Other Risk Factors

Maternal Age

It is controversial whether advanced maternal age is associated with occurrence of neonatal encephalopathy or cerebral palsy after term delivery. Of the nine published studies that address this subject, seven were large, retrospective, population-based cohort studies \((4, 23, 153, 155–158)\). Two of them were not limited to term deliveries and included all gestational ages \((23, 153)\); one did not provide any data \((155)\); and an additional study did not control for confounders \((157)\). Of the remaining three studies, one did not find an association between maternal age of 40 years or older at delivery and risk of cerebral palsy in the offspring \( (P = .58) \) \((156)\); and two found an association between maternal age of 35 years or older at delivery and neonatal encephalopathy in the offspring after controlling for confounders, with adjusted OR of 6.0 \( (95\% CI, 1.3–28.2) \) \((4)\) and OR of 1.3 \( (95\% CI, 1.2–1.5) \) \((158)\). Of the two hospital-based studies that have addressed this issue, one from Nepal found an association between maternal age older than 35 years and occurrence of neonatal encephalopathy \( (adjusted OR, 4.35; 95\% CI, 1.04–18.22) \) \((52)\); the other from Italy did not find maternal age to be significantly different between children with neonatal encephalopathy and controls \( (P = .82) \) \((51)\).

Obesity

Only one population-based study has examined whether maternal weight was associated with neonatal encephalopathy, and it did not find an association \((155)\), although no actual data were provided in the article. Among hospital-based studies, one study assessed the variable obesity among possible risk factors in more than 30,000 infants, and noted a significant association between maternal body mass index (BMI) greater than 30 and risk of neonatal encephalopathy at term \( (OR, 8.5; 95\% CI, 1.7–15.3) \), despite a low prevalence of obesity in the population studied \( (3.8\%) \) \((51)\). The association was independent of diabetes mellitus, hypothyroidism, or hypertension. A collaborative hospital-based case–control study also noted an association between maternal BMI greater than 25 and cerebral palsy among term infants \( (OR, 3.48; 95\% CI, 1.25–8.68) \) \((159)\). At variance with these aforementioned studies, a large population-based study not limited to singleton and term gestations found no association between maternal BMI and cerebral palsy \((34)\). A cohort observational study that examined the effect of BMI in 14,142 women who gave birth at term after a trial of labor after cesarean delivery reported no case of hypoxic–ischemic neonatal encephalopathy (despite uterine rupture or dehiscence in 209 cases, 1,228 admissions to the neonatal intensive care unit, and 44 perinatal deaths) \((160)\). Several comorbidities and obstetric (both antepartum and intrapartum) complications frequently associated with obesity may mediate the risk of neonatal encephalopathy observed among offspring of obese women.

Conclusion

- It is controversial whether advancing maternal age and obesity are associated with increased risk of neonatal encephalopathy or cerebral palsy in term singleton pregnancies.

Research Recommendations

- Large properly designed studies are required to determine if thrombophilias are a significant and independent cause of neonatal encephalopathy and cerebral palsy.
- Studies are needed to determine the association of maternal and fetal and infant thyroid disease with neurologic outcome.
• Large studies are needed to determine whether infection during pregnancy may act as an environmental trigger in those who are genetically susceptible to cerebral palsy.

• Studies are needed that specifically evaluate the relationship between environmental chemical exposure and neonatal encephalopathy or cerebral palsy.

• Large-scale population based studies are needed to better assess the independent relationship between obesity (of different degrees of severity) and neonatal encephalopathy and cerebral palsy.

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The Role of Placental Pathology in Neonatal Encephalopathy and Cerebral Palsy

Adequate placental function is critical for fetal development and survival, and inadequacy of transplacental substrate transfer can lead to fetal growth restriction, which is strongly correlated with neurologic compromise (1–5). Exposure to proinflammatory factors produced by the placenta in response to maternal infection has been linked to cerebral palsy (6–9), whereas impaired thyroid hormone transfer from maternal circulation has been implicated with neonatal encephalopathy (10–13). Abrupt cessation of placental oxygen delivery, as occurs with umbilical cord prolapse, abruptio placentae, and uterine rupture, has been linked to neonatal encephalopathy and cerebral palsy. This chapter reviews current data on placental pathology to better understand the potential relationship between these findings and neurologic outcome.

Reliable correlations between various placental abnormalities and adverse neonatal outcomes are limited and often conflicting. Cerebral palsy and other long-term adverse neurologic outcomes, such as mental retardation, epilepsy, and autism, are not diagnosed until months or years after birth, long after the placentas of most affected children have been discarded. Studies based on convenience samples of placentas, once the neurologic outcome becomes known, may be seriously biased. Because most adverse neurologic outcomes are uncommon, studies of adequate size with appropriate controls are difficult to assemble (14). Placental–clinical correlations are more feasible for neonatal encephalopathy because the delivery of a neurologically depressed infant can enable a decision to send the placenta for pathologic examination immediately. However, consensus is still incomplete on the specific procedures to be followed in placental examination, and interpretations by general pathologists may differ from those of specialist perinatal pathologists.

The paucity of large, controlled studies in representative populations means that the magnitude of the increase in risk associated with specific placental lesions is difficult to quantify. Until controlled studies are available, it is difficult to reach an evidence-based determination of whether or to what degree a given placental finding has contributed to adverse outcome.

Placental Histology and Neonatal Neurologic Outcome

Histologic evaluation of the placenta can provide important, albeit indirect, information regarding placental function and its potential role in neurologic dysfunction in the newborn. In one of the few controlled, population-based investigations of neonatal encephalopathy, abnormal macroscopic appearance of the placenta was observed in 27% of 164 infants with neonatal encephalopathy and 11% of 400 control infants (15). Other studies from smaller convenience samples suggest very high rates of placental pathology (as many as three fourths or more of the examined placentas) in third-trimester stillbirths with brain abnormalities and in infants with low Apgar scores or neonatal encephalopathy (16–20).

Placental Weight

Reference standards for trimmed placental weights published since 1990 are in reasonable agreement. However, there are few studies relating placental weight to neurologic outcome, and the results of these studies are highly discrepant. The few contemporary
prospective population-based studies (21, 22) did not demonstrate a clear association of placental weight with cerebral palsy and did not examine neonatal encephalopathy. The few appropriate studies available (21–24) do not establish that placental weight per se is related to neurologic outcome.

Decidual Vasculopathy
The term **decidual vasculopathy** describes a group of related pathological changes resulting from abnormalities in the spiral arteries of the maternal decidua. The classical histologic feature is acute atherosis with an accumulation of macrophages beneath the endothelium of the vessel. Less severe changes in the spectrum include incomplete trophoblastic invasion of the maternal spiral arteries with or without superimposed vascular thrombosis. The end result of the process is a reduction in maternal spiral artery blood flow with resulting villous ischemia. Mechanisms of the resulting placental tissue damage are complex and involve free radical generation. Decidual vasculopathy is associated with the clinical syndromes of preeclampsia, maternal hypertension, maternal autoimmune disease or thrombophilias, and fetal growth restriction, the latter of which has been associated with neonatal encephalopathy and cerebral palsy.

Placental pathological findings with decidual vasculopathy may be macroscopically apparent, such as gross placental infarction, or may be more subtle with only minor microscopic changes. Histologic features include abnormalities in the decidual vessels of the basal plate, such as frank atherosis and persistence of smooth muscle in the spiral arteries, and secondary changes in the villous architecture (including increased syncytial knot formation; villous hypovascularity; stem villous vasoconstriction and small, abnormally branched terminal villi; and accelerated maturation or distal villous hypoplasia). In a review of 158 medical–legal cases of cerebral palsy complicating singleton pregnancies after 36 weeks of gestation, decidual vasculopathy and other lesions indicative of chronic placental dysfunction were present in 23% and lesions indicative of subacute or chronic hypoxia were present in 15% (25).

Placental Infarction
A placental infarct is a localized area of villous ischemic necrosis that results from a localized reduction of uteroplacental blood flow. Placental infarcts, including those that are peripheral and small in size, may be seen in 2–13% of clinically uncomplicated pregnancies and, thus, data that suggest a linkage of placental infarcts with neonatal encephalopathy or cerebral palsy must be approached cautiously (26). In a Danish study that compared 271 singleton children with spastic cerebral palsy and 217 matched controls, spastic quadriplegia was associated with a fourfold increase in the frequency of placental infarcts (22). The combination of placental infarction and fetal growth restriction was present in approximately 20% of cases of cerebral palsy and associated with a sixfold increased risk. In a cohort study of 175 structurally normal, stillborn infants, 40% of brains showed histologic evidence of ischemic injury, and 55% of the corresponding placentas showed evidence of infarction (27). Another report that examined placental histology and neuropathology in third-trimester stillbirths found that a high proportion of stillborn infants had coexisting vascular or inflammatory lesions in the placenta and neuronal and white matter brain injury (20). Thus, although placental infarcts are identified in a substantial percentage of clinically uncomplicated pregnancies, the presence of infarcts in the placentas of cases of cerebral palsy appears to be increased.

**Intervillous Thrombi, Retroplacental Hematomas, and Abruptio Placentae**
Intervillous thrombi represent well-circumscribed areas of villous-free blood clot within the maternal intervillous space. Small intervillous thrombi can be identified macroscopically in at least 30% of placentas from clinically uncomplicated pregnancies. In most cases, the hematoma is composed of maternal blood. Retroplacental hematomas are areas of abnormal blood clots forming within the decidua between the floor of the placenta and the myometrium. Retroplacental hematomas may be entirely asymptomatic or associated with abruptio placentae and severe fetal hypoxia.

Abruptio placentae is recognized clinically in approximately 1% of live births, but retroplacental hematomas may be demonstrated in up to 5% of placentas; most of these are associated with an unremarkable labor course. The mechanism of placental hematoma formation and subsequent abruptio placentae begins with rupture of maternal decidual vessels, followed by spread of hemorrhage within the decidua. Ultimately, in some cases the hematoma separates the placenta from the uterine wall and the sequelae of abruptio placentae occur (uterine tachysystole, maternal disseminated intravascular coagulation, and fetal hypoxia). Thus, although an association of abruptio placentae and neonatal encephalopathy is well recognized, the relationship between neonatal encephalopathy and placental findings of intervillous thrombi and retroplacental...
hematomas in clinical settings apart from abruption is not established.

**Massive Perivillous Fibrin Deposition**
Massive perivillous fibrin deposition describes a pathological excess of fibrin-type material surrounding the chorionic villi and occluding the intervillous space. Some degree of perivillous fibrin is normal in uncomplicated pregnancies; therefore, the designation of massive or excessive perivillous fibrin deposition is an arbitrary one, usually applied when there is full-thickness involvement of the placenta and when the perivillous fibrin occupies 50% or more of the placental parenchyma on at least one histologic section. Macroscopically, the placenta typically has an abnormal solid and marbled appearance.

Histologically, massive perivillous fibrin deposition is diagnosed when villi are normally arrayed within the intervillous space, but the space itself is replaced by fibrin. Maternal floor infarction, which has a high fetal mortality rate, represents a similar process but with preferential fibrin deposition near the basal plate (“maternal floor”).

Clinically significant massive perivillous fibrin deposition is rare, occurring in approximately 1 in 10,000–20,000 pregnancies, but has a strong association with fetal death and fetal growth restriction. Although an underlying cause is not usually evident, some cases have been described with coexisting maternal autoimmune disease or thrombophilia. The condition may recur in subsequent pregnancies. In a case–control study, infants born to mothers with maternal floor infarction had a higher incidence of intracranial injury (detected on neonatal cranial ultrasonographic examinations) and at follow-up more often had abnormal neurologic examination results than gestational age-matched controls. Cases with maternal floor infarction had lower developmental scores in all areas tested and more often had neurologic or developmental impairment. (28).

**Conclusions**
- The few appropriate studies available do not establish that placental weight per se is related to neurologic outcome.
- Decidual vasculopathy is associated with the clinical syndromes of preeclampsia, maternal hypertension, maternal autoimmune disease or thrombophilias, and fetal growth restriction, the latter of which has been associated with neonatal encephalopathy and cerebral palsy.
- Although placental infarcts are identified in a substantial percentage of clinically uncomplicated pregnancies, the presence of infarcts in the placentas of cases of cerebral palsy appears to be increased.
- Retroplacental hematomas leading to significant abruptio placentae are associated with intrauterine fetal demise and neonatal encephalopathy.
- Clinically significant massive perivillous fibrin deposition is rare, occurring in approximately 1 in 10,000–20,000 pregnancies, but has a strong association with fetal death and fetal growth restriction.
- Cases with maternal floor infarction had lower developmental scores in all areas tested and more often had neurologic or developmental impairment.

**Fetal Vascular Thrombosis**
Fetal vascular thrombosis is an umbrella designation for clotting found within the fetoplacental vascular tree. Fetal vascular thrombosis can manifest at any level of the placenta; in the umbilical vessels, the muscular chorionic and stem arteries, or the downstream vessels in chorionic villi. The term “fetoplacental thrombotic vasculopathy” refers to pathologic changes in downstream villus vessels. The varied causes of fetoplacental thrombosis have mechanisms in common that predispose fetal blood to clotting (ie, vascular stasis, hypercoagulability, and endothelial injury).

With stasis, commonly there is clinical or pathologic evidence of mechanical restriction of umbilical blood flow, such as with oligohydramnios, a nuchal or body-wrapped cord, velamentous or marginal cord insertion, cord hypercoiling, a narrow or long cord (29, 30), or a true knot (31–35). Congenital fetal cardiac anomalies (31) may lead to reduced perfusion pressure that results in vascular stasis. Heritable forms of fetal (36–38) and, to a more controversial degree, maternal hypercoagulability (39–43) may predispose to fetoplacental thrombosis. Poorly controlled maternal diabetes with consequent fetal hyperglycemia may lead to fetal hypertoscyosis and thrombosis (44). Endothelial injury can result from chorionic and umbilical vasculitis, which may promote generalized coagulation by release of inflammatory mediators (45, 46). Rarely, specific placental disorders, such as mesenchymal dysplasia associated with Beckwith–Wiedemann syndrome (47) or twin pregnancy with one nonmolar twin coexisting with a complete molar gestation (48), may be associated with fetoplacental vasculopathy.
Fetal vascular thrombosis, which occurs in 2–4% of placentas, is not an uncommon finding (25, 49). The vast majority of cases have a single microscopic focus or a few small areas of affected vessels within the placental parenchyma, and typically is associated with an unremarkable labor and neonatal course. However, placentas with extensive multifocal or macroscopic lesions (“severe fetoplacental vasculopathy”) have been associated with significant neonatal sequelae, specifically cerebral palsy. In one series of children with either cerebral palsy, neonatal encephalopathy, or both, the prevalence of fetoplacental vascular thrombosis was 18%, of which 51% were graded as severe (50). In another cohort of children with cerebral palsy, 11% had fetoplacental thrombosis, of which 34% were severe (25), whereas in the unaffected comparison group, only 2% had fetoplacental thrombosis with 10% rated as severe.

Several investigations have suggested an association between fetoplacental thrombosis and stillbirth (31, 51–53). Among live births, fetal vascular thrombosis is associated with cerebral and visceral infarcts (34, 52), liver dysfunction (54), neonatal seizures, neonatal hemorrhagic stroke (55), cerebral edema, “birth asphyxia” (16), cerebral palsy and elevated circulating nucleated red blood cells, hypoglycemia, thrombocytopenia in the early postnatal period (25, 32, 56), or a combination of these.

A few studies have attempted to define threshold criteria with respect to “location, severity, multiplicity and timing” (57) of placental–fetal vascular thrombosis in live births associated with or at risk of adverse neurologic outcome. For example, the avascular villi, involving more than 30% of sampled villi, and multifocal lesions were associated with clinical abnormalities, including neonatal thrombosis, acidosis, or death (56). One study has outlined criteria for confident pathologic diagnosis of fetal vascular thrombosis in stillbirth (51). Not surprisingly, the risk of neurologic impairment increases, as do the number of lesions (58). Still, the entire matrix of lesions, antecedent risk factors, and outcomes in placental–fetal vascular thrombosis has not been established in large, well-structured clinicopathologic series.

Conclusions

- Among live births, fetal vascular thrombosis is associated with cerebral and visceral infarcts, liver dysfunction, neonatal seizures, neonatal hemorrhagic stroke, cerebral edema, “birth asphyxia,” cerebral palsy and elevated circulating nucleated red blood cells, hypoglycemia, thrombocytopenia in the early postnatal period, or a combination of these.

- The entire matrix of lesions, antecedent risk factors, and outcomes in placental–fetal vascular thrombosis has not been established in large, well-structured clinicopathologic series.

Inflammation and Infection

Chorioamnionitis

Histologic chorioamnionitis is an inflammatory response directed at microorganisms that reach the placental membranes or amniotic fluid, or both, from the lower genital tract, maternal bloodstream, or contiguous pelvic viscera. The minimal requirement for diagnosis of chorioamnionitis is identification of maternally derived neutrophils in the chorion. Stages preceding this diagnostic threshold include identifying neutrophils in the subchorionic fibrin (early acute subchorionitis) and, more controversially, mononuclear inflammatory cells in the choriodecidual (chronic choriocititis). Clinically significant infections generally feature spread of maternal neutrophils into the amnion or the presence of fetal neutrophils in the muscular walls of umbilical or chorionic vessels (fetal vasculitis), or both.

Chorioamnionitis has been associated with elevated circulating maternal and fetal serum cytokines and chemokines (59, 60). Both maternal and fetal inflammatory responses show a stereotypical pattern of histologic progression providing some insight into severity and duration. Involvement of the umbilical artery (umbilical arteritis and arterial funisitis) has been associated with a greater increase in level of circulating fetal cytokines than other patterns of inflammation (58, 61–64). Also relevant to fetal outcome is the finding of confluent neutrophils in the wall of chorionic plate vessels (high-grade fetal vasculitis). Occasionally, thrombi may develop within severely inflamed fetoplacental veins, which result in a risk of fetal thromboembolic stroke (65). The overall prevalence of histologic chorioamnionitis in all placentas has been reported to be approximately 5% and is observed in approximately 20% of term placentas submitted to pathology. Approximately two-thirds of these placentas also have fetal vasculitis, and approximately 3% have high-grade fetal vasculitis.

The clinical criteria for diagnosis of chorioamnionitis are poorly defined and demonstrate low sensitivity for identifying neonatal encephalopathy when
compared with histologic examination. Only a small fraction of cases of suspected chorioamnionitis are subjected to histologic evaluation of the placenta. The issues relating maternal intrapartum pyrexia and neonatal outcomes are discussed in further detail in Chapter 6.

Regarding neonatal encephalopathy, an Australian case–control study showed an association with maternal intrapartum pyrexia (greater than 37.5°C) (odds ratio [OR], 3.82; 95% confidence interval [CI], 1.44–10.12) (15). In a prospective cohort study of 4,915 low-risk women, intrapartum fever was also strongly associated with neonatal encephalopathy even after adjusting for confounding covariates (OR, 4.72; 95% CI, 1.28–17.40) (66). Chorioamnionitis was associated with cerebral palsy in a case–control study of 327 infants born at 36 weeks of gestation or more (OR, 4.6; 95% CI, 1.28–17.40) (66). Chorioamnionitis was associated with cerebral palsy in a case–control study of 327 infants born at 36 weeks of gestation or more (OR, 4.6; 95% CI, 1.28–17.40) (66). Chorioamnionitis was associated with cerebral palsy in a case–control study of 327 infants born at 36 weeks of gestation or more (OR, 4.6; 95% CI, 1.28–17.40) (66). Chorioamnionitis was associated with cerebral palsy in a case–control study of 327 infants born at 36 weeks of gestation or more (OR, 4.6; 95% CI, 1.28–17.40) (66). Chorioamnionitis was associated with cerebral palsy in a case–control study of 327 infants born at 36 weeks of gestation or more (OR, 4.6; 95% CI, 1.28–17.40) (66). Chorioamnionitis was associated with cerebral palsy in a case–control study of 327 infants born at 36 weeks of gestation or more (OR, 4.6; 95% CI, 1.28–17.40) (66).

Villitis

Chronic villitis is a chronic inflammatory response involving T lymphocytes in the villous stroma that have been shown to be of maternal origin. Chronic villitis has been associated with a distinct signature of circulating maternal and fetal cytokines and chemokines that differs from that observed in chorioamnionitis (76). Clinically significant subgroups include high-grade chronic villitis, defined by multiple foci of 10 or more contiguously involved villi, and chronic villitis with obliterative fetal vasculopathy, defined by a vaso-obliterative fetal vasculitis involving stem villous or chorionic vessels with associated downstream avascular villi (76). Unlike chorioamnionitis, almost all cases of chronic villitis in term infants are idiopathic (also known as villitis of unknown etiology) and are currently viewed as a type of allograft rejection or graft versus host disease–type response of mother against fetus. Rare cases of chronic villitis are associated with infections of toxoplasmosis, rubella, cytomegalovirus, and herpes simplex viruses.

The overall prevalence of villitis of unknown etiology in term placentas is 5–10%, and approximately one third of these are either high-grade or have obliterative fetal vasculopathy. Villitis of unknown etiology has been associated with fetal growth restriction, decreased fetal movement, nonreassuring fetal monitoring results, and elevated maternal alpha-fetoprotein, but antenatal diagnosis is not currently feasible (77).

Few studies have investigated the association of villitis of unknown etiology with neonatal encephalopathy or cerebral palsy, and predominantly derived from medicolegal cases. The prevalence of high-grade villitis of unknown etiology in infants with neonatal encephalopathy, or cerebral palsy, or both, in one of these reports was 13% compared with 3% in controls; high-grade villitis of unknown etiology was an independent risk factor for adverse neurologic outcome when assessed with other placental risk factors (OR, 13.2; CI, 1.2–144) (58). The most recent data from this case series indicate a prevalence of villitis of unknown etiology with obliterative fetal vasculopathy of 23 of 205 (11%) in placenta from infants with cerebral palsy compared with 10 of 350 (3%) in placenta from term infants, submitted to pathology for other indications (25). The prevalence of low-grade villitis of unknown etiology and villitis of unknown etiology without obliterative fetal vasculopathy in these reports was equivalent at approximately 5% for cases and controls.
Conclusions

- Population-based studies demonstrate that the clinical diagnosis of chorioamnionitis is associated with elevated cerebral palsy risk.
- An enlarging literature links some placental lesions with neonatal encephalopathy, perinatal stroke, cerebral palsy, and with risk factors for those conditions. However, the magnitude of these associations has not been established.
- Few studies have investigated the association of villitis of unknown etiology with neonatal encephalopathy or cerebral palsy, and are predominantly derived from medicolegal cases.

Umbilical Cord Abnormalities

Variations in umbilical cord morphology are numerous, ranging from false knot (of little clinical significance) to vasa previa (which may lead to fetal death). As detailed antenatal ultrasonography becomes increasingly used, abnormalities of umbilical cord are diagnosed with increasing frequency.

Single Umbilical Artery

The human umbilical cord has two arteries and a single vein. The presence of a single umbilical artery, thought to occur after thrombosis or atresia of the contralateral artery, is identified in approximately 1 in 200 singletons and in up to 5% of twins (78). Absent left artery is slightly more frequent (60–70%) (79).

Among newborns with single umbilical artery, approximately one third have additional structural anomalies, including cardiovascular abnormalities (OR, 20.3); gastrointestinal defects, including esophageal and anal atresias; and renal malformations (OR, 3.0) (80). In a series of 643 cases identified ultrasonographically and evaluated postnatally (81), the incidence of chromosomal abnormalities was 0% in the group with isolated single umbilical artery. However, with one additional structural defect, 4% were aneuploid, and in those with multiple defects, more than one half were chromosomally abnormal. Trisomy 18, trisomy 13, and triploidy accounted for more than 80% of the abnormal karyotypes.

Single umbilical artery confers increased risk of fetal growth restriction, premature birth, and perinatal mortality, ranging from threefold to fivefold (82, 83), although this occurs predominantly in fetuses with congenital anomalies and chromosomal defects. For fetuses with isolated single umbilical artery, studies that used multivariate analysis to adjust for confounding factors have documented poorer outcome, including increased fetal growth restriction and smaller placental size (84). Researchers compared outcomes of 243 isolated cases of single umbilical artery with 194,809 cases of three-vessel umbilical cords, noting fetal growth restriction in 9.5 versus 1.9%, (P<.001), low 5-minute Apgar scores (3.5% versus 0.4%; P<.001), and excess perinatal mortality (6.6% versus 0.9%, OR, 778; 95% CI, 4.7–13.0; P<.001) (85). Even after adjusting for fetal growth restriction, amniotic fluid abnormalities, maternal hypertension, and diabetes, the OR for perinatal mortality was 3.91 (95% CI, 2.06–7.43, P<.001).

Isolated single umbilical artery has not been directly linked to postnatal neurologic abnormalities or cerebral palsy, but one study (86) that excluded infants who were born preterm, small for gestational age, and with low Apgar scores, documented a 60% excess in neurologic dysfunction (OR 1.60; 95% CI, 1.28–2.00).

Velamentous Cord Insertion

Although the umbilical cord may insert into the placental disc centrally, peripherally, or at the edge (marginal insertion), in approximately 1% of singletons the cord inserts into the membranes some distance from the margin of the placenta. The vessels then course to the placenta across the membranes (velamentous cord insertion). In twin gestation, velamentous cord insertion is not uncommon, occurring in 10% or more of gestations. Regarding etiology, velamentous cord insertion appears to be a very early occurrence and is more frequently found with placenta previa (87), in which the incidence of velamentous cord insertion is reported to be 7.5%.

Velamentous insertion of the cord has been associated with low birth weight, prematurity, and abnormal fetal heart rate in labor (88). Abnormal fetal heart rate patterns and emergency cesarean deliveries occurred with a higher frequency in cases of velamentous cord insertion found in the lower uterine segment than in cases with upper or middle uterine velamentous cord insertion (P<.01) (89). However, there is no present data that directly links velamentous cord insertion found in the lower uterine segment to neonatal encephalopathy or cerebral palsy.

Vasa Previa

A velamentous cord insertion that has umbilical vessels coursing in membranes near or directly over the internal cervical os is termed vasa previa. Alternatively, umbilical vessels coursing over membranes between a succenturiate and the main lobe of placenta may form a vasa previa if near the cervix. If these vessels are disrupted during birth or with prelabor
rupture of membranes, potentially lethal or severely disabling fetal hemorrhage may ensue. The incidence of vasa previa is 1 per 2,000–5,000 deliveries.

Vasa previa is associated with multifetal gestation, in vitro fertilization procedures, and succenturiate placentaion (90), all of which have documented associations with adverse neonatal outcome. Evolution of a velamentous cord insertion near a marginal placenta previa at midtrimester into a vasa previa in the third trimester has been documented (91) and evolution of a midtrimester vasa previa into a velamentous cord insertion well away from the internal cervical os in the late third trimester has been reported. Thus, a high degree of suspicion for vasa previa in at-risk cases is necessary to minimize adverse outcome (92). Transvaginal ultrasound and color Doppler mapping of umbilical vessels is useful.

Significant fetal and newborn morbidity may ensue after rupture of membranes near a vasa previa. In a study of 155 cases, the overall perinatal mortality was 36% (93). However, with planned cesarean delivery before labor (34–35 weeks of gestation), the hemorrhagic morbidity of vasa previa can be substantially reduced (94). Neonatal survival rate was 97% if vasa previa was diagnosed antenatally versus 44% if discovered in labor (93). Neonatal blood transfusion rates were 3.4% among those diagnosed antenatally, whereas 58.5% of the undiagnosed cases required transfusion. The incidence of neonatal encephalopathy and long-term neurologic outcomes of these cases were not reported.

**Umbilical Cord Knots**

There is no evidence that umbilical cord knot is associated with long-term neonatal morbidity. With an incidence in one large series of 1.3%, and associated with advanced maternal age, multiparity, previous miscarriages, obesity, prolonged gravidity, male fetus, long umbilical cord, and maternal anemia (95), the incidence of umbilical cord knot was associated with fetal death (adjusted OR, 3.93; 95% CI, 1.41-11.0), low 1-minute Apgar score (adjusted OR 1.73; 95% CI, 1.10-2.72), but not the 5-minute Apgar score or other perinatal outcome measures (96). Although the incidence of “fetal distress” and meconium-stained amniotic fluid was significantly higher among patients with true knots (7% versus 4%, and 22% versus 16%, respectively, P<.001), as was the rate of cesarean delivery (15.4% versus 1.0%, P<.001), and antepartum death (1.9% versus 0.5%, P<.001) there was no documented difference in neurologic outcome. Although another series of 286 cases of true knot found increased fetal acidosis (pH less than 7.10) with true knots as compared with controls (8.33% versus 4.03%, P<.01), Apgar scores and neonatal intensive care unit admissions were not different. Investigators (22), in a large population-based study, found no association of true cord knot with cerebral palsy.

**Nuchal Umbilical Cord**

Nuchal umbilical cord occurs with progressive frequency as gestation advances. Nuchal cords were observed ultrasonographically in 12% of cases at 24 weeks of gestation and 37% of cases at term (97). At delivery, nuchal cord is frequently encountered with one loop present in approximately 15% of neonates (98) and multiple loops in 2–5% (99).

When a nuchal cord is present, fetal jeopardy can arise when the loop(s) tighten during fetal movements or descent during delivery, potentially constricting umbilical or cerebral blood flow, or both. Reports of associations of nuchal cord with suboptimal perinatal outcome have been contradictory. One study did not find significantly decreased umbilical cord pH at delivery with nuchal cord (100). A case–control study (101) of 5,426 cases of nuchal cord and 3,000 controls reported increased “fetal distress” (OR, 2.7; 95% CI, 2.1–3.4), meconium staining (OR, 2.1; 95% CI, 1.7–2.6), 5-minute Apgar score less than 7 (OR, 1.6; 95% CI, 1.1–2.4), and assisted ventilation (OR, 1.9; 95% CI, 1.4–2.6). Hospital lengths of stay did not differ significantly. When multiple nuchal loops of cord were compared with single or no nuchal cord cases, nonreassuring fetal heart rate patterns during labor, assisted vaginal delivery, and frequency of low umbilical artery pH (7.10 or less) were increased (102). However, the incidence of neonatal encephalopathy and cerebral palsy were not documented.

In a large series of more than 166,000 deliveries higher rates of labor induction and nonreassuring fetal heart rate patterns were observed in the 14.7% of cases with nuchal umbilical cord (103), but cesarean rates and perinatal mortality were actually lower among pregnancies with nuchal umbilical cord. Other studies (104, 105) have similarly shown no effect of a single nuchal cord on short-term perinatal outcomes.

Regarding long-term outcomes associated with nuchal cord, such as cerebral palsy, conflicting data are available. In a landmark case–control study of 46 children with spastic type cerebral palsy and
378 controls, a “tight nuchal cord” was identified in 4% of controls, 17% of the cases had unexplained cerebral palsy, and 42% of the cases had unexplained spastic quadriplegic cerebral palsy, which resulted in an OR for quadriplegia of 18 (95% CI, 6.2–48) (106). Another case–control study also evaluated the potential link between nuchal cord and cerebral palsy, and found nuchal cord at delivery in 17.3% versus 10.1% of children with cerebral palsy compared with controls (OR, 1.9; 95% CI, 1.09–3.21) (22). However, these results were significant only for spastic diplegia, not for quadriplegia, and they were not significant when the analysis was limited to the subgroup with tight nuchal cord; moreover, there was no association between cord around the neck and cerebral palsy delivered at term were compared with 157 controls (OR, 0.5; 95% CI, 0.2–1.4); tight nuchal cord (OR, 1.4; 95% CI, 0.4–4.9). Importantly, in the controls delivered in facilities with elective annotation, a tight nuchal cord was significantly more likely to be noted if the 1-minute Apgar score was less than 7. In summary, nuchal cord is common, and the vast majority of term deliveries with nuchal cord have normal outcomes.

Umbilical Cord Length
Although variations in umbilical cord length can potentially provide useful correlates to fetal and newborn outcomes, problems with cord length measurement limit its clinical usefulness. In reporting umbilical cord length, all portions of the umbilical cord must be measured, including those that have remained attached to the newborn and segments that may have been separately clamped for blood gas analysis.

There are wide variations in the length of the human umbilical cord, ranging from a few centimeters to almost 100 cm. Mean umbilical cord length increases with gestational age, averaging 32 cm at 20 weeks of gestation to 60 cm at 40 weeks of gestation (108). Umbilical cord length has been correlated with maternal prepregnancy weight, maternal body mass index, maternal height, parity, pregnancy weight gain, placental weight and male fetal gender.

An umbilical cord length of at least 25 cm is necessary to prevent traction on the umbilical cord during vaginal delivery (109) and, thus, very short umbilical cords have been associated with abruptio placentae, inversion of the uterus, and umbilical cord rupture. Short umbilical cords also are observed more frequently in cases with longstanding oligohydramnios, urinary tract anomalies, and fetal paralysis (110, 111). Long umbilical cords have been associated with polyhydramnios, cord prolapse, true knots, and entanglement of the cord around fetal neck and limbs (112).

Regarding a potential association between umbilical cord length and long-term neonatal outcomes, only limited data are available. The relationship between abnormal cord length and acid–base abnormalities at delivery was evaluated among 3,019 births after 34 weeks of gestation (113). An abnormally short (less than 40 cm) or long (greater than 80 cm) umbilical cord at birth was not associated with an increased risk of umbilical acidemia. Similarly, negative correlations between umbilical cord length and neonatal acidemia were reported (114). A study of umbilical cord length in 35,779 neonates found that short umbilical cords (less than 40 cm) were associated with increased subsequent psychomotor abnormalities at age 7 years (108). However, the overall predictive value of short umbilical cords was low because of the large range of cord lengths. Short cords were much better predictors of subsequent neurologic impairment when they were combined with other neonatal predictors. For example, the predictive value of a low Apgar score for suboptimal neurologic outcomes was
enhanced by having a coexisting short umbilical cord, which tripled the predictive value of Apgar scores for subsequent low IQ values at age 4 years.

Abnormal Umbilical Cord Coiling
Although the integrity of the umbilical cord and patency of the umbilical vessels are essential for fetal growth and survival, kinking, compression, traction, and torsion of the umbilical cord can present significant threats. A coiled umbilical cord, supported by Wharton’s jelly, is thought to be more resistant to torsion, stretch, and kink. Although the cause of umbilical coiling is not precisely known, theories include fetal movements, differential umbilical vascular growth rates, fetal hemodynamics, and muscular fibers in the umbilical wall (115). Left umbilical cord coiling is more common than right (approximately 80%).

The degree of umbilical cord coiling can be represented by an umbilical coiling index, which is the number of coils per length of umbilical cord. This can be done antenatally using ultrasonography to measure the distance between two adjacent coils of the umbilical artery from the outer surface of the vascular wall to the next twist (antenatal umbilical coiling index = 1/coil distance in centimeters) or postnatally by dividing the total number of umbilical cord coils by the length of the cord. The umbilical coiling index norms are different whether coiling is measured ultrasonographically or in the pathology laboratory, with the intraterine umbilical coiling index higher than the postnatal umbilical coiling index (0.44 ± 0.11 versus 0.28 ± 0.08, r = 0.71, P < .001) (116). Other investigators reported similar but not identical values (antenatal umbilical coiling index 0.20 ± 0.09 standard deviation [SD], postnatal umbilical coiling index 0.36 ± 0.21 SD) (117). Umbilical hypercoiling is defined as umbilical coiling index above the 90th percentile and hypocoiling below the 10th percentile.

The potential perinatal risks associated with abnormal cord coiling are derived from a few case-control and cohort series. Perinatal outcome was assessed in 565 cases and the researchers found increased fetal death (OR, 4.09; 95% CI, 2.22–7.55), chorioamnionitis (OR, 1.77; 95% CI, 1.09–2.88), fetal structural or chromosomal abnormalities (OR, 1.78; 95% CI, 1.08–2.95), and a low Apgar score at 5 minutes (P < .03) with undercoiling (118). With overcoiling, fetal death was increased (OR, 3.74; 95% CI, 1.89–7.40), as was umbilical arterial pH less than 7.05 (OR, 3.63; 95% CI, 1.44–9.17), fetal structural or chromosomal abnormalities (OR, 1.79 95% CI, 1.01–3.16), thrombosis in fetal placental vessels (OR, 2.64; 95% CI, 1.37–5.06), chronic fetal hypoxia–ischemia (OR, 1.82; 95% CI, 1.09–3.05), and lower weight for gestational age (P = .01). However, these results were not subjected to multivariate regression analysis, and long-term outcomes of surviving neonates were not reported.

Another retrospective study of 251 cases with antenatal umbilical coiling index also found elevated preterm birth rate (35%), low birth weight (36%), and neonatal intensive care unit admission rate (27%) in the hypocoiled group, but after adjustment with logistic regression analysis for maternal age, birth weight, and gestational weeks at birth, only preterm delivery was significantly increased (OR, 9.6; 95% CI, 2.0–44.7) (119). Other researchers found no statistically significant correlation between umbilical cord coiling index and low birth weight, 5-minute Apgar score, or meconium staining (120). Long-term outcomes, especially for neurologic injury or cerebral palsy, were not reported. Thus, hypocoiling of the umbilical cord may correlate with increased risk of preterm birth, but there is no present evidence of an association of abnormal umbilical cord coiling and perinatal neurologic injury.

Umbilical Cord Stricture
Umbilical cord stricture is the severe narrowing of the umbilical cord, which leads to occlusion of umbilical vessels that almost invariably results in fetal demise (121). The data on this abnormality derive almost exclusively from case reports or small series. Researchers reviewed 26 cases in a cohort of 139 stillbirths (19%) (122). The etiology of umbilical cord stricture is unknown, but there are commonalities among the reported cases, such as a lack of Wharton’s jelly and an abundance of fibrosis at the stricture site, which is almost always adjacent to the umbilical insertion into the fetal abdomen, and compressed or narrowed umbilical vessels in the stricture, occasionally with thrombosis. Thus, although umbilical cord stricture is a major contributor to fetal death, there is no established link with cerebral palsy.

Umbilical Cord Cysts
Human umbilical cord cysts are found in 1 in 130–200 pregnancies and represent remnants of the allantoic duct, which is obliterated by the early second trimester (123). These remnant cysts have an epithelial lining and are associated with patent urachus, omphalocele, Meckel diverticulum, and cardiac anomalies in 30–40%. The risk of aneuploidy with umbilical cord cyst is elevated (124), but there are no data linking umbilical cord cyst and neonatal encephalopathy or cerebral palsy.
Umbilical Cord Vein Varix
A varix of the umbilical cord vein is a cystic dilatation that typically is observed within the fetal abdomen adjacent to the insertion of the cord at the abdominal wall. Umbilical vein varix can be identified via antepartum sonography as an abnormally wide dilatation in the vein as it courses within the abdomen toward the fetal liver. The diameter of the normal intraabdominal umbilical vein increases linearly from approximately 3 mm at 15 menstrual weeks to approximately 8 mm at term ($R=0.92$). Thus, the criterion for an umbilical vein varix is more than 5 mm width in the second trimester and more than 9 mm (2 SDs) in the third trimester. A study identified a striking association between umbilical vein varix, fetal hydrops, and intrauterine death (125). Subsequently, another study evaluated 91 cases of umbilical vein varix: 32% had coexisting structural malformations, 10% had chromosomal anomalies, and 13% had neonatal or fetal demise, including unexplained intrauterine death between 29 weeks and 38 weeks of gestation in 8% of the cases (126). Similar findings (approximately 30% anatomic anomalies, 10% aneuploidy, and overall 50% perinatal mortality) were reported (127, 128). Additional case reports link umbilical vein varix with varix thrombosis and severe anemia, especially those with turbulent flow in the varix on color Doppler evaluation (129).

Existing studies generally fail to distinguish outcomes between those fetuses with isolated umbilical vein varix and those with chromosomal or structural anomalies. A frequency of isolated umbilical vein varix was reported to be 28 per 65,000 births, or approximately 1/2,200 (130). Among these births managed expectantly, intrauterine growth was normal (fetal growth restriction rate=11%), and there were no perinatal deaths, even in the five cases with turbulent varix flow.

Despite the significant evidence relating umbilical vein varix to increased rates of fetal and neonatal death, no studies to date have linked umbilical vein varix to neonatal encephalopathy or cerebral palsy.

Conclusions
• Abnormally short or long umbilical cords are associated with abnormal amniotic fluid volume, abnormal fetal neuromuscular activity, and acute intrapartum events, such as abruptio placentae.
• Abnormal umbilical cord length is not associated with umbilical acidosis at birth.
• Short umbilical cord length may be associated with increased incidence of abnormal neurologic outcomes beyond 4 years of age if other factors, such as low Apgar score and low birth weight, also are present.
• Single umbilical artery has not been directly linked to postnatal neurologic abnormalities or cerebral palsy.
• Despite the significant evidence relating umbilical vein varix to increased rates of fetal and neonatal death, no studies to date have linked umbilical vein varix to neonatal encephalopathy or cerebral palsy.
• Umbilical cord stricture is a major contributor to intrauterine fetal death, but there is no established link with cerebral palsy.
• Hypocoiling of the umbilical cord may correlate with increased risk of preterm birth, but there is no present evidence of an association of abnormal umbilical cord coiling and perinatal neurologic injury.
• Fetal thrombotic vasculopathy—associated with obstructive lesions of the umbilical cord, including cord hypercoiling and hypocolling, velamentous cord insertion, true knot, nuchal cord, and umbilical cords with decreased Wharton’s jelly—is highly associated with neonatal encephalopathy and cerebral palsy.
• Nuchal cord is common, and the vast majority of term deliveries with nuchal cord have normal outcomes.
• A large population-based study found no association of true cord knot with cerebral palsy.
• If twin gestations and vasa previa are excluded, there are no convincing data linking velamentous cord insertion to neonatal encephalopathy or cerebral palsy.

Guidelines for Examination of the Placenta
A guideline for the indications for placental examination has been developed by consensus of experts (131), and although this guideline is the best available at the present time, placental examination is performed in fewer than one half of all deliveries in which the placenta fulfills those indications for examination (132, 133). Although all placentas of infants with neonatal encephalopathy meet criteria for examination, only 11.2% of placentas were examined in one series (134). In another study, only 24% of placentas of children with cerebral palsy had been examined (135).
THE ROLE OF PLACENTAL PATHOLOGY IN NEONATAL ENCEPHALOPATHY AND CEREBRAL PALSY

Research Recommendations

- A Task Force to be convened jointly by the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the College of American Pathologists is recommended to review and revise the Guidelines for Placental Examination and Biobanking.

- Large, well-structured, clinicopathologic series are needed to establish the entire matrix of lesions, antecedent risk factors, and outcomes in placental–fetal vascular thrombosis.

- When feasible, clinical studies of all neurologically depressed term and late-preterm infants should include gross and microscopic descriptions of placentas. This may include care protocols to hold placentas after delivery for 1 week to facilitate retrieval and examination in cases of neonatal encephalopathy.

- Studies assessing the interobserver variability in the diagnosis of major placental pathologic entities are needed to improve the consistency of diagnosis.

- Standardized examination of placentas of all infants enrolled in therapeutic trials of neonatal neuroprotection will enable more efficient selection and stratification.

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Most cases of cerebral palsy are related to factors other than intrapartum events, such as abnormalities of the placenta and membranes (e.g., chorioamnionitis, intra-amniotic viral infections, abruptio placentae [see also Chapter 4, “The Role of Placental Pathology in Neonatal Encephalopathy and Cerebral Palsy”]), or pathology intrinsic to the fetus (e.g., multifetal pregnancy, congenital or genetic anomalies, low birth weight) (1). In this chapter, elements intrinsic to the fetus that may cause or potentiate the occurrence of neurologic injury are evaluated, such as the role of low birth weight and fetal growth restriction. Regarding multifetal pregnancies, which are at a significantly increased risk of adverse neurologic outcome, the interrelation of gestational age at delivery, chorionicity, birth order and, for monochorionic gestations, co-twin demise and twin–twin transfusion syndrome are summarized. The associations between the fetal postmaturity syndrome and cerebral palsy are detailed.

Defining the Fetus at Risk of Neonatal Encephalopathy and Cerebral Palsy

Because the incidence of neonatal encephalopathy and cerebral palsy is exceedingly low (2–9/1,000) and the list of risk factors for these morbidities is extensive, screening measures designed to detect and prevent impending injury antenatally must be applied to a large proportion of pregnancies, most of which will not experience these untoward outcomes.

Antepartum surveillance regimens were developed primarily to reduce stillbirth and, thus, the effects of antepartum fetal testing on rates of neonatal encephalopathy and cerebral palsy have not been specifically studied. As additional fetal testing indications and techniques evolved, desired outcomes were broadened to include also reduction in operative delivery, low Apgar scores, and neonatal intensive care unit (NICU) admission. Nevertheless, despite presently widespread application to more than one third of pregnancies, antepartum fetal testing has not been definitively demonstrated to improve perinatal outcome or to reduce the incidence of neurologic injury.

Thus, identifying (during ongoing gestation) the fetus at risk of neonatal encephalopathy and cerebral palsy is problematic. Utilizing the proxy-outcomes of stillbirth, low Apgar scores, and NICU admission (which have been used in the development of antepartum fetal surveillance protocols) may allow timely detection of impending fetal jeopardy and possible intervention to reduce the risk of neonatal encephalopathy and cerebral palsy. Pregnancy conditions that are associated with increased risk of short-term and long-term neonatal neurologic sequelae for which antenatal testing may be appropriate include the following (2):

- Maternal conditions—antiphospholipid syndrome, hyperthyroidism, hemoglobinopathies, isoimmunization, cyanotic heart disease, systemic lupus erythematosus, chronic renal disease, preexisting or gestational diabetes mellitus, hypertensive disorders (including preeclampsia and gestational hypertension).
- Feto-placental conditions—fetal growth restriction, oligohydramnios, polyhydramnios, post-term pregnancy, previous fetal demise, decreased fetal movement, significant anatomic anomaly,
multiple gestations with significant growth discordance or twin–twin transfusion syndrome.

Conclusion

• Most cases of cerebral palsy are related to factors other than intrapartum events, such as abnormalities of the placenta and membranes (chorioamnionitis, intraamniotic viral infections, abruptio placentae) or pathology intrinsic to the fetus (multifetal pregnancy, congenital or genetic anomalies, low birth weight).

Antepartum Fetal Surveillance and Neonatal Encephalopathy

Because of the difficulties with long-term follow-up, very few studies have evaluated the relationship between antepartum fetal testing and long-term neurologic outcome. Several randomized prospective trials that used weekly nonstress test surveillance have shown no benefit (3–6). The only prospective randomized trial of antepartum fetal evaluation showed benefit in instructing women in fetal movement counts with a resulting decreased occurrence of fetal death but no effect on long-term neurologic outcomes (7). The remainder of the literature on nonstress tests involves nonrandomized, usually retrospective reviews. In 1983, an Australian study showed that among 72 patients with a nonreactive positive spontaneous contraction stress test result, there was a 28% perinatal mortality rate; of the 52 infants that survived the neonatal period, 45 were assessed and 27% were found to have a neurologic handicap (8). A retrospective study, which used biophysical profile as the primary means of surveillance, reported an incidence of cerebral palsy of 1.33 per 1,000 in the group with biophysical profile and 4.74 per 1,000 in those patients not monitored with biophysical profile testing (9). A Cochrane review found no significant differences in perinatal death and Apgar score between those monitored with biophysical profile as compared with other forms of fetal assessment, mainly fetal heart rate monitoring (10).

Conclusion

• Antepartum surveillance regimens were developed primarily to reduce stillbirth and, thus, the effects of antepartum fetal testing on rates of neonatal encephalopathy and cerebral palsy have not been specifically studied.

Fetal Growth Restriction and Neonatal Neurologic Injury

Birth Weight as a Risk Factor for Neurologic Injury

Extensive evidence supports a strong relationship between low birth weight and neonatal encephalopathy and cerebral palsy. The odds of having birth weight less than the third percentile and between the third percentile and ninth percentile among infants with neonatal encephalopathy are significantly higher than in other infants (odds ratio [OR]; 95% confidence interval [CI], 38.2 [94–154.8] and 4.4 [1.4–13.4], respectively) (11). Cerebral palsy is also strongly associated with birth weight less than the third percentile and between the third percentile and ninth percentile (OR; 95% CI, 6.4 [4.2–10.1] and 2.7 [1.7–4.2], respectively) (12). Supporting a causative association, there is also evidence of dose-response or biological gradient for low birth weight, with more severe fetal growth restriction associated more strongly with downstream neurologic disorders (Fig. 5-1; see color plate) (13–15). The association between fetal growth restriction and abnormal childhood neurologic status also is reinforced by the correlation being consistently observed in multiple studies of different designs and in different populations (11, 14–20).

However, data regarding the rate of cerebral palsy in infants with fetal growth restriction (who were delivered before 34 weeks of gestation) (16) has been conflicted possibly because of the comparison of outcomes to weights of delivered premature infants (which are known to be lower rather than the weights of undelivered fetuses using ultrasound estimation). In a study derived from a large data set aggregated from 10 European cerebral palsy registries, the frequency of cerebral palsy was compared using conventional birth weight standards with standards based on ultrasonographic fetal weight estimates (14). As shown in Figure 5-1 (see color plate), infants of 32–42 weeks of gestation with birth weights below the 10th percentile (using fetal growth standards) were four to six times more likely to have cerebral palsy than were children between the 25th percentile and 75th percentile. Thus, the occurrence of cerebral palsy is strongly linked to abnormalities of the fetal growth process particularly in the early third trimester.

Fetal Growth Restriction Versus Small for Gestational Age

Fetal growth restriction and small for gestational age (SGA) are typically defined in neonates with birth weights below the 10th percentile for gestational age,
yet the pathways to and associated morbidities with this common endpoint are very different. Whereas fetal growth restriction implies a limitation of growth because of inadequate placental nutrient delivery, SGA comprises all newborns whose birth weight is in the lowest decile (compared with relevant population weight statistics), from ultrasonographic estimate of fetal weight calculations (21, 22), or from customized equations that adjust expected weight for key determinants of birth size (eg, ethnicity, sex) (23–25). The two conditions of fetal growth restriction and SGA are not interchangeable. Most newborns born with fetal growth restriction are also SGA, but some newborns with failing growth may have birth weights above the typical 10th percentile cutoff. Further, because fetal growth restriction arises from inadequate placental supply, reduced growth trajectory can be associated with reduced amniotic fluid volume (oligohydramnios) and ultimately fetal hyoxia. There are many other reasons that a newborn may be SGA unrelated to placental nutrient supply, such as ethnic variation, chromosomal anomalies, or early intrauterine infectious insults (eg, toxoplasmosis). In this latter group of SGA, growth is not limited by placental capacity but rather by reduced intrinsic growth potentials.

**Fetal Growth Restriction**

Fetal growth restriction is a dynamic antenatal process characterized by slowing or cessation of growth rate due to a chronic and progressive reduction in nutrient supply from the placenta. With advancing gestational age and fetal size, nutrient demand may progressively outstrip placental capability, and the degree of fetal growth restriction becomes more marked. Fetal compensation for fetal growth restriction involves redistribution of returning blood flow from the placenta away from visceral organs and limbs in favor of critical organs, such as the brain, heart, and adrenals. The resulting growth pattern, characterized by sustained head growth at the expense of reduced abdominal and extremity growth is typically termed asymmetrical.

Detection of fetal growth restriction during pregnancy is important as the diagnosis may lead to alterations in management (biophysical testing, early delivery) that may reduce adverse neurologic sequelae. Researchers compared the outcomes of SGA infants with (n=681) and without (n=573) antenatal diagnosis of growth abnormality and found that the risk of serious fetal complications (hypoxic encephalopathy grade 2 or 3, intracranial hemorrhage, Apgar score less than 4 at 5 minutes, neonatal convulsions, umbilical pH less than 7.0, cerebral palsy, mental retardation, stillbirth, intrapartum or infant death) was fourfold higher in the latter (26). Most SGA fetuses are not identified antenatally because the clinical screening tools for abnormal fetal growth have poor sensitivity (26). Another study reported that the sensitivity of fundal height measurements for detecting SGA (less than 10th percentile) was only 17.3% (27).

Assessment of fetal growth restriction during pregnancy typically is performed by comparing fetal measurements with cross-sectional norms or by plotting a trajectory of growth of individual biometric parameters over several examinations (by using serial ultrasonographic examinations) (26–28). If the biometric measurements demonstrate significant asymmetry (abdominal circumference percentile markedly smaller than the head percentile), the fetus can be tentatively assigned to the fetal growth restriction category, virtually regardless of the estimated fetal weight percentile. Similarly, if serial ultrasonographic measurements of fetal dimensions demonstrate a growth trajectory progressively falling below expectations (eg, biometric percentiles successively decreasing with advancing gestational age), fetal growth restriction is likely. Conversely, if head, limb, and abdominal circumference measurements are in similar percentiles or predictive of similar gestational age, and particularly if the trajectory of growth is sustained over several weeks, SGA is more likely than fetal growth restriction. However, caution should be exercised in categorizing a growth abnormality apparent on ultrasonography as fetal growth restriction, constitutional SGA or pathologic SGA, because of the inherent intraobserver and interobserver variation in biometric measurements, and because early insults, such as fetal viral infections, may markedly attenuate fetal growth potential resulting in a small but symmetrical growth pattern. Most symmetrically SGA infants are constitutionally (genetically) small and carry minimally increased risk of neurologic abnormalities, while others, usually indistinguishable on sonography, may have suffered an early insult or longstanding insult or both (29), such as intrauterine infection, placental infarction, or chromosomal anomaly, which carries a markedly increased risk of neurologic sequelae. Further, fetuses with asymmetrical (“head sparing”) fetal growth restriction may have been subjected to progressively inadequate placental nutrient and oxygen delivery, but with relative sparing of blood flow to the brain, adverse postnatal neurologic sequelae are difficult to predict.

One problem with evaluating the relationship between cerebral palsy and fetal growth restriction is
that the timing and severity of fetal growth restriction is often unclear and, thus, the contribution of fetal growth restriction is difficult to establish. Other coexisting conditions associated with small size at birth may contribute to neurologic abnormality, such as fetal vascular accidents, intrauterine infections, genetic abnormalities, and brain developmental syndromes.

The pattern of neurologic impairment that may follow term birth of a fetus with suboptimal growth is unclear. In a case–control study from Denmark, the combination of placental infarction and SGA was associated with a threefold increase in the risk of spastic quadriplegia (30). Other patterns of cerebral palsy are more difficult to associate with SGA and other growth abnormalities.

A causal pathway from fetal growth restriction to cerebral palsy that includes neonatal encephalopathy is also difficult to establish from current data. For example, preeclampsia, a common cofactor in fetal growth restriction, is also a strong predictor for encephalopathy (11, 31).

Conclusions

• Extensive evidence supports a strong relationship between low birth weight and neonatal encephalopathy and cerebral palsy.

• Neonatal encephalopathy and cerebral palsy are strongly associated with birth weight less than the third percentile and between the third and ninth percentiles.

Doppler Assessment in Fetal Growth Restriction

Fetal Growth Restriction and Organ System Blood Flow

The fetus with growth restriction resulting from inadequacy of placental nutrient and oxygen delivery may experience progressive deterioration in multiple organ systems (32). Thus, evaluation of blood-flow characteristics in placental and fetal vascular beds can provide important clinical information regarding the severity of the fetal growth restriction.

Placenta-based fetal growth restriction first develops during a preclinical phase when decreased umbilical venous blood flow and substrate delivery triggers the redistribution of blood that flows through the ductus venosus away from the liver and toward the fetal heart. This circulatory bypass, which sustains function of the fetal brain and heart, limits hepatic nutrient availability and, thus, alters the endocrine and nutritional milieu of all downstream organs (32). Growth delay of the liver contributes to lagging abdominal circumference growth and ultimately, with increasingly severe nutrient deficits, produces a fetus that progressively has smaller abdominal measurements than head and skeletal measurements. Asymmetrical growth delay of the abdominal circumference below the third to fifth percentiles or symmetrical growth delay of all measurements that produce an ultrasonographic estimate of fetal weight below the 10th percentile are indicators of high likelihood of fetal growth restriction (32).

Doppler Evaluation in Suspected Fetal Growth Restriction

Doppler evaluation in fetal growth restriction allows documentation of the severity of placental disease and assessment of the extent of fetal compensatory responses, and provides an estimate of the rate of clinical progression. It also may provide information in the pregnancy with fetal growth restriction to permit timely intervention, minimizing risk of prematurity while potentially avoiding progressive cerebral hypoxemia, which if allowed to continue may lead to neonatal encephalopathy and cerebral palsy. However, the limitations of indirect Doppler vascular assessment must be understood. Doppler indices, such as the systolic diastolic ratio, the resistance index, and the pulsatility index for arteries and veins, are affected by numerous cardiovascular variables and gestational age that require consideration in their interpretation.

The vessels most commonly studied in clinical practice are the uterine, umbilical, and middle cerebral arteries and the ductus venosus. Doppler interrogation of the maternal uterine arteries reflects the vascular impedance in the maternal compartment of the placenta. An elevation in the uterine artery Doppler resistance index is associated with an increased risk of maternal hypertensive disease and delivery of an SGA infant (33). Doppler evaluation of the umbilical arteries reflects the blood flow characteristics in the fetal villous vascular tree. Increased umbilical artery resistance, which can lead to absent or even reversed end-diastolic velocity, is associated a 30–70% reduction in villous gas exchange area and proportionate reduction in nutrient and oxygenation deficiency (34).

Reduction in blood flow resistance in the middle cerebral arteries is associated with decreased arterial oxygen content. The cerebroplacental Doppler ratio (the quotient of middle cerebral over umbilical artery pulsatility index) mathematically amplifies abnormalities in each vessel and may be abnormally decreased even when index deviations for the component vessels are still within the normal range. A decrease in the
cerebroplacental Doppler ratio has the same clinical associations as abnormal Doppler findings in the umbilical and middle cerebral arteries (35).

Blood-flow velocities in the ductus venosus are related to myocardial performance and placental function. In placental dysfunction, an elevation in the ductus venosus Doppler index, with absence of forward flow during atrial systole in extreme cases, is associated with markedly elevated umbilical artery Doppler impedance, physiologic dilation of the ductus venosus, and fetal acidemia (32).

A methodical Doppler investigation of the placental, fetal cerebral, and venous circulations permits assessment of the severity of placental dysfunction. Based on their timing in the disease process and their association with accelerating circulatory deterioration, Doppler abnormalities in cases of early onset fetal growth restriction can be classified as early and late (32):

- Early findings include Doppler abnormalities confined to the placental and cerebral circulations with preserved forward flow in all other vascular beds described above. These typically are found in cases with late onset fetal growth restriction (late preterm and term).
- Late findings evolve after a considerable period of significant placental insufficiency and include absent or reversed umbilical artery end-diastolic velocities and reduced ductus venosus blood flow leading to absent or reversed flow during atrial systole. These severe circulatory changes often are accompanied by severe growth restriction or growth arrest.

**Antepartum Doppler in Fetal Growth Restriction and Subsequent Neurodevelopment**

The relationship between developmental outcome and umbilical artery Doppler in fetal growth restriction has been evaluated in case-control studies. In early-onset fetal growth restriction presenting before 30 weeks of gestation, survivors with absent or reversed end-umbilical artery diastolic velocity have been found to have lower Bayley motor developmental index scores at age 2 years, lower Kaufman mental processing composite scores after 2 years, higher rates of mental retardation, and lower verbal and composite IQ scores (36). For those with early-onset fetal growth restriction born after 30 weeks of gestation, absent umbilical artery end-diastolic velocity produced lower scores in all domains of the Kaufman mental processing composite scores at age 6 years after correcting for gestational age at delivery. In children surviving until school age, reversed umbilical artery end-diastolic velocity had the strongest association with cognitive delay (14%), visual impairment (56%), hyperactivity, and lower neurologic test scores, independent of gestational age.

In patients with late-onset fetal growth restriction, abnormal umbilical artery Doppler findings are less predictive. Factors contributing to early childhood developmental abnormalities include maternal smoking, lagging head growth, lower ponderal index, higher umbilical cord blood base deficit, longer stay in the neonatal intensive care unit, and lack of breastfeeding (37). In late-onset fetal growth restriction, reduced middle cerebral artery flow resistance is associated with low communication, problem solving, and personal-social scores on the ages and stages questionnaire administered at age 2 years (37).

**Conclusions**

- In early-onset fetal growth restriction before 30 weeks of gestation, survivors with absent or reversed end-umbilical artery diastolic velocity have been found to have lower Bayley motor developmental index scores at age 2 years, lower Kaufman mental processing composite scores after 2 years, higher rates of mental retardation, and lower verbal and composite IQ scores.
- In late-onset fetal growth restriction, reduced middle cerebral artery flow resistance is associated with low communication, problem solving, and personal-social scores on the ages and stages questionnaire administered at age 2 years.

**Neurologic Outcome in Multifetal Pregnancy**

Multifetal gestation is an independent risk factor for cerebral palsy and long-term neurologic impairment. Many studies of cerebral palsy have noted a greater-than-expected contribution from children of multiple gestations (38–47). In these reports, the prevalence of cerebral palsy in multifetal pregnancy ranges from 5.4 (39) to 10.8 per 1,000 (38). The study design in many of these reports is not of the highest scientific quality but the striking similarity of the principal finding lends support to the veracity of this association.

Case series (48, 49) and epidemiologic studies have investigated the prevalence of cerebral palsy in multifetal gestation (17, 50–56). Despite potential
regional differences, variations in standards of medical care, and possible population ascertainment bias, the most reported prevalences of cerebral palsy in multiple pregnancies are remarkably consistent (ranging from 5.0 to 12.6 per 1,000 surviving infants). The most frequently quoted incidence of cerebral palsy for twins is approximately 7 per 1,000 compared with 1–2 per 1,000 in singletons. Despite the abundance of data linking multifetal pregnancy to cerebral palsy in the offspring, there is inadequate information on the incidence of neonatal encephalopathy in multifetal gestation.

Gestational Age at Delivery of Multifetal Pregnancy
Because cerebral palsy is associated with preterm delivery, it is not surprising that the prevalence of cerebral palsy is greater in multiple gestations that result in lower birth weights and from earlier gestational ages (17, 51, 53, 57, 58). Some investigators have reported no difference in rates of cerebral palsy between singletons and twins at low birth weights (1,500–2,499 g) and very low birth weights (less than 1,500 g) (50–54, 59). Indeed, at these very low birth weights, morbidities of extreme prematurity may outweigh those deriving from the plurality of the gestation.

Some authors have reported multiple pregnancy to be an independent risk factor for cerebral palsy at all gestational ages and birth weights (17, 57), although more investigators have found this to be true at higher birth weights (2,500 g or greater) and closer to term (50–54, 58–60). The risk of cerebral palsy has been reported as 3.6–3.8 times more likely in twins with birth weights more than 2,500 g when compared with singletons matched for birth weight (50, 53). Therefore, there appears to be a significant risk of cerebral palsy in offspring of multiple gestations that is not simply related to the greater incidence of preterm delivery.

Zygosity and Chorionicity
Some studies have associated monozygosity with increased risk of neurologic impairment when compared with dizygosity (49). Many investigations have limited documentation of zygosity, and estimates of monozygosity and dizygosity are based on the numbers of like-sex and unlike-sex twin pairs (50, 53, 57). Although there are reports of no significant difference in the rate of cerebral palsy between like-sex pairs and unlike-sex pairs or between monochorionic and dichorionic twins (50, 53, 57, 61), monozygosity seems to be more strongly associated with neurologic impairment than dichorionicity (OR, 6; 95% CI, 1.7–21.3) (62, 63). This is supported by a comparative study of monochorionic and dichorionic pairs born between 24 weeks and 34 weeks of gestation that found that preterm monochorionic twins had a higher incidence of cerebral palsy than dichorionic twins (8% versus 1%, P<.05) at 2 years of age (64).

Birth Order
Most of the literature suggests no correlation between birth order and long-term neurologic impairment (41–43, 47, 49, 57, 65), although one paper (46) reported that twins with cerebral palsy are predominantly first born and the nonsurvivors are predominantly second born. In contrast, a large, multicenter study reported that twins with cerebral palsy were more often second rather than first born (56% versus 44%, P<.05) (58). Thus, relationship of birth order to neurologic outcome is unclear based on currently available data.

Fetal Gender
Some investigators have noted a preponderance of male infants from multifetal gestations affected with cerebral palsy (46, 50). However, other studies reported an equivalent risk of cerebral palsy between genders (45, 49, 53). To date, no conclusive evidence of a gender-associated risk of cerebral palsy can be drawn from the literature.

Weight Discordance
There is remarkably little evidence addressing the effect of weight discordance among fetuses on long-term neurologic function (48, 53, 65). One early study noted that unaffected twins were heavier than those affected with cerebral palsy by an average of 2.8 oz (48). If the analysis was limited to those twins with quadriplegia, the unaffected twins were an average of 8 oz heavier. Another publication noted that in cases of discordant birth weights, the affected twin was heavier in 20 (66%) cases, lighter in 9 (30%), and the same in 1 (3%) (53). In a Swedish series of 5,382 twins, the larger twin in the pair had a significantly higher incidence of cerebral palsy than the smaller one (relative risk [RR] 2.6; 95% CI, 1.4–4.8) (66). Data from the Scottish Register of Children with a Motor Deficit of Central Origin showed that as the level of birth-weight discordance increases, the risk of cerebral palsy increases (10–30% discordance: OR, 1.45; 95% CI, 0.75–2.83; greater than 30% discordance: OR, 5.17; 95% CI, 2.16–130.8) (57). However, there was no consistent relationship between cerebral palsy affecting the larger versus the smaller twin (57). Therefore, although in obstetric practice it traditionally is thought that the smaller twin is at greater risk of cerebral palsy, the limited published evidence suggests
this may not true. Cerebral palsy rates also are reported to be higher in discordant monochorionic twins compared with discordant dichorionic twins (19% versus 1%, P < 0.05) (64).

**Monochorionic Gestation**

The risk of cerebral palsy and long-term neurologic impairment is significantly higher for monochorionic twins. Although the increase in neurologic impairment in monochorionic twin gestations may be most frequently associated with placental vascular anastomoses and twin–twin transfusion syndrome, numerous other factors known to be increased in monochorionic gestations may play a role, such as fetal growth restriction, velamentous cord insertion, preterm premature rupture of membranes, preterm fetal growth restriction, velamentous cord insertion, monochorionic gestations may play a role, such as numerous other factors known to be increased in lar anastomoses and twin–twin transfusion syndrome, be most frequently associated with placental vascular impairment in monochorionic twin gestations may be most frequently associated with placental vascular anastomoses and twin–twin transfusion syndrome, numerous other factors known to be increased in monochorionic gestations may play a role, such as fetal growth restriction, velamentous cord insertion, preterm premature rupture of membranes, preterm delivery, or poor postnatal transition (62, 67–70).

In a prospective observational cohort study, including 202 monochorionic twin pregnancies diagnosed in the first trimester (71), twin–twin transfusion syndrome occurred in 9% and severe discordant growth without twin–twin transfusion syndrome in 14%. In a subsequent prospective cohort study of the long-term neurodevelopmental outcome of surviving infants of monochorionic pregnancies (72), a total of 230 infants were assessed at a mean age of 24 months. Overall, neurodevelopmental impairment was present in 10% (22/230), with 5% having isolated motor delay, 1.5% isolated mental delay, 1.5% a combined motor and mental delay, and 2% cerebral palsy. Significant risk factors for death or developmental impairment of one or both twins were twin–twin transfusion syndrome, early-onset discordant growth, and assisted conception. However, it is noteworthy that neurodevelopmental impairment also occurred in 7% (11/160) of infants resulting from uncomplicated pregnancies who were delivered after 32 weeks of gestation.

In contrast to other investigations, a Dutch study found a considerably lower incidence of neurologic abnormalities and no significant differences between surviving monochorionic and dichorionic twins (61). The incidence of cerebral palsy was 2.2% in monochorionic and 0.5% in dichorionic twins, but developmental delay was present in 0.7% of the monochorionic and 4.2% of the dichorionic twins. A limitation of that study was that it was not population based, and the fetuses of more complex pregnancies with twin–twin transfusion syndrome that involved adverse long-term outcome were delivered at the national referral center for twin–twin transfusion syndrome in the Netherlands and were not included in this series.

An investigation into the antenatal origin of neurologic damage in multiple gestations used ultrasound assessments of the neonatal brain within 3 days of birth (73). Cerebral atrophy and white-matter cavitation were used as indicators of white-matter necrosis. A total of 101 infants (89 twins and 12 triplets) were studied. Antenatal necrosis of cerebral white matter was diagnosed in 14 infants (13.8%). The incidence of white-matter necrosis was greater in monochorionic as opposed to dichorionic infants (30% versus 3.3%; P < 0.001). In this study, cerebral white-matter necrosis was associated with polyhydramnios, intrauterine death of a co-twin, hydrops, and placental vascular connections (particularly vein-to-vein anastomosis).

**Selective Fetal Growth Restriction**

Two studies have investigated the outcome of monochorionic twins with selective intrauterine growth restriction (IUGR) confined to only one of the twins (74, 75). The first study investigated outcome according to umbilical artery Doppler blood-flow waveforms in the smaller twin. In the group with intermittently absent or reversed end-diastolic flow, 20% of the larger twins showed abnormal findings on neonatal scans, suggestive of parenchymal damage. This was also the case in 14% of smaller twins with persistently absent or reversed end-diastolic flow. Intermittently absent or reversed end-diastolic flow in the umbilical artery is indicative of large arterio-arterial anastomoses, and the white matter injury may be the result of the associated hemodynamic imbalances in those anastomoses. Acute events that result in vascular overload on one side and hypovolemia on the other may lead to fetal death or brain damage.

The second study included 117 monochorionic twin pregnancies having two liveborn twins without twin–twin transfusion syndrome (75). In this retrospective study, selective IUGR of one twin was found in 43% with discordance in birth weight of greater than or equal to 25% in 22% of the cases. The incidence of severe cerebral injury (intraventricular hemorrhage grades III and IV, periventricular leukomalacia grade II or greater, porencephalic cysts, ventricular dilatation, or a combination) in infants from pregnancies with and without selective IUGR was 2% and 3%, respectively.

**Intrauterine Demise of One Twin**

One of the first series of children with cerebral palsy noted in 10 cases (among 19 sets of twins affected with cerebral palsy) the co-twin was either stillborn or died shortly after birth (39). Subsequent case series
also have reported a substantial incidence of stillbirth in the co-twin of children with cerebral palsy (46, 64, 73), which has been reproduced in some epidemiologic studies (49, 50, 53, 54). Other studies have found the incidence of cerebral palsy in cases in which one twin died in utero to be 4 (53) to 15 times (54) higher than when both twins survived. One study of a large cohort of twins noted the incidence of cerebral palsy in the surviving twin was 121 per 1,000 (50); 13 times higher than gestations in which both twins survived and 100 times higher than in singletons. A series of 79 sets of triplets noted seven cases in which one fetus died in utero (53) and found a prevalence of cerebral palsy of 154 per 1,000 among those who survived to 1 year, compared with 29 per 1,000 when all of the triplets were born alive. Investigators using data from the Western Australian Cerebral Palsy Register reported an OR for cerebral palsy in survivors of multiple gestations with a co-fetal loss at less than 20 weeks to be 2.65 (95% CI, 0.78–8.98), but after a co-fetal death at or greater than 20 weeks, it was found to be 4.25 (95% CI, 1.12–16.1) (76).

Two large epidemiologic studies investigated the specific issue of long-term follow-up after antenatal death of a co-twin (66, 77). In the earlier of these two studies (1973–1980), long-term follow-up of twin gestations in which one twin had died was compared with twin pregnancies of similar birth weight and date of delivery (65). The study group with a co-twin intrauterine death had a greater proportion of monozygous twins than the control group (69.5% versus 45.4%). The study group also had a greater incidence of cerebral palsy or mental retardation (4.6%) in the surviving twin. The later study (1993–1995) identified 613 twin pregnancies in which one fetus had died in utero (77). Long-term follow-up revealed a rate of cerebral palsy in the surviving twins of 83 per 1,000 (95% CI, 57–117), an increase of 40-fold over the background population prevalence of cerebral palsy.

A more recent study described perinatal outcome and neurologic follow-up of co-twins after single intrauterine death in 10 dichorionic and 13 monochorionic twin pregnancies, which were all managed expectantly (78). Perinatal survival was 100% in the dichorionic and 83% (10/12) in the monochorionic group. Neurodevelopmental follow-up was normal in all but one twin of a dichorionic pregnancy with a suspicion of congenital infection.

In a systematic review of studies reporting on perinatal death (904 pregnancies) and neurodevelopmental delay (267 pregnancies) after co-twin death, the risk of monochorionic and dichorionic co-twin demise was 12% (95% CI, 7–18) and 4% (95% CI, 2–7), respectively (79). The risk of neurologic abnormality in monochorionic and dichorionic co-twin survivors was 18% (95% CI, 11–26) and 1% (95% CI, 0–7), respectively. Where comparative data within studies were available, the OR for co-twin demise of monochorionic twins was six times that of dichorionic twins, and for neurologic abnormality was four times that of dichorionic twins.

Many pathologic lesions can be found in the surviving twin after co-twin demise in monochorionic pregnancy, but renal cortical necrosis and multicystic encephalomalacia are particularly remarkable (80–86). Possible contributing factors include IUGR, marginal and velamentous umbilical cord insertions, extreme fetal growth discordance, and preterm delivery. However, the typical findings of renal cortical necrosis and multicystic encephalomalacia in monochorionic twin gestations point to a common pathologic process. Both circumstantial and objective evidence exist to suggest that this mechanism results from the presence of vascular connections in monochorionic placentation.

The mechanism by which the death of one twin in utero may have effects on the other in monochorionic placentation is unclear. In 1882, Fredereich Schatz documented the existence of vascular connections within monochorionic placentas (87). In an attempt to elucidate the process by which neurologic damage occurs in the survivor, funipuncture was performed on surviving twins after co-twin demise (88). Three of five monochorionic surviving twins had cerebral anomalies postnatally. The fetal blood samples did not reveal coagulopathy but rather significant anemia. This suggests that the likely mechanism for the abnormalities found in the surviving twin is the hemorrhage of the survivor into the circulation of the dead co-twin by placental anastomoses. The subsequent hypotension and tissue hypoxia may lead to cerebral ischemia and infarction in the survivor.

Ultrasoundography and magnetic resonance imaging have been used to evaluate the neurologic effects of antenatal co-twin demise in the survivor, with neurologic injury detectable by ultrasonography in 1–2 weeks of the demise and as early as 1–2 days by magnetic resonance imaging (89).

Most reported cases of intrauterine demise of one twin have been managed expectantly (80–82, 90–99). In some series, expectant and emergency delivery strategies have been pursued (84–86, 100, 101). However, even in cases in which emergency cesarean delivery was performed the same day as diagnosis of the demise of one twin, neurologic impairment still ensued in some of the survivors (84, 85). Although
close fetal surveillance after co-twin death seems prudent, it may be misleading because normal fetal heart rate patterns and biophysical profile scores have been documented even in the presence of multicystic encephalomalacia (85). Thus, there is no reliable evidence that prophylactic delivery of the surviving twin after monochorionic co-twin demise in utero improves outcome.

**Twin–Twin Transfusion Syndrome**

Extremes in hemodynamic imbalance between placental inter-twin vascular communications results in twin–twin transfusion syndrome. This syndrome arises when blood is shunted from one fetus to the other through uncompensated placental vascular anastomoses; as a consequence, one twin becomes the hypovolemic donor and the other the hypervolemic recipient. Without treatment, the survival rate of a twin with twin–twin transfusion syndrome varies from 86% with mild disease to less than 30% with more severe stages (102).

Among the various therapeutic options used to improve outcome in twin–twin transfusion syndrome are serial amnioreduction and fetoscopic laser ablation of the communicating vessels. The former provides symptomatic relief and the latter theoretically interrupts the pathologic basis of the condition (anastomosing vessels) (103–112).

In severe midtrimester twin–twin transfusion syndrome, fetoscopic laser coagulation of vascular anastomoses is superior to serial amnioreduction, with a higher survival rate and lower prevalence of neurologic impairment. A randomized controlled trial comparing laser surgery with serial amnioreduction found that with laser therapy, a significantly higher percentage of pregnancies had at least one survivor (76% versus 56%), the incidence of periventricular leukomalacia was significantly lower (6% versus 14%), and the percentage of children alive without major neurologic complications at 6 months was significantly higher (52% versus 31%) in comparison with the amnioreduction group (113). A follow-up study of long-term neurodevelopment up to age 6 years confirmed these results (114). The children treated with fetoscopic laser coagulation had significantly higher Ages and Stages Questionnaire scores, and 82% and 70% of the children had a normal neurologic evaluation in the laser and amnioreduction groups, respectively ($P=12$). Quintero stage and treatment modality were significant predictors of death or severe neurologic outcome.

In cohort studies investigating the long-term outcome of survivors after laser therapy, the prevalence of minor and major neurologic impairment ranged from 11% to 22% and cerebral palsy from 4% to 11% (115–120). There were no differences between former donor and recipient twins. One study that assessed children who were born preterm and treated by amnioreduction or fetoscopic laser surgery was compared with a cohort of dichorionic twins matched for gestational age at delivery by Ages and Stages Questionnaire scores and a standardized neurologic examination (119). Normal neurologic development was found in 94% of dichorionic children, 89% of children treated by laser surgery, and 81% of those treated by amnioreduction (dichorionic versus twin–twin transfusion syndrome treated by amnioreduction: $P=.07$). The Ages and Stages Questionnaire findings were similar in the laser group and the dichorionic children, whereas scores were lower and domains were more often abnormal in the amnioreduction group (60% versus 27%).

A meta-analysis of studies comparing the outcome of laser therapy with that of serial amnioreductions found a significantly decreased risk of neurologic morbidity with an OR of 0.20 (95% CI, 0.12–0.33) after laser therapy (121). A Cochrane review reached similar conclusions (122). Nevertheless, routine neuroimaging is recommended in twin–twin transfusion syndrome before and after therapeutic interventions, and in cases complicated by single twin demise (123).

**Conclusions**

- Multifetal gestation is an independent risk factor for cerebral palsy and long-term neurologic impairment.
- The risk of cerebral palsy and long-term neurologic impairment is significantly higher for monochorionic twins.
- There is inadequate information on the incidence of neonatal encephalopathy in multifetal gestation.
- In cases of intrauterine fetal demise of one monochorionic twin, there is increased risk of death or neurologic compromise for the surviving co-twin.
- There is no reliable evidence that prophylactic delivery of the surviving twin after monochorionic co-twin demise in utero improves outcome.
- In severe midtrimester twin–twin transfusion syndrome, fetoscopic laser coagulation of vascular anastomoses is superior to serial amnioreduction, with a higher survival rate and lower prevalence of neurologic impairment.
Postterm Birth, Postmaturity, and Cerebral Palsy

Postterm Birth

Perinatal mortality and morbidity—meconium aspiration, neonatal acidemia, oligohydramnios, and non-assuring fetal status in labor, low Apgar scores, fetal macrosomia, and birth injury—increase progressively after 40 weeks of gestation (124). Similarly, rates of neonatal encephalopathy increase at term and post-term. A large, population-based, case–control study identified a significant increase in encephalopathy with each week after 39 weeks of gestation. Compared with newborns delivered at 39 weeks of gestation, the adjusted RR of encephalopathy increased to 1.41 at 40 weeks of gestation, 3.34 at 41 weeks of gestation, and 13.2 at 42 weeks of gestation (11). In utero passage of meconium and meconium aspiration syndrome increase in frequency in late gestation. In one study, 7% of infants that experienced meconium aspiration syndrome developed cerebral palsy (125). However, a causal association between the two has been questioned (126) and chronic rather than acute pathways (eg, intrauterine inflammation, chronic hypoxia) may lead to meconium aspiration syndrome.

The Postmature Newborn

Postterm birth itself is a less important risk factor for neonatal neurologic injury than the underlying condition of the fetus (eg, birth weight, acid–base status, the presence of fetal growth restriction, meconium aspiration). Most reports that address the development of offspring of postterm pregnancy have not segregated appropriately grown infants from those displaying postmature features (eg, dry, peeling skin; meconium staining; decreased subcutaneous fat and muscle mass) (127), those affected by fetal growth restriction and those with evidence of chronic in utero hypoxia–acidosis at birth. One report addressing developmental outcome of offspring of postterm pregnancies with postmature features found an increase in illnesses and sleep disorders, as well as diminished performance on the Vineland Social Maturity Scale (128). Newborns who were “asphyxiated”* before birth had a higher incidence of abnormal neurologic signs in the neonatal period. A second report comparing a group of postmature newborns with term controls, noted that the postmature group demonstrated lower Brazelton interaction and motor scores (129). By age 8 months, the Bayley motor scores were equivalent, but the mental scores were slightly lower in the postmature group (130).

Paralleling the increasing frequency of fetal growth failure, intrapartum hypoxia and meconium aspiration in the postdates period, the rates of cerebral palsy increase steadily after the due date. In one study of 908 cases of cerebral palsy, the rates were 52.2 per 1,000 at 18–31 weeks of gestation (28 cases), 9.79 at 32–36 weeks of gestation (58 cases), 1.46 at 37–41 weeks of gestation (230 cases), and 2.26 at 42 or more weeks of gestation (22 cases) (131).

Conclusions

• Postterm birth itself is a less important risk factor for neonatal neurologic injury than the underlying condition of the fetus (eg, birth weight, acid–base status, the presence of fetal growth restriction, and meconium aspiration).

• Paralleling the increasing frequency of fetal growth failure, intrapartum hypoxia and meconium aspiration in the postdates period, the rates of cerebral palsy increase steadily after the due date.

Fetomaternal Hemorrhage

Fetomaternal hemorrhage, referring to the entry of fetal blood into the maternal circulation before or after delivery, is a pathologic condition with a wide spectrum of clinical outcomes depending on the volume and rapidity of fetal blood lost into the maternal circulation (132). The presently available evidence linking fetomaternal hemorrhage to cerebral palsy or neonatal encephalopathy is inconclusive. Some investigators have suggested a link between antenatal fetomaternal hemorrhage and cerebral palsy associated with the accompanying fetal hypovolemia and anemia (133–136). The probability of neurologic injury among survivors of fetomaternal hemorrhage remains difficult to define because the available literature is limited to case reports and small series.

In a series of 26 children who survived fetomaternal hemorrhage of an estimated 80 mL or greater, one child developed spastic quadriplegia (135). This infant was born severely anemic by emergency cesarean with a 5-minute Apgar score of 0 and remained without a detectable heart rate at 15 minutes; subsequent neonatal imaging demonstrated periventricular cysts. A second series noted abnormal neurologic development in only 1 of 41 fetomaternal hemorrhage survivors (136). In a more recent publication, researchers evaluated long-term outcomes for 31 survivors of

*Throughout the report, the terms “asphyxia” and “birth asphyxia” and their variations appear in quotes when used in reference to a particular study to emphasize the wide variation in study definitions of asphyxia. See Chapter 1 for recommended asphyxia definition (in Table 1-1) and discussion of asphyxia terminology.
fetomaternal hemorrhage (greater than 20 mL) through age 6 years and observed no attributable neurologic sequelae (137). The apparent rarity of neurologic compromise after fetomaternal hemorrhage may reflect survivor bias; those infants who did not suffer either stillbirth or a neonatal death were less likely to have had the devastating bleeds. As a risk factor for neonatal neurologic injury, fetomaternal hemorrhage is problematic because recognition may become apparent only after injury has occurred, if at all.

The most common antenatal presentation of fetomaternal hemorrhage is decreased fetal activity, a nonspecific finding that in most cases heralds biophysical issues other than fetomaternal hemorrhage (132, 138). In summary, although significant fetomaternal hemorrhage may lead to cerebral palsy if the infant survives the event, fetomaternal hemorrhage is unlikely to be a frequent predecessor because the condition is not common, with an estimated incidence of 0.9 per 1,000 births at a cutoff of 80 mL or greater of fetal blood (135).

Conclusion

- Fetomaternal hemorrhage is a pathologic condition with a wide spectrum of clinical outcomes depending on the volume and rapidity of fetal blood lost into the maternal circulation.
- The presently available evidence linking fetomaternal hemorrhage to cerebral palsy or neonatal encephalopathy is inconclusive.

Research Recommendations

- Further epidemiological investigations of the antecedents and associations of encephalopathy in relation to birth weight and percentile, fetal growth patterns, and cerebral palsy are needed to clarify this potential link.
- At present, the evidence linking fetomaternal hemorrhage to cerebral palsy or neonatal encephalopathy is inconclusive.
- Large-scale studies should be performed to evaluate the relationship between currently used antepartum fetal testing regimens and relationship to neonatal encephalopathy and cerebral palsy, as well as long-term neurologic outcome.
- Re-evaluation of the gestational ages for delivery that present the minimum risk of short-term and long-term morbidity to the newborn should be performed.

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Labor and delivery most often proceeds uneventfully but at any moment can become complicated by events or conditions that can lead to potential fetal insult or injury. This chapter focuses on the assessment of acid–base properties and blood gases on umbilical cord arterial and venous samples to provide objective measures of the metabolic condition of the neonate at delivery.

Fetal Heart Rate Monitoring

Physiologic Basis

Alterations in blood flow and oxygen content of the maternal, uteroplacental, umbilical, or fetal circulations can result in interruption of fetal oxygenation. Certain fetal heart rate (FHR) patterns indicate possible mechanisms for interruption of fetal oxygenation.

Fetal oxygenation consists of transfer of oxygen from the environment to the fetus. Oxygen is transferred by maternal and fetal blood along a pathway that includes the maternal lungs, heart, vasculature, uterus, placenta, and umbilical cord. Interruption of oxygen transfer at one or more points along this pathway can result in late, variable, or prolonged FHR decelerations. For example, uterine contractions can produce intermittent interruption of the flow of oxygenated maternal blood to the intervillous space of the placenta, where oxygen exchange occurs (1). If this interruption of the oxygen pathway causes the fetal blood oxygen level to decrease below a critical threshold, the FHR may respond with a pattern of late decelerations. In the absence of metabolic acidemia, a late deceleration is an autonomic reflex response to transient fetal hypoxemia during a uterine contraction (2). Transient fetal hypoxemia stimulates chemoreceptors and initiates reflex sympathetic outflow, causing vasoconstriction in nonessential peripheral vascular beds of the gut, limbs, and kidneys. Perfusion of the vital vascular beds of the brain, heart, adrenal glands, and placenta is preserved or increased (3-11). The resulting blood pressure elevation initiates a baroreceptor-mediated parasympathetic slowing of the heart rate to return the blood pressure to normal. If fetal oxygenation is sufficiently interrupted to produce fetal metabolic acidemia from anaerobic glycolysis, a late deceleration may be the result of direct myocardial depression (2). Under these latter circumstances, FHR variability will be markedly diminished, and in most cases absent. Variable deceleration of the FHR is a common pattern that can result from interruption of the pathway of oxygen transfer from the environment to the fetus by compression of the umbilical cord (12). Variable decelerations are characterized by abrupt onset and resolution and have a variable temporal relationship to uterine contractions. There may be a transient elevation of the fetal Pco₂. The degree of interruption of fetal oxygenation is related to the frequency, duration, and possibly depth of the decelerations.

If oxygen transfer from the environment to the fetus is acutely and substantially interrupted at any point, a prolonged deceleration can result. Examples at the level of the maternal lungs, heart, or vasculature (or all three), and the uterus, placenta, and umbilical cord include conditions, such as maternal apnea during a seizure, maternal cardiac arrhythmia, hypotension after regional anesthesia, uterine rupture, abruptio placentae, or umbilical cord prolapse.
Intrapartum Fetal Monitoring and Neonatal Encephalopathy

Assessment of fetal well-being during labor is the goal of FHR monitoring. The interplay of antenatal complications, inadequate placental perfusion, and intrapartum events can lead to adverse outcomes (13). All women in labor should be monitored in an attempt to prevent “asphyxial” injury and intrapartum death (14, 15).

Before the 1970s, the only widely available clinical techniques used to evaluate the intrapartum condition of the fetus were the appearance of amniotic fluid and auscultated fetal bradycardia. An analysis of the National Collaborative Perinatal Project data concluded that auscultatory FHR monitoring was of little value (16). With the advent of intrapartum electronic FHR monitoring (17), early nonrandomized, mainly historically controlled, and mostly retrospective studies suggested a benefit to intrapartum FHR monitoring, primarily for high-risk patients (18–25). It was hypothesized that FHR monitoring would decrease the incidence of cerebral palsy and mental retardation (26). Specifically, there were fewer cases of intrapartum and neonatal death in patients who had intrapartum FHR monitoring, and some studies showed fewer low Apgar scores, as well as less need for resuscitation.

Although there are no studies comparing fetal heart monitoring with no monitoring, there are 12 randomized trials comparing cardiotocography with careful intermittent auscultation, usually with one-on-one nursing. Researchers summarized the results of these trials and noted that use of continuous monitoring is associated with significantly increased rates of cesarean and operative vaginal deliveries, with a concomitant decrease in the rate of neonatal seizures (27). They reported that electronic fetal monitoring (EFM) was associated with one additional cesarean delivery for every 58 women monitored continuously, and 661 women would have to be monitored during labor to prevent one neonatal seizure. Use of continuous monitoring was not associated with a significantly lower rate of cerebral palsy or neonatal mortality (Table 6-1). Thus, the American College of Obstetricians and Gynecologists, the Society of Obstetricians and Gynecologists, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, and the Royal College of Obstetricians and Gynaecologists of Canada have acknowledged that there are no long-term benefits of EFM as currently used (28–30).

A recent addition to the methods of intrapartum FHR monitoring involves the evaluation of the fetal electrocardiogram pattern as an adjunct to the traditional FHR monitoring. Changes in the fetal ST segment have been associated with fetal acidosis. Five randomized trials have been completed in Europe using this technology. When compared in a systematic review with continuous electronic FHR monitoring, the use of adjunctive ST waveform analysis made no significant difference to births by cesarean delivery, the number of neonates with severe metabolic acidosis at birth, or babies with neonatal encephalopathy. Since the studies completed in Europe, there were on average fewer fetal scalp pH samples taken during labor. There were also fewer operative vaginal deliveries and admissions to a special care unit. There were no significant differences in the number of newborns with low Apgar scores at 5 minutes or newborns requiring neonatal intubation. The results of a large randomized trial conducted in the United States have not been published at the time of this report.

Throughout the report, the terms “asphyxia” and “birth asphyxia” and their variations appear in quotes when used in reference to a particular study to emphasize the wide variation in study definitions of asphyxia. See Chapter 1 for recommended asphyxia definition (in Table 1–1) and discussion of asphyxia terminology.

### TABLE 6-1. Outcomes With Continuous Electronic Fetal Heart Rate Tracing Versus Intermittent Auscultation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Trials</th>
<th>N</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative vaginal delivery</td>
<td>9</td>
<td>18,515</td>
<td>1.16 (1.01, 1.32)</td>
</tr>
<tr>
<td>Cesarean delivery for abnormal fetal heart rate tracing</td>
<td>11</td>
<td>33,379</td>
<td>2.37 (1.88, 3.00)</td>
</tr>
<tr>
<td>Neonatal seizures</td>
<td>9</td>
<td>32,386</td>
<td>0.50 (0.31, 0.80)</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>2</td>
<td>13,252</td>
<td>0.00 (0.97, 3.11)</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>11</td>
<td>33,513</td>
<td>0.85 (0.59, 1.23)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

Standardization of Intrapartum Fetal Heart Rate Monitoring

Definitions and Interpretation
In 2007, the National Institute for Health and Clinical Excellence (31) and the Society of Obstetricians and Gynaecologists of Canada (32) produced expert-based consensus documents with recommendations for FHR pattern classification and intrapartum management actions (31, 32). The Society of Obstetricians and Gynaecologists of Canada recommends a three-tier system (ie, normal, atypical, abnormal), as does the National Institute for Health and Clinical Excellence (ie, normal, abnormal, pathologic). In 2008, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the American College of Obstetricians and Gynecologists, and the Society for Maternal-Fetal Medicine jointly published updated guidelines for FHR monitoring (33), which also recommended a three-tier terminology (Category I, II, III). The classification of fetal heart rate patterns is as follows:

- **Category I** FHR tracings are defined by a baseline FHR of 110–160 beats per minute, moderate variability, and no late or variable decelerations. Such tracings are strongly predictive of normal fetal acid–base status at the time of observation.

- **Category III** FHR tracings are defined by at least one of the following: absent variability with recurrent late decelerations, absent variability with recurrent variable decelerations, or absent variability with bradycardia or a sinusoidal pattern for at least 20 minutes. Category III FHR tracings identify fetuses at increased risk of abnormal fetal acid–base status at the time of observation.

- **Category II** FHR tracings include all FHR tracings that do not meet criteria to be included in Category I or Category III. Category II tracings are not indicative of abnormal fetal acid–base status.

Conclusion
- The NICHD three-tier system is similar to those recommended by other organizations and is the accepted standard in the United States.

Association of Electronic Fetal Monitoring Patterns With Acidemia

Before the development of the three-tiered category system for EFM interpretation, a few investigators examined the associative and predictive abilities of elements of EFM patterns for various short-term markers of neonatal morbidity. In 1987, researchers described EFM baseline changes in the second stage of labor and their association with acidemia and its subtypes in 277 women in labor at term (37 weeks of gestation or more) (34). They reported an association between bradycardia and tachycardia and umbilical artery pH less than 7.20. Another study (35) examined the association between EFM patterns and base deficit, comparing 71 cases with an umbilical artery base deficit greater than 16 mmol/L (metabolic acidemia) to 71 gestational age-matched controls and birth weight-matched controls with a base deficit less than 8 mmol/L. These authors found no association between tachycardia and a base deficit greater than 16 mmol/L but did find both absent variability and late decelerations to be associated with metabolic acidemia. However, even when seen together, absent variability and late decelerations were poorly predictive of a base deficit greater than 16 mmol/L, with a sensitivity of 17% and a positive predictive value of 18%.

The findings from a retrospective cohort study of 488 term births were reported in two reports. In the first report, the authors estimated the association of EFM patterns in the period 2 hours before delivery with umbilical artery pH less than or equal to 7.0 (36). They found that the presence of normal variability (now called moderate) and accelerations was associated with a pH greater than 7.0; 97% of EFM tracings with these findings resulted in an umbilical artery pH greater than 7.0. However, the predictive value of EFM features for a pH less than 7.0 was poor. Tracings with minimal or absent variability and late decelerations had a positive predictive value for acidemia of 31–50%.

In the second report, the authors examined the patients who experienced an episode of bradycardia (37), comparing those who recovered with those who did not, with and without preceding reduced variability. They found that decreased variability before unrecovered bradycardia was weakly associated with an umbilical artery pH less than 7.0 (adjusted odds ratio [OR], 1.28; 95% confidence interval [CI], 1.15–1.40). However, all of these early reports were limited in their inability to adjust for clinical factors known to affect the risk of acidemia and adverse outcomes.

In 2004, the authors of another retrospective cohort study of 10,030 births in Japan estimated the association between EFM patterns and umbilical blood gases and between EFM and cerebral palsy in low risk pregnancies (38). They found increased numbers of late, variable, and prolonged deceleration in those who gave birth to infants with an umbilical artery pH of less than 7.10. However, the false-positive rate for predicting low pH was very high, ranging
from 63% to 89%. In addition, they described six cases of cerebral palsy; only three had late decelerations, and three had prolonged decelerations in their EFM patterns during the 2 hours before delivery (38). In a subgroup analysis of EFM patterns in those women with intrauterine bacterial infections, they reported a significant association between fetal tachycardia and risk of cerebral palsy (adjusted OR, 1.10; 95% CI, 1.8–67.0), but no association between deceleration characteristics and risk of cerebral palsy (39). In a subanalysis of women with late decelerations, they estimated the association between recurrent late decelerations (occurring with more than 50% of contractions) and decreased variability with an umbilical artery pH less than 7.10. They found that women with recurrent late decelerations and decreased (minimal or absent) variability, compared with those with moderate variability, had a higher incidence of pH less than 7.10 (10/19 versus 6/80, \( P < .001 \)) (40). In contrast, in 2003, researchers examined 51 term births using computer analyses to estimate the association between EFM patterns and metabolic acidosis at birth in those who labored and those who did not, and found no evidence of association (41).

Following these findings, in 2007, results were published of a case–control study of 107 nonanomalous, chromosomally normal infants born with umbilical artery pH less than 7.0 and an umbilical artery base deficit greater than 12 mmol/L (13 of whom developed hypoxic–ischemic encephalopathy [HIE]) and 107 control infants with an umbilical artery pH greater than 7, which were matched on gestational age and mode of delivery (42). Upon examining the last 60 minutes of EFM before delivery, the authors found that bradycardia, absence of accelerations, and reduced variability—but not the presence of late or variable decelerations—were associated with HIE. However, despite these associations, they found that even in combination, the predictive value of bradycardia and absence of accelerations and reduced variability for HIE was poor, with a sensitivity of 77% and a positive predictive value of 50% (42). The 2003, 2004, and 2007 studies together provide some evidence to suggest that EFM patterns may have some association with umbilical artery pH, but specific patterns fail to emerge as those most consistently associated with acidemia. Further, significant variation in the umbilical artery pH chosen as the primary outcome makes interpretation in aggregate challenging. Despite the differences in conclusions reached by these investigators, there remains excellent consensus regarding the significance of two specific FHR patterns, namely moderate variability and accelerations. Differences exist in the fetal effects of hypoxic stresses associated with late and variable decelerations, and different fetuses may have differing thresholds for damaging degrees of metabolic acidemia. However both variability and accelerations are reliably depressed with degrees of metabolic acidemia sufficient to cause central nervous system injury and neonatal encephalopathy, as well as in a variety of noninjurious situations. Thus, in a fetus exhibiting either moderate variability or accelerations of the FHR, damaging degrees of hypoxia-induced metabolic acidemia can reliably be excluded. In contrast, because of the poor predictive value of most abnormal FHR patterns, prediction of the fetus at risk of neurologic injury is much less certain. To date, no evidence exists demonstrating that electronic FHR monitoring reduces the rate of neonatal encephalopathy.

In 2006, the Cochrane Database of Systematic Reviews published a meta-analysis of 11 randomized controlled trials that compared maternal and neonatal outcomes after continuous EFM versus intermittent auscultation during labor (more than 33,000 women). The women in the continuous EFM group had an increase in cesarean delivery (relative risk [RR], 1.66; 95% CI, 1.30–2.13; \( n = 18,761; 11 \) trials) and operative vaginal deliveries (RR, 1.16; 95% CI, 1.01–1.32; \( n = 18,515; 10 \) trials) but no difference in perinatal mortality (RR, 0.85; 95% CI, 0.59–1.23; \( n = 33,513; 11 \) trials), rates of cerebral palsy (RR, 1.74; 95% CI, 0.97–3.11; \( n = 13,252; 2 \) trials) or rates of Apgar of less than 7 at 5 minutes (RR, 0.97; 95% CI, 0.72–1.31; \( n = 4,037 \)). There was a 50% decrease in the incidence of neonatal seizures in the continuous EFM group compared with the intermittent auscultation group (RR, 0.50; 95% CI, 0.31–0.80; \( n = 32,386; 9 \) trials). However, a follow-up study of the infants who had seizures at 4 years of age found an equal number of children in each group with cerebral palsy, leading the authors to conclude that continuous EFM offers little if any benefit (27).

The limited published evidence and inherent weaknesses of many of the studies themselves were acknowledged at the 2008 NICHD consensus conference on EFM (33). Importantly, the group acknowledged that little evidence had emerged on EFM since the 1997 consensus conference and again called for well-designed studies to fill the significant knowledge gaps that continue to exist. One of the areas of highest importance cited was observational studies that focused on indeterminate (Category II) EFM patterns, as well as outcomes-based science. Because of the rarity of neonatal severe neurologic morbidity and mortality in infants born at term, surrogates have been used
as outcome measures of association with EFM patterns. Because in the 2003 document umbilical artery pH less than 7.0 was considered as a necessary but not sufficient criteria for a subsequent diagnosis of HIE, it has frequently been chosen as a primary outcome measure for EFM research (41). Similar rationale has been used for using a base deficit greater than 12 mmol/L as the outcome of interest. However, given that those values carry a significant association with risk of neurologic injury, many investigators have chosen an umbilical artery pH cutoff greater than 7.0 but less than normal (7.2) in an effort to use EFM to identify and predict fetal pH at a level that is amenable to intervention before injury has occurred. With this in mind, many investigators have chosen an umbilical artery pH less than 7.10 as the acid–base abnormality that would be of greatest clinical use for EFM to be able to predict the fetal pH. Table 6-2 summarizes the EFM associations with acidemia.

There is no evidence in the current literature to support the ability of practitioners to predict neonatal neurologic injury, cerebral palsy, or stillbirth using EFM. Additional systems to risk-stratify the infants with Category II patterns based on components, such as decelerations, baseline changes, and minimal variability seem in greatest need given the high incidence of those patterns and the wide variability of umbilical artery pH that results. Some of the variation in findings of association may be because of a lack of true association. Thus, although future directions for research in EFM include determining which EFM patterns are associated with

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>N</th>
<th>Acidemia Definition</th>
<th>Baseline</th>
<th>Variability</th>
<th>Accelerations</th>
<th>Decelerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilstrap¹ (1987)</td>
<td>227</td>
<td>pH&lt;7.20</td>
<td>Tachycardia</td>
<td>n/r</td>
<td>n/r</td>
<td>n/r</td>
</tr>
<tr>
<td>Low² (1999)</td>
<td>142</td>
<td>Base deficit&gt;16 mmol/L</td>
<td>Tachycardia</td>
<td>Absent</td>
<td>n/r</td>
<td>Early Variable Late Prolonged</td>
</tr>
<tr>
<td>Williams³,4 (2002, 2003)</td>
<td>488</td>
<td>pH≤7.00</td>
<td>n/r</td>
<td>Absent Minimal</td>
<td>Absent</td>
<td>Variable Late Prolonged</td>
</tr>
<tr>
<td>Sameshima⁵,6 (2004, 2005)</td>
<td>10,030</td>
<td>pH&lt;7.10</td>
<td>Tachycardia</td>
<td>Absent Minimal</td>
<td>n/r</td>
<td>Variable Late Prolonged</td>
</tr>
<tr>
<td>Agrawal⁷ (2003)</td>
<td>51</td>
<td>n/r</td>
<td>Mean</td>
<td>Absent Minimal Marked¹</td>
<td>Absent</td>
<td>Variable Late Prolonged¹</td>
</tr>
<tr>
<td>Larma⁸ (2007)</td>
<td>214</td>
<td>pH&lt;7.00 and Base deficit≥ 12 mmol/L</td>
<td>Tachycardia</td>
<td>Absent Minimal</td>
<td>Absent</td>
<td>Variable Late Prolonged</td>
</tr>
<tr>
<td>Cahill⁹ (2012)</td>
<td>5,388</td>
<td>pH≤7.10</td>
<td>Tachycardia</td>
<td>Minimal</td>
<td>Absent</td>
<td>Variable¹ Late¹ Prolonged¹</td>
</tr>
</tbody>
</table>

Abbreviation: BD, base deficit; n/r, not reported.
¹Bold: evidence for association with acidemia; N/0: no evidence of association with acidemia.
²Standard definitions not used.
³Only when repetitive (occurring with greater than 50% of contractions).
meaningful neonatal outcomes using visual as well as computer interpretation, there remain important improvements to be made in terms of system-wide use of the technology (including education) as well as adoption of uniform nomenclature.

**Uterine Tachysystole**

*Tachysystole* is defined as more than five contractions in 10 minutes, averaged over a 30-minute interval. The presence or absence of associated FHR abnormalities is the key issue in management (43). For women with spontaneous labor, tachysystole coupled with recurrent FHR decelerations requires evaluation and treatment. Tachysystole occurring with less frequent FHR abnormalities may or may not require treatment, depending on the specific clinical situation and associated FHR characteristics, such as variability and accelerations. The management of tachysystole for women who are in labor and receiving oxytocin generally involves efforts to reduce uterine activity to minimize the risk of evolving fetal hypoxemia or acidemia (44).

In labor induction or augmentation or both, a decrease in the oxytocin dose should be considered if tachysystole occurs in the presence of a Category I tracing. If there is a Category II or Category III tracing, oxytocin should be reduced or stopped and intrauterine resuscitation techniques should be initiated (43, 45). In addition, simultaneous initiation of multiple resuscitative measures may improve fetal condition more rapidly than the use of individual therapies. If tachysystole-induced FHR abnormalities do not resolve with these initial maneuvers, then tocolytic medications (eg, terbutaline) may be warranted (46, 47).

**Conclusions**

- No evidence exists demonstrating that electronic FHR monitoring reduces the rate of neonatal encephalopathy.
- When compared with intermittent auscultation, however, electronic FHR monitoring does reduce the rate of neonatal seizures.

**Iatrogenic Heat in Labor**

Iatrogenic heat in labor—such as the use of hot showers, warm baths, and hot packs—was not associated with an increased risk of cerebral palsy (OR, 0.47; CI, 0.36–0.61) in a large case-control study (48). However, such interventions for relaxation and pain relief are available more often to low-risk pregnancies, which may have confounded this observation, and the safety of applied heat in labor is not established. In a randomized trial of immersion in warm water during the first stage of labor, more neonates in the immersion group required active resuscitation (RR, 1.41; CI, 1.06–1.89) (49). The Cochrane review of three such trials shows no increase in admissions to neonatal intensive care units (NICU) after the use of immersion during the first stage of labor (50).

**Conclusion**

- No evidence exists of a relationship between iatrogenic heat in labor and cerebral palsy.

**Chorioamnionitis and Intrapartum Fever**

The clinical signs of intraamniotic infection and chorioamnionitis appear relatively late in the inflammatory process and probably after a fetal inflammatory response has been initiated. Intrauterine infection can be hard to detect in its early stages, but a clinical history of prolonged labor and membrane rupture—and signs that include maternal and fetal tachycardia, fever, offensive amniotic fluid, and raised maternal blood inflammatory markers—suggest clinical chorioamnionitis.

After delivery, placental histology can provide definitive diagnosis of intrauterine infection via evidence of chorioamnionitis and funisitis. Placental histology can yield a wealth of information regarding both acute and chronic infection, noninfective villitis, and other placental and systemic disease in a pregnancy complicated by neonatal encephalopathy (51, 52), summarized in Chapter 4. The associations between intrapartum maternal fever and chorioamnionitis with neonatal encephalopathy and cerebral palsy (53) are summarized in Chapter 6. Gross and microscopic examination of the placenta, if still available, should be performed in cases of neonatal encephalopathy and can contribute significantly to the differential diagnosis.

**Maternal Intrapartum Fever**

In the past, it was widely assumed that maternal fever during labor was strong evidence for maternal and fetal infection, in particular chorioamnionitis. For example, an important paper in *JAMA* in 1997 used maternal temperature in labor as the main risk factor, linking this with the diagnosis of chorioamnionitis. It reported that “maternal fever exceeding 38 degrees C in labor was associated with increased risk of unexplained [cerebral palsy] (OR, 9.3; 95% CI, 2.7–31.0), as was a clinical diagnosis of chorioamnionitis” (54). However, there is growing evidence that in developed
countries, infection is not the most common cause of increased maternal temperature during labor; rather, it is the use of regional (epidural) anesthesia.

**Epidural-Associated Fever**

Fusi and colleagues were the first to establish a link between the use of epidural anesthesia and an increase in maternal temperature (55). Despite initial scepticism, this link has subsequently been confirmed by many investigators (56–60). Perhaps the most striking demonstration of the effect was reported in a 2001 study at Tripler Army Medical Centre (61). In the year after the introduction of epidural analgesia on request, the incidence of maternal temperature in labor greater than 37.5°C increased from 8.2% to 26.2%, and the incidence of temperature greater than 38°C increased from 0.6% to 11%. There was no other identifiable change in risk factors or in practice between the 2 years. Although the increase in the pyrexia rate was associated with an increase in the incidence of neonatal blood cultures from 8.6% to 30.7% (RR, 1.7; 95% CI, 1.2–2.4), there was no change in the median neonatal length of stay in the hospital, which suggests that there was no significant increase in the actual rate of intrapartum infection.

Another study suggesting that clinicians were inappropriately linking intrapartum pyrexia with chorioamnionitis, rather than epidurals, was published in 1997 (62). The authors studied 1,657 nulliparous women (who were afebrile at admission for delivery) with term pregnancies and singleton cephalic fuses. Without epidural, the rate of fever remained low regardless of length of labor. With the epidural, the rate of fever increased from 7% for labors up to 6 hours to 36% for labors longer than 18 hours. Neonates whose mothers received epidurals more often were evaluated for sepsis (34.0% versus 9.8%; adjusted OR, 4.3; 95% CI, 3.2, 5.9) and treated with antibiotics (15.4% versus 3.8%; adjusted OR, 3.9; 95% CI, 2.1, 6.1).

Further evidence that epidural fever is not associated with chorioamnionitis was published in an observational analysis of placental cultures and serum cytokine levels in 200 low-risk women (63). Fever was much more frequent in women receiving labor epidural analgesia (22.7% versus 6% no epidural; P=.009), but they were not more likely to have placental infection (4.7% epidural, 4.0% no epidural; P=.99). Infection was similar regardless of maternal fever (5.4% febrile, 4.3% afebrile; P=.7). At delivery, febrile and afebrile women receiving epidural had higher interleukin-6 levels than women not receiving analgesia.

**Maternal Intrapartum Fever and Neonatal Outcomes**

Although there is little or no evidence linking epidural labor analgesia with an increased rate of intrapartum infection, there is evidence that the increased incidence of pyrexia has an adverse effect on the condition of a neonate at birth. A subsequent study examined the neonatal outcomes for 1,218 nulliparous women in spontaneous labor without any clinical signs of infection other than fever (64). Of these women, 123 had fever greater than 38°C, and of these, 120 had epidurals. Of the women with fever, 23% had neonates with a 1-minute Apgar score less than 7. Comparatively, only 8% of the women without fever had neonates with a 1-minute Apgar score less than 7. Similarly, the incidence of neonatal seizures was 3.3% versus 0.2%. In a more recent paper from this group, the incidence of pyrexia greater than 38°C was 19.2% in women receiving epidural anesthesia compared with 2.4% in those not receiving an epidural (65). Among women receiving an epidural, a significant linear trend was observed between maximum maternal temperature and all adverse neonatal outcomes examined, including hypotonia, assisted ventilation, 1- and 5-minute Apgar scores less than 7, and early-onset seizures.

Other studies also have confirmed a strong association between maternal intrapartum fever and neonatal encephalopathy. For example, in 2001, researchers reported that maternal intrapartum fever was strongly associated with neonatal encephalopathy (crude OR, 10.8; 95% CI, 4.0–29.3) and that this relationship persisted after adjustment for covariates (66). In a subsequent study, they reported that although there was an increased risk of encephalopathy when neonates were born acidic (adjusted OR, 11.5; 95% CI, 5.0–26.5), when there was intrapartum fever and fetal acidosis at birth the risk of encephalopathy was greatly increased (adjusted OR, 93.9; 95% CI, 28.7–307.2) (67).

A possible explanation for this interaction is that an increased temperature of the tissues increases their metabolic rate and, therefore, their oxygen requirements; thus, exacerbating the effects of hypoxia. Moreover, increasing temperature increases the release of oxygen free radicals and glutamate, which are neurotoxic (68). There also may be dysfunction of the blood–brain barrier and accelerated cytotoxic proteolysis (68). It is known that hyperthermia worsens the effect of brain ischemia in dogs (69) and may increase the extent of damage in human stroke (70). Moreover, the beneficial effects of neonatal head cooling as protection against the effects
of hypoxia have been attested to by many studies over the past decade (71–79). The authors of a 2001 study suggested that “there are now strong case control data to suggest that even mild pyrexia during labour has an adverse impact on fetuses exposed to hypoxia ischaemia, increasing the risk of subsequent encephalopathy. Thus, when maternal pyrexia develops, as well as appropriate screening and treatment for infection, lowering the maternal fever should be the desired goal” (80). In this context, it needs to be remembered that the core temperature of the fetus is approximately 0.9°C higher than that of the woman giving birth; the fetus needs to dissipate the heat generated by its metabolism, and heat loss requires that there be a temperature gradient down which the heat can flow (81–84). Thus, with maternal temperatures of 39°C, the fetal temperature approaches 40°C.

**Conclusion**

- Placental histology can provide important information regarding the type of inflammatory processes in a pregnancy complicated by neonatal encephalopathy.
- There is growing evidence that in developed countries, infection is not the most common cause of increased maternal temperature during labor; rather, it is the use of regional (epidural) anesthesia.
- There is evidence that pyrexia during labor increases the risk of neonatal encephalopathy.

**Acid–Base Parameters of Umbilical Cord Blood**

The determination of pH, blood gases, and base deficit in umbilical cord blood is commonly performed to assess the metabolic status of the newborn in conjunction with Apgar scores and the neonatal clinical course (85). Hypoxia is the most common stress to the fetus during labor and, depending on the degree and duration, it may result in significant metabolic acidosis. Although all newborns have a modest degree of metabolic acidosis, it is the metabolic acids produced in response to anaerobic metabolism during hypoxia–ischemia that, if severe, correlate with the risk of permanent neurologic abnormalities in some newborns. Notably, the overwhelming majority of cases of cerebral palsy are unrelated to events during parturition and, thus, most infants who develop cerebral palsy are not severely acidotic at birth. Furthermore, most severely acidotic newborns do not develop cerebral palsy. Nevertheless, the measure of an umbilical cord blood acid–base provides an important index of the status of the newborn.

Under normal conditions, oxygen and carbon dioxide diffuse across the placental membrane, traversing the layers of trophoblast and fetal endothelial cells. With the aid of fetal hemoglobin and the Bohr and Haldane effects, the fetus is able to maintain an oxygen saturation of approximately 65% in the blood supplying the heart and brain, despite the relatively low Po₂ (ie, Po₂ 30–36 mm Hg). Oxygen and carbon dioxide diffusion rates are limited primarily by the relative amounts of maternal and fetal blood flow (ie, flow limited) rather than by the diffusion barrier of the placental tissues themselves (ie, diffusion limited). In contrast to the rapid diffusion of oxygen and carbon dioxide, lactic acid (the most prevalent anaerobically produced acid) is cleared slowly (86).

**Respiratory and Metabolic Acidosis**

Blood pH may be influenced by respiratory (carbon dioxide) and metabolic (lactate) changes. Whereas normal adult levels of arterial Pco₂ generally do not exceed 50 mm Hg, newborn levels in the umbilical cord artery may exceed 100 mm Hg at birth. Transient increases in Pco₂ values that occur, for example, during umbilical cord compression in labor or before expulsion of the fetal body in the second stage of labor, may result in respiratory acidosis (reflected in lower pH values) in the absence of significant metabolic acidosis. A predominantly respiratory acidosis is believed not to be detrimental to the fetus nor associated with newborn neurologic damage (87).

As pH represents the inverse logarithm of the hydrogen ion concentration, it does not change linearly with hydrogen ion concentration. During periods of reduced organ oxygen delivery, cellular responses to hypoxia and ischemia result in the accumulation of lactic acid in proportion to the degree and duration of the hypoxic stress; but pH, being an exponential function and affected by changes in carbon dioxide and lactate, has limited use for quantitating the degree of accumulated metabolic acidosis and tissue ischemia. In contrast, base deficit, a calculated value derived from the measured values of pH and Pco₂ in blood, does have a linear relationship to the accumulation of lactic acid and, thus, also correlates with the risk of newborn neurologic injury, especially when it becomes severe (base deficit greater than 12 mmol/L). Base deficit may be quantified as base deficit blood or extracellular fluid levels, with the extracellular fluid value important in cases of marked respiratory acidosis.
A single standard algorithm to calculate and define base deficit in blood gas analyzers is lacking. Because lactic acid (lactate) is the end product of anaerobic metabolism and, in contrast to base deficit, is a measured product and not an estimate, it therefore, might provide improved precision in prediction of neonatal outcome. However, large studies of umbilical cord blood lactate levels are few and the variation in mean values surprisingly large, ranging from 2.55 mmol/L to 4.63 mmol/L (88, 89). The large variation in mean values may be because of the differences in calibration in blood gas meters. Therefore, the use of cord blood lactic acid as an index of fetal metabolic status is less well defined than the base deficit.

**Umbilical Artery pH Across Gestation**

Normal fetal umbilical cord blood gas values have been obtained across gestation via cordocentesis. Although several studies have been reported in the literature, some of the values may have been influenced by sedation of the pregnant patient or the indication for the blood sampling (eg, fetal growth restriction) (90–94). Umbilical artery blood obtained by cordocentesis was evaluated from 70 uncomplicated patients from 18 weeks to 38 weeks of gestation (95). Mean values for pH and base deficit were 7.39 ± 0.05 (standard deviation [SD]) and 2.3 ± 0.6 (SD) mmol/L, respectively. These investigators demonstrated that with advancing pregnancy, fetal arterial Po2 and pH decrease and Pco2 increases (95) as a result of changes in placental function and increased placental and fetal oxygen consumption. Notably, base deficit values did not change with gestational age. Although the fetal arterial Po2 decreases with advancing gestation, the total oxygen content in the fetal blood remains relatively stable because of fetal physiologic adaptive mechanisms (eg, increasing hemoglobin). The metabolic increase in oxygen consumption contributes to the slight increase in fetal Pco2 with advancing gestation. Fetal umbilical artery blood was obtained in 35 normally grown fetuses (96). Based on the authors' graphic data presentation, the mean (95% CI) values at 38 weeks of gestation were approximately pH 7.35 (7.29–7.41), Po2 23 (14–32) mm Hg, and Pco2 42 (38–46) mm Hg. Similar data have been reported from cord blood obtained immediately after elective cesarean delivery. Among 26 cases of scheduled cesarean births, the mean umbilical artery pH was 7.32 ± 0.06 (SD), Pco2 44.2 ± 0.9 (SD), and base deficit 2.3 ± 3.9 (SD) mmol/L (97). These data confirm that the fetus is slightly acidic compared with the mother, with a markedly lower arterial Po2 and slightly increased Pco2; 2 SDs above the mean for fetal base deficit reported from this study was 10.1 mmol/L.

The fetal adaptations to this chronically hypoxic environment include increased hemoglobin F with its enhanced affinity for oxygen, alterations in fetal erythrocyte 2,3-DPG levels, efficient placental oxygen transfer from the mother, and a relatively reduced fetal basal metabolic rate resulting from the temperature-controlled environment and passive, placental-derived nutrition.

**Normal Values for Umbilical Artery and Vein pH at Term**

Values for umbilical arterial and venous pH and Pco2 at delivery have been widely reported. In a study of normal term vaginal deliveries, mean umbilical arterial values were pH 7.28 ± 0.05, Pco2 49.2 ± 8.4 mm Hg, Po2 18.0 ± 6.2 mm Hg, and bicarbonate 22.3 ± 2.5 mEq/L. Umbilical venous values were pH 7.35 ± 0.05, Pco2 38.2 ± 5.6 mm Hg, Po2 29.2 ± 5.9 mm Hg, and bicarbonate 20.4 ± 4.1 mEq/L (98). Note that pH, Po2, and Pco2 data may be the result of rapid and acute changes in placental gas transfer, resulting in the broad range of normal values. In contrast, base deficit reflects the long-term metabolic fetal acid–base status. Among more than 15,000 newborns with 5-minute Apgar scores equal to or greater than 7.0, a 1996 study reported mean umbilical artery base deficit values of 4 ± 3 and 3 ± 3 mmol/L, respectively, with 2 SDs above the mean for base deficit being 9 mmol/L (99). A 2000 study reported mean umbilical artery and umbilical vein base deficit values among more than 1,500 liveborn neonates of 4.8 and 3.9 mmol/L, respectively (100). These values are slightly more acidic than those reported in the 1996 study, reflecting the fact that the former study included only infants with Apgar scores equal to or greater than 7.0. The authors of a 2004 study collected umbilical artery pH from more than 20,000 unselected singleton infants born at term (101). Umbilical artery pH and base deficit values averaged 7.24 ± 0.07 (SD) and 5.6 ± 3.0 (SD) mmol/L, respectively. Two SDs above the mean base deficit was 11.6 mmol/L.

**Fetal Metabolic Changes During Labor**

During labor, uterine contractions cause transient decreases in maternal–placental perfusion and, thus, a reduction of placental oxygen and carbon dioxide exchange. In addition, umbilical cord compression, reduced uteroplacental blood flow due to maternal hypotension, or impaired maternal oxygenation may also adversely affect fetal oxygenation. Consequently, the process of labor and vaginal delivery, with
intermittent reductions in fetal oxygen delivery, results in the development of mild acidosis in almost all labors.

In one study, regression equations were used to correlate umbilical artery blood gases at delivery with the duration of first-stage and second-stage labor among 1,255 singleton term infants with nonoperative vaginal deliveries (102). Based on the results, the latent phase of the first stage of labor typically results in minimal change in base deficit among normal fetuses. In contrast, an increase in the frequency and intensity of uterine contractions in the active phase of the first stage of labor increases the mean fetal base deficit by approximately 1 mmol/L every 3 hours. The second stage of labor further increases the average base deficit by approximately 1 mmol/L every hour in the normal fetus. These changes occur in response to the reduced oxygen delivery during uterine contractions and, in the second stage of labor, with coincident maternal pushing efforts. It should be noted that the rates of projected base deficit change in response to stages of labor and FHR patterns quoted previously are meant as approximations only because there may be significant individual variability. In conclusion, when an infant presumed to be normal upon entering the intrapartum period is subsequently born with or develops an encephalopathy in the early neonatal period, the term birth asphyxia should be reserved for those cases meeting the criteria that are discussed in Chapter 13. Acute intrapartum asphyxia, sufficient to result in neonatal encephalopathy, will most often result in multiple organ system injury. The absence of evidence of such injury should call into question the diagnosis of significant intrapartum asphyxia (103).

Collecting Umbilical Artery pH

Because newborn umbilical artery pH and particularly base deficit can provide an index of fetal acid-base status at the time of delivery and, thereby, risk of organ system injury, these should be obtained in cases for which fetal metabolic status is in question. The umbilical vein, which represents metabolic status after gas and acid transfer in the placenta, has higher Po2 and lower Pco2 levels than the umbilical artery, which represents the metabolic milieu of the fetal tissues before placental gas exchange. Most studies demonstrate superior correlation with neonatal morbidity of umbilical artery pH and base deficit over the umbilical vein. Nevertheless, both the umbilical vein and artery should be sampled primarily to ensure that the artery has been sampled. Exposure of either umbilical artery or umbilical vein samples to air (eg, air bubble in the syringe) results in a tendency toward atmospheric values and, thus, a tendency for an increase in Po2 and a decrease in Pco2. Most commonly, one can discern significant differences in the Po2 and Pco2 values between umbilical artery and vein.

The reliability of cord gas specimens obtained from clamped versus unclamped umbilical vessels up to 2 hours after delivery has been evaluated in several studies. These show that pH, Po2 and Pco2 values remain essentially unchanged for up to 60 minutes in clamped vessels but change significantly in specimens obtained from the placenta via an unclamped vessel (ie, vessel in continuity with placental vessels). However, base deficit values do change significantly over time. In specimens obtained from a clamped section of umbilical cord, umbilical artery base deficit increased by only 1.2 mmol/L after 20 minutes in room air but increased by 4.5 mmol/L after 60 minutes. In the case of lactate measurements in umbilical artery blood, these were the most affected by delay in analysis, with values increasing by 44% after 20 minutes and by 245% at 60 minutes (104).

Thus, efforts should be made to doubly clamp the umbilical cord promptly after birth, and obtain and analyze the sample expeditiously. If there is an expected delay (more than 20 min) in analyzing the sample, it may be helpful to store the syringe on ice (104), but in all such cases, the base deficit and lactate values should be interpreted with caution.

Fetal Acidosis and Newborn Encephalopathy

A number of studies have demonstrated a correlation between metabolic acidosis at the time of delivery and the risk of newborn encephalopathy or neurologic deficit, or both. A series of investigations were published comparing neonatal outcomes with fetal metabolic status as indicated by umbilical artery pH and base deficit. In a study of 233 term newborns stratified by umbilical artery base deficit (4 to 8 mmol/L, 8 to 12 mmol/L, 12 to 16 mmol/L, greater than 16 mmol/L), outcomes were assessed with a composite morbidity score for mild to severe neurologic, cardiovascular, and renal morbidities in the newborn period (105). Among those with a base deficit of 12 or less (ie, less acidotic; n=116), one case of moderate and no cases of severe morbidity occurred (less than 1%), whereas among those with a base deficit more than 12 (ie, more acidotic; n=117), 14 cases of moderate and 13 cases of severe morbidity were seen (23% moderate–severe overall). In the subgroup with a base deficit greater than 16, 37% had moderate–severe morbidity. A subsequent study confirmed a 14% incidence of major neurologic deficits and a 27% incidence of minor deficits at 1 year of age among...
infants experiencing severe metabolic acidosis at delivery (106). In an observational cohort study of umbilical cord arterial samples from term, nonanomalous live neonates the median arterial pH was 7.22 (interquartile range 7.17–7.27). The absolute risk of an adverse neurologic outcome was significantly increased below a pH of 7.10 (0.36%) and was lowest between 7.26 and 7.30 (0.16%). Even below a pH of 7.00 the risk was only 2.95%. The authors concluded that the threshold pH for increased risk of adverse neurologic outcomes is 7.10 and the ideal umbilical cord pH is 7.26–7.30. Most neonates with neurologic morbidity have normal pH values and, therefore, other variables must influence adverse outcomes (107).

With regard to the correlation with umbilical cord blood gases and long-term outcomes, researchers conducted a systematic review of 51 studies of term infants correlating neonatal mortality, HIE, and cerebral palsy (108). Various thresholds for umbilical artery pH were used (less than 7.00, less than 7.10, less than 7.20). They documented a graded increase in risk of perinatal mortality and morbidity with increasingly acidemic status at birth, with OR for mortality increasing from 4.3 (95% CI, 2.2–8.7) for pH less than 7.20 to 6.1 (95% CI, 0.90–41.6) for pH less than 7.00, and similarly for perinatal morbidity from 2.2 (95% CI, 1.3–3.7) for pH less than 7.20 to 12.5 (6.1–25.6) for pH less than 7.00. The correlation with umbilical artery pH and cerebral palsy was much weaker, with seven studies showing nonsignificant increases in risk at various degrees of acidosis (for pH less than 7.0 to pH less than 7.2). However, when subjected to meta-analysis, the OR for cerebral palsy with umbilical artery acidemia was significantly but moderately increased (OR, 2.3; 95% CI, 1.3–4.2) (108) (see Table 6-3).

Together, these studies indicate that unless the newborn has accumulated significant metabolic acidemia, the likelihood of subsequent neurologic and cardiovascular morbidities attributable to perinatal events is very low. Less severe levels of acidosis as measured by pH greater than 7.0 also may be predictive of neonatal morbidity (108). Conversely, reports exist of well-documented intrapartum events leading to severe or moderately severe neonatal encephalopathy with umbilical artery pH greater than 7.0 or base deficit less than 12 mmol/L (103). Such cases are frequently associated with a sentinel event, such as shoulder dystocia, cord prolapse, or uterine rupture and they tend to occur in appropriate for gestational age or large-for-gestational-age newborns, with no preexisting maternal conditions identified, and with unremarkable placental pathology (109–113). The mechanism underlying neonatal encephalopathy in such cases is thought to be complete occlusion of the umbilical cord or sudden and severe hypotension (105, 114).

There are a number of conditions in which umbilical artery pH may not match the infant’s Apgar score or newborn course. In conditions where the umbilical artery pH is normal but the Apgar scores low, there may be other etiologies for newborn compromise, including maternal narcotic administration, inadequate newborn resuscitation, neonatal infection, or congenital anomalies. Similar to in utero cord compression-induced bradycardia, umbilical cord clamping at birth induces a marked bradycardic response. Thus, newborn heart rate is often low and sometimes undetectable, despite a normal FHR just before delivery. Cases in which the umbilical cord base deficit indicates a greater degree of acidosis not reflected by the infant’s status may result from excess heparin in the syringe. Umbilical blood gas values (ie, Po2 and Pco2) are more variable as they may change with acute alterations in maternal and fetal perfusion of the placenta in the final stages of labor.

**Conclusions**

- Newborn umbilical artery pH and particularly base deficit can provide an index of fetal acid–base status at the time of delivery.
- Umbilical cord artery metabolic acidemia has a relatively weak predictive value for longer-term complications, such as neonatal encephalopathy or cerebral palsy.

**TABLE 6-3. Umbilical Artery pH and Neonatal Outcome**

<table>
<thead>
<tr>
<th>pH</th>
<th>Perinatal Mortality (Odds Ratio)</th>
<th>Perinatal Morbidity (Odds Ratio)</th>
<th>Cerebral Palsy (Odds Ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7.00</td>
<td>6.1 (0.90–41.6)</td>
<td>12.5 (6.1–25.6)</td>
<td></td>
</tr>
<tr>
<td>&lt;7.10</td>
<td>7.1 (3.3–15.3)</td>
<td>2.4 (1.3–4.2)</td>
<td></td>
</tr>
<tr>
<td>&lt;7.20</td>
<td>4.3 (2.2–8.7)</td>
<td>2.2 (1.3–3.7)</td>
<td>2.3 (1.3–4.2)*</td>
</tr>
</tbody>
</table>

*Seven reports, 1,117 cases and controls with pH thresholds of 7.00–7.20.

Neonatal Neurologic Outcome Following Acute Intrapartum Events: The Effect of Time From Diagnosis to Delivery

Animal data show that the duration and degree of fetal hypoxia are related to the occurrence and extent of brain damage. The data in humans, however, are not as clear because the situation in humans does not allow experimental manipulation to determine the different factors involved. In humans, information is extrapolated from actual cases of umbilical cord prolapse, abruptio placenta, shoulder dystocia, maternal cardiac arrest, and uterine rupture. A multitude of clinical factors surrounding these conditions affect the neurologic outcome of the fetus. Included are the degree and duration of umbilical cord compression (complete versus variable), the degree and duration of placental separation, the effectiveness and duration of maternal cardiopulmonary resuscitation, and the fetal condition before the event (a normal fetus versus one compromised by preexisting uteroplacental insufficiency or intermittent umbilical cord occlusion). Fetal outcome also will likely be affected by the length of time between actual occurrence of the event, diagnosis, and the ability to effect termination of the insult.

The pattern of neurologic injury after acute hypoxic–ischemic insult can involve the thalami and basal ganglia predominantly and may be different from the common pattern after chronic insult in the term newborn that involves predominantly the cerebral cortex and the subcortical white matter (115, 116). The former pattern was found to be highly predictive of poor outcome and corresponds closely to experimental models of acute total perinatal “asphyxia” (117). In a review of infants hospitalized in an infant special care unit, 85 developed neonatal seizures. Eleven of those infants had a gestational age beyond 37 weeks at birth and had experienced persistent prolonged decelerations without recovery just before birth (116). Radiologic and clinical findings showed a consistent pattern of injury in the subcortical brain nuclei with complete or relative sparing of the cerebral cortex and white matter, along with absent or only subtle injury to organs other than the brain.

As noted, fetal hypoxic–ischemic brain injury secondary to acute intrapartum events may not be associated with other multiorgan system injury (116, 118). In a review of 14 cases of severe fetal brain injury with absent multiorgan system dysfunction associated with acute intrapartum asphyxial events (six uterine ruptures, five prolonged FHR decelerations, one fetal exsanguination, one umbilical cord prolapse, and one maternal cardiopulmonary arrest), the average duration of the prolonged FHR deceleration was 32.1 ± 9.1 minutes (range: 19–51 minutes) (118). The higher metabolic rate of subcortical nuclei compared with the cerebral hemispheres and the higher metabolic rate of the brain compared with other organs may explain the distribution of cerebral damage and the sparing of other organs that can be seen with an abrupt decrease in oxygenation after acute near-total asphyxia. Alternatively, the shunting of blood flow from other organs to the brain and from the cerebral hemispheres to the thalamus and brain stem may explain the involvement of the cerebral hemispheres and multiorgan dysfunction seen with the more prolonged type of fetal hypoxia associated with uteroplacental ischemia. The pattern of the hypoxic–ischemic insult (chronic versus acute), the gestational age of the fetus, and the effectiveness of resuscitation all will have bearing on the ultimate neurologic outcome. For example, in sheep, complete umbilical cord occlusion of up to 20 minutes did not result in neurologic damage in midgestation (119), whereas repeated brief umbilical cord occlusions in late-preterm fetal lambs did result in neurologic damage (120). The lower level of cerebral metabolism in early gestation compared with term gestation and the more cytotoxic effects of the ischemia–reperfusion insult compared with continuous ischemia may explain these differences. Many of the published data were obtained before the advent of whole-body or selective hypothermia for prevention of neurologic injury in neonates with HIE, many of whom had acute intrapartum asphyxia (76, 77).

Umbilical Cord Prolapse
Fetal hypoxia in umbilical cord prolapse is the result of impediment to blood flow to and from the placenta. This occlusion may or may not be continuous or complete. Thus, one would postulate that injury patterns might resemble acute total fetal “asphyxia,” acute partial intermittent “asphyxia,” or a hybrid of the two. The relationship between time to delivery and neurologic outcome in umbilical cord prolapse depends on fetal presentation, station, and the frequency of contractions in addition to the other factors that affect neurologic outcome listed previously. Umbilical cord compression in cephalic presentation generally would be more severe than in a transverse lie.

Most of the data regarding neonatal outcome after umbilical cord prolapse dates back 20 or more years and may have limited applicability today. Historical differences in FHR monitoring practice, choice of delivery method (vaginal versus cesarean delivery, especially for breech presentation), neonatal resusc-
tation, and the changing threshold for viability of pre-term neonates as well as gestational-age-specific long-term morbidity all affect fetal outcome. Because the variability is so great, only the following broad generalizations can be made, and, even then, exceptions will be common:

- Fetal mortality and umbilical artery pH are affected by the time from diagnosis to delivery (121–123).
- Perinatal mortality is greatest with frank prolapse, followed by occult prolapse, and least in controls without prolapse (124, 125).
- By far the most common long-term neurologic outcome with either frank or occult cord prolapse is a normal infant (124–126).

Shoulder Dystocia

The issues with shoulder dystocia are similar to those of cord prolapse, with the exception that the degree of umbilical cord compression usually can be assumed to be at least as severe as or more severe than that seen with umbilical cord prolapse. The same generalizations regarding outcome can again be assumed.

In a review of 56 cases of fatal shoulder dystocia, the head-to-body delivery interval was recorded by the clinical staff involved as less than 5 minutes in 47% of cases and greater than 10 minutes in 20% of cases (127). The authors determined that “nonreassuring fetal status” (“fetal distress”*) was present in 14 cases before delivery of the head. The incidence of fetal compromise during labor was not different between neonates who died after a short head-to-body versus long head-to-body delivery interval. Thirty-eight (68%) newborns had no signs of life at delivery, and 23 of these could not be resuscitated and were classified as stillborn. Twenty-one (38%) neonates were transferred to a neonatal unit, most with major postnatal complications, such as HIE. Adequate autopsies were performed on 18 cases, with evidence of acute hypoxic organ damage in 96% of cases and birth trauma in 24%. Details regarding the site and type of organ injury were not provided.

Shoulder dystocia (defined as need for ancillary maneuvers to deliver the anterior shoulder or a head-to-body delivery interval longer than 1 minute) occurred in 210 pregnancies (0.34% of singletons delivered vaginally between 1995 and 2009) at a tertiary care hospital in Hong Kong. Two hundred of these cases were included in a retrospective review of the risk of fetal acidosis and HIE in relation to the head-to-body delivery interval. Head-to-body delivery interval and presence of nonreassuring fetal heart rate pattern were both independent determinants of umbilical artery pH, and the head-to-body delivery interval was the only significant determinant of umbilical artery base deficit. The arterial pH dropped at a rate of 0.011 per minute (95% CI, 0.017–0.004; \(P = .002\)) of head-to-body delivery interval. The risk of severe acidosis (pH less than 7) was 0.5% (1/183) when the head-to-body delivery interval was less than 5 minutes and 5.9% (1/17) when the head-to-body delivery interval was prolonged to 5 minutes or more (\(P = .034\)). There were five cases (2.5%) of HIE, four of which had head-to-body delivery intervals at or beyond 5 minutes. The risk of HIE for head-to-body delivery interval less than 5 minutes was 0.5%, compared with 23.5% for head-to-body delivery interval of 5 minutes or longer (\(P = .001\)). Although this review found a statistically significant association between head-to-body delivery interval and neonatal acidosis, that association was weak, as the head-to-body delivery interval accounted for relatively little of the variance in umbilical artery pH or base deficit (128). The findings of another retrospective review are consistent with a weak association between shoulder dystocia and umbilical artery acidosis. In this study, 134 cases of shoulder dystocia (defined as need for ancillary maneuvers regardless of the head-to-body delivery interval) were included in the analysis. The umbilical artery pH was 7.23 ± 0.082. Only two infants had an arterial pH less than 7.00, neither of whom exhibited signs of HIE during hospitalization. No infant had a 10-minute Apgar score less than 4 (129, 130). What these data indicate is that the neonatal acidosis and central neurologic injury are relatively rare in shoulder dystocia, and that head-to-body delivery interval is not the only, nor the major, determinant of their occurrence.

Uterine Rupture

In addition to the numerous maternal and fetal factors listed previously, perinatal mortality and morbidity with uterine rupture is greatly affected by whether the fetus is extruded from the uterus. One review of all cases of uterine rupture—defined as symptomatic uterine scar separation that required emergency laparotomy—identified 106 cases out of 11,179 women with a previous cesarean delivery who underwent trial of labor (131). Of the 99 cases with complete maternal and neonatal records, the fetuses were totally extruded in 28, partially extruded in 13, and

*The term “fetal distress” is imprecise and nonspecific. Although still used in the literature, its continued use as an antepartum or intrapartum diagnosis is discouraged. It is recommended that the term “fetal distress” be replaced with “nonreassuring fetal status,” followed by a further description of findings.
not extruded in 58. The number of fetuses with perinatal death, cases of *perinatal asphyxia* (defined as an umbilical artery pH less than 7.0 with seizures and multiorgan dysfunction), need for ventilatory support, 5-minute Apgar score less than 7, and umbilical artery pH less than 7.0 were all much worse with total or partial fetal extrusion from the uterine cavity than when the fetus remained in utero.

The authors did not comment on the neurologic outcome of the neonates or specifically analyze the relationship between neurologic outcome and the time from diagnosis to delivery, but some of the data provided may be useful in this regard. Four of the perinatal deaths (three of the four deaths with total extrusion and one of two deaths in the nonextrusion group) occurred in 13 women who had nonreassuring fetal status (“acute fetal distress”) on admission and who underwent immediate cesarean delivery. In these cases, fetal damage may well have occurred before presentation, and the duration of the insult cannot be determined. Of the remaining nine cases, three had an umbilical artery pH less than 7.0. It could be inferred from this that the insult may have occurred long before admission and that intrapartum management could not have prevented the outcome. Fetal heart rate patterns were analyzed for abnormalities on the remaining cases after excluding the 13 patients who were delivered immediately and the eight patients (without nonreassuring fetal status) who were delivered vaginally. Prolonged decelerations that provoked operative delivery occurred in 55 of the remaining 78 women (Fig. 6-1). No significant perinatal morbidity occurred in patients whose only FHR abnormality was prolonged deceleration when delivery occurred within 17 minutes of the onset of the prolonged deceleration. Perinatal asphyxia occurred as early as 10 minutes after the onset of prolonged deceleration when the prolonged deceleration was preceded by a period of severe late decelerations ranging from 36 minutes to 90 minutes in duration. There was significant overlap in the time from onset of prolonged deceleration to delivery between cases with perinatal morbidity and those without complications, regardless of the presence or absence of antecedent FHR abnormalities. The time from the onset of the prolonged deceleration to delivery was 13 ± 6.5 minutes in the neonates without significant morbidity.

A retrospective study identified 11 women who had intrapartum uterine rupture among 3,353 women who attempted vaginal birth after previous cesarean delivery between 1990 and 1995 (132). Nine of the 11 women (73%) had FHR bradycardia before delivery, all lasting longer than 15 minutes, with five episodes lasting between 18 minutes and 37 minutes. Before the bradycardia, four had late decelerations, eight had variable decelerations, and three had early decelerations. All but one of the neonates had an umbilical cord blood pH less than 7.0, and five had a base deficit greater than 15 mEq/L (not specified arterial or venous). The author noted a trend toward lower pH and higher base deficit (more acidotic) that appeared to be related to the length of the bradycardia but did not provide the data. Eight of the 11 neonates were admitted to the NICU, but only one required hospitalization beyond age 5 days. None of the neonates had seizures or multiorgan dysfunction, and none required ventilatory assistance. One neonate was referred to the neurology clinic but was lost to follow-up. None of the neonates had sustained brain damage at the time of publication.

In a small retrospective series from Japan, the effect of the interval between onset of sustained fetal bradycardia and cesarean delivery on neurologic outcome at 2 years was evaluated in 19 pregnancies with umbilical cord prolapse (n=5), abruptio placentae (n=4), uterine rupture (n=3), maternal respiratory failure (n=1), or other causes (n=6). All three neonates in the uterine rupture group had normal neurologic outcome at 2 years of age. The bradycardia to delivery interval ranged between 19 minutes and 28 minutes, and the umbilical artery pH ranged between 6.76 and 6.95 (122).

A recently published series analyzed 36 cases of uterine rupture, which occurred during 11,195 cases
of labor after cesarean delivery in nine hospitals of the Intermountain Healthcare system and the University of Utah (133). Signs of the uterine rupture were fetal (n=24), maternal (n=8), or a combination of the two (n=3), and in the other case the rupture was occult. Fetal heart rate characteristics associated with the uterine rupture included variable decelerations in 30.5% of the patients and prolonged fetal bradycardia in 19.4%. Thirteen of the 36 neonates (36.1%) had an umbilical artery pH less than 7.0 or a 5-minute Apgar score less than 7. When compared with 23 neonates without either of those outcomes the median time to delivery in the adverse outcome group was 19 (9–40) minutes, compared with 14 (0–38) minutes in the others. Seventeen neonates were delivered less than 18 minutes after identification of uterine rupture, and none of them had an umbilical cord pH less than 7.0 or a neurologic injury. Eighteen infants were delivered more than 18 minutes after suspicion of uterine rupture and 11 had either an umbilical cord pH of less than 7.0 or a 5-minute Apgar score less than 7. Three of those infants had an adverse neurologic outcome, and all of them had an initial umbilical cord pH less than 6.88.

**Maternal Cardiopulmonary Arrest**

A number of case studies have attempted to report on the relationship between the interval from cardiopulmonary arrest to delivery and neonatal outcome. As with other acute causes of fetal asphyxia, neonatal outcome after cardiopulmonary arrest depends on a number of factors that may be independent of the duration of the asphyxial episode, including the cause of cardiopulmonary arrest (eg, trauma, amniotic fluid embolism, or medical complications), the maternal status and maternal stability or instability before the arrest, the efficacy of cardiopulmonary resuscitation, and the gestational age of the fetus. One report on neonatal outcomes in women with amniotic fluid embolism included in a national registry identified 69 cases, of which 25 met strict inclusion criteria and had cardiac arrest while the fetus was alive in utero (134). The precise arrest-to-delivery time was available in 16 of the 25 women. Neurologically intact survival was inversely related to the time from cardiac arrest to delivery. The limitations of these data include reporting bias, unknown criteria for ascertainment of outcome, lack of information regarding associated obstetric conditions (eg, abruptio placenta, uterine rupture), maternal status before cardiac arrest, or efficacy of cardiovascular resuscitation. A review of the topic summarized the data published from 1900 to 1985 regarding neonatal outcome in relation to the time from maternal death to delivery (135). The authors noted that most fetal survivors were delivered within 5 minutes, and only rare healthy survivors were reported among fetuses delivered more than 10 minutes after cardiopulmonary arrest (Table 6-4). A subsequent review summarized the data published from 1986 to 2004 and found somewhat similar relation between timing of cesarean delivery and neonatal outcome (Table 6-4) (136). The limitations of these data include reporting bias, unknown criteria for ascertainment of outcome, and unclear number of postmortem cesarean deliveries performed for non-surviving infants.

### TABLE 6-4. Postmortem Cesarean Deliveries With Surviving Infants According to Time From Death of the Mother Until Delivery (Reports Published 1900–2004)

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Number of Cases, Infant Outcome</th>
<th>Percentage of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–5</td>
<td>50 normal</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>1 retinopathy of prematurity and hearing loss</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 condition not reported</td>
<td></td>
</tr>
<tr>
<td>6–10</td>
<td>8 normal</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>3 neurologic sequelae</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 condition not reported</td>
<td></td>
</tr>
<tr>
<td>11–15</td>
<td>7 normal</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>2 neurologic sequelae</td>
<td></td>
</tr>
<tr>
<td>&gt;15</td>
<td>5 normal</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>5 neurologic sequelae</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 respiratory sequelae</td>
<td></td>
</tr>
<tr>
<td></td>
<td>86 surviving infants</td>
<td>100</td>
</tr>
</tbody>
</table>

Survival of an infant delivered 22 minutes after medically documented maternal cardiac arrest has been reported (137). At age 18 months, the child was clinically normal, except for persistent mild hypotonia, and results of the child’s Denver Developmental Screening Test Scores were normal.

The 30-Minute Rule
There has been much controversy regarding the so-called “30-minute rule,” which is the capability to begin a cesarean delivery within 30 minutes of the decision to perform it (45). This arbitrary time limit was implemented to encourage hospitals with obstetric services to provide anesthetic resources and operating rooms, as well as nursing, obstetric, and pediatric personnel who can perform cesarean delivery and neonatal resuscitation in a timely fashion. Cesarean delivery should be accomplished as soon as possible for a given hospital for certain conditions, such as prolapsed umbilical cord or uterine rupture. Likewise, it is not always necessary or even desirable to accomplish a cesarean delivery within 30 minutes for some conditions, such as failed induction of labor or failure to progress in labor.

In a review of 11,481 primary cesarean deliveries in laboring women with singletons weighing 2,500 g or more performed between 1999 and 2001 (at 13 institutions that were members of the NICHD Maternal–Fetal Medicine Units Network across the United States), 24% were performed for a primary emergency indication. Of these, only 65% were commenced within 30 minutes of the decision to operate. The most common indication for an emergency cesarean delivery was nonreassuring fetal heart rate, and in these, 62% were begun within 30 minutes. Of the 170 cesarean deliveries performed for the other emergency indications, 98% were commenced within 30 minutes of the decision to operate. Measures of newborn compromise, including umbilical artery pH less than 7.0 and intubation in the delivery room, were significantly greater when the cesarean delivery was commenced within 30 minutes, likely attesting to the need for expedited delivery. Of the infants with indications for an emergency cesarean delivery who were delivered more than 30 minutes after the decision to operate, 95% did not experience a measure of newborn compromise. There were no significant differences in HIE between the less than 30 minutes versus more than 30 minutes group (0.7% versus 0.5%). This large study confirmed that the 30-minute rule is not always attainable, even in academic medical centers, and that the neonatal outcome is not necessarily compromised if the decision to incision interval is longer than 30 minutes (138). Other studies both in and outside of the United States have confirmed these results.

The relationship between timing of acute asphyxia and neonatal neurologic outcome is not simple and depends on a number of independent and elusive factors. As seen in the multiple studies summarized previously, adverse neonatal outcome may occur even when the decision-to-delivery interval is only a few minutes.

Conclusions
• Even in the presence of significant acidemia, most newborns will be neurologically normal (139).
• Most neonates who survive an acute intrapartum hypoxic event have a normal neurologic outcome.

Operative Vaginal Delivery
Use of Instruments During Labor
Obstetric forceps and vacuums are used to assist a vaginal delivery for their potential to increase the expelling force (adding or replacing the maternal expelling forces), decrease the resistance force of the maternal birthing canal by modifying the perimeter of the fetal head (through the correction of malpositions, asynclitism, and deflection), and decrease the resistance of the birthing canal by increasing the perimeter of the soft pelvis (in the case of forceps) (140, 141).

The use of instruments in a delivery is in itself a surrogate parameter of difficulty in the birthing process (142, 143). From the fetal standpoint, umbilical cord lactate concentrations (a marker of acidosis) have been found to be significantly higher in cases of instrumental delivery compared with spontaneous delivery, which reflects a higher rate of instrumental delivery in a group of fetuses with intrapartum diagnoses of distress as manifested by abnormal FHR monitoring patterns (144).

Morbidity Associated With Instrumental Delivery
The incidence of serious neonatal complications and mortality is low for both forceps and vacuum-assisted deliveries (142, 145–149). Birth injuries can be divided into two categories based on their etiology: insults from mechanical forces during the process of labor and delivery, including spontaneous or unassisted delivery, and insults from hypoxia and ischemia (150).

Physical (Mechanical) Injuries
Because of their mechanisms of action, the application of instruments to the fetus has the potential for
maternal and fetal injury (151–154). The patterns of potential injuries are different for forceps than vacuums. The Cochrane meta-analysis of 13 prospective studies comparing the outcomes of vacuum with the outcomes of forceps in 3,338 women between 1964 and 2008 reports more facial injuries with the use of forceps and a trend toward more cephalohematomas with the vacuum, and no difference in death or severe morbidity (HIE, organ failure, NICU admission longer than 7 days) (155).

In one study, the authors found the rate of injury in the groups of vacuum, forceps, and vacuum followed by forceps were not significantly higher than the rate of injury in the cesarean group after failed instrumental delivery. Their interpretation was that an intracranial injury associated with any type of operative delivery may be due to dysfunctional labor rather than to the operative intervention (152).

Hypoxia and Ischemia

In a cohort study of operative vaginal deliveries, a need for ventilation was reported in 1.46% of unassisted deliveries, 2.93% of forceps-assisted deliveries, and 2.5% of vacuum-assisted deliveries (142). Prolonged ventilation (more than 30 minutes) was required for 2.59/1,000 spontaneous births, 5.5/1,000 forceps-assisted births, and 4.76/1,000 vacuum-assisted births. Neonatal seizures were reported in 0.5/1,000 unassisted births, 0.87/1,000 forceps-assisted births, and 0.65/1,000 vacuum-assisted births. Although the causes for neonatal seizures are multiple, this group represents a cohort of children at risk of neonatal encephalopathy. As evidenced in the results of other studies, the vast majority of neonates delivered with the assistance of instruments have a normal transition in the neonatal period and continue to do well long term (142, 153)

Case-control studies performed in Western Australia and Nepal report an association between instrumental delivery and neonatal encephalopathy (156, 157). To estimate the proportion of infants who had been exposed to possible intrapartum hypoxia, the Australians used the following criteria: presence of an abnormal intrapartum cardiotocogram or abnormal FHR on auscultation or fresh meconium in labor, or both, together with a 1-minute Apgar score of less than 3 and a 5-minute Apgar score of less than 7 (156, 158).

Less than one third (29%) of the infants had evidence of intrapartum hypoxia, and of these, only 4% did not have other antenatal risk factors; 25% had risk factors (156, 159). In the study from Nepal, 43% of cases met similar criteria of intrapartum hypoxia, and a further 17% had evidence of a significant intrapartum event (157, 160).

Risk factors for HIE included catastrophic intrapartum events (such as hemorrhage, maternal convulsions, uterine rupture, and umbilical cord accidents), which occurred in 7–8% of the cases; nonspontaneous vaginal delivery; and meconium-stained liquor (156, 157, 159, 160). Both studies found thick meconium was associated with higher odds of neonatal encephalopathy than the use of instruments for delivery. In the Nepalese study, the diagnosis of obstructed labor and induction also were associated with higher odds of neonatal encephalopathy than the use of instruments (157, 160).

Long-Term Outcomes

The effective use of instruments to deliver fetuses who manifest intrauterine signs of compromise has the potential to decrease the exposure to a prolonged second stage of labor (in the absence of a traumatic injury), which prevents or minimizes the effect of intrapartum insults. Some studies have found that dysfunctional labor patterns were associated with a lower IQ in the child at 4 years of age, suggesting that protracted labors and arrest disorders can have a negative effect on the fetal brain (161, 162); however, others have not found this association (163). The vast majority of neonates delivered with the assistance of instruments have a normal transition in the neonatal period and continue to do well long term, including in some studies up to 18 years of age (142, 153, 164–168).

Caveats on the Available Evidence

Experts often provide conflicting evidence for and against the use of instruments during delivery (141, 169, 170). It has been recognized that the prospective randomized trials available in the literature do not use the same inclusion criteria or instruments, and do not evaluate the same outcomes, making comparison of the techniques difficult.

In addition, the analysis of morbidities (particularly long term) associated with the use of instruments is fraught with bias (selection, ascertainment, response, recall), lack of power to find true differences by route of delivery, lack of prepregnancy baseline data, lack of long-term follow-up, inconsistencies, unaddressed covariables, and an incomplete understanding of physiologic processes being evaluated (171, 172).

Because few studies have prospectively evaluated the elective use of forceps when seemingly no assistance was required, it is difficult to ascertain what proportion of the morbidity over the baseline the instruments are actually responsible for (attributable
risk) (173–175). The timely and skilled use of instruments to assist delivery could therefore have a role in decreasing the effect and contribution of intrapartum factors leading to neonatal encephalopathy and HIE (176).

Conclusions

- The effective use of instruments to deliver fetuses who manifest intrauterine signs of compromise has the potential to decrease the exposure to a prolonged second stage of labor (in the absence of a traumatic injury), which prevents or minimizes the effect of intrapartum insults.
- The timely and skilled use of instruments to assist delivery could therefore have a role in decreasing the effect and contribution of intrapartum factors leading to neonatal encephalopathy and HIE.

Cesarean Delivery

Cesarean delivery as an obstetric intervention to reduce neonatal encephalopathy and cerebral palsy has been considered unsuccessful. The dramatic increase in cesarean delivery has many drivers, including increased numbers of repeat cesareans coupled with a decrease in vaginal birth after cesarean deliveries, an increase in nonindicated (elective) cesarean deliveries, and medicolegal pressure with a desire to reduce adverse outcomes. Despite the continued increase in cesarean deliveries, which now represent approximately one third of all births in the United States, there has been no parallel reduction in cerebral palsy rates (177). Some have proposed that the failure of epidemiologic studies to demonstrate a reduction in neonatal encephalopathy and cerebral palsy as a result of interventions, such as EFM and cesarean delivery, may be attributed to the high frequency of cerebral palsy among preterm infants (who are now more likely to survive than in the past) as well as a reduction in intrapartum stillbirth rates, such that infants who once would have died may now survive with damage and those who once would have survived with damage may now survive intact (178).

Although intrapartum hypoxia is believed to contribute to a minority of cases of cerebral palsy, there is general agreement that the potential for such injury presents itself when labor is accompanied by certain events, such as umbilical cord prolapse, abruptio placentae, or uterine rupture. In these cases, particularly when fetal bradycardia ensues, decision-to-incision times are recommended to be as short as safely possible. There are, however, no prospective data available evaluating outcomes stratified according to specific time intervals, such as decision-to-incision, in these obstetric emergencies. A retrospective study of 235 urgent cesarean deliveries performed for fetal bradycardia, which included 30 cases of umbilical cord prolapse or abruption categorized as “irreversible bradycardia,” found that umbilical cord arterial pH decreased significantly with the “bradycardia-to-delivery” interval in these cases. In contrast, no relationship was found in the larger number of cases deemed “reversible bradycardia” or in unspecified cases of “fetal distress” (123).

Recognizing that major adverse perinatal outcomes can occur in institutions providing maternity care, The Joint Commission has recommended that hospitals regularly conduct simulated emergency cesarean delivery drills (179). The benefit of enhancing teamwork and communication aside, limited data at present suggest that such drills actually can improve fetal outcomes (180). As efforts to provide simulation training increase, it will be important to carefully track perinatal outcomes associated with this process.

The term “emergency cesarean” carries with it a broad range of clinical circumstances and degrees of fetal compromise. It should therefore not be surprising that absent conditions associated with fetal bradycardia—such as umbilical cord prolapse, abruptio placentae, or uterine rupture—there remains considerable uncertainty about the necessary time interval to intervene to prevent fetal neurologic damage in the face of a wide spectrum of FHR abnormalities. Recognizing that there were no prospective studies describing the relationship between cesarean response times and subsequent infant outcomes in the setting of emergency cesarean delivery, the Maternal–Fetal Medicine Units Network conducted a secondary analysis of their cesarean registry to examine this issue (138). Among 2,808 emergency procedures, 1,814 (65%) were begun within 30 minutes of the decision to operate. Measures of newborn compromise, including umbilical artery pH less than 7.0 and intubation in the delivery room, were significantly greater when the cesarean delivery was commenced within 30 minutes, likely attesting to the need for expedited delivery. Of the infants with indications for an emergency cesarean delivery who were delivered more than 30 minutes after the decision to operate, 95% did not experience a measure of newborn compromise. Thus, exceeding 30 minutes from decision to incision in many clinical circumstances, which were categorized as an emergency cesarean delivery, may not represent
substandard care. Although this analysis did not analyze outcomes according to specific clinical details in the 1,647 cases of emergency cesarean deliveries performed for “nonreassuring fetal heart rate,” clinical judgment would appear to contribute to the variation in decision-to-incision times. An analysis of 109 “crash emergency” cesarean deliveries also confirmed that longer decision-to-incision intervals may be associated with better umbilical cord pH and Apgar scores, which suggests that less critical situations may have been managed with less urgent action (181).

Planned or elective cesarean delivery before labor may be associated with a reduced incidence of HIE of the newborn. A case–control study found an adjusted OR of 0.17 compared with spontaneous vaginal delivery (156). This finding has been confirmed in women with prior cesarean deliveries who underwent elective repeat operations when compared with those who underwent trials of labor (182, 183). The reported rate of HIE unrelated to uterine rupture at term was 5/15,777 in trials of labor compared with no cases in a similar number of women who underwent elective scheduled repeat cesarean deliveries. An additional seven cases of HIE were found in 114 cases of uterine rupture at term in laboring women. However, these findings must be interpreted cautiously, and counseling is essential as it is not possible to assure a patient that she will have an elective cesarean before labor; the patient may require a cesarean for an indication or may go into labor before elective cesarean.

**Conclusions**

- Cesarean delivery before labor may be associated with a reduced incidence of HIE.
- Exceeding 30 minutes from decision to incision in many clinical circumstances, which were categorized as an emergency cesarean delivery, may not represent substandard care.

**Intrauterine Resuscitation**

Intrauterine resuscitation involves one or more of a series of interventions in an attempt to improve oxygen delivery to the fetus when the FHR pattern during labor is suggestive of fetal hypoxemia. These interventions range from repositioning the mother laterally to further measures, such as maternal oxygen administration, an intravenous (IV) fluid bolus, reduction of uterine activity, amnioinfusion, modification of second-stage labor maternal pushing efforts, medication administration, or a combination. The choice of intervention is based on the presumed etiology of the FHR pattern (Table 6-5) (43).

Lateral positioning, either to the left or right side, is more advantageous for enhancing fetal oxygenation when compared with a supine position and may be

<table>
<thead>
<tr>
<th>Goal</th>
<th>Associated Fetal Heart Rate Abnormality*</th>
<th>Potential Intervention(s)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promote fetal oxygenation and improve uteroplacental blood flow</td>
<td>Recurrent late decelerations or bradycardia</td>
<td>Initiate lateral positioning (either left or right)</td>
</tr>
<tr>
<td></td>
<td>Prolonged decelerations or bradycardia</td>
<td>Administer intravenous fluid bolus</td>
</tr>
<tr>
<td></td>
<td>Minimal or absent fetal heart rate variability</td>
<td></td>
</tr>
<tr>
<td>Reduce uterine activity</td>
<td>Tachysystole with Category II or III tracing</td>
<td>Discontinue oxytocin or cervical ripening agents</td>
</tr>
<tr>
<td>Alleviate umbilical cord compression</td>
<td>Recurrent variable decelerations</td>
<td>Initiate maternal repositioning</td>
</tr>
<tr>
<td></td>
<td>Prolonged decelerations or bradycardia</td>
<td>If prolapsed umbilical cord is noted, elevate the presenting fetal part while preparations are underway for operative delivery</td>
</tr>
</tbody>
</table>

*Evaluation for the underlying suspected cause(s) is also an important step in management of abnormal fetal heart rate tracings.

†Depending on the suspected underlying cause(s) of fetal heart rate abnormality, combining multiple interventions simultaneously may be appropriate and potentially more effective than doing individually or serially (Simpson KR, James DC. Efficacy of intrauterine resuscitation techniques in improving fetal oxygen status during labor. Obstet Gynecol 2005;105:1362–8).


beneficial if the FHR pattern is indeterminate or abnormal (categories II and III) (184–186). There is no significant difference between the right or left side.

If the FHR pattern is suggestive of evolving fetal hypoxemia (eg, recurrent late decelerations) or the mother is hypotensive, an IV fluid bolus may be beneficial. An IV bolus of a non–glucose-containing fluid, such as Ringer’s lactate has been shown to improve fetal oxygen status (186). Generally, at least 500 mL appears to be beneficial, and the effects last approximately 15 minutes (186).

There is limited evidence that maternal oxygen administration at 10 L/min via nonrebreather face mask improves fetal oxygen status, with a greater increase when the fetus is hypoxic (186, 187). The benefits appear to last for at least 30 minutes after the oxygen has been discontinued. However, there is not enough evidence to evaluate its effectiveness (188).

Uterine contractions produce an intermittent decrease of blood flow to the intervillous space, where oxygen exchange occurs. If this intermittent interruption of blood flow reaches an abnormal level as a result of too-frequent contractions, such as with tachysystole, the fetus is at risk of hypoxemia. When fetal oxygenation is sufficiently impaired to produce fetal metabolic acidosis from anaerobic glycolysis, direct myocardial depression occurs. As fetal deterioration progresses, the fetus will likely respond with a decrease in variability and late decelerations. If the FHR is indeterminate or abnormal while uterine tachysystole is occurring, reduction of uterine activity will optimize fetal oxygenation as more time between contractions facilitates maximal perfusion of the placenta and delivery of oxygen to the fetus. Reduction of uterine activity can occur either by reducing oxytocin dosage, discontinuing oxytocin administration, or administering tocolytics (43). A lateral position and an IV fluid bolus may be helpful as simultaneous interventions; simultaneous use resulted in resolution more quickly (6.1 minutes) than with discontinuation of oxytocin and an IV fluid bolus (9.8 minutes) or discontinuation of oxytocin alone (14.2 minutes) (44). Administration of tocolytics is another option, such as subcutaneous terbutaline 0.25 mg (47). A management algorithm for treatment of tachysystole can be found in the American College of Obstetricians and Gynecologists Practice Bulletin, Management of Intrapartum Fetal Heart Rate Tracings (43).

Correction of maternal hypotension secondary to regional analgesia that has resulted in an indeterminate or abnormal FHR pattern may be accomplished with maternal position change and an IV bolus of non–glucose-containing fluids. If these measures fail, IV administration of ephedrine or phenylephrine most often will correct the hypotension and result in correction or improvement of the FHR pattern. Indirect evidence (186, 189, 190) suggests that conventional IV volumes (125 mL/h) of fluid administered in labor are often insufficient to maintain optimal uterine performance and, by inference, optimal intravascular volume. Thus, administering higher than 125 mL/h volumes of IV fluids in labor, especially for nulliparous women, has the potential to avoid often-seen FHR changes that are due to hypotension with regional anesthesia. Amnioinfusion may be beneficial when recurrent variable decelerations during first-stage labor have not been resolved with maternal repositioning (191–194).

Conclusion

- Intrauterine resuscitation involves one or more of a series of interventions in an attempt to improve oxygen delivery to the fetus when the FHR pattern during labor is suggestive of fetal hypoxemia.

**Meconium and Cerebral Palsy**

Like the Apgar score, meconium staining of the amniotic fluid has been used as a marker for newborn hypoxia. However, meconium staining of the amniotic fluid has proved to be an inconsistent predictor of neonatal encephalopathy or long-term neurologic disability, such as cerebral palsy, in the term infant. In a prospective collaborative perinatal project from 1959 to 1966, 45,559 infants were monitored for up to 9 years, and 189 (0.4%) developed cerebral palsy. Among infants who weighed more than 2,500 g, the rate of cerebral palsy was not significantly different between cases with meconium staining of the amniotic fluid versus those without (0.4% versus 0.3%) (195). Similarly, a population-based case–control study performed in four California counties from 1983 to 1985 comparing birth records of 46 children with disabling spastic cerebral palsy and 378 randomly selected control children weighing 2,500 g or more at birth and surviving to age 3 years failed to note an association between meconium staining of the amniotic fluid and cerebral palsy (196).

However, several studies from several countries around the world reported findings at variance with the aforementioned results. The authors of one study examined data from the National Institute of Neurological Disorders and Stroke Collaborative Perinatal Project and reported that infants born through meconium staining of the amniotic fluid had a significantly
increased risk of neurologic abnormalities at 7 years of age, including cerebral palsy (197). The authors of another study in the United Kingdom found meconium staining of the amniotic fluid to be significantly more common among 141 singleton infants with cerebral palsy born at term than matched controls (24.2% versus 9.9%; OR, 3.0; 95% CI, 1.7–5.4) (198). Similar findings were reported in a case–control study of cerebral palsy cases (78% born at term) from Turkey. The authors found meconium staining of the amniotic fluid to be present more often in the group of children with cerebral palsy compared with controls (5% versus 1%, P = .05) (199). A population-based cohort study from Norway (200) found that meconium staining of the amniotic fluid was significantly more common among 93 singleton term births who subsequently developed cerebral palsy than 146,891 who did not (31.2% versus 17.4%; OR, 2.1; 95% CI, 1.4–3.3). The increased rate was uniformly distributed among births from 37 weeks to 44 weeks. Multivariate analysis was used in a case–control study from Victoria, Australia, which found that meconium staining of the amniotic fluid was a predictor of cerebral palsy among term infants after controlling for cigarette smoking, abnormal antenatal cardiotocogram, choioamnionitis, and nuchal cord, among other variables (OR, 5.29; 95% CI, 1.96–14.27) (201).

Indirect supporting evidence for an association between meconium staining of the amniotic fluid and adverse neurologic outcome comes from several studies that reported increased rates of seizures during the neonatal period, an important predictor of subsequent neurologic handicap, in the presence of meconium staining of the amniotic fluid. As for the association between meconium staining of the amniotic fluid and neonatal encephalopathy, a population-based cohort study from Western Australia found that meconium at delivery was more common in infants with neonatal encephalopathy than controls (33% versus 12%; OR, 3.72; 95% CI, 2.33–5.95), and grade III meconium in particular was much more common (13% versus 1.0%; OR, 16.7; 95% CI, 5.76–50.0) (156). A case–control study from Nepal used multivariate analysis to assess whether the association between meconium staining of the amniotic fluid and adverse neurologic outcomes is independent of other confounders. Obstetric characteristics were compared between 131 children with neonatal encephalopathy and 635 controls; presence of meconium was significantly associated with neonatal encephalopathy after controlling for sex of the infant, plurality, birth weight, maternal age, and antenatal care, among other confounders (thin meconium: adjusted OR, 6.0; 95% CI, 2.6–14.2, and particulate meconium: OR, 18.2; 95% CI, 8.0–41.2) (157).

The potential mechanisms of injury associated with meconium staining of the amniotic fluid are unknown. However, association does not imply causality, and it is likely that processes occurring antepartum or during labor may lead to both meconium staining of the amniotic fluid and development of cerebral palsy, which may explain the diversity of findings previously chronicled. One such process may be infection; clinical, laboratory, or placental pathology evidence of uterine infection is indeed more frequent in the presence of meconium staining of the amniotic fluid at term (see also “Inflammation and Infection” in Chapter 4). Placental vascular lesions and fetal growth restriction are also more frequent among term neonates with meconium staining of the amniotic fluid, suggesting that chronic ischemia may be another such process.

Conclusion
- Meconium has proved to be an inconsistent predictor of neonatal encephalopathy or long-term neurologic disability, such as cerebral palsy.

Research Recommendations
- Studies are needed on refining the management of Category II FHR patterns.
- Observational studies examining EFM patterns associated with and predictive of meaningful clinical outcomes are needed.
- Development and evaluation of new technologies for intrapartum fetal monitoring to augment EFM interpretation and clinical decision making at the bedside is needed.
- Exploration of computer interpretation of EFM as an aid, or even replacement, to visual interpretation is needed.
- Quality and safety research validating education and credentialing systems, as well as interpretation and decision-making algorithms are needed.
- Systems-based research exploring alternative paradigms to the bedside use of EFM is needed.

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Neonatal Assessment

Major intrapartum events capable of compromising oxygen supply to the fetus, such as abruptio of the placenta, umbilical cord prolapse, or uterine rupture, may result in hypoxic–ischemic brain injury in the fetus, especially if accompanied by fetal bradycardia (see also Chapter 6, “Intrapartum Considerations and Assessment”). However, catastrophic intrapartum events are present in only a small portion of cases of neonatal encephalopathy, and it is not unusual to find more than a single factor contributing to adverse outcome. Thus, even when there is an obvious obstetric complication, it is important to explore other diagnostic possibilities for which treatment might improve the ultimate outcome. The purpose of this chapter is to outline the steps in the assessment of an encephalopathic newborn.

In the delivery room, birth of a seriously depressed infant should lead to skillful and preemptive resuscitation and an immediate effort to gather information that may be helpful in understanding etiology, especially after a seemingly uncomplicated delivery. The Apgar score for infants undergoing resuscitation at birth should be recorded on an expanded Apgar score form. Umbilical cord blood samples should be drawn to determine arterial cord pH and base deficit levels (see also Chapter 6, “Intrapartum Considerations and Assessment”).

The mother’s history should be reviewed, as well as data regarding maternal and family medical conditions, including thyroid or other autoimmune disorders, deep vein and other thrombotic disorders, early stroke or myocardial infarction, and history of prior pregnancy loss. The history should evaluate whether a twin fetus died, even early in the pregnancy. A history of maternal infection should be sought, including clinical markers of chorioamnionitis or sexually transmitted disease. The history also should look for evidence of intrapartum maternal fever (see also Chapter 6, “Intrapartum Considerations and Assessment”). The results of prenatal ultrasound evaluations and other antepartum test results should be included as part of the maternal medical history.

A sepsis evaluation of the infant is warranted in every seriously depressed infant. However, a significant percentage of neonates with clinical and laboratory evidence of infection will have negative bacterial cultures (1, 2). Abnormal findings in the complete blood count, such as increased immature-to-total neutrophil ratio (greater than 0.2), thrombocytopenia, low white blood cell count (less than 5,000), or absolute neutrophil count (2,000) with elevated acute phase reactants (C-reactive protein) are highly suggestive of sepsis, even in the face of negative cultures.

Neuroimaging plays a unique and crucial role in the assessment of neonatal encephalopathy and is comprehensively reviewed in Chapter 10. Brain magnetic resonance imaging (MRI) and magnetic resonance spectroscopy performed at the appropriate time and interpreted by a neuroradiologist with expertise in neonatal neuroimaging can provide invaluable information regarding the following five questions: 1) Is there evidence of brain injury or malformation? 2) What area of the brain is involved? 3) What type or pattern of brain injury is evident? 4) Is there a time window during which this injury likely occurred? 5) What is the long-term neurodevelopmental prognosis? The following sections describe additional key components in the evaluation of an encephalopathic neonate.
Apgar Scores

The Apgar score provides a universally accepted and convenient system for reporting the status of an infant within minutes of birth and an infant’s response to resuscitation, when needed (3). A 5-minute Apgar score of 7–10 is considered reassuring, whereas a score of 4–6 is considered moderately abnormal in the term and late-preterm infant. A very low Apgar score of 0–3 at 5 minutes or more is a nonspecific indicator of illness and may be one of the first indications of encephalopathy.

There are numerous factors that can influence the Apgar score, including maternal sedation or anesthesia, congenital malformations, trauma, and the interobserver variability of the individuals assigning the score (4). Cardiorespiratory conditions may decrease the newborn’s heart and respiratory rate and tone. Infection may negatively affect tone, color, and response to resuscitative efforts. Normal transition from the intrauterine to the extrauterine environment is gradual, and it generally takes several minutes before a neonate’s oxygen saturation increases from intrauterine levels of 50–60% (cyanotic) to more than 90% (5, 6). Thus, to attribute a low Apgar score solely to hypoxia–ischemia represents a misuse of the score.

The Apgar score is an expression of an infant’s physiologic condition at a certain point in time. Furthermore, it has a limited time frame and includes subjective components (3). Elements of the score, such as tone, color, and reflex irritability can depend on the physiologic maturity of the infant (7). The Neonatal Resuscitation Program guidelines (8) state that Apgar scores should not be used to dictate appropriate resuscitative actions, nor should interventions for depressed infants be delayed until the 1-minute assessment. Although its predictive reliability has not been studied, an Apgar score that is assigned during resuscitation is termed an “assisted Apgar score” and is not equivalent to one assigned to a spontaneously breathing infant (3, 9); that is, it would be misleading to assign a “2” for respirations to an intubated infant with no spontaneous respirations at 5 minutes of age who is being ventilated at 30 breaths per minute. To describe such infants correctly, the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists have proposed an expanded Apgar score form that accounts for concurrent resuscitative interventions (Fig. 7-1).

The use of Apgar scores to predict neurologic outcome was assessed comprehensively using data from

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**Apgar Score**

<table>
<thead>
<tr>
<th>Sign</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Blue or pale</td>
<td>Acrocyanotic</td>
<td>Completely pink</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>Absent</td>
<td>Less than 100 min</td>
<td>More than 100 min</td>
</tr>
<tr>
<td>Reflex Irritability</td>
<td>No response</td>
<td>Grimace</td>
<td>Cry or active withdrawal</td>
</tr>
<tr>
<td>Muscle Tone</td>
<td>Limp</td>
<td>Some flexion</td>
<td>Active motion</td>
</tr>
<tr>
<td>Respiration</td>
<td>Absent</td>
<td>Weak cry; Hypoventilation</td>
<td>Good, crying</td>
</tr>
<tr>
<td></td>
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<td></td>
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</tbody>
</table>

**Comments:**

**Resuscitation**

<table>
<thead>
<tr>
<th>Minutes</th>
<th>1</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>PPV/NCPAP</td>
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<td>ETT</td>
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<tr>
<td>Chest compressions</td>
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<tr>
<td>Epinephrine</td>
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</tbody>
</table>

FIG. 7-1. Expanded Apgar score form. Record the score in the appropriate place at specific time intervals. The additional resuscitative measures (if appropriate) are recorded at the same time that the score is reported using a check mark in the appropriate box. Use the comment box to list other factors, including maternal medications and the response to resuscitation between the recorded times of scoring. Abbreviations: ETT, endotracheal tube; PPV/NCPAP, positive-pressure ventilation/nasal continuous positive airway pressure. (Reprinted from The Apgar Score. ACOG Committee Opinion No. 333. American College of Obstetricians and Gynecologists. Obstet Gynecol 2006;107:1209–12.)
the National Collaborative Perinatal Project, a prospective study in which Apgar scores were recorded for approximately 49,000 singleton neonates at 1 minute and at 5 minutes by an independent observer with a stopwatch to ensure objectivity (10). Scoring continued every 5 minutes thereafter until a score of 8 or higher was reached or the neonate left the delivery room. Study infants were observed to the age of 7 years with a systematic schedule of neurologic, psychometric, and sensory examinations.

In the group of neonates who weighed greater than 2,500 g at birth, the risk of cerebral palsy was higher if the Apgar score at 5 minutes was 0–3 compared with 7–10 (4.7% versus 0.2%), a difference that was statistically significant. Low Apgar scores at 10, 15, or 20 minutes were better indicators of cerebral palsy risk than low scores at 1 minute and 5 minutes. Of the 14 survivors who weighed more than 2,500 g at birth and had an Apgar score of 0–3 at 20 minutes, eight neonates (57%) had a diagnosis of cerebral palsy. In contrast, the rate of cerebral palsy among infants with Apgar scores of 0–3 at 5 minutes who achieved a higher score at 10 minutes was 0.9%, which suggests that a failure to respond to resuscitation was an important predictor of adverse outcome.

A study 10 times larger than the National Collaborative Perinatal Project also confirmed that the Apgar score is a significant predictor of cerebral palsy. In a Norwegian population of 543,064 births, a 5-minute Apgar score of 0–3 was associated with a 125-fold increased risk of cerebral palsy among infants who weighed more than 2,500 g at birth (11). Compared with infants with 5-minute Apgar scores greater than 8, the risk of cerebral palsy was significantly elevated in infants with 5-minute Apgar scores of 0–3 (relative risk [RR], 125; 95% confidence interval [CI], 91–170), in infants with Apgar scores 4–6 (RR, 28; 95% CI, 21–36), and even in those with Apgar scores of 7–8 (RR, 3.7; 95% CI, 2.8–4.8). Similarly, in a California population of infants born at or near term, cerebral palsy was diagnosed in 24% of those with 5-minute Apgar scores less than 7, compared with 0.9% of those with an Apgar score of 7 or greater (RR, 34; 95% CI, 8–294) (12). Low Apgar score is also predictive of neonatal mortality in term infants. Among 132,228 term infants born in Texas over a 10-year period, death within 28 days of age was seen in 24.4% of infants with 5-minute Apgar scores of 0–3, in 0.9% of infants with Apgar scores of 4–6, and in only 0.02% of infants with 5-minute Apgar scores of 7 or greater (13).

In statements regarding the Apgar score, AAP and the American College of Obstetricians and Gynecologists indicate that the change in the Apgar score between 1 minute and 5 minutes is a useful index of the response to resuscitation, a low 1-minute Apgar score is a poor predictor of long-term neurologic outcome, and an Apgar score of 0–3 at 5 minutes of age may correlate with neonatal mortality but does not predict future neurologic dysfunction (3).

To fully understand the association between low Apgar scores and future risk of cerebral palsy, it is important to distinguish between relative risk and absolute risk. Population studies evaluating the relationship between low Apgar scores and cerebral palsy have uniformly reassured us that most infants with low Apgar scores will not develop cerebral palsy; that is, the absolute risk of cerebral palsy remains very low in the setting of a low Apgar score alone. However, low 5-minute and 10-minute Apgar scores clearly confer an increased relative risk of cerebral palsy, despite the high false-positive rate associated with this clinical measure if used as a predictor for neonatal encephalopathy or cerebral palsy. For instance, population studies suggest that the relative risk of cerebral palsy in the setting of a low 5-minute Apgar score ranges from 21 to 125 (11, 12, 14). The risk of cerebral palsy increases by 20-fold to 120-fold in the setting of a low 5-minute Apgar score, depending on how “low Apgar” is defined. It is no surprise then that clinical trials of induced hypothermia have typically listed a low Apgar score as an inclusion criterion (15–18).

Conclusions

• The Apgar score is an expression of an infant’s physiologic condition at a certain point in time, has a limited time frame, and includes subjective components.

• A low 1-minute Apgar score is a poor predictor of long-term neurologic outcome.

• Most infants with low Apgar scores will not develop cerebral palsy; that is, the absolute risk of cerebral palsy remains very low in the setting of a low Apgar score alone.

• Low 5-minute and 10-minute Apgar scores clearly confer an increased relative risk of cerebral palsy, despite the high false-positive rate associated with this clinical measure if used as a predictor for neonatal encephalopathy or cerebral palsy.

• The degree of Apgar abnormality at 5 minutes and 10 minutes correlates with the risk of cerebral palsy.

• The Apgar score for infants undergoing resuscitation at birth should be recorded on an expanded Apgar score form.
Physical Examination

A careful physical examination may reveal clues to the etiology and timing of neonatal encephalopathy, and is an essential component of neonatal assessment. Anthropometric data including weight, length, and head circumference should be plotted using modern growth charts adapted to the ethnicity of the parents and the geographic area in which the neonate is born. Measured head circumference can be variable over several days because of variances in measurement technique and alterations in head shape after birth. Microcephaly at birth (defined as less than 2 standard deviations below the mean) may result from a prenatal insult early in pregnancy or abnormal development of the brain. Symmetrically small-for-gestational-age infants often have suffered a severe and longstanding insult (19), such as intrauterine infection, placental infarction, or chromosomal anomaly and, thus, have an increased risk of neurologic sequelae. Infants with asymmetrical (head sparing) fetal growth restriction may have suffered from progressive placental dysfunction and suboptimal nutrient and oxygen delivery, but with relative sparing of blood flow to the brain. Such infants have an increased risk of acquired brain injury leading to neonatal encephalopathy and cerebral palsy when compared with normally grown infants. Calculation of the weight-to-length ratio (ponderal index) can provide clues to the adequacy of placental function and growth in the last several months of pregnancy (see Chapter 5, “Fetal Considerations and Assessment”).

The physical examination should include a careful search for dysmorphic features and minor congenital anomalies. The finding of three or more minor anomalies is closely associated with major anomalies and often with neurodevelopmental consequences in later life (20). Generally, neonates who have experienced recent neurologic insults will go through stages of tone changes, progressing from hypotonia to normal tone and then to hypertonia. Hypertonia in the first 24 hours after birth is evidence of a remote injury, unless the increased tone is due to repetitive seizures (21). The Sarnat classification of neonatal encephalopathy distinguishes three distinct stages based on level of consciousness, spontaneous activity, muscle tone, reflexes, autonomic function, and presence of clinical seizure activity (21). A modified Sarnat scoring system (see Table 11-1 in Chapter 11) often is used in clinical studies to classify the severity of encephalopathy (ie, mild, moderate, severe) (15, 22).

Conclusions

- A careful physical examination may reveal clues to the etiology and timing of neonatal encephalopathy, and is an essential component of neonatal assessment.
- A modified Sarnat scoring system often is used in clinical studies to classify the severity of encephalopathy (ie, mild, moderate, severe).

Blood Gases

Interpretation of umbilical cord blood gases is discussed in Chapter 6. An umbilical artery pH less than 7.0–7.1 or a base deficit of 12–16 mmol/L is associated with increased neonatal mortality, moderate to severe neonatal encephalopathy, multisystem organ failure, and long-term neurologic disability, including cerebral palsy (23–26).

Neonatal arterial blood gases obtained within 1 hour after birth also have been linked to neonatal outcome and can be interpreted in a similar fashion to umbilical cord arterial blood gas samples. In contrast, capillary blood gas values in the first several hours after birth often do not accurately reflect true acid–base status and are poorly predictive of outcome (27). Because of poor peripheral circulation, capillary blood samples can show an increased metabolic acidosis that is not confirmed when compared with simultaneously drawn arterial samples. A discordant metabolic acidosis documented in an early neonatal arterial gas sample compared with a more normal umbilical cord arterial blood gas result may arise from reperfusion acidosis, the recruitment of metabolic acids from tissue into the circulation, or ineffective resuscitation efforts.

Conclusion

- Neonatal arterial blood gases obtained within 1 hour after birth have been linked to neonatal outcome and can be interpreted in a similar fashion to umbilical cord arterial blood gas samples. In contrast, capillary blood gas values in the first several hours after birth often do not accurately reflect true acid–base status and are poorly predictive of outcome.

Organ Dysfunction

Organ systems within the human body maintain a baseline homeostasis of function that can be measured clinically or by laboratory evaluation. This baseline is altered in acute injury, usually worsens over time and, if the patient recovers, will usually return to baseline. Multisystem organ dysfunction may be seen after an
acute hypoxic–ischemic injury or as part of the sepsis cascade (28) and is physiologically related to the phenomenon of the dive reflex. This reflex redirects blood flow to the brain, heart, and adrenal glands and away from other organ systems in the face of a significant hypoxic–ischemic stress. Multisystem organ failure can involve renal injury, hepatic injury, hematologic abnormalities, cardiac dysfunction, metabolic derangements, and gastrointestinal injury (29, 30).

Encephalopathic neonates should be monitored for multisystem organ injury, including metabolic, renal, hepatic, and cardiac dysfunction. Multisystem organ failure that occurs after 48–72 hours of life is unlikely to result from an intrapartum insult (29).

Clinical and laboratory measures of organ function include urine output, renal and liver function studies, blood glucose and calcium, and vital signs (ie, heart rate, oxygen saturation, and blood pressure measurements). Each organ system and each individual have a unique threshold of injury. Significant brain injury may occur even in the absence of any signs of organ injury (31). That is, although presence of organ dysfunction increases the risk of hypoxic–ischemic encephalopathy in the setting of neonatal encephalopathy, severity of brain injury seen on neuroimaging does not always correlate with the degree of organ injury (32).

Conclusions

- Encephalopathic neonates should be monitored for multisystem organ injury, including metabolic, renal, hepatic, and cardiac dysfunction.
- Although presence of organ dysfunction increases the risk of hypoxic–ischemic encephalopathy in the setting of neonatal encephalopathy, severity of brain injury seen on neuroimaging does not always correlate with the degree of injury to other organ systems.

Hypoglycemia

Hypoglycemia can adversely affect the neonatal brain (33–35) and has been associated with transient deficits in visual evoked potentials and edema of the parieto-occipital white matter on early neuroimaging (36–39). In later childhood, neonatal hypoglycemia has been associated with a triad of cortical visual deficits, occipital localization-related epilepsy, and developmental delay (40–42).

Data from rodent models suggest that brain injury associated with hypoglycemia is more severe when hypoxia–ischemia and seizures also are present (43, 44). Neonates with suspected perinatal “asphyxia”* and hypoglycemia have more severe encephalopathy (45), a higher incidence of corticospinal tract injury on early neuroimaging, as well as later impaired motor and cognitive outcome, when compared with encephalopathic infants who are normoglycemic (46, 47). This suggests that hypoglycemia and hypoxia–ischemia may act synergistically to cause neonatal brain injury. Because hypoglycemia is common in infants with neonatal encephalopathy (48), glucose levels of infants who are encephalopathic should be monitored closely. Immediate intervention of symptomatic hypoglycemia using intravenous dextrose infusion has been recommended by AAP (49) and the Canadian Paediatric Society (50).

Other conditions that lead to neonatal hypoglycemia include sepsis, transient neonatal hyperinsulinemia, placental insufficiency (especially if associated with fetal growth restriction), and inborn errors of metabolism. Etiologies, such as hyperinsulinemic hypoglycemia and structural or functional abnormalities of the hypothalamic–pituitary axis, are less common but typically result in severe, persistent hypoglycemia (51).

Although hypoglycemia can be harmful, the exact level and duration of hypoglycemia needed to cause brain injury is unknown. Despite the existence of many case reports on the sequelae of neonatal hypoglycemia, almost no large prospective studies exist to date. A 2011 clinical report from the AAP Committee on Fetus and Newborn concluded that current evidence did not support a specific concentration of glucose that can discriminate normal from abnormal outcomes or that can potentially result in acute or chronic irreversible neurologic damage (49). An expert panel convened by the National Institutes of Health also concluded that there had been no substantial evidence-based progress in defining what constitutes clinically important neonatal hypoglycemia, particularly regarding how it relates to brain injury (52).

Conclusions

- Because hypoglycemia is common in infants with neonatal encephalopathy, glucose levels of infants who are encephalopathic should be monitored closely.
- Although hypoglycemia can be harmful, the exact level and duration of hypoglycemia needed to cause brain injury is unknown.

*Throughout the report, the terms “asphyxia” and “birth asphyxia” and their variations appear in quotes when used in reference to a particular study to emphasize the wide variation in study definitions of asphyxia. See Chapter 1 for recommended asphyxia definition (in Table 1–1) and discussion of asphyxia terminology.
• Hypoglycemia and hypoxia–ischemia may act synergistically to cause neonatal brain injury.

Electroencephalography

Neonatal electroencephalogram (EEG) is a widely available, inexpensive, and noninvasive neurologic test of the functional integrity of the newborn brain. Electroencephalogram may provide early evidence of the presence and severity of encephalopathy, but EEG does not indicate the cause of encephalopathy. The prognostic value of neonatal EEG is well recognized. If, at the height of an illness, the background shows marked abnormalities (eg, burst suppression, isoelectricity, or extremely low voltage), there is a reasonable expectation for a high risk of death or subsequent chronic static encephalopathy in the survivors (53–56). If the EEG result is normal or only mildly abnormal, a favorable outcome can be anticipated (21). The prognostic accuracy of the EEG is high also in infants treated with prolonged moderate hypothermia for presumed hypoxic–ischemic encephalopathy (HIE): burst suppression or low-voltage background persisting for 24–48 hours correlates with moderate or severe abnormalities on MRI and with death or major neurologic sequelae, whereas a normal or mildly discontinuous background almost always is associated with a normal MRI and a normal neurologic outcome subsequently (57, 58).

The diagnostic specificity of the EEG is very limited. In acute causes of global encephalopathy (eg, perinatal hypoxia–ischemia, shock, meningitis, or hypoglycemia), there are no distinctive kinds of diffuse EEG abnormalities that uniquely reveal the cause of the encephalopathy. An abnormal neonatal EEG result only reveals how potently the abnormality has disturbed brain function. Likewise, for acute causes of focal encephalopathy (eg, localized stroke or hemorrhage), the EEG may reveal the magnitude of the disturbance (the abundance of focal slowing, seizures, or excessive sharp waves) but does not reveal the identity of the cause.

Scant attention has been paid to the use of neonatal EEG in determining the timing of the onset of an acute encephalopathy. There is such great individual patient variation in the type, evolution, and severity of EEG abnormalities observed in acute encephalopathies that the question of timing cannot be answered by EEG alone.

Electroencephalography is the premier tool for identifying neonatal seizures and distinguishing them from other phenomena. Electroencephalography is a valuable tool for assessing neurologic function following encephalopathy during the first 72 hours after birth. Cerebral function monitoring devices that record the amplitude-integrated EEG and standard EEG typically from one to two channels are increasingly used for long-term trend monitoring and seizure detection in neonatal intensive care units. The clinical recognition of neonatal seizures is often difficult, and such continuous monitoring improves the diagnostic acumen of seizure detection. The amplitude integrated EEG has a similar prognostic accuracy as the standard EEG in infants with HIE but is less accurate for seizure detection, although this may improve with automated seizure detection programs (59–61).

Conclusions

• Electroencephalogram may provide early evidence of the presence and severity of encephalopathy, but EEG does not indicate the cause of encephalopathy.
• Electroencephalogram is the premier tool for identifying neonatal seizures and distinguishing them from other phenomena.
• Electroencephalogram is a valuable tool for assessing neurologic function following encephalopathy during the first 72 hours after birth.

Biomarkers of Neonatal Brain Injury in Hypoxic–Ischemic Encephalopathy

As yet, there are no proven biomarkers that are diagnostic for neonatal HIE or the timing of a potential brain injurious event, or prognostic for long-term outcome following early symptoms. It is likely that a battery of such markers in conjunction with clinical findings and brain imaging, rather than a single metabolite or protein, will be more predictive. Biomarkers that accurately reflect the degree of brain injury, the timing and evolution of injury, and response to therapy would improve clinical management of these patients and facilitate new research (62). Ideal biomarkers would differentiate infants who do not require treatment from those at risk of permanent sequelae, and those infants who might benefit from intervention from those for whom treatment is futile. If the biomarkers accurately reflected timing of injury, not only would this be important for diagnosis, but they also might identify infants who are within a therapeutic window for specific treatments. Predictive biomarkers are also critical to research because providing accurate identification of at-risk infants will decrease the variability of enrolled participants, thereby decreasing the number of patients required
to adequately power studies. Ideal biomarkers also would provide short-term surrogates for long-term outcomes. This would permit the more rapid evaluation of potential neuroprotective strategies in phase III trials, which are costly and, because they use human resources, they would be reserved for only the most promising therapies. It is unlikely that a single biochemical or imaging biomarker measured at a single time point will achieve all these goals. Magnetic resonance imaging and magnetic resonance spectroscopy have shown promise for diagnosis of brain injury (63), but optimal timing for study is undetermined (64).

Nucleated Red Blood Cells
An association of hypoxia and an increased nucleated red blood cell (RBC) count has been noted in animal models (65) and in human neonates (66–68). Other studies have correlated high-nucleated RBC count at birth with cerebral palsy, periventricular leukomalacia, intraventricular hemorrhage, and retinopathy of prematurity. In a study of more than 30,000 neonates, the authors confirmed an earlier observation by Nicolaides that there is an inverse relationship of the nucleated RBC count and gestation (69, 70). However, no relationship was noted between the nucleated RBC count and umbilical cord pH or 1-minute or 5-minute Apgar scores in the first day of life. The pathophysiologic explanation for an elevated nucleated RBC count in some neonates with HIE has not been completely defined, but it very likely involves a hypoxia-mediated increase in fetal erythropoietin production and release (65, 71, 72).

Potential Markers Measured in Blood, Cerebrospinal Fluid, or Urine
Ideally, a circulating biomarker would reflect damage to a specific organ. Several potential biomarkers for brain injury that fit this criterion include phosphorylated axonal neurofilament heavy chain protein, ubiquitin C-terminal hydrolase 1 (73), neuron-specific enolase (74–76), gliarial fibrillary acidic protein (77, 78), and S100B (76, 79–81). Elevations of these proteins have been associated with hypoxia brain injury in animal models and in clinical trials, but large-scale definitive studies have not yet been done. Several investigators have measured specific proteins and metabolites that reflect hypoxic metabolism or hypoxia-mediated injury. To date, associations have been found between hypoxia–ischemia and erythropoietin (80, 82), troponin I (83), 8-iso prostaglandin F2α (84), amyloid A (85), matrix metalloproteinase-9, tissue inhibitor of metalloproteinases-1 (86), lactate, succinic acid, malate and arachidonic acid (87, 88), and S100B (81). The clinical use of these potential markers for the prediction, etiology, or timing of hypoxic–ischemic injury remains to be determined.

A meta-analysis was performed to determine if any biomarkers were sufficiently sensitive and specific as predictors of long-term neurologic outcome (89). Serum interleukin-1β (P=.04), serum interleukin-6 (P=.04), cerebrospinal fluid neuron-specific enolase (P=.03), and cerebrospinal fluid interleukin-1β (P=.003, n=2) were identified as putative predictors of abnormal neurologic outcome in survivors when measured before age 96 hours. Further validation of these markers, either alone or in combination, is required before widespread use can be recommended. Other potential biomarkers include urinary thiobarbituric acid–reacting substances (90), malondialdehyde, uric acid and protein (91), S100B, and lactate to creatinine ratio (92).

Conclusion
• As yet, there are no proven biomarkers that are diagnostic for neonatal HIE, the timing of a potential brain injurious event, or prognostic for long-term outcome following early symptoms. It is likely that a battery of such markers in conjunction with clinical findings and brain imaging, rather than a single metabolite or protein, will be more predictive.

Research Recommendations
• The degree and duration of hypoglycemia required to result in brain injury in encephalopathic infants deserves further study.
• Additional studies are needed to further clarify the prognostic and diagnostic value of EEG in the setting of hypothermia.
• The role of neonatal seizures as a cause of long-term brain injury needs to be elucidated.
• Additional studies are needed to identify biomarkers that are predictive of brain injury and of response to neuroprotective therapy in neonates with encephalopathy. Biomarkers also are needed to improve prediction of long-term neurologic outcome.

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Pediatrics 2010;125:e382–95. (Meta-Analysis) [PubMed] [Full Text] ⇧


Focal Ischemic Stroke

Perinatal focal ischemic stroke may present with neonatal seizures and other signs of neonatal encephalopathy. Focal ischemic stroke also has received attention as a distinct cause of cerebral palsy, especially hemiplegic cerebral palsy. A National Institute of Neurological Disorders and Stroke (part of the National Institutes of Health) workshop on perinatal stroke defines perinatal ischemic stroke as “a group of heterogeneous conditions in which there is focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis, occurring between 20 weeks of fetal life through the 28th postnatal day, and confirmed by neuroimaging or neuropathological studies.” Modern imaging-based classification systems facilitate the accurate diagnosis of four perinatal ischemic stroke syndromes based on consideration of the three following variables: 1) the timing of injury, which encompasses the fetal period (8 weeks to birth), the perinatal period (28 weeks to 7 days), and neonatal period (birth to 28 days) periods; 2) the clinical presentation, whether acute neonatal symptoms (usually seizures) or in utero events occur before delivery, typically asymptomatic at birth and presenting later in infancy (usually with hemiplegic cerebral palsy); and 3) the blood vessel affected (arterial or venous). This chapter focuses on the diagnosis, evaluation, treatment, and management of perinatal focal ischemic stroke.

The four different types of perinatal ischemic stroke are demonstrated in Figure 8-1 with their mechanisms, risk factors, treatments, and outcomes elaborated as follows:

1. Symptomatic neonatal arterial ischemic stroke. There is no more focused period of risk of ischemic stroke than the first week of life, and arterial ischemic stroke is most common. Incidence rates likely exceed approximately 1 in 3,000 live births and may still be underestimated. Approximately one half of neonatal arterial ischemic strokes are acutely symptomatic, usually presenting with seizures in the first days of life without focal deficits or encephalopathy. Diffusion magnetic resonance imaging (MRI) confirms recent brain infarction in an arterial territory. Lesions typically occur within middle cerebral artery territories, involve cortical structures, are more common on the left, and are multifocal in 20–30% of cases.

2. Symptomatic neonatal cerebral sinovenous thrombosis. The neonatal period also carries the highest incidence of cerebral sinovenous thrombosis. Neonatal cerebral sinovenous thrombosis can present with seizures, but diffuse neurologic dysfunction is also common. Imaging confirms cerebral vein or venous sinus thrombosis, or both, with or without parenchymal edema, infarction (in approximately 40–50% of cases), or hemorrhage. The superficial venous system (e.g., superior sagittal sinus) is more commonly affected. However, deep system cerebral sinovenous thrombosis (e.g., straight sinus) has additional clinicoradiographic presentations, including thalamic and intraventricular hemorrhage. Approximately 25% of untreated neonates will propagate their thrombosis in the first week of life.

3. Presumed perinatal ischemic stroke. Many fetal and perinatal strokes lack acute neonatal symptoms. They are subsequently diagnosed retrospectively.
in the first years of life when hemiparesis manifests or other neurologic concerns, such as seizures, arise. Parents usually notice an early hand preference or other motor signs at 4–6 months (18, 28, 29), but diagnosis of presumed perinatal ischemic stroke usually is delayed until the second year of life (29). Neuroimaging confirms a remote, focal ischemic injury (see Fig. 8-1 [A], right). Such cases were previously described as presumed prenatal or perinatal infarction (28) but are now defined as presumed perinatal ischemic stroke (1). The exact timing of injury can therefore only be implied but, assuming events in infancy would likely be symptomatic, events must be either fetal or immediately approximate to the time of birth.

Imaging studies have defined recognizable presumed perinatal ischemic stroke patterns of injury, which help to define mechanisms of injury and predict long-term outcomes (4, 5). Many presumed perinatal ischemic stroke are obvious arterial occlusions within middle cerebral artery territories (20, 28, 30) and virtually indistinguishable from chronic imaging in neonatal arterial ischemic stroke (see Fig. 8-1[C]). Combined with indirect evidence from risk-factor studies (29), this suggests arterial presumed perinatal ischemic stroke, and symptomatic neonatal arterial ischemic stroke may represent the same disease, differing only in timing of recognition. Isolated subcortical infarcts also occur and may be arterial (31), particularly in preterm arterial ischemic stroke (32). However, studying subcortical presumed perinatal ischemic stroke lesions has helped establish an additional, common, and unique mechanism of fetal stroke.

4. Periventricular venous infarction. Preterm germinal matrix hemorrhage may result in obstruction of medullary venous drainage of the periventricular white matter. The venous infarction that results often damages descending corticospinal tracts, resulting in hemiplegic cerebral palsy (33, 34). This process has been well described to occur postnatally in preterm infants for decades, but more recent evidence suggests in utero occurrence is also common (35, 36), presenting as a subtype of presumed perinatal ischemic stroke called periventricular venous infarction (37, 38). Periventricular venous infarction is therefore a retrospective diagnosis but one that can be made accurately with attention to details evident on modern neuroimaging (see Fig. 8-1[C]). In fact, both early imaging cerebral palsy studies (39–41) and more recent population-based (42) and advanced imaging (4) studies suggest such periventricular venous infarction lesions may account for up to 50% of term infants who develop hemiplegic cerebral palsy. The ability to accurately confirm a nonarterial, preterm and fetal mechanism of injury in periventricular venous infarction carries substantial implications for future research and the assignment of causation.

**Diagnosis**

Accurate perinatal stroke diagnosis depends on neuroimaging. Pediatric neuroradiology advances have enhanced recognition and understanding of
mechanisms. Ultrasound applications are limited (12, 20, 43, 44), and although computerized tomography can confirm arterial ischemic stroke, cerebral sinovenous thrombosis, and hemorrhage (45), there are substantial limitations with this modality as well as concerns of radiation exposure.

Magnetic resonance imaging is therefore the neuroimaging investigation of choice in all perinatal stroke syndromes. Modern MRI sequences afford important opportunities to better classify, understand, and prognosticate perinatal stroke (see Fig. 8-1). In symptomatic neonatal arterial ischemic stroke, diffusion-weighted imaging provides highly sensitive and specific confirmation of acute, focal, neonatal brain infarction, including detection of smaller lesions and valuable information on timing (10). Evidence of early corticospinal tract Wallerian degeneration on diffusion-weighted imaging also may help predict motor outcome (46, 47). Magnetic resonance angiography of the head and neck may demonstrate large artery occlusions or, less often, evidence of arteriopathy, and probably is underutilized (10, 12, 48, 49).

In symptomatic neonatal cerebral sinovenous thrombosis, MRI is superior at differentiating regional venous edema from infarction (45). Hemorrhage-sensitive modalities, such as gradient echo and susceptibility-weighted sequences, can demonstrate distinct patterns of parenchymal hemorrhagic changes related to venous ischemia (see Fig. 8-1 [B]). Magnetic resonance venography can confirm cerebral sinovenous thrombosis and provide surveillance for propagation and response to treatment (21, 27, 45).

Presumed perinatal ischemic stroke syndromes that present later in infancy also require MRI for accurate classification. This includes specific arterial lesions, including different patterns of middle cerebral artery arterial ischemic stroke (4, 28, 30). A substantial effect of modern neuroimaging in perinatal stroke care has been an improved understanding and diagnostic accuracy for periventricular venous infarction. Imaging features that confirm the nature and timing of periventricular venous infarction lesions appear distinct and are highly recognizable (4, 50). These include the parenchymal lesion itself, which is typically a well-circumscribed, unilateral area of cystic periventricular encephalomalacia with surrounding gliosis and ex vacuo ventricular dilatation (see Fig. 8-1 [C]). Additional features include relative sparing of the basal ganglia and subcortical white matter, increased T2 or fluid attenuated inversion recovery signal in the posterior limb of the internal capsule, and atrophy of the ipsilateral cerebral peduncle. The most pathognomonic imaging finding is the presence of old blood product in the region of the germinal matrix or of venous infarct, or both (4, 37, 38, 50). Although such signal may fade over years (4), its detection would appear to confirm antenatal timing (presumably less than 34 weeks of gestation) in term-born children.

Fetal MRI has improved the antenatal diagnosis of in utero strokes identified by prenatal ultrasonography (44). The role of advanced imaging applications applied to neonatal hypoxic–ischemic encephalopathy, such as magnetic resonance spectroscopy and diffusion tensor imaging, remain to be established for perinatal stroke.

Conclusions

- There are four perinatal ischemic stroke diseases that are distinguished by the timing of injury, the clinical presentation, and the blood vessel affected (arterial or venous).
- The four perinatal ischemic stroke diseases are the following: 1) symptomatic neonatal arterial ischemic stroke, 2) symptomatic neonatal cerebral sinovenous thrombosis, 3) presumed perinatal ischemic stroke, and 4) periventricular venous infarction.
- Magnetic resonance imaging is the neuroimaging investigation of choice in all perinatal stroke syndromes.

Risk Factors, Pathophysiology, and Evaluation

Despite a lengthy list of proposed etiologies, evidence for a causative factor cannot be found in most perinatal stroke cases (2, 10, 21, 28, 51). The temptation to assign causation to any factor potentially deviating from “typical” must be avoided. A review of perinatal stroke pathogenesis aptly states that “none of these factors can be considered as the unique and direct cause of the infarction” (7). However, thorough diagnostic evaluation typically is required and some children may be discovered to have multiple potential risk factors (10, 21, 23, 52, 53). Well-powered, case–control studies using consistent, imaging-based classifications of well-characterized perinatal stroke populations are eagerly awaited. Several major categories are considered, each with variable, often limited, evidence to support them.

Prothrombotic

Prothrombotic factors have been widely studied in relation to perinatal stroke. However, the magnitude
of the association between prothrombotic factors and perinatal stroke is modest, and studies of thrombotic factors and perinatal stroke have produced inconsistent results. Studies have been limited by inconsistent disease classifications, lack of appropriate controls, different laboratory methods and disorders evaluated, and variable age at testing (54–60). Detection estimates range widely, from 20% to 68% in neonatal arterial ischemic stroke (28, 61–65), with lower estimates in smaller cerebral sinovenous thrombosis studies (21, 24). Studies in presumed perinatal ischemic stroke and periventricular venous infarction populations have been limited (28, 29, 66). Unlike many other potential risk factors, case–control studies do exist, and one meta-analysis supports an association (67). However, only 6 of 22 studies examining thrombophilia in childhood arterial ischemic stroke and cerebral sinovenous thrombosis included perinatal stroke, and analysis combined different diseases and age ranges. With these limitations in mind, associations with several conditions, including factor V Leiden (odds ratio [OR], 3.56; 95% confidence interval [CI], 2.29–5.53) and prothrombin gene G20210A mutation (OR, 2.02; 95% CI, 1.02–3.99) (67) were identified. Several studies have examined associations between maternal thrombophilia and perinatal stroke with multiple factors described, which suggests additional prothrombotic mechanisms of pathogenesis (65, 68).

Placental
Disorders of the placenta are a highly suspicious but mostly unproven factor in perinatal stroke pathogenesis (69). With no risk of recurrence and modern imaging confirming both acute timing and often multifocal infarcts consistent with proximal embolism, indirect evidence supports placental embolism. Early anatomic studies attempted to support such a mechanism, (70–72). Multiple placental disorders have been associated with perinatal stroke (73–79). Thrombi are commonly found in placentas (80, 81), and strokes are common in autopsy studies of fetal thrombotic vasculopathy (79). Studies linking chorioamnionitis to perinatal stroke have been inconsistent (52, 82, 83). Limited studies of well-defined perinatal stroke diseases have suggested a role for placental disease but have been underpowered to identify specific diseases (3, 84). Some have suggested that male predominance of stroke and placental disease and associations with maternal thrombophilia provide additional evidence (7). With most children diagnosed days or months after birth and placentas usually destroyed within hours of delivery, prospective tissue banking studies are likely required to establish the true role of placental disease.

Maternal and Pregnancy Factors
Most maternal and pregnancy histories in perinatal stroke are unremarkable. However, significant case–control evidence suggests associations between several maternal and pregnancy factors and perinatal stroke, most notably neonatal arterial ischemic stroke (69, 85). These include primiparity, infertility, pre-eclampsia, fetal growth restriction, prolonged rupture of membranes, and clinically diagnosed chorioamnionitis (52, 82, 83, 86). Most of these factors are not consistently found across all studies, which are limited by heterogeneous populations and small sample sizes. Many other common maternal conditions suggested by case reports and small case series remain unproven, including hypertension, bleeding, smoking, and diabetes (21, 23, 28, 65). Cases of perinatal stroke in twins are well reported, including after fetal demise of the co-twin (87–90). A study comparing arterial presumed perinatal ischemic stroke and periventricular venous infarction found no differences in prenatal or maternal factors (29).

Intrapartum
With few identifiable risk factors in many cases, attention often is focused on intrapartum management in a search for causation. A series of case–control studies examined these factors (52, 82, 83, 86). Suggested associations include prolonged rupture of membranes, prolonged second-stage labor, fetal heart rate and umbilical cord abnormalities, vacuum extraction, and emergency cesarean delivery. Less robust evidence associating perinatal stroke with obstetric issues or implied trauma must be interpreted with caution (6, 91–95). Any association with obstetric factors is difficult to interpret. For example, an emergent cesarean delivery is unlikely to be the cause of perinatal stroke, given lack of biologic plausibility. More likely, an underlying pathogenetic factor led to both the stroke and the need for cesarean delivery. Alternatively, it is possible that an acute stroke in a fetus could compromise the labor process, leading to the need for cesarean delivery. However, the exact relationship between obstetric factors and perinatal stroke is poorly understood because the diagnosis of perinatal stroke is invariably made after delivery.

Some children with perinatal stroke are born after application of vacuum or forceps. Literature suggesting a direct association between vacuum deliveries and stroke consists of isolated cases that should not be mistaken for significant evidence of causation (91, 94). There is no existing evidence supporting the biological plausibility that controlled, external mechanical manipulations could lead to clot formation in deep
arterial structures resulting in arterial ischemic stroke. Evidence suggests that cervical arterial dissection, which theoretically could occur with the forces of assisted delivery, rarely accounts for neonatal arterial ischemic stroke (70–72, 93, 95).

The recent ability to confirm fetal timing of periventricular venous infarction provides an important example of previous errors in assigning causation. Despite strong imaging evidence of an event occurring months before delivery, many would continue to erroneously assert that obstetric factors could be responsible for a periventricular venous infarction lesion.

Neonatal
Multiple clinical elements of the newborn have been associated with perinatal stroke. Although most neonates with stroke look well and present with isolated seizures (71, 96), a significant proportion are otherwise unwell. Case-control data suggest neonates with arterial ischemic stroke have increased proportions of low Apgar scores, umbilical cord pH less than 7.0, neonatal resuscitation, and need for transfer to the neonatal intensive care unit (52, 83, 86). A relationship between perinatal stroke and both extremes of birth weight has been suggested, but studies are inconsistent (3, 82, 86, 97). Global hypoxic–ischemic encephalopathy can certainly co-occur with focal ischemic stroke, and they may share common risk factors (11, 25, 98). Many neonates with cerebral sinovenous thrombosis have perinatal complications, including “asphyxia,” sepsis, disseminated intravascular coagulation, meconium aspiration, extracorporeal membrane oxygenation, and dehydration (21, 23).

By definition, cases of presumed perinatal ischemic stroke and periventricular venous infarction lack neonatal neurologic concerns (1, 28). However, a study comparing arterial presumed perinatal ischemic stroke with periventricular venous infarction demonstrated a higher occurrence of acute perinatal factors in the former, indirectly supporting the possibility that many neonatal arterial lesions are the same, differing only in their age at recognition (29).

Infection
Multiple mechanisms support an association between infection and perinatal stroke. Neonatal sepsis and disseminated intravascular coagulation have been linked to symptomatic neonatal stroke (6, 99). Although diagnostic accuracy is a concern in some, multiple studies have suggested chorioamnionitis as a risk factor in neonatal arterial ischemic stroke (52, 77, 82, 83, 100–102). Bacterial meningitis has shown varying degrees of association with neonatal arterial ischemic stroke and cerebral sinovenous thrombosis (103–105). Consecutive case series suggest a high rate of stroke (106), whereas those using diffusion-weighted MRI are now defining specific patterns of ischemic stroke in bacterial meningitis (107). Selective involvement of bilateral lenticulostriate and other penetrating arteries traversing infected meninges may suggest new avenues for treatment. Whether antenatal or otherwise asymptomatic perinatal maternal and congenital infections may play a role in presumed perinatal ischemic stroke and periventricular venous infarction has not been well examined (10, 101, 106). Consistent with management of neonatal encephalopathy and suspicion of a highly treatable disease, most newborns with symptomatic stroke will undergo a full septic evaluation.

Cardiac
Complex congenital heart disease is a well-established neonatal arterial ischemic stroke risk factor (10, 108–110). However, it is found in only a minority of cases. In a prospective series of 100 neonatal arterial ischemic stroke cases, none were found with congenital heart disease (86). Catheter angiography, procedures (particularly balloon atrial septostomy), and surgery appear to further increase the risk (111, 112). The physiologically patent foramen ovale in the newborn provides the opportunity for cerebral embolism of venous (or placental) thrombosis (113). Additional considerations include neonatal cardiomyopathies, valvular disease, and arrhythmia (114). Extracorporeal membrane oxygenation has been associated with both cerebral sinovenous thrombosis (23) and arterial ischemic stroke (25). Minimal if any association has been found between cardiac disease and presumed perinatal ischemic stroke, periventricular venous infarction (28, 29), or cerebral sinovenous thrombosis (21, 23). Cardiac evaluation is likely indicated in acute symptomatic neonatal arterial ischemic stroke (10, 113, 115, 116), but the yield in the other perinatal stroke syndromes appears low (28, 29).

Genetic
Although familial perinatal stroke appears to be uncommon, genetic mechanisms—including spontaneous mutations, low penetrance or expressivity rates, multiple gene interactions, and others—may exist. In addition to genetic thrombophilias, isolated

*Throughout the report, the terms “asphyxia” and “birth asphyxia” and their variations appear in quotes when used in reference to a particular study to emphasize the wide variation in study definitions of asphyxia. See Chapter 1 for recommended asphyxia definition (in Table 1–1) and discussion of asphyxia terminology.
single gene mutations have been linked to arterial perinatal strokes and periventricular venous infarction, including \(\text{COL4A1}\) (99). A single case-control study of candidate thrombosis, cytokine, vascular, and cell adhesion polymorphisms was negative (57). Emerging genetic technologies may shed additional light on perinatal stroke pathogenesis.

**Additional Considerations**

Maternal exposure to drugs has been associated with perinatal stroke (117, 118). Most are isolated case reports in which coincidental occurrence is difficult to exclude (119). Perinatal stroke in the context of cocaine exposure has been reported (96, 120, 121), but large studies suggest the risk is low (117, 122, 123). Occipital bone compression of the superior sagittal sinus may represent a mechanical risk of neonatal cerebral sinovenous thrombosis (124).

**Conclusions**

- Despite a lengthy list of proposed associations, evidence for a true causative factor in most perinatal stroke cases cannot be found.
- The temptation to assign causation to any factor potentially deviating from “typical” must be avoided.
- Prothrombotic factors have been widely studied in relation to perinatal stroke. However, the magnitude of the association between prothrombotic factors and perinatal stroke is modest, and studies of thrombotic factors and perinatal stroke have produced inconsistent results.

**Acute Treatment**

Evidence-based treatments for perinatal stroke are lacking. Three consensus-based guidelines for childhood stroke management (125–127) are limited in their attention to perinatal stroke. Principles of management of global hypoxia–ischemia and other mechanisms of acquired neonatal brain injury may be applicable to neonatal stroke. However, the focal nature of stroke dictates specific differences in mechanisms of injury, including the potential salvage of penumbral areas immediately adjacent to circumscribed areas of infarction, the integrity of which may influence outcomes (128). Such neuroprotective interventions are primarily based on evidence extrapolated from animal models (129, 130), adult stroke studies (131), and neonatal hypoxic–ischemic encephalopathy (132). The development of neuroprotective strategies faces unique challenges in the neonate, in whom multiple mechanisms of injury combine with constant early developmental changes (132, 133).

Factors to consider in acute symptomatic neonatal strokes include the normalization of blood sugar, ventilation and oxygenation, blood pressure, and temperature. Hyperthermia worsens neonatal ischemic brain injury and should be treated aggressively (134, 135). Current evidence of improved outcomes in neonates with hypoxic–ischemic encephalopathy who were treated with hypothermia remains untested in neonatal stroke. Consistent with all neonatal seizures, there is no evidence to support specific agents, but control of seizures is indicated in the interests of preventing secondary brain injury (135). With many events being subtle or subclinical, continuous electroencephalography or other cerebral function monitoring could be considered. Duration of therapy is unstudied, but early recurrence beyond the first week of age appears to be uncommon; suggested long-term anticonvulsants only may be indicated once chronic epilepsy has been diagnosed.

Reasonable evidence supports the consideration of anticoagulation therapy in selected symptomatic forms of neonatal stroke. In cerebral sinovenous thrombosis, substantial safety data and consensus-based opinions (126, 136) are now supported by new evidence that a high proportion of untreated newborns will propagate their thrombosis in the first week of life compared with those receiving anticoagulation (27). In neonatal arterial ischemic stroke, recommendations for anticoagulation generally are limited to infants with an identified cardioembolic source potentially conferring an ongoing risk of recurrent stroke (126, 127, 137).

Mortality attributable to neonatal stroke is very uncommon—likely less than 5%—with cranial sutures accommodating cerebral edema and brain-stem involvement being rare (13, 65, 86). Recurrence of all perinatal stroke types appears to be exceedingly rare, likely less than 1% (133, 138). Therefore, unless a chronic, high-risk condition exists (eg, congenital heart disease), secondary prevention rarely is required. With variable and unpredictable event timing and no well-established maternal risk factors, primary prevention strategies are nonexistent, although the risk of recurrence in subsequent pregnancies also appears extremely low. There are no data that support the treatment of women with known prothrombotic conditions as a preventative measure for perinatal stroke.

**Conclusion**

- Evidence-based treatments for perinatal stroke are lacking.
Long-Term Outcomes and Management

Neurologic deficits or epilepsy occur in up to 75% of perinatal ischemic stroke survivors (13, 21, 24, 28, 49, 139, 140). The increased plasticity of the developing brain often is suggested to confer an advantage toward better recovery in perinatal stroke compared with adult stroke (10). However, most children suffer long-term neurologic morbidity, and some studies even suggest that children with perinatal injuries fare worse than children with similar lesions acquired later in infancy or childhood (141, 142). The complexities of how developmental plasticity affects the more basic deficits of perinatal stroke, namely cerebral palsy, are only just beginning to be understood (143, 144).

Congenital hemiplegia is the most common form of long-term motor dysfunction, following perinatal arterial ischemic stroke and periventricular venous infarction (145). Stroke is the predominant cause of hemiplegic cerebral palsy (10, 146). Proportions of motor deficits vary by syndrome, with selection bias likely conferring a very high percentage (80–100%) in presumed perinatal ischemic stroke and periventricular venous infarction (4, 13, 18, 28, 65, 83, 147) compared with 22–48% in arterial ischemic stroke (13, 49, 148–150) and less than 30% in cerebral sinovenous thrombosis (21, 24, 151). Motor deficits typically emerge in the first year, but evolution and effects on quality of life change through life. Early initiation of multimodal rehabilitation therapy is likely beneficial (125, 152). A comprehensive team includes physical, occupational, and speech therapists; orthopedic surgeons; pediatric physiatrists; and others.

Evidence for several new interventions is just emerging; although rehabilitation clinical trials in the developing brain are particularly challenging. Rapidly expanding evidence from randomized trials supports the efficacy of constraint-induced movement therapy in patients with congenital hemiplegia (153–158), most of whom have perinatal stroke. The role of botulinum toxin injections in both upper and lower extremities specific to perinatal stroke is emerging but unclear (158–160). Consensus guidelines support muscle strengthening and ankle-foot orthoses for gait and contracture prevention (125).

Nonmotor neurologic morbidities—including deficits in language, vision, cognition, behavior, and other higher brain functions—are less studied but occur in 20–60% of cases (18, 28, 49, 114, 161). Improved long-term neuropsychological studies are now defining the evolution and spectrum of these complex deficits (162, 163). Isolated subcortical lesions, most notably periventricular venous infarction, appear to have a much lower risk of cognitive, behavioral, language, or seizure disorders (4). As such higher brain functions only emerge over many years of child development, perinatal stroke children tend to “grow into their deficits,” and problems may not become evident until school age or later (163). Therefore, long-term developmental surveillance and timely administration of neuropsychological testing is recommended.

Children with arterial perinatal strokes carry the highest risk of epilepsy (compared with periventricular venous infarction and cerebral sinovenous thrombosis), although rate estimations have varied from 15% to 67% (4, 164–167). Bilateral electroencephalogram abnormalities, infantile spasms, and other epileptic encephalopathies can occur despite a unilateral lesion (164, 165). Despite these concerns, many children may eventually “outgrow” their epilepsy (164, 165). Children with perinatal stroke may be excellent surgical candidates for epilepsy (168). Presence of a seizure disorder appears to be associated with cognitive, behavioral, and other developmental sequelae (165–167, 169), although mechanisms are not well understood.

The education, support, and counseling of the growing child and family are essential. Mothers may harbor enormous feelings of unjustified guilt, particularly when a cause cannot be determined. The risk of recurrent stroke in the child and the risk of recurrent perinatal stroke in future pregnancies is extremely low, and should be emphasized (13, 138, 170). Connections to educational and support resources should be sought. The morbidity of perinatal stroke lasts a lifetime, which amplifies the burden to individuals, families, and society (171).

Conclusions

- Congenital hemiplegia is the most common form of long-term motor dysfunction, following perinatal arterial ischemic stroke and periventricular venous infarction.
- Nonmotor neurologic morbidities—including deficits in language, vision, cognition, behavior, and other higher brain functions—are less studied but occur in 20–60% of cases.
- The risk of recurrent stroke in the child and the risk of recurrent perinatal stroke in future pregnancies is extremely low, and should be emphasized.

Research Recommendations

- Fully powered, population-based, case–control studies are required to better establish the clinical
variables associated with specific perinatal stroke types and their possible role in pathophysiology.

- Prospective controlled studies are needed to explore potentially novel mechanisms of perinatal stroke and can be elucidated by such strategies as placental tissue banking or advanced biomarker technologies if prevention strategies are ever to be realized.

- Clinical trials are needed to improve outcomes from perinatal stroke. Possible examples include antithrombotic therapy, seizure monitoring and treatment, erythropoetin, and hypothermia.

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Focal Ischemic Stroke


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Role of Genetics

Genes and their protein products create the basis of all cellular structure and function. Their actions control, regulate, and modulate cell proliferation, migration, differentiation, and specialization. Intracellular chemistry, cell-surface markers and receptors, angiogenesis, and neurogenesis reflect but a few functions conferred and controlled by genes. Susceptibility to extraneous influences often is conveyed by inherited polymorphisms or inherited epigenetic changes, as are the body’s reaction to such challenges. It is no surprise then, when the normal complexity of brain structure and function is considered, that the role of genes is seen as paramount.

This chapter briefly reviews neuronal reaction to exogenous insults (such as hypoxia and ischemia), which inevitably invoke multigenic responses. This is especially the case when perinatal hypoxia supervenes and is further compounded by the secondary cellular neurochemical damage that follows (1), which is due, for example, to the up-regulation of specific genes by hypoxia (2–9). Moreover, challenges to neuronal integrity will frequently involve more than a single hostile challenge; for example, hypoxia, ischemia, and infection (chorioamnionitis) may be acting in concert. This chapter also addresses genetic conditions and metabolic disorders that may mimic neonatal encephalopathy, and suggests appropriate genetic evaluation in the presence of neonatal encephalopathy.

Neuronal Reaction to Exogenous Insult: Genetic Aspects

Induction of the hypoxia-signaling pathway results in the activation of the hypoxia-inducible transcription factors (HIF-1 and HIF-2) (2–4). These factors have been shown to trigger the expression of genes involved in oxygen transport, glycolytic metabolism, angiogenesis, cell cycle control, cell proliferation, apoptosis, and energy metabolism. In addition, microRNAs, which are non–protein-coding RNAs made up of 20–24 nucleotides, mediate hypoxic stress responses because they are able to modify gene expression both rapidly and reversibly (10). Besides infection (eg, chorioamnionitis) (11, 12), chronic fetal hypoxemia triggers a fetal inflammatory response with release of a cytokine cascade and activation of apoptosis leading to cell death (13, 14).

Genetic susceptibility, together with number, duration, severity, and timing of insult(s); gestational stage; established fetal growth restriction; and placental function affect neuronal structural and functional integrity. Hypoxia may be a compounding problem in a fetus already affected by a genetic disorder. For example, in one study, 23% of children with Prader–Willi syndrome had had “birth asphyxia”* (15). Similarly, the rate of intrapartum complications (defined as sustained cyanosis, need for oxygen or ventilatory support, cardiopulmonary resuscitation or prolonged admission to the neonatal intensive care unit) is significantly higher in children with malformations of cortical development compared with a control group of children with idiopathic epilepsy (16). The profound multigenic control of brain structure and function most likely explains the range of reactions

*Throughout the report, the terms “asphyxia” and “birth asphyxia” and their variations appear in quotes when used in reference to a particular study to emphasize the wide variation in study definitions of asphyxia. See Chapter 1 for recommended asphyxia definition (in Table 1–1) and discussion of asphyxia terminology.
encountered after hypoxia. Following similar degrees of hypoxia, some affected infants recover without sequelae, whereas others are left with varying degrees of intellectual and physical handicap. Fundamental genomics also may serve to explain how the frequency of cerebral palsy has hardly changed in the Western world despite available surveillance, sophisticated technology, and a soaring cesarean delivery rate.

Single nucleotide polymorphisms in genes involved in inflammation and coagulation have been implicated as risk factors for cerebral palsy. More than 20 studies of cerebral palsy have evaluated alterations in genes that regulate the inflammatory and coagulation cascades, and polymorphisms in more than 15 genes have been associated with cerebral palsy (17–27). However, such genetic association studies are hampered by multiple comparisons, small sample size, and population heterogeneity, thus leading to inconsistent findings (18, 26–29).

A promoter region polymorphism in the interleukin-6 gene has been associated with increased risk of cerebral palsy in two separate populations (19, 20). These findings suggest that an altered fetal inflammatory response that is due to genetic variation in inflammatory genes could contribute to an increased risk of cerebral palsy (19, 23).

Two other genetic variations have been linked to cerebral palsy in separate populations. The ε4 allele of the apolipoprotein E gene has been associated with cerebral palsy in some (27, 30, 31) but not all studies (32, 33). Given that the apolipoprotein E ε4 allele is associated with ischemic stroke in adults (34, 35), it is possible that this polymorphism might predispose to a subset of cerebral palsy related to perinatal stroke. The inducible nitric oxide synthase gene was first evaluated in relation to cerebral palsy because of its role in ischemic and inflammatory brain injury. Overexpression of the inducible nitric oxide synthase in the brain has been reported in newborn periventricular white matter injury (36) and in adult stroke (37), and the inducible nitric oxide synthase is a key mediator of oligodendrocyte injury in newborn brain injury that is due to intrauterine infection (38). Inducible nitric oxide synthase-231 polymorphism has been associated with cerebral palsy in two separate populations (18, 21), but the findings were of borderline significance and the effect sizes were small. Therefore, the significance of these findings is unclear.

The growing number of studies evaluating genetic risk factors for cerebral palsy with comprehensive genomic testing (eg, whole genome or exome sequencing) may eventually establish the contribution of genomic variants to the occurrence of neonatal encephalopathy and cerebral palsy. Indeed several lines of evidence strongly support a contribution of multiple genetic factors to the etiology of cerebral palsy (39, 40). It is likely that neonatal encephalopathy results from multiple interactions between genomic variants or abnormalities and environment; the role of the individual components is so far unclear.

Candidate gene association studies using single nucleotide polymorphism arrays have been disappointing because of the limitations of this methodology and the large size of studies needed. Exome and whole genome sequencing are likely to be much more revealing and rewarding. Studies of copy number variations and potentially pathogenic mutations in the exome affecting neurodevelopmental pathways are soon to be reported and may reveal new genetic causes and genetic susceptibility in many cases of cerebral palsy, thus changing the understanding of causation (40).

The contribution of monogenic syndromes to neonatal encephalopathy and cerebral palsy is currently small. The risk of recurrent isolated cerebral palsy following a first affected child was 0.5% in a U.S. population (41). Among children with cerebral palsy that is not due to a brain malformation, genetic syndrome, or neurometabolic disease, the risk of recurrence is likely to be even smaller. Indeed, very few new single gene causes of idiopathic cerebral palsy have been reported even in the more recent literature (39).

Conclusions

- Genetic susceptibility, together with number, duration, severity, and timing of insult(s); gestational age; established fetal growth restriction; and placental function affect neuronal structural and functional integrity.
- Single nucleotide polymorphisms in genes involved in inflammation and coagulation have been implicated as risk factors for cerebral palsy.
- The contribution of genetic polymorphisms to neonatal encephalopathy and cerebral palsy is currently unknown.
- Although neonatal encephalopathy may result from multiple gene–environment interactions, the role of the individual components is so far unclear.

**Genetic Conditions Mimicking Neonatal Encephalopathy**

Careful attention is necessary to distinguish neonatal encephalopathy from features of genetic disorders that may mimic encephalopathy. The recurring problem is
the realization of intellectual deficits, various sensory abnormalities, or physical problems months to years after a difficult delivery or stormy neonatal period, or both. Clear documentation of appropriate care and evaluation should support evidence-based conclusions. The passage of time since birth also may enable definitive recognition of an evolving genetic disorder not readily apparent (or diagnosed) in the early days, weeks, or months of life. Precise diagnosis in such cases is important, not only for establishing the causal pathways, but also to enable parents to plan the care of a child with a defined disorder and, where applicable through genetic counseling, to understand future risks of recurrence and their specific options. It is beyond the scope of this chapter to consider the enormous number of genetic disorders characterized by intellectual deficits, impaired physical abilities (walking, running, balance, coordination), or speech and language delays, any one of which may have occurred in a child who had neonatal complications. Rather, the focus is on listing the steps in the evaluation that might highlight an underlying genetic condition.

The medical history of a parent subsequent to the birth of an affected child may be informative (Box 9-1). Many different findings on examination of an affected child years after birth may be diagnostic and provide the reason for the child's deficits previously thought to be due to neonatal encephalopathy. Careful examination for dysmorphic features is important given that there are more than 2,000 recognized syndromes. Evaluation by a clinical geneticist may provide the necessary insight and guide in the choice of the diagnostic tests necessary. Observation of dysmorphic features, developmental delay, or congenital defects invariably raise the question of a microdeletion and microduplication syndrome. Although such syndromes, the reported numbers of which are increasing exponentially, do not usually cause neonatal encephalopathy, subsequent recognition of these molecular–cytogenetic abnormalities establish the cause of the child's deficits and abnormalities. The reported phenotypes of these many microdeletion and microduplication syndromes (42–44) (Box 9-2 and Box 9-3) reflect considerable variability. Careful evaluation by a geneticist and chromosomal microarray analysis may be necessary in cases of neonatal encephalopathy suspected to have an underlying genetic cause. Chromosomal microarray analysis is indicated whenever a clear etiology has not been established for psychomotor deficits thought to be due to neonatal encephalopathy resulting in various neurodevelopmental abnormalities that may be misdiagnosed as cerebral palsy.

Recognition of dysmorphic features in the newborn is not simple, even for the seasoned dysmorphologist. Observations suggesting a genetic disorder (Box 9-4) are easily compromised in the encephalopathic newborn, with features often distorted by recent birth, particularly if following a complicated delivery. Obvious congenital defects (eg, cleft lip and palate, microtia, macroglossia, choanal atresia, and severe micrognathia) should prompt further evaluation and consideration of additional diagnosis or diagnoses in infants presenting initially with neonatal encephalopathy. The inevitable performance of brain imaging—with magnetic resonance imaging being most revealing—

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**BOX 9-1. Maternal or Paternal Medical History Since the Birth of An Affected Child and Physical Changes in the Child That May Become Apparent Over Time**

- Information concerning the birth of a new sibling or relatives since the birth of the affected child
- New information about genetic disorders in the family history
- Child history of developmental regression
- History of prematurity
- History of developmental milestones
- Child's behavioral phenotype
- History of early swallowing or choking

**Physical changes in an affected child:**
- Dysmorphic features
- Macrocephaly
- Microcephaly
- Graph of head circumference over time
- Skin pigmentation
- Multiple hemangiomas
- Abnormalities of gait
- Neuropsychological report
- Involvement of other nonnervous system organ involvement
- Brain imaging reports
**BOX 9-2. Phenotypes in Microdeletion and Microduplication Syndromes**

<table>
<thead>
<tr>
<th>Phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental delay</td>
</tr>
<tr>
<td>Hypertonia</td>
</tr>
<tr>
<td>Speech/language delay</td>
</tr>
<tr>
<td>Brain abnormalities (imaging)</td>
</tr>
<tr>
<td>Autism (autism spectrum disorder)</td>
</tr>
<tr>
<td>Eye abnormalities</td>
</tr>
<tr>
<td>Abnormal behavioral phenotype</td>
</tr>
<tr>
<td>Hearing impairment</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
<tr>
<td>Skeletal abnormalities</td>
</tr>
<tr>
<td>Dysmorphism</td>
</tr>
<tr>
<td>Digital abnormalities</td>
</tr>
<tr>
<td>External ear or auricle abnormalities</td>
</tr>
<tr>
<td>Growth abnormalities</td>
</tr>
<tr>
<td>Cleft lip, cleft palate, and velopharyngeal insufficiency</td>
</tr>
<tr>
<td>Congenital cardiac disease</td>
</tr>
<tr>
<td>Microcephaly</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
</tr>
<tr>
<td>Ectodermal dysplasia</td>
</tr>
<tr>
<td>Genitourinary defects</td>
</tr>
<tr>
<td>Recurrent infections</td>
</tr>
<tr>
<td>Macrocephaly</td>
</tr>
<tr>
<td>Hypotonia</td>
</tr>
</tbody>
</table>

**BOX 9-3. Chromosomal Locations of Known Selected Microdeletion and Microduplication Syndromes**

<table>
<thead>
<tr>
<th>Chromosomal Location</th>
<th>1p36</th>
<th>1q21.1</th>
<th>1q41–42</th>
<th>2p15–16.1</th>
<th>2p21</th>
<th>2q31</th>
<th>3q24</th>
<th>3q29</th>
<th>5p13.2</th>
<th>5q14</th>
<th>5q21</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5q35.3</td>
<td>6p21</td>
<td>6q16.3</td>
<td>6q24</td>
<td>7p14.1</td>
<td>7p21.1</td>
<td>7q11.23</td>
<td>8p23.1</td>
<td>8q12.2</td>
<td>8q13.3</td>
<td>8q21.3–22.1</td>
</tr>
</tbody>
</table>

**BOX 9-4. Selected Neonatal Factors That May Point to a Genetic Cause for Encephalopathy**

Dysmorphic features

Observation of abnormal findings (head circumference: body length ratio; marked hypotonia; impaired level of consciousness; seizures; apneic attacks) with no (or minimal) intrapartum labor or delivery factors

“Sick” neonate—not sucking, not feeding, vomiting, obtundated

Major congenital anomalies

Prolonged hyperbilirubinemia

Metabolic abnormalities (eg, refractory metabolic acidosis, hyperammonemia)

Brain imaging findings that indicate any of the following: cerebral dysgenesis, agenesis of the corpus callosum, polymicrogyria, lissencephaly, pachygyria, hydrocephalus, hydranencephaly, schizencephaly, heterotopias
in the newborn manifesting signs of encephalopathy—may show structural abnormalities of cerebral dysgenesis (see Box 9-4). For example, detection of lissencephaly will point directly to the need for DNA mutation analysis of certain genes (45–47). Various other structural abnormalities may be seen, including agenesis of the corpus callosum, focal or generalized cortical dysplasia, heterotopias, holoprosencephaly, hydranencephaly, hydrocephalus, pachygyria, polymicrogyria, and schizencephaly (48). Initially easily confused with the effects of hypoxia are the telltale findings of hypoplasia of the cerebellum (especially the vermis) and the pons for the classical diagnosis of the autosomal recessive pontocerebellar hypoplasia, for which DNA mutation analysis of the TSEN54 gene establishes the diagnosis (49). Brain imaging distant from birth may be important if the only imaging performed was in the first week of life or if the imaging was limited to ultrasonography.

Of particular importance is the recognition of disproportionate fetal growth (see Box 9-4). A small or large head circumference compared with body length may point to a genetic neurologic disorder. Similarly, a lack of (or minimal) intrapartum concerns (eg, fetal bradycardia or tachycardia, abnormal electronic fetal monitor results, prolonged second stage of labor, Apgar score of less than 4 at 5 minutes) raises serious considerations of a genetic disorder when marked hypotonia, impaired level of consciousness, seizures, or apneic attacks occur without clear explanation.

Various antecedent cues or clues serve to alert the health care provider before or during pregnancy to a possible genetic basis for the subsequently occurring encephalopathy (Box 9-5). The obviously ill newborn who may appear encephalopathic but also is vomiting, not feeding, and not sucking will invariably raise suspicions of a biochemical genetic disorder. Inborn metabolic errors may manifest in the first days or week of life with features mimicking neonatal encephalopathy (Box 9-6). The underlying biochemical genetic disorders are listed in Box 9-7. An important example is medium-chain acyl-CoA dehydrogenase deficiency, associated with a high mortality rate (50). Although a diagnosis can be established by measurement of medium-chain fatty acids or assay of the enzymatic defect in leukocytes, rapid mutation analysis can quickly reveal the common mutation that occurs in most cases. Other biochemical disorders that may

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**BOX 9-5. Cues and Clues That Signal a Potential Genetic Cause for Neonatal Encephalopathy**

<table>
<thead>
<tr>
<th>FAMILY HISTORY</th>
<th>MEDICAL HISTORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of mental retardation or epilepsy</td>
<td>Maternal disease (eg, hypothyroidism, myotonic</td>
</tr>
<tr>
<td>Previous child with a known or suspected genetic disorder</td>
<td>muscular dystrophy)</td>
</tr>
<tr>
<td>Previous child (or family history) with neonatal or infantile onset epilepsy</td>
<td></td>
</tr>
<tr>
<td>Previous stillbirth or unexplained neonatal death</td>
<td></td>
</tr>
<tr>
<td>History of recurrent spontaneous abortions</td>
<td></td>
</tr>
<tr>
<td>Personal or family history of deep vein thrombosis, pulmonary embolism,</td>
<td>Consanguinity</td>
</tr>
<tr>
<td>early-age strokes</td>
<td></td>
</tr>
<tr>
<td>Maternal or paternal chromosome abnormality</td>
<td></td>
</tr>
<tr>
<td>Infertility*†</td>
<td></td>
</tr>
<tr>
<td>In vitro fertilization pregnancy‡</td>
<td></td>
</tr>
</tbody>
</table>

**PREGNANCY HISTORY**

- Unexplained high-second-trimester maternal serum alpha-fetoprotein
- Intrauterine growth restriction
- Oligohydramnios
- Polyhydramnios
- Decreased fetal movements
- Extensive placental thrombosis

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Potential Early Neonatal Signs of a Metabolic Genetic Disorder in the First Week of Life

Lethargy–stupor–comatose
Poor feeding or sucking
Hypotonia
Jitteriness
Seizures
Hiccups
Vomiting
Acidosis
Apnea or respiratory difficulties
Hypoglycemia
Hyperventilation
Hypoventilation
Hyperbilirubinemia
Hyperammonemia
Temperature instability
Dysmorphic features (eg, glutaric aciduria type II, fumaric aciduria, Zellweger syndrome)

Conclusions

- Hypoxic–ischemic encephalopathy may occasionally mimic encephalopathy and other features associated with a genetic disorder.
- Precise diagnosis in such cases is important, not only for establishing the causal pathways, but also to enable parents to plan the care of a child with a defined disorder and, where applicable through genetic counseling, to understand future risks of recurrence and their specific options.
- Careful evaluation by a geneticist and chromosomal microarray analysis may be necessary in cases of neonatal encephalopathy suspected to have an underlying genetic cause.
- Inborn metabolic errors may manifest in the first days or week of life with features mimicking neonatal encephalopathy.
- It is important to identify infants with metabolic disorders as early as possible because, in some cases, prompt institution of therapy and diet changes may be lifesaving.
- Genetic and metabolic disorders may cause or contribute to some cases of neonatal encephalopathy.
BOX 9-7. **Metabolic Genetic Disorders in Which Neonatal Encephalopathy May Occur**

- Alpha-ketoglutarate dehydrogenase deficiency
- 4-Aminobutyrate aminotransferase deficiency
- Argininosuccinic acid synthetase deficiency
- Argininosuccinase deficiency
- Beta-ketothiolase deficiency
- Biotinidase deficiency
- Carbamoyl phosphate synthetase deficiency
- Carnitine-acylcarnitine translocase deficiency
- Congenital disorders of glycosylation
- Cytochrome oxidase (mitochondrial complex IV) deficiency
- Dihydropyrimidine dehydrogenase deficiency
- Folinic acid-responsive seizures
- Fructose 1,6-diphosphatase deficiency
- Fumaric aciduria
- Glucose transporter defect (Glut-1 deficiency)
- Glutamate transporter deficiency
- Glutaric aciduria type II (multiple acyl-coenzyme A dehydrogenase deficiency)
- Glycine encephalopathy (nonketotic hyperglycinemia)
- Glycine encephalopathy (ketotic hyperglycinemia)
- Glycogen storage disorders types I, II, III, VIII
- Guanidinoacetate methyltransferase deficiency
- Holocarboxylase synthetase deficiency (multiple carboxylase deficiency)
- 3-Hydroxyisobutyric aciduria
- Hydroxymethylglutaryl-CoA lyase deficiency
- Hyperammonemia–hyperornithinemia–homocitrullinuria syndrome
- Isovaleric acidemia
- Leigh syndrome
- Long-chain hydroxyacyl-CoA dehydrogenase deficiency
- Lysine protein intolerance
- Maple syrup urine disease
- Medium-chain acyl-CoA dehydrogenase deficiency
- Medium-chain 3-ketoacyl-CoA thiolase deficiency
- 3-Methylglutaconic aciduria
- Methylmalonic acidemia
- Mevalonic aciduria
- Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes
- Molybdenum cofactor deficiency
- Ornithine transcarbamylase deficiency
- 5-Oxoprolinuria
- Peroxisomal disorders (eg, Zellweger syndrome)
- 3-Phosphoglycerate dehydrogenase deficiency
- Propionic acidemia
- Pyridoxal-dependent and pyridoxine-dependent seizures
- Pyruvate carboxylase deficiency
- Pyruvate dehydrogenase deficiency
- Short-chain acyl-CoA dehydrogenase deficiency
- Sulfite oxidase deficiency
- Very-long-chain acyl-CoA dehydrogenase deficiency


**Research Recommendations**

- Explore the genetic and nongenetic epidemiology of the neonatal encephalopathy trait.
- Further research is needed into the role of microarray analysis in cases in which a clear etiology has not been established for psychomotor deficits thought to be the result of neonatal encephalopathy or cerebral palsy.
- As in other multifactorial conditions, genome or exome sequencing may, in the future, shed light on the genetic contribution to the genesis of neonatal encephalopathy.

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Neonatal encephalopathy describes “a clinically defined syndrome of disturbed neurologic function in the earliest day after birth in the term infant” and affects 1–6 per 1,000 live term births within the developed world. This neurologic condition frequently results in lifelong disability in affected children, with serious effects on the child, family, and society: 15–20% of affected newborns will sustain permanent neurodevelopmental disability, including dysfunction in motor skills and cognition. Altered neonatal behavior can result from many processes, which can include congenital central nervous system dysgenesis, viral and bacterial infection, trauma, hemorrhage, and metabolic disorders. It has been estimated in prospective longitudinal studies that hypoxic–ischemic cerebral injury is attributable to approximately 50–75% of infants born at term with neonatal encephalopathy presenting within the first 3 days of life; this highlights the importance of the consideration of other diagnoses. Neuroimaging plays a critical role in the diagnosis of the neurologic symptoms in the newborn period. Neuroimaging can identify patterns of acute and chronic brain injury, which are both of diagnostic importance and critical for predicting long-term neurologic outcome. Although challenging, neuroimaging may also be able to identify the timing and risk factors for acute brain injury in neonatal encephalopathy. It is, however, important to recognize that neuroimaging techniques and their application to the newborn infant is a rapidly developing field.

Given these issues, this chapter will address the following four topics: 1) common patterns of neuropathology related to hypoxic–ischemic cerebral injury (more extensively reviewed in Chapter 1, “Background”), 2) neuroimaging modalities that are used in the term newborn with encephalopathy, 3) common patterns of neuroimaging abnormalities in neonatal encephalopathy and the effect of therapeutic hypothermia on imaging evaluation, and 4) the relationship of patterns of injury to neurodevelopmental outcome.

Patterns of Brain Injury in the Encephalopathic Term Infant

The patterns of injury in the term newborn have been delineated on both neuropathology and magnetic resonance imaging (MRI). In this chapter, neuropathologic classification is reviewed, which is also well visualized on MRI, with a summary of the terms provided in Table 10-1. The injury types discussed include the broad spectrum of patterns observed after hypoxic–ischemic injury in the neonatal brain: selective neuronal injuries, parasagittal cerebral injury, white-matter injury, and focal and multifocal ischemic brain necrosis. These lesions are discussed as separate discrete entities, but overlap between the patterns of brain injury is common.

Selective Neuronal Injury

The selective vulnerability of specific neuronal populations appears to be due to factors such as their high-energy demand and glutamate distribution. Four patterns of selective neuronal injuries are seen and reflect the severity, duration, and nature of the insult. The first form of selective neuronal injury that is seen is that of diffuse neuronal injury with widespread injury in the cerebral cortex, basal ganglia, hippocampus, brain stem, and cerebellum. Injury of this magnitude can result from a severe or prolonged
TABLE 10-1. Summary of Terminologies in Neuropathology and Magnetic Resonance Imaging for the Common Cerebral Lesions Observed in Neonatal Encephalopathy in the Term Infant*

<table>
<thead>
<tr>
<th>Neuronal injuries</th>
<th>Widespread neuronal injury</th>
<th>Diffuse or global injury (almost all include deep nuclear gray matter)</th>
<th>5–10%</th>
<th>Profound or prolonged insult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral—deep nuclear neuronal injury</td>
<td>Deep nuclear gray matter</td>
<td>Common 25–75% cases</td>
<td></td>
<td>Severe partial insult of prolonged duration or a combined partial with profound terminal insult</td>
</tr>
<tr>
<td>Deep nuclear gray—brain stem</td>
<td>Deep nuclear gray matter</td>
<td>5%</td>
<td></td>
<td>Acute total hypoxic–ischemic insult</td>
</tr>
<tr>
<td>Pontosubicular necrosis</td>
<td>Pons in the brain stem and parahippocampal</td>
<td>5%</td>
<td></td>
<td>Premature infant</td>
</tr>
<tr>
<td>Parasagittal cerebral injury</td>
<td>Parasagittal cortical neuronal necrosis at regions between the major cerebral vessels</td>
<td>Watershed</td>
<td>Common 15–45% cases</td>
<td>Hypotension maternal fever</td>
</tr>
<tr>
<td>White matter injury</td>
<td>Periventricular leukomalacia or white-matter injury</td>
<td>White-matter injury</td>
<td>Severe isolated uncommon; milder noncystic forms seen in 10–20%</td>
<td>Earlier gestation (eg, preterm infant) or inflammation, or both</td>
</tr>
<tr>
<td>Vascular lesions</td>
<td>Focal arterial distribution infarct</td>
<td>Ischemic perinatal focal infarction</td>
<td>5–10% cases</td>
<td>Multifactorial</td>
</tr>
</tbody>
</table>

*Note that the specificity of magnetic resonance imaging for neuropathology and etiology has not been confirmed.


FIG. 10-1. Total injury. Axial T2-weighted imaging (A) and apparent diffusion coefficient map (B) at 24 hours of age for an infant of 37 weeks of gestation who was noted by his mother to have decreased fetal movements 24 hours before onset of labor and 36 hours before delivery. He was comatose and ventilator dependent with impaired brain-stem function. Note the large hemorrhagic infarction in the right occipital hemisphere (thick arrow) and the widespread cortical gray-matter restriction (dark signal, bilateral thin arrows) throughout all of the left and most of the right hemisphere. Note also the loss of cortical gray-matter signal (dashed arrow) over the same region on T2-weighted imaging throughout the left hemisphere that demonstrates restricted diffusion. The combined findings of changes in T2 signal characteristics and prominent restriction in diffusion (on hypothermia therapy) support a likely timing of 48–72 hours before magnetic resonance imaging. This infant died at 5 days of life. ☞
near-total perinatal ischemic insult immediately before or during labor and delivery, such as a ruptured uterus, severe abruptio placentae, umbilical cord prolapse, amniotic fluid embolus with coincident severe and prolonged maternal hypotension and hypoxemia, maternal cardiovascular collapse or fetal exsanguination or both from either vasa previa or massive fetomaternal hemorrhage. This lesion often is referred to as global, total, or diffuse injury on MRI. In a study of patterns of brain injury following perinatal sentinel events, 13 infants with uterine rupture (n=9), maternal collapse (n=2), and umbilical cord separation (n=2) were reported among a total of 48 term infants. These infants all displayed thalamic and basal ganglia injury, with 50% displaying cortical and brain-stem injury and 25% displaying hippocampal injury (11). There was no comment on the cerebellum.

The second form of selective neuronal injury is the cerebral–deep nuclear neuronal injury, which combines neuronal damage in the deep nuclear gray matter with injury in the cerebral cortex, usually the parasagittal areas of the perirolandic cortex (Fig. 10-2 and Fig. 10-3). This is referred to on imaging studies as “deep nuclear gray matter” or “basal nuclei predominant” pattern. Affected areas of the deep nuclear gray matter that are more vulnerable include the putamen and the ventrolateral thalamus. This pattern appears in more than one third of term infants after hypoxic–ischemic insults (12–14). Clinically, this pattern of injury is recognized most commonly after an acute near-total hypoxic–ischemic insult. With an increasing duration of hypoxia–ischemia, the distribution of cortical injury expands. In experimental models, the mechanism responsible for this pattern of cerebral insult is described as a “prolonged, partial with final total asphyxia” with a moderate to severe insult evolving in a gradual manner leading to a potential complete “asphyxia” (15). The severity of the extent of deep nuclear gray matter involvement appears to relate to the severity of the “prolonged partial asphyxia” (16, 17). This pattern of injury has been described in

The third form is deep nuclear gray-matter brain stem that often results from an abrupt–severe insult. This pattern of neuronal injury only seems to affect the deep gray matter without other cerebral neuronal involvement. Affected areas include the basal ganglia, the thalamus, and the tegmentum of the brain stem. (16, 17). This pattern of injury has been described in

FIG. 10-2. Deep nuclear gray-matter injury. An infant at 36 weeks of gestation, birth weight 2.6 kg, born after abruptio placentae with Apgar score 1 at 1 minute, 3 at 5 minutes, and 4 at 10 minutes. Cord pH 6.6. Magnetic resonance imaging undertaken at 72 hours of life demonstrated no abnormality noted on axial T2-weighted imaging (A); high signal on diffusion-weighted imaging (B); and low signal in the deep nuclear gray matter (arrowheads) and insula region (arrows) on the apparent diffusion coefficient map (C). Notably, this imaging sequence was initially reported as within normal limits until review with the clinical team was undertaken; this emphasizes the challenge of neuroradiologic interpretation.

FIG. 10-3. Deep nuclear and cerebral injury. An infant at 35 weeks of gestation with a history of abruptio placentae for several hours before hospital admission. Apgar score 1 (at 1 minute), 3 (at 5 minutes), and 7 (at 10 minutes). No hypothermia therapy was commenced. Magnetic resonance imaging of axial imaging on the first day of life demonstrated no abnormality noted on axial T2-weighted imaging (A), apparent diffusion coefficient map imaging (B), T1-weighted imaging (C), and T2-weighted imaging (D) reveal isolated thalamic and deep nuclear gray-matter injury that is most apparent on the diffusion imaging (A, B, thick arrows). At day 10 there is now evolution, with more prominent T1- and T2-weighted signal changes in the deep nuclear gray matter and thalamus (G, H, thin arrows) but also prominent restriction in the cortical ribbon on diffusion-weighted (E, thick arrow) and apparent diffusion coefficient map (F, thick arrow) imaging, which suggests a secondary neuronal degeneration. (Images courtesy of Dr. Joshua Shimony, neuroradiologist at Washington University, St. Louis, MO.)

Throughout the report, the terms “asphyxia” and “birth asphyxia” and their variations appear in quotes when used in reference to a particular study to emphasize the wide variation in study definitions of asphyxia. See Chapter 1 for recommended asphyxia definition (in Table 1-1) and discussion of asphyxia terminology.
the total asphyxia model in the primate when total umbilical cord occlusion was undertaken for greater than 15 minutes. The pattern of vulnerability in the brain stem (inferior colliculi), superior olives, sensory nuclei of the trigeminal nerve, gracile and cuneate nuclei, and the posterior and lateral ventral thalamic nuclei followed the known perfusion gradient determined by C14 labeled diffusion studies (18). This pattern of brain injury is rare in imaging studies of neonatal encephalopathy in the infant born at term, occurring in less than 5%, as most instances of severe, abrupt hypoxic–ischemic insults are near-total rather than total “asphyxia.” The presence of intact myelination signal characteristics within the posterior limb of the internal capsule have been shown to be of prognostic significance and are frequently altered in significant deep nuclear gray matter and thalamic injury (Fig. 10-4).

The final form of selective neuronal injury is pontosubicular necrosis with injury to the neurons of the ventral pons and the subiculum of the hippocampi (19). Etiologies for this injury are more diverse and include hypoxia, acute ischemia, hypcapnia, hyperoxemia, and hypoglycemia (20–23). This pattern—the least common form of selective neuronal injury in the term infant—is more recognized in the preterm infant and often associated with periventricular leukomalacia. Studies by Bruck and colleagues indicate that in pontosubicular necrosis, neuronal cell death is apoptotic in nature on pathological examination (24).

Parasagittal Cerebral Injury (Neuronal and White Matter)

Parasagittal cerebral injury is unique to the term infant, occurring over the cerebral cortex and the underlying subcortical white matter of the parasagittal regions. It was first reported in 1977 by Volpe and Pasternak (25). Parietal–occipital regions are the most commonly affected (Fig. 10-5; see color plate). Injury is usually bilateral in distribution and results from mild to moderate hypoperfusion in this watershed region between the anterior, middle, and posterior cerebral circulation. This lesion often is referred to as a “watershed injury” or “border zone injury” in MRI publications. The neuropathology is not well established in the human, as most affected infants survive. A pattern of selective cortical injury was noted in isolated partial insult or hypotensive injury in the immature primates described in Chapter 2. Of note, the macaque differs in its cerebral vasculature, with a single azygous median anterior cerebral artery, which may alter vulnerability to anterior watershed patterns (26, 27). Only a few of these primates displayed any injury to the deep nuclear gray matter or thalamus, with no injury in the brain stem or cerebellum. The authors also noted that brief periods (less than 40 minutes) of profound hypotension (mean arterial pressure [MAP] less than 25 mm Hg) could be tolerated without neurologic sequelae. This is in contrast to the total insult model, in which injury occurred consistently after a duration of 15 minutes. Exposure to milder forms of hypotension (mean arterial pressure greater than 35 mm Hg) was tolerated for several hours. Watershed cortical infarcts have been well recognized in the term infant, occurring in 30–45% of published series of infants born at term with neonatal encephalopathy, dependent on the enrollment criteria and commonly involve the underlying white matter (Table 10-2).

White-Matter Injury

Damage to the white matter dorsal and lateral to the external angles of the lateral ventricle has been well described in the preterm infant, but also is seen in the term infant after hypoxic–ischemic injury (Fig. 10-6; see color plate). In one series of term encephalopathic
infants, white-matter injury was identified in 23% of newborns with encephalopathy of presumed hypoxic–ischemic origin (28). In this series, the white-matter injury was thought to have been acquired near birth because almost all lesions demonstrated restricted diffusion on apparent diffusion coefficient maps. Because newborns with white-matter injury had milder encephalopathy relative to other newborns in the cohort, these lesions may have been underdetected in the past. Lower gestational age at birth was associated with an increasing severity of white-matter injury, suggesting a role for brain maturation in the etiology of this specific pattern of injury pattern (28). It is also important to note that preterm

<table>
<thead>
<tr>
<th>Table 10-2: Characteristics and Magnetic Resonance Imaging Findings From Studies on Term Encephalopathy</th>
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<tr>
<td>Inclusion criteria</td>
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<tr>
<td>Either fetal heart rate monitoring abnormalities or Umbilical cord pH &lt; 7.1 or Delayed respiration or 5-min Apgar score &lt; 7 or Multiorgan failure</td>
</tr>
<tr>
<td>Acute sentinel event: umbilical cord prolapse (19%), uterine rupture (23%), abruptio placenta (46%)</td>
</tr>
<tr>
<td>Neonatal encephalopathy and one of “fetal distress” Umbilical cord acidemia, 5-min Apgar score ≤ 5, or both</td>
</tr>
<tr>
<td>Neonatal encephalopathy and abnormal EEG and Umbilical cord pH &lt; 7.0 or Delayed respiration or 10-min Apgar score &lt; 5, or both</td>
</tr>
<tr>
<td>Seizures or stupor Coma or hypothermia or Apgar score at 5 min &lt; 3</td>
</tr>
<tr>
<td>Two of: Apgar score ≤ 5 Need for mechanical ventilation at 10 min pH &lt; 7.0, BD &gt; 12</td>
</tr>
<tr>
<td>Term neonatal encephalopathy and MRI in first 6 weeks Apgar score ≤ 5 at 5 min or pH &lt; 7.1, or both “fetal distress”</td>
</tr>
<tr>
<td>Number of infants</td>
</tr>
<tr>
<td>Day of MRI scan (range)</td>
</tr>
<tr>
<td>No abnormality</td>
</tr>
<tr>
<td>Basal ganglia–thalamus</td>
</tr>
<tr>
<td>Cortical injury</td>
</tr>
<tr>
<td>White-matter injury</td>
</tr>
<tr>
<td>Other diagnosis</td>
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Abbreviations: BD, base deficit; EEG, electroencephalogram.


infants (median gestational age of 35 weeks) display a pattern of cerebral injury with both neuronal and white-matter lesions. In a study of 55 infants with a median gestational age of 35 weeks who presented with low Apgar and the need for major resuscitation, basal ganglia injury occurred in 75%, white-matter injury in 89%, and cortical injury in 58% of infants (29). Note that most infants displayed more than one region of injury. Brain-stem injury was seen in infants with severe diffuse injury. Of the infants in this study, 80% were born between 34 weeks and 36 weeks of gestation.

**Ischemic Perinatal Stroke**

In human infants, the incidence of ischemic perinatal stroke ranges from 1/2,300 to 1/5,000 live births (30–33) and is now recognized (with magnetic resonance imaging studies) as the second-most common etiology for neonatal encephalopathy (34–36), commonly presenting as neonatal seizures. Arterial lesions, usually unilateral, most commonly involve the middle cerebral artery, with the left cerebral hemisphere being more frequently affected than the right. Venous thrombosis most commonly affects the superior sagittal sinus. In an observational study of 62 newborns with focal or multifocal stroke, 36 had stroke alone, and 26 had stroke with a concurrent pattern of nonfocal hypoxia–ischemia (37). For a comprehensive discussion of perinatal stroke see Chapter 8, “Focal Ischemic Stroke.”

**Evolution of Neuropathology on Neuroimaging**

The unique patterns of injury in the brain of the infant born at term reflect selective vulnerabilities combined with the nature and severity of the insult. This vulnerability reflects developmentally regulated biochemical processes that mature at different rates in specific anatomic brain structures (eg, expression of glutamate receptor subunits, antioxidant enzymes, and nitric oxide synthase) that render neurons particularly vulnerable (2, 38, 39). The neuropathology following a cerebral insult evolves over a period of days to weeks. Initial extensive injuries may be accompanied by hemorrhages, especially in the cerebellum and the choroid plexus (39). By 3–5 days after initial injury, the subacute phase is characterized by “reactive processes” targeting parenchymal cleanup and repair: vascular proliferation with endothelial hypertrophy, activation and proliferation of resident microglia, and macrophage influx (see Fig. 10-5 and Fig. 10-6; see color plate). A severe insult may result in total infarction with damage to all cellular elements. The proliferation of astrocytes in response to the neuronal loss (ie, gliosis) is usually not prominent until 1 week or more after the injury. In the chronic phase, weeks to months after the insult, small collapsed glial scars or calcification are observed with larger parenchymal cysts observed after severe injuries (Fig. 10-7) (39). In this chronic stage, ulegryia and multicystic encephalomalacia are observed after severe hypoxic–ischemic injury in the term newborn (Fig. 10-8; see color plate) (39).

**Conclusions**

- Neuroimaging is critical to assist in defining the presence, nature, and severity of cerebral injury in infants born at term with neonatal encephalopathy and children with subsequent neurodevelopmental disabilities that are being attributed to perinatal events.
- The common patterns of brain injury in the encephalopathic term infant include selective neuronal injuries, parasagittal cerebral injury, white-matter injury, and focal and multifocal ischemic brain necrosis (Table 10-1).

![Fig. 10-7. Thalamic injury. A. Gross appearance of status marmoratus (marbled appearance of neuronal loss and scarring with calcification) in a 7-year-old child with cerebral palsy; note white patches in the thalamus and streaks in the caudate and putamen (arrow). B. Focal neuronal loss, gliosis, and mineralization (arrows) in the thalamus (hematoxylin and eosin stain; original magnification X 200). (Folkerth R. Neuropathological Substrate of Cerebral Palsy. J Child Neurology 2005;20:940-949, Copyright 2005 by SAGE Publications. Reprinted by Permission of SAGE Publications.)](image-url)
• The cerebral lesions associated with hypoxic-ischemic injury in the term infant have characteristic patterns related to the underlying cellular and vascular vulnerabilities. These patterns assist in distinguishing the etiology of abnormal neurologic behavior in infancy or childhood from that of other potential etiologies, such as genetic or metabolic.

• The nature of the neuropathology, reflected by the MRI, evolves during the first few days to weeks or months after injury.

**Major Neuroimaging Modalities**

The accurate diagnostic application of all neuroimaging modalities in the newborn with encephalopathy is related to the level of radiologic expertise for the acquisition and interpretation of the studies, regardless of the neuroimaging method. The methods of acquisition and level of experience in the interpretation of neuroimaging studies in the newborn can vary greatly between institutions. Integration of neonatal and radiologic physicians by joint conference and review of case materials on a regular basis (eg, weekly) may assist in improved communication and application of modern neuroimaging methods. Alternatively, expert interpretation at a center of excellence in perinatal and neonatal neurology should be requested.

**Cranial Ultrasonography**

Cranial ultrasonography relies on the reflection of ultrasound waves from tissue to provide images. It can be performed at the bedside with minimal risk to the patient. Cranial ultrasonography is performed through an open fontanelle; thus, its use is restricted to the first 6 months of life. It remains the most commonly used neuroimaging modality in the neonatal intensive care unit (NICU) setting. In the Vermont Oxford Neonatal Encephalopathy Registry, cranial ultrasonography was acquired in close to 40% of all infants with neonatal encephalopathy on a median of day 4 of life. Cranial ultrasonography may be the only possible imaging modality if an infant is too clinically unstable to transport out of the NICU. Cranial ultrasonography is sensitive for hemorrhage (although subdural hematomas can be missed because of the angle of the transducer), ventricular size, gross brain malformations, and cystic changes in the brain parenchyma. It is less sensitive for smaller and more subtle anomalies within the brain, including noncystic white-matter abnormalities and minor cerebral dysgenesis. It is a very useful screening evaluation in the term infant with encephalopathy, identifying cerebral dysgenesis in approximately 2–4% of infants who had been diagnosed with hypoxic-ischemic injury (see Table 10-2). Cranial ultrasonography often is used to look for the presence of slit-like ventricles, sulcal effacement to represent cerebral edema, and hemispheric or basal ganglia echodensity. However, cranial ultrasonography lacks sensitivity in defining the full extent of the cerebral lesions, even in severe encephalopathy and particularly in the first 24 hours of life (40, 41). Because cranial ultrasonography more reliably detects abnormalities after the first 24 hours after the occurrence of the inciting injury, abnormalities that it detects on the first day of life may assist in establishing the presence of severe hypoxic–ischemic encephalopathy before the onset of labor or the immediate period before birth (42).

**Computed Tomography**

Computed tomography (CT) scanning is performed by passing an X-ray beam (ionizing radiation) through a subject at a series of different angles. Based on the attenuation of these beams, an image can be constructed. Computed tomography scanning has several advantages, including providing a quantitative measurement of tissue diffusivity, high sensitivity for the detection of acute hemorrhage and bone abnormalities, a short examination time, and wide availability. These advantages are useful in the evaluation of acute brain pathology, particularly in the setting of traumatic brain injury. However, MRI appears to be more sensitive, particularly for injury to the deep nuclear gray matter and white matter. This is demonstrated in the results of neuroimaging in 1,421 term infants with neonatal encephalopathy in the Vermont Oxford Neonatal Encephalopathy Registry from 2006–2008 (Table 10-3).

In addition to its limited diagnostic role, there are increasing concerns regarding the effect of radiation exposure from CT on the developing brain (ie, the risk of future malignancy and later cognitive impairments). The adverse effect of non-CT cranial irradiation on cognitive development after radiation treatment of brain tumors has been clearly shown and is dose related. However, the threshold value for the effect is not known. It has been suggested that even low doses of ionizing radiation, similar to those delivered by CT scans, may adversely affect brain and cognitive development (43). In relation to the risk of subsequent malignancy, a 0.1% risk of lifelong fatal malignancy from a head CT at age 12 months has been estimated (44). However, the risk of tumor may be significantly greater with cranial irradiation exposure at a younger age. The risk of development of brain tumor was found to be 10-fold higher in infants exposed to
craniocerebral irradiation at younger than 5 months in comparison with those older than 7 months. Until further data are available, this neuroimaging technique should be restricted to select settings in which the information obtained from the imaging study is clearly of benefit to the patient and cannot be readily obtained using some other modality. This may include infants with severe head trauma at risk of major epidural bleeding and infants who require more definitive imaging in a very brief period because of severe clinical instability.

**Magnetic Resonance Imaging**

Magnetic resonance imaging provides the highest sensitivity for both anatomic and functional detail. It also offers an array of imaging options that can be tailored to the specific clinical question. The techniques that may be applied, and their interpretation, may differ as to whether they are targeted in the investigation during the newborn period (on which most of this chapter is focused) or in childhood after the diagnosis of neurologic abnormality, such as cerebral palsy. In the investigation of cerebral palsy, neuroimaging with MRI is recommended by the American Academy of Neurology (45). On meta-analysis, it appears that detectable abnormalities are present in 80% of children with cerebral palsy (46). However, it is worthy to note that this meta-analysis includes studies that have mixed populations of preterm and term infants from clinic-based populations. The authors conclude that neuroimaging in cerebral palsy is useful, but care must be taken in ascertainment of etiology and timing when neuroimaging is taken at this later time (46).

Magnetic resonance imaging does, however, have some drawbacks compared with other imaging modalities, particularly in the neonatal period. Unlike cranial ultrasonography, patients typically must be transported to a radiology suite from the NICU for MRI, which may pose some risk to those infants who are unstable. Some facilities sedate infants and children for MRI, which also carries risk, but this practice is not routinely required for MRI in the newborn period. Magnetic resonance imaging sessions typically take longer than CT or cranial ultrasonography, and the infant or child is less readily accessible for evaluation in the event of an emergency, such as displacement of an endotracheal tube. Magnetic resonance scanners are much more expensive to install and maintain than cranial ultrasonography or CT scanners. Despite these issues, MRI is in widespread use because of its superior neurodiagnostic information.

Safely imaging encephalopathic neonates is a unique challenge. Studies have shown that at least 20% of infants born at term with severe hypoxic-ischemic encephalopathy cannot be safely transported to the MRI scanning suite because of the severity of their illness (47). Few centers have experience in routinely imaging critically ill infants, making it an intimidating proposition for less-experienced centers. Multiple considerations must be addressed before taking a neonate to the scanner. All infants should have a thorough search for any ferrous objects that would interfere with the magnet. Commonly overlooked items include snaps on clothing, electroencephalography leads, intraventricular shunts, and rectal thermometers, which are frequently used for systemic cooling. To maximize signal-to-noise ratio, a dedicated neonatal head coil is ideal, but if not available, an adult knee coil can be used as a substitute. Because of the noise from certain MRI sequences, such as diffusion-weighted imaging, ear protection


<table>
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<tr>
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<th>Ultrasonography</th>
<th>Computed Tomography</th>
<th>Magnetic Resonance Imaging</th>
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</thead>
<tbody>
<tr>
<td>Number of infants</td>
<td>729 (51%)</td>
<td>477 (34%)</td>
<td>1,074 (75%)</td>
</tr>
<tr>
<td>Mean (SD) age (days)</td>
<td>3.1 (4.4)</td>
<td>3.2 (3.5)</td>
<td>7.3 (8.7)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>232 (32%)</td>
<td>271 (57%)</td>
<td>717 (67%)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVH/SE</td>
<td>56 (8%)</td>
<td>59 (12%)</td>
<td>79 (7%)</td>
</tr>
<tr>
<td>Extra-axial</td>
<td>24 (3%)</td>
<td>165 (35%)</td>
<td>212 (20%)</td>
</tr>
<tr>
<td>Parenchymal</td>
<td>37 (5%)</td>
<td>57 (12%)</td>
<td>105 (10%)</td>
</tr>
<tr>
<td>Deep nuclear gray-matter injury</td>
<td>70 (10%)</td>
<td>50 (10%)</td>
<td>309 (29%)</td>
</tr>
<tr>
<td>White-matter injury</td>
<td>16 (2%)</td>
<td>15 (3%)</td>
<td>271 (25%)</td>
</tr>
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</table>

Abbreviations: IVH, Intraventricular hemorrhage; SD, standard deviation; SE, subependymal hemorrhage.
for the infant is recommended. Neonatal earmuffs have been used, but other options—such as moldable ear putty or shielding with 2x2 gauze pads—are acceptable (48). Some baseline level of monitoring should be done on all infants in the MRI scanner, including healthy term controls, such as oxygen saturation monitoring to ensure safety of airway patency and respiration. Magnetic resonance imaging-compatible intravenous pumps, pulse oximetry, cardiorespiratory monitors, and ventilators are needed when imaging infants in more critical condition.

To maximize the quality of the study, infants must remain still. As anyone who has tried to image a neonate can attest, this is not a simple task. An organized approach can avoid wasting hours of effort only to get inadequate images. Often feeding and bundling the infant about half an hour before the study can result in exceptional images during natural sleep. This requires feeding and wrapping the infants beforehand in the unit, allowing time for the infant to settle into sleep before transportation to the scanner. Furthermore, placing all MRI-compatible monitoring devices, such as the heart and pulse oximetry leads, before wrapping the infant can be beneficial. Devices, such as vacuum packs, can be extremely helpful in ensuring minimal motion artifact. As another alternative, many centers have success with mild sedation, such as midazolam, lorazepam, or oral chloral hydrate. These medications should always be administered under the watchful eye of a physician experienced in sedating neonates. Ideally, a nurse and a physician should accompany the sedated or sick patient and remain throughout the entire study (48).

A risk-benefit assessment of timely acquisition of MRI should be considered by the attending physician. If the information potentially available from MRI can guide care and management of the infant, effort should be made to obtain the study. If the information from the MRI is unlikely to affect the acute current care and management of an infant, neuroimaging may be delayed until the second week of life or later, when the infant is more stable. The logistics and ease of obtaining MRI at the hospital should be considered, including location of the MRI suite; appropriate staff availability; care of the infant preceding, during, and after the MRI; and need for neonatal transport. Neuroimaging should be performed in accord with American Academy of Neurology guidelines, but consideration should be given to the extended timeline for the evolution of neuroimaging findings in infants receiving therapeutic hypothermia (see also “The Effect of Hypothermia on the Evolution and Patterns of Injury on Magnetic Resonance Imaging in Neonatal Encephalopathy” later in this chapter).

An important consideration for the utility of MRI is the optimal sequences to be obtained. Magnetic resonance imaging can be successfully obtained on a 1-Tesla, 1.5-Tesla, or 3-Tesla scanner, but the sequences need to be adapted for the newborn brain. Specialized sequences are essential because of the high water content of the neonatal brain when compared with that of the adult. An example of sets of acquisition parameters that are applied in the newborn brain during the neuroimaging evaluation of neonatal encephalopathy in the term infant are outlined in Table 10-4 for 1.5-Tesla and 3-Tesla magnetic resonance systems.

**Conventional Images**

Conventional images include T1-weighted (short repetition and short echo times) and T2-weighted images (long repetition times and long echo times). These sequences offer superiority in differentiating cortical gray matter from cerebral white matter and myelinated from unmyelinated white matter when compared with ultrasonography and CT. Injury will appear hypointense on T1-weighted and hyperintense on T2-weighted images in the acute phase (first few days), then hyperintense on T1-weighted and hypointense on T2-weighted later within the first week. T1-weighted hyperintensity may persist for weeks, whereas T2-weighted hypointensity transitions to hyperintensity over that interval. Conventional images alone can lack sensitivity to visualize injury in the acute phase (less than 4 days) (see Fig. 10-3 and Fig. 10-7).

**Diffusion-Weighted Imaging**

Diffusion-weighted imaging measures the random self-diffusion of water through the brain tissue. This self-diffusion of water in tissue is referred to as apparent diffusion, thus the term *apparent diffusion coefficient*, which is the quantitative measure of tissue diffusivity. In MRI, a diffusion-weighted image of water motion is acquired. From this image, susceptibility influences from T2 signal should be removed and an apparent diffusion coefficient map calculated and presented for clinical and radiologic interpretation, including the measurement of the apparent diffusion coefficient value in several cerebral regions. After ischemic injury, brain tissue will experience a decrease in water diffusion compared with healthy adjacent tissue, which will be reflected in a decrease of the apparent diffusion coefficient value. This is sometimes referred to as a
“restriction” of the apparent diffusion coefficient value or “restricted diffusion” of water. After neonatal ischemic brain injury, apparent diffusion coefficient values can decrease more slowly than documented in adult stroke, with up to 30% of infants having normal apparent diffusion coefficient values in the first 12–24 hours of life (49). Diffusion-weighted imaging progresses with a pseudo-normalization of the apparent diffusion coefficient occurring by 7–10 days of life (see Fig. 10-9; see color plate), a time when injury should be apparent on conventional MRI. Secondary alterations in cerebral regions, such as Wallerian degeneration in axonal pathways after a primary neuronal injury, can alter the representation of these acute changes. For example, a reduction in the apparent diffusion coefficient value from the diffusion imaging in the posterior limb of the internal capsule or corpus callosum may become noticeable on day 6–10 of life (50, 51). Thus, one must take care in the interpretation of the timing of the insult based solely on apparent diffusion coefficient values but consider the pattern of restriction.

**Magnetic Resonance Spectroscopy**

Magnetic resonance spectroscopy is based on the ability of identical nuclei, predominantly the 1H proton, in various molecules to demonstrate different resonant frequencies as a result of different electron densities. The signal is expressed in parts per million (ppm) and can detect N-acetylaspartate, creatine + phosphocreatine, choline, myo-inositol, glutamine, glutamate, glucose, taurine, and lactate. N-acetylaspartate (a free amino acid) is present in large quantities in the developing brain (in neuronal tissue and developing oligodendrocytes), making it a great indicator of intact central nervous tissue (52). Multiple studies have used N-acetylaspartate ratios (N-acetylaspartate/creatine + phosphocreatine and N-acetylaspartate/choline) to assess the degree of brain injury in animal models and human infants (53–55). Proton magnetic resonance spectroscopy also detects this presence of lactate, a doublet peak at 1.3 ppm that is upright at 288s echo time and inverted at 144s echo time (Fig. 10-10), and is a useful marker for tissue injury.

FIG. 10-10. Magnetic resonance spectroscopy evolution. Day 1 (A) and day 10 (B) point resolved magnetic resonance spectroscopy over the left thalamus in a term infant with fetal bradycardia, emergent cesarean delivery, acidemia (pH 6.9, base deficit 15), and Apgar scores 1, 2, and 3 at 1 minute, 5 minutes, and 10 minutes, respectively. This infant received 72 hours of therapeutic hypothermia therapy. Note the elevated lactate doublet (arrow) on Figure A at day 1. By day 10, this lactate peak resolved, but the level of N-acetylaspartate has decreased. Abbreviations: Cho, choline; Cr, creatine + phosphocreatine; ppm, parts per million; NAA, N-acetylaspartate.
Magnetic Resonance Angiography and Magnetic Resonance Venography

Magnetic resonance angiography and venography are noninvasive techniques used to delineate arterial and venous supply and topography while avoiding catheterization and contrast administration (56–58). However, in the newborn there are limitations with small-caliber vessels and slow cerebral flow, which make apparent absence of flow more frequent than in children and adults (59).

Conclusions

- Cranial ultrasonography is a bedside technique that can be easily accessible. Cranial ultrasonography on admission and in the first 2–3 days of life will assist in excluding major cerebral dysgenesis and antenatal lesions, which have been reported in 2–5% of encephalopathic infants and 10% of children with cerebral palsy. 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 scanning has the advantage of being a fast or rapidly acquired neuroimaging technique that has sensitivity for hemorrhage. However, CT lacks sensitivity for brain injury in the newborn and will often not reveal abnormalities in the first 24–48 hours after an injury. Computed tomography scanning in the newborn period also may be associated with an increased risk of subsequent cancer and later cognitive impairments.

- Magnetic resonance imaging has the major advantage of being the broadest method for the evaluation of macrostructural and microstructural cerebral and vascular anatomy, as well as biochemistry. Magnetic resonance imaging will best define the nature and extent of cerebral injury in neonatal encephalopathy. The major disadvantage of MRI is the need to transport a potentially very unstable infant out of the neonatal intensive care unit for up to 1 hour.

Patterns of Neuroimaging Abnormalities Found in Neonatal Encephalopathy in the Newborn Infant

There is wide variation in current clinical practice for the use of neuroimaging modalities in the term infant with encephalopathy. We have used the term neonatal encephalopathy in preference to hypoxic–ischemic encephalopathy, as suggested by current research and clinical leaders (60) and to recognize the clinical syndrome in the infant that often is being evaluated by neuroimaging. However, once the clinical history, examination, electrophysiological study, and neuroimaging study have been undertaken, the term hypoxic–ischemic encephalopathy may be applied as a diagnosis if appropriate (4, 5).

It is notable that in current neonatal practice, there are still a significant number of infants with neonatal encephalopathy who do not receive any neuroimaging evaluation or receive inadequate neuroimaging to define the nature and severity of brain injury. Within the Vermont Oxford Network Neonatal Encephalopathy Registry from 2006–2008, 88,527 infants were screened from 70 centers (61). Of these infants, 1,743 (2%) met criteria for neonatal encephalopathy with either an Apgar less than 3 at 5 minutes or stupor and coma or neonatal seizures in the first 72 hours of life. Thirty four (2%) infants were excluded because of evidence of cerebral dysgenesis on neuroimaging that had not been previously detected. Of the remaining infants, 1,421 (82%) underwent some form of neuroimaging evaluation. There were 322 infants (18%) who did not have any neuroimaging. Of these 322 infants, there were 62 deaths. Thus, 15% of living term infants with neonatal encephalopathy did not undergo any neuroimaging (62).

Of those infants who did undergo neuroimaging, the type and timing of imaging is shown in Table 10-3. Approximately 34% of the infants received a CT scan, 51% received a cranial ultrasonography, and 63% received MRI. The major abnormality detected on CT scanning was extra-axial blood. Magnetic resonance imaging had higher detection rates than CT scans for deep nuclear gray matter and white-matter injury (see Table 10-3). To more accurately evaluate these imaging modalities, a comparison was made of a subset of 317 (20%) infants, who received a CT scan and an MRI. White-matter injury was 10 times more likely to be diagnosed and deep nuclear gray-matter injury was three times more likely to be diagnosed with MRI than CT scans in the same infants. In one study, patterns of brain injury detected by CT were compared with those diagnosed on diffusion-weighted imaging in a cohort of term newborns (neonatal encephalopathy was studied uniformly with both modalities on the third day of life). The extent of cortical injury and focal-multifocal lesions, such as infarcts and white-matter injury, were less apparent on CT relative to diffusion-weighted imaging. Although the
detection of deep nuclear gray-matter injuries were similar with both modalities in this study, on the third day of life diffusion-weighted imaging was still the most sensitive technique, particularly for cortical injury and focal-multifocal lesions (63). Thus, although the American Academy of Neurology recommendations for MRI between day 2 and day 8 of life have been present for close to a decade as the neuroimaging modality for neonatal encephalopathy in the term infant (64), a translational gap remains.

With the increased use of MRI, the recognition of different patterns of injury has become established. 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, 2) more importantly, there are little to no data on the neuropathological correlate of the MRI pattern. However, two main patterns often are distinguished on MRI: 1) the basal–ganglia–thalamus pattern and 2) the watershed or border zone predominant pattern.

The basal–ganglia–thalamus pattern predominantly affects bilaterally the central gray nuclei and periolandic cortex (see Fig. 10-1, Fig. 10-2, and Fig. 10-3). This pattern of injury is consistent with the selective neuronal necrosis described previously and has been associated with a prolonged partial near-total “asphyxia.” Basal ganglia involvement also can occur in other mechanisms of brain injury, particularly if the injury is severe in nature. The presence of brain-stem or cerebellar involvement with basal ganglia injury may suggest a total “asphyxia” event. Basal ganglia injury is reported in 25–80% of term infants with neonatal encephalopathy undergoing neuroimaging evaluation (see Table 10-4). The variation in the rates of injury may relate to selection bias in the patient populations; subjective differences in the reporting or interpretation of signal abnormalities in the basal ganglia and thalamus; and the use, including timing, of diffusion-weighted imaging.

The watershed or border zone predominant pattern of injury affects mainly the white matter and, in more severely affected infants, the overlying cortex in the vascular watershed zones (anterior-middle cerebral artery and posterior-middle cerebral artery; see Fig. 10-4) (65). The lesions can be unilateral or bilateral and predominantly posterior and anterior. Although loss of the cortical ribbon and, therefore, the gray-white matter differentiation, can be seen on conventional MRI, diffusion-weighted imaging highlights the abnormalities and is especially helpful in making an early diagnosis. A repeat MRI may show cystic evolution, but more often atrophy and gliotic changes will be recognized. This will be considerably later (typically more than 21 days). This pattern of injury typically is seen after partial insult (15), which may be prolonged (not clearly defined in time). The frequency of this lesion has varied between studies. This may reflect the enrollment criteria of infants in these neuroimaging studies (ranges from 25% to 60%, Table 10-3) or the use, including timing, of diffusion-weighted imaging.

When either of these patterns of injury become extreme, a total injury pattern results. Additionally, there are infants with lesions restricted to the periven-tricular white matter not dissimilar from the so-called punctate white-matter lesions described in preterm infants; these lesions can be distinguished as a separate pattern of injury, although less common than the patterns outlined earlier. Researchers pointed out that infants with this type of injury are more immature in gestation and tend to have a milder encephalopathy and fewer clinical seizures compared with newborns with the two more common patterns of injury. In the setting of neonatal encephalopathy, perinatal arterial ischemic infarction and perinatal hemorrhagic infarction can occur in isolation or in the context of either the basal–ganglia–thalamus pattern or watershed pattern of injury (28).

**Clinical Interpretation of Magnetic Resonance Imaging in the Term Encephalopathic Infant**

The aim in undertaking neurologic imaging of a term infant with encephalopathy is to enhance the information obtained from the history and examination to aid the physician in answering the following questions: Is there an MRI abnormality? If so, what is the nature and extent of brain injury? What was the likely etiology of the injury? When did the injury occur? Are there ways to intervene other than supportive care that could affect outcome? What is the prognosis for this patient? The family should be fully informed regarding the reasons for acquiring neuroimaging and how the information will be incorporated into clinical decision making for their infant.

**Conventional Imaging**

In the first 48 hours after hypoxic–ischemic injury, there may be no visible abnormalities on conventional MRI. If MRI abnormalities are present at this time, T1-weighted images will appear hypointense or display no abnormalities, whereas T2-weighted images may be hyperintense. The hyperintensity in affected areas on T2-weighted images evolves into hypointensity by 6–10 days of life, whereas the T1-weighted imaging will become hyperintense (9, 49). Acutely affected infants may only demonstrate diffuse edema.
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of the cortical tissue on conventional images. This increase in water content of the brain tissue causes the cortex to become isointense with adjacent white matter, making differentiation of the border between the two tissues difficult. Areas of involvement vary according to the nature and severity of the insult, as described in Table 10-1. If the lesion resulted from total loss of all perfusion, then there is likely to be brain-stem or cerebellar involvement, or both. Affected areas include the basal ganglia, the thalamus, and the tegmentum of the brain stem (see Fig. 10-3). More severe injuries or prolonged insults of a partial (less common) and partial with total insult pattern will also include diffuse areas of the deep and superficial gray matter, along with diffuse white-matter involvement. Chronically, this may evolve into a picture of multicystic encephalomalacia, characterized by cystic evolution that often is accompanied by atrophy and gliotic changes.

**Diffusion-Weighted Imaging and Diffusion Tensor Imaging**

In contrast to conventional MRI, diffusion imaging is sensitive to acute cerebral injury. By 24–48 hours after hypoxic–ischemic injury, reduction in the apparent diffusion coefficient, otherwise more precisely referred to as mean diffusivity, is clearly visible with brain injury, although it may underestimate the full extent or be difficult to visualize with moderate injury (66–68). The evolution in diffusion over time in infants with hypoxic–ischemic encephalopathy has been described with basal ganglia injury in the early postnatal period (69). In the first 12–24 hours, some infants may have no visible changes on diffusion imaging (see Figs. 10-3 and 10-7) (49). The pattern of the early predominance of the ventrolateral nucleus of the thalami (first 48 hours) becomes more evident in the putamen, corticospinal tracts, and the perirolandic cortex by 3–5 days of life. Subcortical white

**TABLE 10-4. Suggested Magnetic Resonance Imaging Parameters for Acquisition on 1.5-Tesla and 3-Tesla Magnet Sequences for Neonates**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1.5 Tesla</th>
<th>3 Tesla</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2-weighted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TE: 280 ms</td>
<td>TE: 161 ms</td>
<td></td>
<td>Sensitivity encoding can be X2</td>
</tr>
<tr>
<td>TR: 3,000 ms</td>
<td>TR: 8,950 ms</td>
<td></td>
<td>Acquired in coronal plane</td>
</tr>
<tr>
<td>Flip: 120°</td>
<td>Flip: 120°</td>
<td></td>
<td>isotropic and reconstructed for axial and sagittal</td>
</tr>
<tr>
<td>Slice thickness: 1 mm³</td>
<td>Slice thickness: 1 mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time: 6:12 min</td>
<td>Time: 6:35 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-weighted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TE: 3.09 ms</td>
<td>TE: 3.05 ms</td>
<td></td>
<td>MP-RAGE</td>
</tr>
<tr>
<td>TR: 2,000 ms</td>
<td>TR: 1,550 ms</td>
<td></td>
<td>For pure T1 TR: 1,100 ms</td>
</tr>
<tr>
<td>Flip: 120°</td>
<td>Flip: 120°</td>
<td></td>
<td>Acquired in sagittal plane</td>
</tr>
<tr>
<td>Slice thickness: 1 mm³</td>
<td>Slice thickness: 1 mm³</td>
<td></td>
<td>isotropic and reconstructed for axial and sagittal</td>
</tr>
<tr>
<td>Time: 3:36 min</td>
<td>Time: 3:45 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TE: 96 ms</td>
<td>TE: 96 ms</td>
<td></td>
<td>12 directions in addition to b=zero</td>
</tr>
<tr>
<td>TR: 9,000 ms</td>
<td>TR: 9,300 ms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flip: 120°</td>
<td>Flip: 120°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slice: 2.5 mm³</td>
<td>Slice thickness: 2 mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b-value: 1,000</td>
<td>b-value: 1,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time: 4:05 min</td>
<td>Time: 4:13 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnetic resonance spectroscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TE: 144 ms</td>
<td>TE: 144 ms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TR: 1,710 ms</td>
<td>R: 1,710 ms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time: 3:44 min</td>
<td>Time: 3:44 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnetic resonance venography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TE: 5.43 ms</td>
<td>TE: 7.05 ms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TR: 22 ms</td>
<td>TR: 27 ms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slice: 1 x 1 x 3 mm</td>
<td>Slice: 0.8 x 0.8 x 2 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time: 4:03 min</td>
<td>Time: 3:55 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnetic resonance arteriography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TE: 4.06 ms</td>
<td>TE: 3.59 ms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TR: 20 ms</td>
<td>TR: 20 ms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slice: 0.8 mm³</td>
<td>Slice: 0.9 x 0.6 x 0.5 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time: 3:20 min</td>
<td>Time: 4:54 min</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: TE, echo time; TR, repetition time.
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matter and white-matter pathways, such as the corpus callosum and the cingulum, may show involvement early, or this may appear as a secondary change by 7 days after hypoxic–ischemic injury. Therefore, clues to the timing and extent of brain injury can be elucidated by diffusion-weighted imaging within the first 24–96 hours of life (Fig. 10-10 and Fig. 10-11). Changes in diffusion can be detected as early as 6 hours after injury, but the most significant change in diffusion occurs between 2 days and 4 days after the injury (49, 70). These changes in the diffusion not only correlate with later conventional imaging but also with neurodevelopmental outcome (71).

Quantitative measures of diffusion-weighted imaging have been studied in term-born infants with neonatal encephalopathy and appear to give useful prognostic information. One study demonstrated that if diffusion weighted imaging shows involvement of the posterior limb of the internal capsule with an apparent diffusion coefficient of 0.74 or less, poor neurodevelopmental outcome is highly likely (72). The presence of Wallerian degeneration in the posterior limb of the internal capsule on diffusion-weighted imaging also appears a strong predictor for hemiplegia in infants with perinatal cerebral infarcts (see Fig. 10-4) (73, 74), although is not specific for hypoxic–ischemic injury. Measuring anisotropy (relative anisotropy or fractional anisotropy) with diffusion tensor imaging may give additional information. Anisotropy decreases with both severe and moderate white-matter and basal ganglia injury during the first week of life, whereas apparent diffusion coefficient decreases only for severe injury. Fractional anisotropy values continue to decrease during the second week of life and do not undergo pseudonormalization like apparent diffusion coefficient values. Thus, the pairing of fractional anisotropy values with apparent diffusion coefficient can add information on severity and timing of injury. In the mild and moderate hypoxic–ischemic encephalopathy population, fractional anisotropy correlated with short-term neurodevelopmental outcome (75).

Magnetic Resonance Spectroscopy

The in vivo assessment of metabolites was first described in neonates by investigators, who observed high lactate and low N-acetylaspartate values in the basal ganglia in infants with poor outcome at 3 months after encephalopathy (53). Since this, observation studies have looked at both metabolite ratios (lactate/choline, lactate/creatine, N-acetylaspartate/choline) and absolute levels (lactate, N-acetylaspartate) and correlated them with outcome. The abnormal rise in lactate and fall in N-acetylaspartate are most significant within the first week after injury, with lactate being detected within 24 hours following injury and N-acetylaspartate beginning to decrease after 48 hours (55). An elevated lactate/choline ratio early in the first week and a decrease in N-acetylaspartate/choline later in the first week have been shown to be most predictive for neurodevelopmental outcome (74, 76–82). These metabolite levels can remain abnormal for long periods. Elevated lactate levels are seen for months after injury and, thus, do not always indicate acute injury. The persistence of lactate signifies a worse prognosis (78). When magnetic resonance spectroscopy of the basal ganglia and parasagittal cortex (watershed area) has been compared with diffusion-weighted imaging in the acute postnatal period, magnetic resonance spectroscopy appeared superior in predicting poor outcome (83).

![Fig. 10-11. Evolution of conventional and diffusion changes.](image-url)
A study of term infants who underwent conventional diffusion spectroscopy measurements in the basal ganglia on imaging at a median of day 4 showed that the addition of quantitative measures of apparent diffusion coefficient or lactate/\(N\)-acetylaspartate ratio in the basal ganglia, or both, improved the predictive power of conventional imaging for adverse neurodevelopmental outcome (area under the curve [AUC]= 0.85 with lactate/\(N\)-acetylaspartate ratio \(P=.006\); AUC = 0.93 with apparent diffusion coefficient in basal ganglia, \(P<.001\)) (74).

In a meta-analysis of 32 studies grouping 806 newborns with neonatal encephalopathy, the ratio of lactate over \(N\)-acetylaspartate in the deep gray matter had strong prognostic accuracy for disability (84), with a pooled sensitivity of 82% and a specificity of 92%. Although this measure was useful for predicting death or profound disability, more detailed anatomic imaging may assist in refining prognostic information.

**Evaluation of the Timing of Cerebral Injury**

Magnetic resonance imaging studies have defined that the vast majority of cerebral injury that is seen in term-born infants with neonatal encephalopathy is acute (34), contrasting with epidemiologic studies that have suggested that 70% of causation is related to chronic antenatal factors (85). This apparent contradiction relates to the fact that some of these imaging studies are based on imaging findings in the first 2–3 weeks of life and demonstrate a subacute pattern (34). They 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 timing of ischemic cerebral injury. Magnetic resonance imaging can provide mutual information from diffusion-weighted imaging, conventional imaging, and magnetic resonance spectroscopy, which can inform timing. However, 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 an MRI in the clinical setting).

If the hypoxic–ischemic injury occurs in the hours immediately preceding and after birth, the early imaging in the first 24–96 hours of life would show no changes in conventional imaging, no reduction (first 24 hours of life) to mild reduction (24–96 hours of life) in the apparent diffusion coefficient value on diffusion imaging, and an elevated lactate (from birth to 96 hours of life) but no alteration in \(N\)-acetylaspartate on magnetic resonance spectroscopy. By day 4–5 of life, diffusion imaging remains restricted with the evolution of early conventional imaging changes, and lactate remains elevated. By day 7–14 of life, apparent diffusion coefficient values on the diffusion imaging will be pseudonormalized (timing appears related to whether therapeutic hypothermia treatment was undertaken in the region of primary injury but may have reduction in the apparent diffusion coefficient values in secondary areas of injury undergoing Wallerian degeneration) (86). After 14 days of life, the apparent diffusion coefficient value will increase on diffusion imaging associated with tissue dissolution. Conventional imaging will typically reveal signal abnormality to confirm the nature and extent of injury, and magnetic resonance spectroscopy will show a reduction in \(N\)-acetylaspartate, with lactate potentially persisting or resolving. Thus, an infant who suffered an insult associated with decreased fetal movements 48 hours before delivery would display a pattern for day 4 of life imaging findings at day 2 of life. It is important to note that imaging studies with the predominant MRI studies obtained after day 7 of life can discern the absence of chronic findings, such as cystic changes and atrophy, but are not able to discern the acute or subacute nature of an insult. It is also important to note that MRI can assist in timing in terms of days and not hours or minutes (Table 10-5).

There are few imaging studies that have attempted to undertake MRI in the first 24 hours of life to define the timing and evolution of injury. Although some of these studies have tended to have a priori inclusion of infants with sentinel acute events near the time of birth and, thus, may be biased, (49), they nonetheless suggest the presence of intrapartum injuries. However, it is also important that clinicians recall that fetal stillbirth rates in the third trimester remain higher than neonatal encephalopathy by a factor of three (87), indicating that injury and death can occur outside the setting of labor. Thus, research into the timing of cerebral injury remains critical to our understanding of the pathway to neonatal encephalopathy. 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 over 24 hours before delivery. This area is worthy of greater investigation—combined with investigation of the placenta—and may be more plausible as NICUs acquire access to MRI scanners within their nursery setting. The role of postmortem MRI
should be considered in cases of neonatal death when the infant was too unstable to be taken for MRI. Neuroimaging postmortem should include high-resolution T1-weighted and T2-weighted imaging and can assist in defining the nature of injury. Magnetic resonance spectroscopy cannot be used postmortem, and diffusion imaging has limited use, requiring modification of the acquisition and interpretation only of the anisotropy measures.

The Effect of Hypothermia on the Evolution and Patterns of Injury on Magnetic Resonance Imaging in Neonatal Encephalopathy

Systemic hypothermia reduces the risk of death and disability in term-born infants with hypoxic-ischemic encephalopathy (88–93). In the TOBY (Whole Body Hypothermia for the treatment of Perinatal Asphyxial Encephalopathy) trial, total body cooling therapy was associated with less injury in the basal ganglia, thalami, and posterior limb of the internal capsule on MRI in the second week of life (94). In another study of total body cooling, systemic hypothermia down to 33–34°C reduced cortical injury (95). In an experimental study of 42 newborn piglets, optimal neuroprotection by delayed hypothermia was found to occur at different temperatures in the cortical and deep gray matter (96). Whether a cooling protocol could be tailored to provide more optimal brain protection to a particular pattern of brain injury is an important question for future research. Importantly, therapeutic hypothermia does not affect the predictive value of conventional MRI for subsequent neurologic impairment (63, 95–99). However, further studies are needed to define the optimal timing of brain imaging for newborns treated with hypothermia because there are some data that suggest that therapeutic hypothermia may slow the evolution of diffusion and conventional MRI findings (86) (Fig. 10-9 [see color plate] and Fig. 10-12). A serial MRI imaging study in term encephalopathic infants undergoing therapeutic hypothermia (97) demonstrated injury in 4/12 infants (33%) that was readily detected by diffusion and magnetic resonance spectroscopy on day 2 of life (but not within the first 24 hours). The injury on day 2 of life predicted the presence of conventional abnormalities at day 10 of life. A larger population study of the evolution of imaging findings in infants who received therapeutic hypothermia

| TABLE 10-5: Evolution of Magnetic Resonance Imaging Changes With and Without Therapeutic Hypothermia After Neonatal Cerebral Injury | \hline
<table>
<thead>
<tr>
<th><strong>Therapeutic Hypothermia</strong></th>
<th><strong>Conventional T2/T1-Weighted Imaging</strong></th>
<th><strong>Diffusion-Weighted Imaging</strong></th>
<th><strong>Magnetic Resonance Spectroscopy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>First 24 hours</td>
<td>No TH</td>
<td>No abnormality</td>
<td>30% negative</td>
</tr>
<tr>
<td></td>
<td>TH</td>
<td>No abnormality</td>
<td>30–50% negative</td>
</tr>
<tr>
<td>24–96 hours</td>
<td>No TH</td>
<td>Abnormalities will begin to evolve</td>
<td>Prominent restriction in ADC</td>
</tr>
<tr>
<td></td>
<td>TH</td>
<td>Minimal–no abnormality</td>
<td>Prominent restriction in ADC</td>
</tr>
<tr>
<td>4–7 days</td>
<td>No TH</td>
<td>Abnormalities become prominent by day 4–8</td>
<td>Pseudonormalization in ADC by day 5–7 with elevation of ADC in primary region of injury &gt;7 days</td>
</tr>
<tr>
<td></td>
<td>TH</td>
<td>Minimal abnormality may be visible by day 4 evolving fully by day 8–10</td>
<td>Persisting restriction in ADC in primary region of injury to day 10–12</td>
</tr>
<tr>
<td>7–21 days</td>
<td>No TH</td>
<td>Abnormalities prominent after day 8</td>
<td>Restriction in ADC may be present up to 10–12 days following insult Wallerian degeneration</td>
</tr>
<tr>
<td></td>
<td>TH</td>
<td>Abnormalities prominent after day 8</td>
<td>Reduction NAA</td>
</tr>
<tr>
<td>&gt;21 days</td>
<td>No TH or TH</td>
<td>Cystic degeneration and atrophy</td>
<td>Elevated ADC and reduction in anisotropy with injury</td>
</tr>
</tbody>
</table>

Abbreviations: ADC, apparent diffusion coefficient; NAA, N-acetylaspartate; TH, therapeutic hypothermia.
will be required. However, it may be difficult to interpret the nature and timing of the injury in some infants undergoing therapeutic hypothermia (Table 10-5).

**Conclusions**

- Neuroimaging in the neonatal period should be obtained on all term newborns with moderate or severe encephalopathy.
- Magnetic resonance imaging is the neuroimaging modality of choice to define the pattern of cerebral injury, as recommended by the American Academy of Neurology in 2002, although a translational gap into clinical practice for all term infants with neonatal encephalopathy exists.
- Two common patterns of brain injury in hypoxia–ischemia in the term infant have been established: 1) basal-ganglia-thalamus and 2) watershed or border zone predominant. Involvement of the brain stem and cerebellum may suggest a total asphyxia event.
- Distinct patterns of neuroimaging abnormalities are recognized in hypoxic–ischemic cerebral injury in the 35-week-or-older infant and have prognostic value for predicting later neurodevelopmental impairments.
- Optimal acquisition and interpretation of MRI is critical. Ongoing education in the interpretation of neonatal neuroimaging studies is encouraged. If there is limited expertise in neonatal neuroimaging with persisting clinical concerns, then an expert neonatal neuroradiological opinion should be sought.
- The timing of MRI relates to both the clinical needs of the physician team and family in the management decision and knowledge of the optimal window for defining the nature and timing of the injury.
- Magnetic resonance imaging and magnetic resonance spectroscopy are the most sensitive neuroimaging modalities to assist with the timing of cerebral injury. Magnetic resonance imaging—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.
- If MRI or magnetic resonance spectroscopy undertaken after the first 24 hours of life is 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 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.
• Imaging obtained optimally at 10 days of life, with an approximate window of 7–21 days of life, depending on the logistics of acquiring MRI in the clinical setting, will better define the full extent or pattern of cerebral injury. The further one is from birth for imaging, the broader the range of injury and the less precisely one can define the timing of the injury.

• 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.

• Despite the advances in neuroimaging, our ability to precisely time the occurrence of a hypoxic–ischemic event is still limited, estimating within days rather than hours or minutes.

• Neuroimaging studies of infants undergoing therapeutic hypothermia confirm a reduction in the severity of brain injury. Importantly, the prognostic power of MRI is not altered by hypothermia therapy. The evolution of MRI findings after hypothermia therapy may be altered in some infants, with delays in the typical evolution of findings.

• 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.

**Neurodevelopmental Correlates of Neuroimaging Patterns**

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 relating 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 done after a week from the initial insult, correlating well with neurodevelopmental outcome (83–85). Conventional MRI in the first 24–96 hours of life may underestimate the total extent of the injury but is better in timing.

Studies have demonstrated that the extent of brain injury on MRI is more strongly associated with long-term outcome than the severity of injury in any given region (101, 103, 107). Several studies have divided patterns of injury into either watershed predominant or deep nuclear gray matter predominant with long-term follow-up. Deep nuclear gray matter (basal ganglia, thalamus) predominance is associated with more intensive need for resuscitation, more severe encephalopathy, increased seizure burden, and worse neurodevelopmental outcome as far out as 5 years of age (14, 104, 105). The basal nuclei pattern and abnormal signal intensity in the posterior limb of the internal capsule on MRI are both predictive of severely impaired motor and cognitive functions (101–104). An area to pay particular attention to is the posterior limb of the internal capsule, as previously noted. In images of healthy neonates, the internal capsule appears hypointense on T1-weighted images and hypointense on T2-weighted images compared with adjacent structures. If injured, the posterior limb of the internal capsule will appear hypointense on T1 images relative to the thalamus and putamen by 5 days after the injury. Abnormal signal intensity in the posterior limb is a powerful prognostic indicator for poor neurodevelopmental outcome, correctly predicting outcome in 92% of infants with Sarnat stage II hypoxic–ischemic encephalopathy (see Fig. 10-4) (101).

Although the motor and cognitive deficits following the basal nuclei pattern of injury often are evident during the first years of life, the cognitive deficits following the watershed pattern may appear later after 2 years of age (104). Importantly, cognitive deficits at 4 years of age are more strongly related to the severity of watershed injuries rather than the severity of injury in the deep nuclear gray matter (98).

Researchers reported findings on a large cohort of infants with encephalopathy, collected over a 15-year period at the Hammersmith and Queen Charlotte’s Hospitals in London (107, 109). Infants were included if they were 35 weeks of gestational age or older and exhibited altered neurologic behavior, signs of fetal compromise, and poor condition at birth. The researchers focused on infants who had an injury to the basal ganglia and thalamus identified on an MRI scan within the first 6 weeks of life and who were evaluated for outcome after 12 months of age. Over the course of the study, of the 555 infants in their neonatal database, 175 infants fulfilled the inclusion criteria. The researchers defined basal ganglia and thalamus injury by a practical three-tier classification system comprising mild basal ganglia and thalamus (focal and subtle abnormalities), often with a normal posterior
limb of the internal capsule; moderate basal ganglia and thalamus (multifocal discrete areas of damage or more diffuse injury) and a posterior limb of the internal capsule with an equivocal or abnormal appearance; and severe basal ganglia and thalamus with widespread basal ganglia and thalamus injury and an abnormal posterior limb of the internal capsule in almost all cases (107). A large proportion of the cohort displayed severe brain injury, particularly in the posterior limb of the internal capsule (76% of infants) and brain stem (67% of infants). They found that only the severity of basal ganglia and thalamus injury predicted motor outcomes, with a predictive accuracy for severe motor impairment of 89%. Damage to white matter, the cortex, and brain stem, by contrast, showed no significant correlation with motor impairment.

Interestingly, a dystonic or athetoid pattern of cerebral palsy, which traditionally would be associated with basal ganglia and thalamus lesions, was only observed in 46% of cases. The remaining 54% of cases with cerebral palsy showed a spastic pattern, which may result from the substantial concurrent neuropathology in these infants, namely moderate to severe white matter and cortical lesions in 82% and 57% of cases, respectively. The presence of brain-stem lesions was shown to be predictive of death, as has been demonstrated in traumatic head injury in children and adults (108). Brain-stem injury was displayed in 79 infants, with 49% of these infants dying in the first 3 years of life. In contrast to motor outcomes, the severity of basal ganglia and thalamus injury was not associated with an increased risk of death. Thus, neuroimaging markers in the newborn period were clearly demonstrated for death (brain-stem lesion) and cerebral palsy (basal ganglia and thalamus injury).

A previous report on the same cohort (109) investigated the association of basal ganglia and thalamus lesions with disability in the domains of feeding, speech and language, vision, and intellect, as well as the risk of epilepsy. This report summarized the risk of disability in six domains in relationship to the extent of basal ganglia and thalamus injury: mild, moderate, or severe. Within these categories, it also incorporated brain-stem lesions for the prediction of feeding difficulties and cortical injury for epilepsy. For cases of mild basal ganglia and thalamus, cerebral palsy occurs in 10–15%, with similar risks of impairments in the other domains with IQ greater than 84 in 80%. In cases of moderate basal ganglia and thalamus, cerebral palsy occurs in 60–75%, with 30–50% experiencing challenges in each of the other domains with IQ less than 70 in 35%. For cases of severe basal ganglia and thalamus, cerebral palsy is universal (98%), with 90–95% speech and feeding difficulties, 50–75% visual impairment, and 25–75% epilepsy. This report assists in providing expanded and clinically relevant outcomes, other than motor impairment or death, to understand the relationship between cerebral lesions and the spectrum of disabilities that affect children with perinatal brain injury.

Conclusions

- The nature and severity of brain injury on MRI in the first 21 days of life is an important marker for subsequent neurodevelopmental outcome.
- Injury to the brain stem is associated with a high risk of death in the first 3 years of life.
- Injury to the basal ganglia and thalamus can be graded as 1) mild, 2) moderate, or 3) severe, with increasing risk of cerebral palsy, speech and feeding difficulties, and epilepsy. An abnormal signal in the posterior limb of the internal capsule on MRI has high prognostic value for motor impairments.
- Injury to the watershed region is associated with milder neurodevelopmental consequences but cognitive impairments may be apparent in later childhood.

Research Recommendations

- Research initiatives to address several key gaps in knowledge relating to the role of MRI in determining the relationship of a perinatal insult to the pattern of brain injury would assist in the acute management of the term encephalopathic infant and allow more informed counseling of families regarding the likely nature and timing of a cerebral insult.
- 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 over 24 hours before delivery. Thus, studies of early (first 48 hours) and serial (eg, day 1, 4, 10) MRI in term-born encephalopathic infants will assist in determining the evolution of imaging findings. These studies should include careful evaluation of the placenta.
- Combined neuropathological and neuroimaging studies should be done in appropriate animal models of hypoxic–ischemic cerebral injury to assist in defining the sensitivity, specificity, and evolution of neuroimaging findings.
• Studies should be done to correlate MRI with neuropathology in human infants at autopsy, including histopathology, to define the sensitivity and specificity of the MRI signal characteristics. This could include postmortem MRI studies. These studies should include careful evaluation of the placenta.

• Comparative studies should be done of intra-observer and inter-observer variability in the neuroradiologic reporting of neuroimaging in neonatal encephalopathy, particularly in relation to MRI. Investigation of imaging findings in infants born at or beyond 35 weeks without fetal acidemia, resuscitation, admission to any neonatal facility, or a combination can be used to define the baseline incidence of abnormalities.

• Collaborative investigative teams should be developed to provide research evidence to base care practices comprising specialists in maternal–fetal medicine, neonatology, neurology, and neuroradiology.

• Outcomes morbidities and diagnostic accuracy of an MRI performed after transport should be compared with an in-suite MRI.

• Affordable MRI scanner equipment should be developed, such as self-shielded small MRI systems for neonates, which can be located in the neonatal intensive care unit to facilitate the acquisition of MRI without the risk of transportation and habitation outside the intensive care unit.

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Neonatal Interventions

The focus of this chapter is to describe common interventions for infants presenting with neonatal encephalopathy. Care of the neonate begins with basic delivery room management, including the Neonatal Resuscitation Program guidelines. Airway, breathing, and circulation are attended to, as well as temperature management. If needed, assisted ventilation is administered for infants with primary or secondary apnea, as well as those with respiratory compromise. General medical management can continue if needed in an appropriate neonatal care setting.

Infants at risk of or those who have encephalopathy require general supportive care that includes monitoring vital signs and attention to systems that may be compromised. Respiratory and cardiovascular support may be required. Attention to metabolic status, including blood glucose, hematologic, and electrolytes, is essential. Management of infants with encephalopathy may require additional evaluation and treatment depending on individual circumstances.

Temperature management is essential. Once stabilized, infants with encephalopathy can be assessed for potential cooling management. Therapeutic hypothermia for infants with moderate to severe encephalopathy has been a significant advance. Cooling reduces the combined rate of death and disability. Safety during cooling therapy is necessary, and protocols as well as checklists for individual centers are often useful. Despite cooling therapy, there are still a significant number of infants who suffer untoward outcome and, thus, there is a need for adjuvant therapies. This chapter presents a summary of interventions for infants with encephalopathy.

Effect of Neonatal Resuscitation on Outcomes

Even with timely provision of effective neonatal resuscitation, neonatal encephalopathy cannot be completely prevented. However, a number of studies have shown a significant reduction in perinatal mortality and morbidity after implementation of educational programs in neonatal resuscitation methods, such as the Neonatal Resuscitation Program. In 2000, standardized guidelines for neonatal resuscitation were developed by the International Liaison Task Force on Resuscitation (1). These guidelines are reviewed and revised based on a review of evidence at 5-year intervals. The state of Illinois evaluated the effect of Neonatal Resuscitation Program instruction on Apgar scores of neonates born in the state. Compared with neonates born before the Neonatal Resuscitation Program instruction was routine, neonates born after the providers of newborn care received the Neonatal Resuscitation Program instruction were more likely to have an Apgar score of 7–10 and less likely to have an Apgar score of 0–3 or 4–6. Further, neonates with 1-minute Apgar scores of 6 or less were more likely to have an increase in Apgar score at 5 minutes (2). The latter was true regardless of the level of neonatal care available at the hospital of birth.

Similar effects of resuscitation education have been reported in medium-resource and low-resource settings. Investigators found an increase in Apgar scores and a decrease in length of hospital stay among neonates with perinatal “asphyxia” after implementation.*

*Throughout the report, the terms “asphyxia” and “birth asphyxia” and their variations appear in quotes when used in reference to a particular study to emphasize the wide variation in study definitions of asphyxia. See Chapter 1 for recommended asphyxia definition (in Table 1–1) and discussion of asphyxia terminology.
of Neonatal Resuscitation Program training in a region of Turkey (3); there also was a subsequent decrease in the incidence of cerebral palsy, seizures, and abnormal electroencephalogram (EEG) (4). A meta-analysis of resuscitation in low-resource health care facilities found that training in basic resuscitation—defined as provision of drying, stimulation, and bag-mask ventilation—was associated with a 30% decrease in mortality at birth and a 38% decrease in the incidence of death in the first week after birth. A study of resuscitation by traditional birth attendants in Tanzania found that in infants with initial apnea, the risk of neonatal death or a prolonged hospital stay increased 16% for every 30-second delay (up to 6 minutes after birth) in initiating positive pressure ventilation with bag or mask; the risk of these two complications also increased 6% for every minute of positive pressure ventilation provided before achieving a normal heart rate and spontaneous respirations (5).

These results suggest that prompt initiation of neonatal resuscitation improves short-term and long-term outcomes in low-resource settings. One study, however, suggests that the in utero status of the fetus also may affect the outcome of resuscitation (6). A secondary analysis of a study that compared neonatal resuscitation with room air or 100% oxygen found that heart rate and Apgar scores increased in moderately and severely affected infants during resuscitation, suggesting that effective resuscitation was being provided (6). However, heart rate and Apgar scores remained significantly lower in infants who had poor outcomes compared with those with good outcomes. Infants with a heart rate of 60 beats per minute or less or an Apgar score of less than 4 at 5 minutes, or both, had a 16-fold greater chance of death in the first week of life or Sarnat stage 2/3 encephalopathy than infants with higher heart rates, Apgar scores, or both (6).

Researchers formally reviewed a series of consecutive cases of neonatal encephalopathy for quality of care provided during labor and delivery (7). Among the 59 deaths and 49 cases of neonatal encephalopathy examined, 21 instances of delayed or inappropriate resuscitation were identified. More than 100 incidents of inappropriate intrapartum management were noted (7). Similarly, other researchers reviewed all neonatal resuscitations over a 2-year period in Stockholm County and identified a number of instances of suboptimal ventilation and failure to have skilled practitioners available (8). Taken in combination, these data suggest that resuscitation skills and policies should be reviewed periodically to ensure optimal practice.

Conclusions

- Prompt initiation of neonatal resuscitation improves short-term and long-term outcomes in low-resource settings.
- Neonatal encephalopathy may reflect the effects of preceding in utero events that may not be able to be reversed by immediate resuscitation efforts.

Common Diagnostic Issues in the Delivery Room and Neonatal Intensive Care Unit

In dealing with sick neonates in the delivery room and upon admission to neonatal intensive care unit, there are common diagnostic strategies that can be used to guide our management for optimal care. These strategies are described in the next sections, with special emphasis on infants who have signs of encephalopathy and who are at risk of cerebral palsy and other neurodevelopmental impairment.

Neurologic Issues

Values of Umbilical Cord Blood pH and Base Deficit

Umbilical cord blood pH and base deficit are useful diagnostic parameters in the evaluation of an infant who requires resuscitation at birth. An umbilical cord blood pH of less than 7.0 and a base deficit of 12 mmol/L or greater are suggestive of fetal hypoxia leading to metabolic acidosis. This finding—along with other risk events, such as pregnancy complications (eg, preeclampsia), abnormal fetal heart rates, poor biophysical profiles, low Apgar scores (less than 3 at 2 minutes, 5 minutes, and 10 minutes), meconium-stained amniotic fluid, and multiorgan failure (including signs of encephalopathy)—suggests the diagnosis of nonreassuring fetal status.

Assessment of Infants’ Severity of Encephalopathy Using Physical Examination

An important task in assessing an infant with signs of encephalopathy is to evaluate its severity using the Sarnat score (Table 11-1) (9). It has been shown that a high Sarnat score is significantly associated with the incidence of death or neurologic impairment, including cerebral palsy (10–13). The scoring is an important diagnostic and prognostic instrument in assessing the outcome of these infants and is useful in counseling parents.

Diagnostic Approach in Infants With Seizures

Seizure is a common sign in an infant with encephalopathy. The standard EEG is done when clinical assessment cannot definitively establish the occurrence of seizure. Its prognostic value is limited;
however, a more useful diagnostic method for prog-
nostication is the use of amplitude-integrated EEG. Several studies have established close association 
between specific types of amplitude-integrated EEG and neurodevelopmental outcome at a later age 
(14–18). However, a study found that amplitude-
integrated EEG performed at less than 9 hours of age 
does not offer additional advantage in predicting out-
come of infants with hypoxic–ischemic encephalopa-
thy when compared with severity classification by 
neurologic examination (19).

**Imaging Studies for Brain Injury**

Several imaging techniques are available for the assessment 
of brain injury in an infant who has perinatal hypoxia. Cranial ultrasonography is a noninvasive procedure 
that can be done at the bedside and provide valuable information. It is routinely done in infants at 
less than 34 weeks of gestation to detect intraventricular hemorrhage. Classification of the severity of hemor-
rhage (20) provides useful information in predicting potential long-term outcome and is helpful in parental 
counseling. Because of limited exposure through the anterior fontanel during examination, some lesions 
that are located in the peripheral portion of the brain may be missed. Computed tomography scan or mag-
netic resonance imaging (MRI) offer a distinct advantage in detecting brain pathology in that they provide a 
clear picture of the lesion. In term infants with potential intracranial hemorrhage, MRI is useful in defining 
the exact location and extent of the lesion.

**Metabolic Complications**

**Hypoglycemia**

Hypoglycemia is a common neonatal metabolic comp-
plication. Infants with perinatal hypoxia are at risk of 
this complication. Although there is no consensus on 
the cutoff value for the definition of hypoglycemia 
(21), most clinicians consider 40 mg/dL as the cutoff 
for the diagnosis (22). Because infants with neonatal 
depression and those who are premature often are 
admitted to the neonatal intensive care unit and given 
glucose-containing parenteral fluid, hypoglycemia is 
not generally observed. However, if the infant is being 
oberved in a transitional or normal nursery, periodic 
glucose screening using point of care reflectance 
meter should be done. The guidelines published by 
the American Academy of Pediatrics provide useful 
and practical guides in screening and management of 
this condition (22).

**Hypocalcemia**

Hypocalcemia is another common neonatal metabolic 
complication. Total and ionized serum calcium deter-
mination should be done in all at-risk infants, including 
those with perinatal hypoxia. The mechanism of this

| TABLE 11-1. Modified Sarnat Stage* | 
| Stage** | Stage 1 | Stage 2 | Stage 3 |
| Level of Consciousness | Hyperalert | Lethargic or obtunded | Stupor or coma |
| Activity | Normal | Decreased | Absent |
| Neuromuscular Control | Normal | Mild hypotonia | Flaccid |
| Posture | Mild distal flexion | Strong distal flexion | Intermittent decerebration (extension) |
| Stretch Reflexes | Overactive | Overactive | Decreased or absent |
| Complex/Primitive Reflexes | Suck | Weak | Absent |
| Moro (startle) | Weak or Absent | Absent |
| Tonic Neck | Slight | Strong | Absent |
| Autonomic function | Pupils | Mydriasis | Miosis |
| Heart Rate | Tachycardia | Bradycardia | Variable |
| Seizures | None | Common; focal or multifocal | Uncommon (excluding decerebration) |

**STAGE 0=Normal
complication is unclear. It has been speculated that elevated calcitonin and relative hypoparathyroid state may be responsible for the association between hypocalcemia and “asphyxia” (23). The diagnosis generally is based on the total or ionized calcium level of less than 8.0 mg/dL or less than 1.1 mM/L, respectively, for term infants and less than 7.0 mg/dL or less than 0.75 mM/L, respectively, for preterm infants. Hypomagnesemia is a common concurrent metabolic abnormality because its hormonal regulation is similar to that of calcium. Thus, a serum magnesium level also should be done when evaluating for hypocalcemia.

**Hematologic Issues**

**Anemia**
Fetal anemia—which can be due to a variety of factors, such as fetomaternal hemorrhage and hemolytic diseases (blood group incompatibility or gestational parvovirus infection)—is a frequent cause of fetal hypoxia and neonatal depression. If the infant shows sign of pallor, hemoglobin and hematocrit tests should be done immediately to identify anemia and promptly correct it by blood transfusion. A maternal blood sample also should be obtained as soon as possible to confirm the presence of fetal red blood cells in the maternal circulation using the Kleihauer–Betke method. The presence of fetal red blood cell confirms the diagnosis of fetomaternal hemorrhage, and in some cases the degree of fetomaternal hemorrhage can be assessed by the amount of fetal red cells in the maternal circulation.

**Polycythemia**
Polycythemia—defined as venous hematocrit greater than 65%—is a frequent complication of infants with perinatal hypoxia. The mechanism is well established in that the presence of hypoxia stimulates erythropoiesis with an elevated level of erythropoietin. The clinical suspicion is based on the observation of a ruddy color and a confirmation of the condition by the hematocrit measurement. The abnormal clinical manifestation is a result of hyperviscosity with multiorgan circulatory sludging. Ideally, measurement of blood viscosity by a viscometer is preferred; however, viscometer for measurement of blood viscosity is not available in most routine clinical laboratories. Thus, we generally rely on hematocrit for the diagnosis. One important consideration in interpreting the hematocrit value for the diagnosis of polycythemia is the source of blood sampling. If the blood sample is obtained by an unwarmed heel puncture, the hematocrit will be approximately 10% higher than the simultaneously obtained central venous blood (24). It is essential that if the unwarmed capillary blood hematocrit is greater than 65%, a venous or arterial blood be obtained for hematocrit determination to establish the diagnosis of polycythemia. The hematocrit value of a blood sample obtained from a warmed heel puncture is still higher than the central venous blood although the gap is smaller (approximately 5%) (25).

**Hyperbilirubinemia**
Hyperbilirubinemia is a common hematologic disorder in the newborn. Jaundice that is due to an elevated serum bilirubin level has a multitude of causes, including blood group incompatibility, hemolytic disease that is due to red cell abnormality, and infection. In infants with neonatal depression, hyperbilirubinemia may result from increased red cell breakdown in those with excess red cell volume with or without polycythemia. Diagnostic measures should include maternal blood type and Rh and antibody screening. If jaundice appears in the first 24 hours, maternal and infant blood type and direct and indirect Coombs tests should be done to rule out Rh and ABO incompatibility as the cause of hyperbilirubinemia. Time-specific serum bilirubin determination is useful in predicting the occurrence of hyperbilirubinemia and is useful in making a decision of infant discharge or continuing nursery observation, as well as guiding therapy with either phototherapy or exchange transfusion (26).

**Respiratory Distress**
Respiratory distress is common after neonatal depression. The most common cause is the failure of cardiopulmonary transition. The most useful diagnostic parameter is chest roentgenogram. Streaking infiltrates is a common finding reflecting the presence of lung fluid that results from lack of transition and clearance of lung fluid. Chest roentgenogram is useful in confirming such diagnoses as aspiration syndromes, pneumothorax, congenital pulmonary abnormality (eg, congenital diaphragmatic hernia), tracheoesophageal fistula, and other conditions involving the upper respiratory system.

**Birth Injury**
Infants with neonatal depression, particularly those with difficult delivery and required instrument assistance during delivery (forceps, vacuum extraction), are at increased risk of birth injury. A thorough physical examination can reveal such condition as brachial plexus palsy (also known as Erb’s palsy), phrenic nerve injury, and clavicular fracture. Brachial plexus palsy can be diagnosed by performing a Moro reflex
maneuver. Infants with this condition will not move the affected upper extremity during the maneuver. Phrenic nerve palsy often presents as respiratory distress because of hemidiaphragmatic functional failure. Diagnosis is confirmed by ultrasonography or fluoroscopy with a visualization of failure of movement of the affected diaphragm.

Conclusions

- An umbilical cord blood pH of less than 7.0 and a base deficit of 12 mmol/L or greater, high Sarnat score, and imaging to assess brain injury are useful diagnostic methods in evaluating the level of severity of hypoxic–ischemic encephalopathy.
- Metabolic complications, such as hypoglycemia and hypocalcemia, can be identified by blood glucose and serum calcium determination.
- Anemia and polycythemia are frequent associated findings in infants who experience perinatal hypoxia and can be identified with hematocrit determination.
- Hyperbilirubinemia is a common neonatal complication. Assessment of etiology and serum bilirubin level is essential to avoid bilirubin-induced encephalopathy.
- Respiratory distress in infants who required delivery room resuscitation has a multitude of etiologies that require careful physical examination and a chest roentgenogram to determine the cause.
- Birth injury should be ruled out with thorough physical examination and appropriate imaging.

Assisted Ventilation for Infants With Neonatal Encephalopathy

Initiation of Ventilation

The decision of whether to initiate mechanical ventilation depends on the clinician’s assessment of the extent of the infant’s central nervous system injury and its prognosis. This is usually unclear in the early stages and, therefore, it may be necessary to initiate ventilation while information relevant to prognosis is being gathered. The decision not to initiate ventilation may be irreversible, whereas ventilation may be withdrawn if subsequent information suggests that it is futile. The physiologic processes that lead to cardiorespiratory failure and, thus, the need for ventilation, tend to improve over the first few days of life. Prognostic ability concerning outcome increases over the same period. The clinician thus may be faced with the decision as to the appropriate time to withdraw ventilation if the goal is to avoid survival with severe disability.

Approach to Ventilation

The technical approach to mechanical ventilation in this population depends on the type and degree of lung disease and in that sense is similar to any other group of newborns. Lung disease in babies with neonatal encephalopathy runs the spectrum from virtually normal lungs in neonates with apnea secondary to central nervous system damage to the most severe degree of parenchymal disease complicated by pulmonary hypertension. There are no data supporting one type or mode of ventilation as superior to another in terms of long-term outcome in infants with encephalopathy.

Optimal Blood Gas Values

During mechanical ventilation for infants with encephalopathy, the available evidence supports maintaining blood gases and pH in the physiologic range. Hyperventilation with resulting hypocapnia and respiratory alkalosis was once an accepted approach to treatment of the pulmonary hypertension that often accompanies encephalopathy. The use of inhaled nitric oxide has rendered this treatment obsolete.

There is scant information available on hyperventilation and neurologic outcome in asphyxiated neonates. Researchers examined a retrospective cohort of 244 infants with hypoxic–ischemic encephalopathy. They found that infants with Pco2 less than 20 mm Hg when assessed at 24 months of age were more likely to have died or, among surviving infants, to have severe cerebral palsy, any cerebral palsy plus blindness, deafness, or developmental delay. This association was not found with less severe (Pco2 less than 25 mm Hg) hypocapnia. Other researchers examined the relationship between hypocapnia and outcome from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network trial of hypothermia for neonatal encephalopathy. They found that minimum Pco2 and cumulative Pco2 less than 35 mm Hg were associated with increased death or disability at 18–22 months. In 2010, researchers did not find any difference in mean Pco2 between infants with normal outcome versus abnormal outcome in the retrospective data analysis, but only 6 of the 52 infants studied were normocapnic. In an older study of infants treated with hypocapnia to less than 25 mm Hg, the authors found normal growth and neurodevelopment in a group of 16 infants. Given
these findings and the availability of nitric oxide for treatment of pulmonary hypertension, should it occur in an infant with encephalopathy, hyperventilation is no longer recommended as a therapeutic approach (28).

**Hypercapnia**
There have not been prospective trials of permissive hypercapnia in infants with neonatal encephalopathy. In the 2010 retrospective review, the authors did not find an association between hypercapnia and outcome, but few of the patients were normocapnic (32). Given a lack of demonstrated pulmonary benefit and the potential effect on cerebral perfusion, there is no basis to recommend permissive hypercapnia for infants with encephalopathy (34).

**Hyperoxemia**
The current recommendation for term infants is to initiate resuscitation with room air and modify as clinically indicated according to pulse oximetry (1). There have not been studies of oxygenation and outcome over longer periods in “asphyxiated” newborn infants. Researchers did examine the effect of hyperoxemia in the first hours of life on outcome in their retrospective analysis of 244 “asphyxiated infants” (30). They found that severe hyperoxemia (Po2 greater than 200 mm Hg) was associated with a poor outcome at 24 months but found no association with Po2 greater than 100 mm Hg.

**Effect of Hypothermia on Pulmonary Function**
With the advent of hypothermia as a major therapeutic modality for neonatal encephalopathy, the question of its effect on pulmonary function has arisen. There have been no comparisons of pulmonary mechanics during hypothermia, but two groups have looked at clinical indices of pulmonary function (35, 36). Neither group found any significant differences between newborns who were deeply cooled (30–33˚C) versus those who were mildly cooled (33–34˚C) or between infants undergoing head cooling versus whole-body cooling.

**Effect of Hypothermia on Measured Blood Gases**
Cooling affects blood gases by changing metabolic rate, increasing the solubility of gases in blood, shifting the hemoglobin saturation curve to the left, and through complex interactions of these factors and pH (37). The change in Pco2 is a 4% increase per Celsius degree. The normal range of Pco2 at normal body temperature is 36–44 mm Hg, resulting in a corrected range for infants cooled to 34˚C of 41–51 mm Hg (38). Using this range for making ventilator adjustments would result in a respiratory acidosis with its potential effect on cerebral perfusion. Given a lack of clear-cut data and the complex nature of the issue, it is prudent to stay in familiar territory and use blood gas values measured at 37˚C, not corrected for body temperature.

**Nitric Oxide**
Inhaled nitric oxide is the mainstay of treatment of the pulmonary hypertension that often accompanies respiratory failure in infants with neonatal encephalopathy (29). It has been shown to improve oxygenation and reduce the need for extracorporeal membrane oxygenation. Theoretically, inhaled nitric oxide should have minimal effect on organs other than the lung, including the brain, because of its rapid metabolism. The investigators of the Neonatal Inhaled Nitric Oxide Study Group examined the outcome of 199 newborns enrolled in their randomized trial of inhaled nitric oxide for treatment of persistent pulmonary hypertension (39). The investigators found no difference in neurodevelopmental outcome at 18–24 months of age between the inhaled nitric oxide-treated and control groups. Given the frequent combination of encephalopathy and persistent pulmonary hypertension of the newborn, the limited follow-up studies suggest that treatment with inhaled nitric oxide is not likely to be harmful to the brain.

**Surfactant Therapy**
Meconium aspiration syndrome frequently accompanies neonatal encephalopathy, and meconium is known to inhibit surfactant function. Use of exogenous surfactant for treatment of meconium aspiration has been examined in several clinical trials (40–43) and a meta-analysis (44). The combined studies did not show a decrease in mortality, but there was an overall trend toward better pulmonary outcomes in the surfactant-treated groups. In those studies in which extracorporeal membrane oxygenation was available as a rescue treatment, there was less extracorporeal membrane oxygenation use in the surfactant-treated groups (40, 41). No studies have evaluated the effect of surfactant on neurologic outcomes in this population.

In summary, there is little information in the literature dealing specifically with the optimal approach to mechanical ventilation in infants with encephalopathy complicated by respiratory failure. Given this situation, the best approach is to use the mode of ventilation best suited to the infant’s lung disease and to maintain blood gases in the usual physiologic range, if possible.
Conclusions

- The decision to initiate assisted ventilation in a newborn with encephalopathy depends on the clinician's assessment of the extent of the infant's central nervous system injury and its prognosis and may be withdrawn if subsequent information suggests that it is futile. The technical aspects of approach to ventilation depend on the type and degree of lung disease independent of encephalopathy.

- Blood gas concentrations should be maintained in the usual physiologic range.

Cooling for Neuroprotection

Moderate cooling by 3–4°C is the first efficacious neural rescue therapy for neonatal encephalopathy. The development of treatment with moderate cooling for neural rescue in newborns with hypoxic–ischemic brain injury is the culmination of research spanning decades that proved the potential for neural rescue after “perinatal asphyxia” (45), consistently showed benefit in appropriate experimental models (46, 47), examined safety and feasibility in preliminary clinical studies (48, 49), confirmed efficacy by synthesis of the results of several well-conducted randomized clinical trials in newborns (50), and was followed by rapid implementation into clinical practice and ongoing surveillance (51). The positive results of randomized clinical trials led to recommendations by expert groups, specialist advisory committees, and professional bodies for the rapid implementation into clinical practice of treatment with cooling for neonatal encephalopathy (52–54).

Preliminary Trials

The safety and feasibility of cooling infants with hypoxic–ischemic encephalopathy were investigated in a number of small preliminary studies before the large randomized controlled trials (48). Subsequently, a commercial device for providing selective head cooling with mild body cooling was developed and used in the first large randomized trial of neural rescue with cooling in infants with perinatal hypoxic–ischemic injury: the CoolCap trial (55).

Safety concerns were raised in a pilot randomized controlled trial of 65 infant's allocated whole-body cooling to 33°C for 48 hours or standard care (56). The group allocated to cooling had significantly higher prothrombin times and lower platelet counts and a greater requirement for inotropes and infusions of plasma and platelets. Seizures also were reported to be more frequently observed in the cooled group compared with the noncooled infants. These complications were considered to be of mild to moderate severity and easily manageable. These findings may be related to the lower rectal temperature aimed for in this study compared with the other trials (33°C versus 33.5–34.5°C).

Researchers investigated a protocol that might be used to enroll infants in prospective randomized controlled trials of neural rescue with hypothermia (49). The aim was to use objective criteria to select infants (within 6 hours of birth) with suspected “birth asphyxia” with a high risk of developing moderate to severe encephalopathy. Because clinical criteria alone were considered poorly predictive of subsequent outcome when applied so soon after birth, they proposed staged entry criteria: Infants suspected of having suffered perinatal hypoxic–ischemic injury were defined using clinical criteria and were entered into the study. These infants then underwent objective assessment of their neurologic prognosis using amplitude-integrated EEG, and those infants with a poor prognosis were selected for treatment with hypothermic neural rescue therapy. The researchers suggested that this approach increased specificity, which would allow a smaller study size. This method was subsequently used in three large trials of therapeutic cooling in infants with suspected “birth asphyxia” (55, 57, 58).

Clinical Trials of Neural Rescue With Cooling 
Outcomes to at Least 18 Months of Age

The initial studies were too small to assess the neuroprotective effect of therapeutic cooling or only reported short-term outcomes. The author of the pilot randomized study of 65 infants found that cooling was associated with a lower rate of death or severe motor scores up to 12 months of age (14/27 [52%] in the cooled group compared with 21/25 [84%] in the noncooled group, \( P = .019 \)), but 12-month motor follow-up data were only available in 28/41 survivors (59). In this study, more than 75% of the infants were born outside the cooling centers, but cooling could be initiated during transport. Outborn infants were 10 times more likely to die than inborns, but no explanation for this observation could be found.

Several large randomized controlled trials of hypothermic neural rescue therapy in newborns with hypoxic–ischemic encephalopathy with outcomes to at least 18 months of age were published from 2005 to 2011 (55–58, 60–63). These studies had a similar study design, largely based on the CoolCap study (see Box 11-1), but there were some differences: In two trials the intervention was selective head cooling with mild
body cooling (55, 61), and three trials used amplitude-integrated EEG or EEG for assessment of the severity of encephalopathy and enrollment of infants (55–58). In all trials, infants were full term or near term (35 weeks or 36 weeks of gestation), and randomization was completed within 6 hours of birth in all but one study. The intervention period was 72 hours followed by slow rewarming at 0.5˚C per hour, and in all the trials the primary outcome measure was the combined rate of death and disability assessed at 18–24 months of age. The target rectal temperature was 33.5˚C in all the trials that used whole-body cooling. All but one study used specific cooling equipment to achieve and maintain hypothermia. The whole-body hypothermia for term and late-preterm newborns with hypoxic–ischemic encephalopathy trial (the ICE trial) (63) differed from the other trials in that the investigators expected most infants to be born outside tertiary centers (outborn) and, therefore, trained dedicated retrieval teams to identify infants at risk of brain injury. Furthermore, in order for cooling to be used at the birth hospital, refrigerated gel packs were placed around the infant.

Outcomes were remarkably similar among the trials. All showed a reduction in the combined rate of death and disability with cooling, and this reached statistical significance in four of the six studies. The rates of death and disability in the control groups were similar in four of the studies (53–66%), suggesting that patient selection and standard of care were likely similar in these trials; the event rate was higher in one study (83%) and lower in another (49%) (58, 61). The studies are summarized in Table 11-2.

Synthesis of Trial Data
Although no formal prospective meta-analysis was set up, trial investigators recognized from the outset that meta-analysis of trial data would be required to confirm the safety and efficacy of therapeutic hypothermia for neonatal encephalopathy. Accordingly, the major trials had a similar trial design: Clinical enrollment criteria, duration and depth of cooling, and outcome measures were similar, albeit different methods of cooling were used. Synthesis of the trial data shows remarkable consistency with minimal heterogeneity among the studies.

The results of a meta-analysis of randomized controlled trials with outcomes to at least 18 months of age and published in the English literature are displayed as risk ratios and 95% confidence interval (CI) in Figures 11-1–11-7. These data confirm that prolonged mild cooling, whether provided by a cooling cap or systemically, reduces the rate of death and of severe disability and increases the rate of intact survival at 18–24 months of age. The size of the effect (calculated from data from the six large randomized trials with similar entry criteria) is clinically important. For every seven infants (95% CI, 5–11) treated, one infant is prevented from dying or becoming disabled.

Typical risk ratios for selective head cooling and whole-body cooling are similar (see Fig. 11-6). In view of the simplicity of whole-body cooling and the close temperature control achieved with servo-controlled
TABLE 11-2. Summary of the Main Randomized Trials of Cooling for Neonatal Encephalopathy With Outcome to 18–24 Months of Age

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Method</th>
<th>Criteria</th>
<th>Rate of Death or Disability in Controls (%)</th>
<th>Rate of Death or Disability in Cooled Infants (%)</th>
<th>Risk Ratio (RR)</th>
<th>Lower Limit of RR</th>
<th>Upper Limit of RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoolCap (Gluckman 2005)</td>
<td>USA, New Zealand, UK</td>
<td>Selective head with mild body</td>
<td>Clinical plus aEEG</td>
<td>73/110 (66.36)</td>
<td>59/108 (54.62)</td>
<td>0.82</td>
<td>0.66</td>
<td>1.02</td>
</tr>
<tr>
<td>NICH (Shankaran 2005)</td>
<td>USA</td>
<td>Whole body</td>
<td>Clinical</td>
<td>64/106 (60.37)</td>
<td>45/102 (44.11)</td>
<td>0.73</td>
<td>0.56</td>
<td>0.95</td>
</tr>
<tr>
<td>TOBY (Azzopardi 2009)</td>
<td>UK, Hungary, Ireland, Sweden, Finland, Israel</td>
<td>Whole body</td>
<td>Clinical plus aEEG</td>
<td>86/162 (53.08)</td>
<td>74/163 (45.39)</td>
<td>0.86</td>
<td>0.68</td>
<td>1.07</td>
</tr>
<tr>
<td>Li 2009</td>
<td>China</td>
<td>Whole body</td>
<td>Clinical</td>
<td>21/44 (47.7)</td>
<td>7/38 (18.4)</td>
<td>0.39</td>
<td>0.18</td>
<td>0.81</td>
</tr>
<tr>
<td>Zhou 2010</td>
<td>China</td>
<td>Selective head with mild body</td>
<td>Clinical</td>
<td>46/94 (48.93)</td>
<td>31/100 (31)</td>
<td>0.63</td>
<td>0.44</td>
<td>0.91</td>
</tr>
<tr>
<td>neo.nEURO. network (Simbruner 2010)</td>
<td>Germany, France, Belgium, Denmark, Italy, South Africa, Singapore</td>
<td>Whole body</td>
<td>Clinical plus aEEG</td>
<td>48/58 (82.75)</td>
<td>27/53 (50.94)</td>
<td>0.62</td>
<td>0.46</td>
<td>0.82</td>
</tr>
<tr>
<td>ICE (Jacobs 2011)</td>
<td>Australia, New Zealand, Canada, USA</td>
<td>Whole body (cool packs)</td>
<td>Clinical</td>
<td>67/101 (66.34)</td>
<td>55/107 (51.4)</td>
<td>0.77</td>
<td>0.62</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Abbreviation: aEEG, amplitude-integrated electroencephalogram.


cooling equipment, this likely will become the most widely practiced method of inducing and maintaining cooling therapy in newborns.

Synthesis of trial results grouped by severity of encephalopathy suggests that cooling reduced the rates of death and disability at 18–24 months of age both in the moderate and the severe encephalopathy subgroups (see Fig. 11-6). However, the assessment of encephalopathy very soon after birth is problematic, and the criteria and method of assessment differed between the studies. Some studies used the amplitude-integrated EEG for assessing encephalopathy, but the amplitude-integrated EEG grade is not necessarily equivalent to the clinical grade of encephalopathy. This was evident in the CoolCap study, in which the combined rate of death and disability in the subgroups differed according to the method of assessment of encephalopathy (55, 64). Furthermore, there were a higher proportion of infants with severe encephalopathy noted in the trials in which assessment of encephalopathy was by amplitude-integrated EEG, yet the outcomes were broadly similar among all the trials. Assessment of severity of encephalopathy by amplitude-integrated EEG is less precise during the first 6 hours after birth, because even in the precooling era, a proportion of cases with severely suppressed amplitude-integrated EEG show return of cerebral electrical activity over the subsequent
NEONATAL INTERVENTIONS

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Li 2009</td>
<td>7</td>
<td>38</td>
<td>21</td>
<td>44</td>
</tr>
<tr>
<td>Zhou 2010</td>
<td>31</td>
<td>100</td>
<td>46</td>
<td>94</td>
</tr>
<tr>
<td>neo.nEURO 2010</td>
<td>27</td>
<td>53</td>
<td>48</td>
<td>58</td>
</tr>
<tr>
<td>NICHD 2005</td>
<td>45</td>
<td>102</td>
<td>64</td>
<td>106</td>
</tr>
<tr>
<td>ICE 2011</td>
<td>55</td>
<td>107</td>
<td>67</td>
<td>101</td>
</tr>
<tr>
<td>TOBY 2009</td>
<td>74</td>
<td>163</td>
<td>86</td>
<td>162</td>
</tr>
<tr>
<td>CoolCap 2005</td>
<td>59</td>
<td>108</td>
<td>73</td>
<td>110</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>671</td>
<td>675</td>
<td>100.0%</td>
<td>0.74 [0.66, 0.84]</td>
</tr>
</tbody>
</table>

Total events: 174

Heterogeneity: Tau²=0.00; Chi²=0.81, df=6 (P=.24); I²=0%

Test for overall effect: z=4.86 (P<.001)

FIG. 11-2. Forest plot of risk ratios of the rate of survival with normal neurologic outcome in cooled infants and controls at 18–24 months of age.

Safety outcomes were assessed in several preliminary and randomized controlled trials of moderate cooling for neonatal encephalopathy. Although several short-term adverse events occurred in cooled infants and control infants, only a low platelet count occurred significantly more frequently in the cooled infants (see Fig. 11-7). The other adverse events were related to the systemic hypoxic–ischemic injury that accompanied neonatal encephalopathy. The mortality rate at 18 months of age was similar in the treated and control infants in most of the trials but was significantly reduced with cooling in the ICE trial and on meta-analysis of trial data (see Fig. 11-4).

A mild coagulopathy occurred commonly in cooled infants and noncooled infants, and bleeding...
### 1.3.1 Major neurodevelopmental disability in survivors

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Li 2009</td>
<td>6</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>neo.nEURO 2010</td>
<td>7</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Zhou 2010</td>
<td>11</td>
<td>80</td>
<td>19</td>
</tr>
<tr>
<td>NICHD 2005</td>
<td>21</td>
<td>78</td>
<td>26</td>
</tr>
<tr>
<td>CoolCap 2005</td>
<td>23</td>
<td>72</td>
<td>31</td>
</tr>
<tr>
<td>ICE 2011</td>
<td>28</td>
<td>80</td>
<td>25</td>
</tr>
<tr>
<td>TOBY 2009</td>
<td>32</td>
<td>120</td>
<td>42</td>
</tr>
<tr>
<td><strong>Subtotal (95% Cl)</strong></td>
<td>500</td>
<td>442</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 128 / 176

Heterogeneity: $\tau^2=0.01$; $\chi^2=7.17$, $df=6$ ($P=.31$); $I^2=16$

Test for overall effect: $z=4.11$ ($P<.001$)

### 1.3.2 Rate of cerebral palsy in survivors

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Li 2009</td>
<td>2</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>neo.nEURO 2010</td>
<td>4</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>Zhou 2010</td>
<td>10</td>
<td>80</td>
<td>19</td>
</tr>
<tr>
<td>NICHD 2005</td>
<td>15</td>
<td>77</td>
<td>19</td>
</tr>
<tr>
<td>ICE 2011</td>
<td>21</td>
<td>79</td>
<td>17</td>
</tr>
<tr>
<td>CoolCap 2005</td>
<td>23</td>
<td>72</td>
<td>29</td>
</tr>
<tr>
<td>TOBY 2009</td>
<td>33</td>
<td>120</td>
<td>48</td>
</tr>
<tr>
<td><strong>Subtotal (95% Cl)</strong></td>
<td>497</td>
<td>437</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 108 / 150

Heterogeneity: $\tau^2=0.00$, $\chi^2=7.61$, $df=6$ ($P=.27$); $I^2=21$

Test for overall effect: $z=3.51$ ($P=.004$)

### 1.3.3 Rate of severe neuromotor delay (PDI<70) in survivors

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>ICE 2011</td>
<td>19</td>
<td>73</td>
<td>14</td>
</tr>
<tr>
<td>NICHD 2005</td>
<td>20</td>
<td>74</td>
<td>22</td>
</tr>
<tr>
<td>CoolCap 2005</td>
<td>21</td>
<td>69</td>
<td>23</td>
</tr>
<tr>
<td>TOBY 2009</td>
<td>27</td>
<td>114</td>
<td>37</td>
</tr>
<tr>
<td><strong>Subtotal (95% Cl)</strong></td>
<td>330</td>
<td>277</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 87 / 96

Heterogeneity: $\tau^2=0.00$, $\chi^2=0.62$, $df=3$ ($P=.89$); $I^2=0$

Test for overall effect: $z=2.21$ ($P=.03$)

### 1.3.4 Rate of severe neurodevelopmental delay (MDI<70) in survivors

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Li 2009</td>
<td>4</td>
<td>37</td>
<td>10</td>
</tr>
<tr>
<td>ICE 2011</td>
<td>17</td>
<td>73</td>
<td>14</td>
</tr>
<tr>
<td>NICHD 2005</td>
<td>19</td>
<td>75</td>
<td>24</td>
</tr>
<tr>
<td>CoolCap 2005</td>
<td>21</td>
<td>70</td>
<td>24</td>
</tr>
<tr>
<td>TOBY 2009</td>
<td>28</td>
<td>115</td>
<td>38</td>
</tr>
<tr>
<td><strong>Subtotal (95% Cl)</strong></td>
<td>370</td>
<td>324</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 89 / 110

Heterogeneity: $\tau^2=0.00$, $\chi^2=1.20$, $df=4$ ($P=.88$); $I^2=0$

Test for overall effect: $z=2.86$ ($P=.004$)

---

**FIG. 11-3.** Forest plots of the risk ratios of individual neurologic outcomes in cooled infants and controls at 18–24 months of age. Abbreviation: CI, confidence interval. (Figure originally published in Edwards AD and Azzopardi DV. Chapter 4 “Clinical trails of hypothermic neural rescue” in Neonatal Neural Rescue, A.D. Edwards, D.V. Azzopardi, A.J. Gunn [Eds]. Published by Cambridge University Press, 2013. Reproduced with permission.)
### NEONATAL INTERVENTIONS

#### Hypothermia vs. Normothermia: Risk Ratio

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robertson 2008</td>
<td>7</td>
<td>21</td>
<td>1</td>
<td>0.5% 5.00 [0.69, 36.50]</td>
</tr>
<tr>
<td>Lin 2006</td>
<td>2</td>
<td>32</td>
<td>2</td>
<td>0.8% 0.94 [0.14, 6.24]</td>
</tr>
<tr>
<td>Akisu 2003</td>
<td>0</td>
<td>11</td>
<td>2</td>
<td>1.0% 0.18 [0.01, 3.41]</td>
</tr>
<tr>
<td>Li 2009</td>
<td>1</td>
<td>38</td>
<td>3</td>
<td>1.1% 0.39 [0.04, 3.56]</td>
</tr>
<tr>
<td>Shankaran 2002</td>
<td>2</td>
<td>9</td>
<td>3</td>
<td>1.1% 0.74 [0.16, 3.48]</td>
</tr>
<tr>
<td>Eicher 2005</td>
<td>10</td>
<td>32</td>
<td>14</td>
<td>11.2% 0.27 [0.09, 0.82]</td>
</tr>
<tr>
<td>Zhou 2010</td>
<td>20</td>
<td>100</td>
<td>27</td>
<td>11.2% 0.70 [0.42, 1.15]</td>
</tr>
<tr>
<td>neo.nEURO 2010</td>
<td>20</td>
<td>53</td>
<td>33</td>
<td>12.6% 0.66 [0.44, 1.00]</td>
</tr>
<tr>
<td>NICHD 2005</td>
<td>24</td>
<td>102</td>
<td>38</td>
<td>14.9% 0.66 [0.43, 1.01]</td>
</tr>
<tr>
<td>CoolCap 2005</td>
<td>36</td>
<td>108</td>
<td>42</td>
<td>16.7% 0.87 [0.61, 1.25]</td>
</tr>
<tr>
<td>ICE 2011</td>
<td>27</td>
<td>108</td>
<td>42</td>
<td>16.8% 0.65 [0.43, 0.97]</td>
</tr>
<tr>
<td>TOBY 2009</td>
<td>42</td>
<td>163</td>
<td>44</td>
<td>17.7% 0.95 [0.66, 1.36]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>777</td>
<td>781</td>
<td>100.0%</td>
<td>0.77 [0.66, 0.90]</td>
</tr>
</tbody>
</table>

**Total events**: 191 vs. 251

**Heterogeneity**: Chi²=8.37, df=11 (P=.68); I²=0%

**Test for overall effect**: z=3.29 (P=.001)

#### Hypothermia vs. Normothermia: Subgroup Analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li 2009</td>
<td>3</td>
<td>24</td>
<td>15</td>
<td>3.7% 0.27 [0.09, 0.82]</td>
</tr>
<tr>
<td>Zhou 2010</td>
<td>9</td>
<td>41</td>
<td>19</td>
<td>10.5% 0.47 [0.24, 0.92]</td>
</tr>
<tr>
<td>TOBY 2009</td>
<td>20</td>
<td>65</td>
<td>30</td>
<td>22.8% 0.69 [0.44, 1.08]</td>
</tr>
<tr>
<td>NICHD 2005</td>
<td>22</td>
<td>69</td>
<td>30</td>
<td>25.0% 0.67 [0.43, 1.03]</td>
</tr>
<tr>
<td>ICE 2011</td>
<td>26</td>
<td>61</td>
<td>34</td>
<td>38.0% 0.64 [0.45, 0.91]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>260</td>
<td>254</td>
<td>100.0%</td>
<td>0.62 [0.50, 0.77]</td>
</tr>
</tbody>
</table>

**Total events**: 80 vs. 128

**Heterogeneity**: Tau²=0.00; Chi²=3.25, df=4 (P=.52); I²=0%

**Test for overall effect**: z=4.29 (P=.001)

#### Infants with moderate encephalopathy

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li 2009</td>
<td>4</td>
<td>14</td>
<td>6</td>
<td>1.5% 0.57 [0.21, 1.56]</td>
</tr>
<tr>
<td>Zhou 2010</td>
<td>22</td>
<td>38</td>
<td>27</td>
<td>14.3% 0.75 [0.54, 1.04]</td>
</tr>
<tr>
<td>NICHD 2005</td>
<td>23</td>
<td>32</td>
<td>34</td>
<td>23.8% 0.85 [0.66, 1.09]</td>
</tr>
<tr>
<td>TOBY 2009</td>
<td>54</td>
<td>98</td>
<td>56</td>
<td>25.3% 0.93 [0.73, 1.19]</td>
</tr>
<tr>
<td>ICE 2011</td>
<td>25</td>
<td>30</td>
<td>24</td>
<td>35.0% 0.94 [0.76, 1.15]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>212</td>
<td>209</td>
<td>100.0%</td>
<td>0.88 [0.78, 0.99]</td>
</tr>
</tbody>
</table>

**Total events**: 128 vs. 147

**Heterogeneity**: Tau²=0.00; Chi²=2.37, df=4 (P=.67); I²=0%

**Test for overall effect**: z=2.05 (P=.04)

#### Infants with severe encephalopathy

**FIG. 11-4. Forest plot of the risk ratios of mortality rate in cooled infants and controls.** Abbreviation: CI, confidence interval. (Figure originally published in Edwards AD and Azzopardi DV. Chapter 4 “Clinical trails of hypothermic neural rescue” in Neonatal Neural Rescue, A.D. Edwards, D.V. Azzopardi, A.J. Gunn (Eds). Published by Cambridge University Press, 2013. Reproduced with permission.)

**FIG. 11-5. Forest plot of the risk ratios of the combined rates of death and disability in cooled infants and controls at 18–24 months of age, grouped by the severity of encephalopathy.** The severity of encephalopathy was by amplitude-integrated electroencephalogram (aEEG) grade in the TOBY and n.nEURO studies, by aEEG and clinical grade in the CoolCap study (data from clinical assessment only displayed in forest plot), and by clinical grade only in the other studies. Abbreviation: CI, confidence interval. (Figure originally published in Edwards AD and Azzopardi DV. Chapter 4 “Clinical trails of hypothermic neural rescue” in Neonatal Neural Rescue, A.D. Edwards, D.V. Azzopardi, A.J. Gunn (Eds). Published by Cambridge University Press, 2013. Reproduced with permission.)
did not occur more frequently with cooling. In the
TOBY trial, mild intracranial hemorrhage on MRI
was observed in approximately 30% of cooled and
control infants (57, 67). Sinus bradycardia and prolon-
gation of the QT interval in the electrocardiogram are
physiologic responses to hypothermia and were
almost universally observed in the cooled infants (63).
However, clinically significant arrhythmias were very
rare and not more frequent with cooling. Minor skin
changes, such as reddening or hardening of the skin,
was observed in a few infants treated with whole-
body cooling, and similar changes occurred rarely on
the scalp with head cooling. Subcutaneous fat necro-
sis occurred in one infant allocated whole-body cool-
ing in the NICHD trial. This complication is notified
in approximately 1% of cases registered with the U.K.
Cooling Register and is probably directly related to
surface cooling in “asphyxiated” infants (68).

Neither sepsis nor pneumonia was found to be
associated with cooling in the trials. The frequencies
of other pulmonary complications were similar in
cooled and noncooled infants; the incidence of persis-
tent pulmonary hypertension varied with individual
trials occurring most frequently (approximately 25%)
in the NICHD trial.

**Exploratory Analysis**

Post hoc exploratory analyses of data from the ran-
domized trials have been performed to attempt to
address some of the clinical uncertainties surround-
ing therapeutic hypothermia in newborns with
eencephalopathy, such as the influence of temperature
control on outcomes (64, 69), effect of cooling on cli-
cinal predictors of outcome (70, 71), cardiovascular
effects of cooling (72), and others (31).

The effect of pyrexia on neurologic outcome in an
infant’s allocated standard care without cooling was
examined in the CoolCap and NICHD trials (64, 73).
A rectal or esophageal temperature of 38°C or greater
was observed in approximately 30% of controls, and a direct relationship was
found between elevated core temperature and sub-
sequent outcome. The odds of death or disability were
increased threefold in the infants with pyrexia in the

![Forest plot of the risk ratios of the combined rates of death and disability in cooled infants and controls at 18–24 months of age, grouped by the method of cooling.](image)
CoolCap trial and increased 3.6–4-fold with each Celsius degree increase in the highest quartile of esophageal temperature in the NICHD trial. These observations strongly suggest that pyrexia is injurious after hypoxic–ischemic injury and is consistent with experimental data.

In the clinical trials, excessive cooling commonly occurred in the infants allocated cooling, most often during the induction phase of cooling. An esophageal temperature of less than 32˚C was observed in approximately 30% of infants allocated cooling in the NICHD trial, despite using servo-controlled cooling equipment. It occurred more frequently in the infants with low birth weights but did not cause systemic or cardiovascular complications and was not associated with a worse neurologic outcome (69). Although this is reassuring, there are several case reports of cardiac arrhythmias and other adverse events following accidental hypothermia to less than 32˚C, so excessive cooling should be avoided.

In experimental studies, the brain-sparing effect of moderate hypothermia is critically affected by the interval between the insult and start of cooling; delay in induction of hypothermia beyond 8 hours is associated with attenuation or loss of neuroprotection (74). In the cooling trials, cooling was initiated at a median age of approximately 4 hours with little variability among the trials. Therefore, it is not surprising that no interaction effect was seen between age at initiation of cooling and outcome. Further information about the effect of delay in starting cooling may be available from a clinical trial currently under way examining the effects of cooling after 6 hours of age (Evaluation of Systemic Hypothermia Initiated After 6 Hours of Age in Infants with Hypoxic Ischemic Encephalopathy: A Bayesian Evaluation NCT00614744), as well as from data from the cooling registries. Another trial, Optimizing Hypothermia as Neuroprotection at Less Than 6 Hours of Age for Neonatal Hypoxic Ischemic Encephalopathy, also is planned by the NICHD to determine the optimal duration of cooling therapy and the depth of cooling.

The ability to predict outcome and the response to cooling treatment soon after birth is vitally important for clinical management of infants with hypoxic–ischemic encephalopathy. This was investigated by the CoolCap and NICHD trial investigators (11, 64, 70). In the CoolCap study, following multivariate analysis, treatment with cooling, low grade of encephalopathy, increased amplitude-integrated EEG amplitude, low birth weight, and absence of seizures were associated with a better outcome. The encephalopathy grade at randomization was the strongest predictor of outcome, closely followed by an amplitude-integrated EEG background amplitude. There was no evidence of interaction between treatment with cooling and these variables. The NICHD investigators used two approaches: 1) a score was developed from the most predictive variables following logistic regression analysis, and 2) prognostic algorithms were developed from classification and regression tree analysis. Prediction of death or death and disability by either method was

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total Events</td>
<td>Weight</td>
<td>M-H, Random, 95% Cl</td>
</tr>
<tr>
<td>Eicher 2005</td>
<td>20</td>
<td>31</td>
<td>9.4%</td>
<td>2.88 [1.03, 8.07]</td>
</tr>
<tr>
<td>ICE 2001</td>
<td>56</td>
<td>110</td>
<td>26.3%</td>
<td>1.25 [0.73, 2.13]</td>
</tr>
<tr>
<td>neo.nEURO 2010</td>
<td>16</td>
<td>62</td>
<td>15.2%</td>
<td>0.70 [0.32, 1.51]</td>
</tr>
<tr>
<td>NICHD 2005</td>
<td>20</td>
<td>102</td>
<td>15.7%</td>
<td>1.74 [0.82, 3.73]</td>
</tr>
<tr>
<td>TOBY 2009</td>
<td>94</td>
<td>163</td>
<td>33.4%</td>
<td>1.38 [0.89, 2.14]</td>
</tr>
<tr>
<td>Zhou 2010</td>
<td>6</td>
<td>100</td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>568</td>
<td>469</td>
<td>100.0%</td>
<td>1.35 [0.96, 1.89]</td>
</tr>
</tbody>
</table>

| Total events      | 212         | 177          |

Test for overall effect: z=1.73 (P=.08)

Heterogeneity: Tau²=0.04; Chi²=5.42, df=4 (P=.25); I²=26%

FIG. 11-7. Forest plot of the odds ratio of the occurrence of thrombocytopenia in cooled infants and controls. Thrombocytopenia was defined as a platelet count less than 150,000 cells/microliter in the Eicher, TOBY, and ICE trials, and less than 100,000 cells/microliter in the CoolCap, n.nEURO, and Zhou trials. For the Eunice Kennedy Shriver National Institute of Child Health and Human Development trial, the rates of infants who required platelet transfusion are shown. Abbreviation: CI, confidence interval. (Figure originally published in Edwards AD and Azzopardi DV. Chapter 4 “Clinical trials of hypothermic neural rescue” in Neonatal Neural Rescue, A.D. Edwards, D.V. Azzopardi, A.J. Gunn (Eds). Published by Cambridge University Press, 2013. Reproduced with permission.)
comparable or better than the grade of encephalopa-
thy before randomization and was not altered by
treatment with cooling; approximately 75% of infants
were correctly classified. It is uncertain whether this
is sufficiently precise for guiding clinical manage-
ment. Interestingly, abnormal posture, absence of
spontaneous activity, and absent suck were the only
features of the neurologic examination that contrib-
uted to the prognosis.

Childhood Outcomes of Cooling for
Encephalopathy
The outcomes of school-aged children enrolled in the
CoolCap trial (75) and the NICHD Whole Body Cool-
ing trial (76) have been reported. The CoolCap inves-
tigators concluded that they had insufficient power to
directly assess the effect of therapeutic hypothermia.
They did find an association between a favorable out-
come at 18 months of age and a favorable outcome at
7–8 years of age when they assessed 62 of the 135 sur-
vivors from their original trial. The NICHD investiga-
tors showed a trend ($P=0.06$) toward a reduced risk of
the combined outcome (death plus IQ less than 70) in
the hypothermia-treated children when compared
with control children at age 6–7 years. The hypo-
thermia treatment favored a benefit for the secondary
outcomes of mortality (relative risk [RR] 0.66; 95% CI,
0.45–0.97) and of the combined outcomes of death or
cerebral palsy (RR 0.71; 95% CI, 0.54–0.95). Disability
among survivors did not differ between the
hypothermia and usual care groups. The long-term
follow-up results of these studies are reassuring with
respect to safety and efficacy of hypothermia for
hypoxic–ischemic encephalopathy.

Societal Benefits
In well-resourced countries, where the incidence of
moderate or severe neonatal encephalopathy is
approximately 1–2/1,000 births, the societal benefits
are likely to be large. Treatment with cooling for 72
hours is cost saving by 18 months of age and can be
calculated to have major benefits to the health econ-
omy in countries where the intervention is applied
widely (77).

Therapeutic hypothermia treatment will also
likely prove to be of significant benefit to the health
economy of poorly resourced countries, where neo-
natal encephalopathy is the largest cause of mortality
and serious morbidity affecting children and accounts
for more than 1 million deaths annually (78). Prelimi-
ary investigation of therapeutic hypothermia in
these settings has been carried out, and large clinical
trials are planned, such as the Therapeutic Hypo-
thermia for Birth Asphyxia in a Low Resource Setting
(ISRCTN 89547571) (61, 71).

Conclusions
• Therapeutic hypothermia improves outcome for
some newborns with encephalopathy of a hypoxic–
ischemic origin.
• The implementation of therapeutic hypothermia
for neonatal encephalopathy is a milestone in neo-
natal medicine. In view of the simplicity of whole-
body cooling and the close temperature control
achieved with servo-controlled cooling equipment,
this likely will become the most widely practiced
method of inducing and maintaining cooling ther-
apy in newborns.
• The results of a meta-analysis of randomized con-
trolled trials with outcomes to at least 18 months of
age and published in the English literature confirm
that prolonged mild cooling, whether provided by
a cooling cap or systemically, reduces the rate of
death and of severe disability and increases the rate
of intact survival at 18–24 months of age.
• Safety outcomes were assessed in several prelimi-
nary and randomized controlled trials of moderate
cooling for neonatal encephalopathy. Only a low
platelet count occurred significantly more fre-
quently in the cooled infants. The other adverse
events were related to the systemic hypoxic–ishe-
mic injury that accompanied neonatal encephalop-
athy.
• The outcomes of school-aged children enrolled
in the CoolCap trial and the NICHD Whole Body
Cooling trial have been reported, and the long-term
follow-up results of these studies are reassuring
with respect to the safety and efficacy of hypother-
mia for hypoxic–ischemic encephalopathy.
• The success of treatment with moderate cooling
has shown that neural rescue therapy for neonatal
encephalopathy is achievable. However, the risk
of an adverse neurologic outcome after treatment
with cooling for neonatal encephalopathy remains
high (40–50%), so there still is scope and a press-
ing need for additional therapies to further improve
outcomes following this devastating condition.

Adjuvant Therapies for Treatment of
Encephalopathy
Therapeutic hypothermia improves outcome for
some newborns with encephalopathy of a hypoxic–
ischemic origin (50). In spite of this, death or dis-
ability occurs in 40–50% of infants treated with
hypothermia, so there still is scope and a pressing
need for additional therapies to further improve outcomes following this devastating condition. Hypothermia suppresses many pathways that contribute to cell death, but there is little evidence that hypothermia promotes repair of neural tissue. The following reviews potential adjuvant therapies for therapeutic hypothermia.

**Erythropoietin**

Erythropoietin is the major hematopoietic growth factor, but it also has prominent neuroprotective properties. Receptors for erythropoietin are expressed in the brain across development (79); gene expression for erythropoietin and its receptor are up-regulated during hypoxia and ischemia; and expression is found in neurons, microglia, and endothelial cells (80, 81). Systemic hypoxia and ischemia; and expression is found in neuroprotective properties. Receptors for erythropoietin are expressed in the brain across development (79); gene expression for erythropoietin and its receptor are up-regulated during hypoxia and ischemia; and expression is found in neurons, microglia, and endothelial cells (80, 81). Systemic hypoxia and ischemia; and expression is found in neurons, microglia, and endothelial cells (80, 81).

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Recombinant erythropoietin administration after hypoxia–ischemia reduced histologic injury and improved functional outcome in rat pups (83, 84). Erythropoietin treatment after brain ischemia in rat pups improved brain structure and function even when assessed at 3 months (85). It affects multiple pathways involved in injury, including reduced susceptibility to excitotoxic neurotransmitters (86), nitric oxide–mediated injury (87), apoptosis (88), and brain inflammation (89). Erythropoietin has the potential to repair neural tissue (90) because it stimulates neurogenesis, angiogenesis, and oligodendrogenesis (91, 92).

A pilot study of escalating high-dose erythropoietin for safety and pharmacokinetics has completed enrollment of encephalopathic infants born at 36 weeks of gestation and beyond (NCT 00719407). Similar studies are planned using erythropoietin (NCT 00491413) or darbepoetin (longer-acting erythropoietin, NCT 01471015). A trial in China randomized term encephalopathic infants to low-dose erythropoietin (300 units/kg or 500 units/kg) or conventional treatment, and death or disability was lower with erythropoietin (24.6% versus 43.8%, P=.017) (93). A prospective case–control study in Egypt reported fewer neurologic and developmental abnormalities (P=.03) at 6 months of age among encephalopathic infants given high-dose erythropoietin (2,500 units/kg daily) (94).

**Xenon**

Xenon is an anesthetic gas that readily crosses the blood–brain barrier and in high concentrations (50–70%) provides neuroprotection in older animals after cardiac arrest (95, 96). It also provides neuroprotection after hypoxia–ischemia in 7-day rat pups using concentrations of 50%; the extent of neuroprotection provided by xenon was additive when combined with therapeutic hypothermia and persisted over the 3-month follow-up (97, 98). Similar results have been found in newborn pigs (99). Xenon has a good safety profile in adults (100), although use in neonates is limited (101).

Xenon is an antagonist of excitatory neurotransmitters and may inhibit multiple subtypes of glutamate receptor channels (102). The latter may be linked to reduced apoptosis (103). Because hypothermia reduces neurotransmitter release (104) and xenon blocks neurotransmitter receptors (102), the two therapies converge on a common pathway. Other mechanisms of neuroprotection are under investigation.

Feasibility of using 50% xenon in ventilated infants undergoing therapeutic hypothermia indicated that xenon was well tolerated but accompanied by sedation (104). Other studies will assess biomarkers of brain injury (magnetic resonance spectroscopy, NCT 00934700). Important questions remain. Xenon is expensive, and a closed-circuit breathing system is needed for efficiency and economy (105). Hypoxia–ischemia complicated by pulmonary pathology may require high-oxygen concentrations and limit xenon delivery. Neurodegeneration after exposure to anesthetics occurs in developing animals, and the effect in human infants remains in question (106).

**Antiepileptic Drugs**

Seizures associated with encephalopathy are common. A controversial issue is whether seizure control improves outcome after hypoxia–ischemia (107). Accumulating animal data indicates that neonatal seizures alter brain development with long-term sequelae (108). Secondary analyses from two hypothermia trials, however, are in conflict: Seizures were an independent predictor of worse 18-month outcome in the CoolCap trial (64), but clinical seizures were not independently associated with 18-month outcome in the NICHD trial (109). Conflicting results reflect the difficulty in separating effects of seizures from the underlying hypoxia–ischemia. Adjustment for MRI-detected brain injury in term infants at risk of hypoxia–ischemia supported an association between seizures and worse neurodevelopmental outcome (110). This is important because commonly used antiepileptic drugs have limited efficacy (111).

Topiramate suppresses seizures after perinatal hypoxia–ischemia (112) and has multiple neuroprotective properties (ie, neurotransmitter receptor blockade, stabilization of membrane ionic gradients) (113).
It provides short-term neuroprotection in piglets (114) and rats (115) after hypoxia–ischemia but was effective only when started within 2 hours of hypoxia–ischemia and apoptosis was increased (in piglets). Topiramate given 15 minutes after hypoxia–ischemia in 7-day rats extended the therapeutic window for hypothermia-associated neuroprotection (116). It is unclear whether neuroprotection associated with topiramate reflects solely antiepileptic effects. Topiramate appears to be well tolerated by infants undergoing therapeutic hypothermia (117, 118). Pilot trials of topiramate (NCT 01241019) and other drugs with antiepileptic properties, such as bumetanide (119), are under way (NCT 00830531). Evaluation of treatment for electrographic compared with clinical seizures is planned (NCT 01027715).

**Stem Cells**

Stem cells may represent an endogenous repair response to brain injury. During brain development, specific cortical zones provide progeny cells that migrate to their final location. In late-preterm and term newborns, the subventricular zone remains prominent and contains neural stem cells and progenitors at different stages of cell commitment. After hypoxia–ischemia in 10-day mice, the subventricular zone expands, and cells move from this area to the surrounding injured brain. Survival of these new cells is limited and may reflect a suboptimal local environment (120, 121). These data, however, suggest that augmenting the stem cell response could improve neural repair.

Animal studies support stem-cell transplants as a viable therapy. Injection of multipotent astrocytic stem cells from mice into the somatosensory cortex of rat pups after hypoxia–ischemia demonstrated that transplanted cells survive, move to the area of injury, and differentiate into neurons and astrocytes (122). Intraparenchymal transplantation of human umbilical cord mononuclear cells after hypoxia–ischemia in rat pups entered the brain, migrated to sites of injury, and minimized spastic paresis (123). Hippocampal cell preservation after hypoxia–ischemia in rat pups was similar whether adult progenitor cells were administered intracerebrally or intravenously, supporting feasibility (124). Pilot studies of autologous umbilical cord blood infusions for encephalopathic infants are ongoing to determine safety and feasibility (NCT 00593242, preliminary results) (125).

**Conclusions**

- Potential adjuvant treatments include erythropoietin, xenon, antiepileptic drugs, and stem cells. In spite of this, death or disability occurs in 40–50% of infants treated with hypothermia, justifying the need for adjuvant therapies.
- Hypothermia suppresses many pathways that contribute to cell death, but there is little evidence that hypothermia promotes repair of neural tissue. Most of the current potential adjuvant therapies have been targeted for study because they may be additive or synergistic with the effects of hypothermia. Work is moving to preclinical and clinical trials.

**Research Recommendations**

- Research for timing for initiation, depth, duration, and rewarming strategies for therapeutic hypothermia is needed.
- Targeting of the population most likely to benefit from therapeutic hypothermia is needed.
- Impact of inflammatory process on therapeutic hypothermia is needed.
- Transport management of infants with encephalopathy is needed.
- Adjuvant therapies to therapeutic hypothermia are needed.
- Impact of therapeutic creep in cooling on outcomes is needed.

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Patient Safety Efforts and Neonatal Encephalopathy

Modern medicine is a complex, fast-paced, and technologically oriented field. Perinatal care providers must additionally work as part of multidisciplinary teams that provide round-the-clock care in a dynamic environment. Effective communication and teamwork is essential to provide the highest quality of care. Yet there is evidence from statistics and publicized tragedies that health care needs to be made safer. The Institute of Medicine report *To Err is Human: Building a Safer Health System* estimated that errors cause as many as 98,000 patient deaths each year in hospitals (1). This means that medical errors are the eighth-leading cause of death in the United States. As concluded in the report, most of those errors are caused by correctable faults. The report serves as a “call to arms” to improve the quality and safety of care, providing a series of recommendations to recruit national leadership, organize adverse event reporting efforts, empower oversight groups and, most importantly, establish internal safety systems within individual health care organizations. The World Health Organization has summarized the goal of patient safety eloquently: “Every patient receives safe health care, every time, everywhere” (2).

The most important consequence of efforts to improve safety in any complex, potentially risky activity has been recognition of the ubiquity of human and system deficiencies that contribute to errors. By understanding that some medical errors are inevitable, but most are preventable, patient safety efforts focus on human fallibility and seek to enhance communication, as well as improve knowledge and technical skills with the goal of decreasing the likelihood that an error will manifest itself at the bedside. This chapter reviews patient safety efforts directed at preventing neonatal encephalopathy.

Patient safety initiatives in perinatology have tended to lag behind many other medical specialties, despite the fact that childbirth is one of the most common reasons for hospital admission in the United States, accounting for more than 4 million hospitalizations each year and ranking second only to cardiovascular disease (3). Although good outcomes generally are expected in obstetrics, adverse events occur in as many as 16% of deliveries (4–6). The anticipation of a favorable outcome among largely young and healthy women, and the fact that two patients—mother and child—can be affected, make any adverse outcome particularly devastating. Despite this, few published models exist to guide health care providers in reducing obstetric adverse outcomes.

To achieve the goal of patient safety, the field of medicine can learn a lot from the processes used by high-reliability industries, such as aviation and nuclear power. Like medicine, these organizations are high risk, extremely technical, and require effective communication in dynamic environments, yet they have admirable safety records. There certainly are differences between commercial aviation and the practice of clinical medicine. For example, when a plane crashes, hundreds of people can die at the same time and the accident instantly becomes front-page news, whereas deaths and major adverse sequelae caused by medical errors occur in relative isolation and usually with a low prevalence. As a consequence, public pressure can force improvements to be made in the first instance, but this is less of a factor in the second. Furthermore, the pilot has a very personal stake in the plane’s safety. Crews do not change during a flight,
 Unlike teams of physicians and nurses caring for a patient over periods exceeding the lengths of their shifts. And finally, the complexities of rendering the safest clinical care for a multitude of illnesses in modern medical facilities vastly exceeds the variables to be considered in any of the other high-reliability enterprises to which the practice of medicine often is compared. Flights are frequently delayed or canceled because of adverse conditions, but the physician or obstetric team is frequently confronted with emergent conditions that require immediate action under unfavorable circumstances. Nevertheless, understanding how the high-reliability industries have achieved their remarkable safety records can be extremely informative because the principles underlying that success do apply to the practice of medicine.

Flight simulation is an integral part of pilot training, and interdisciplinary simulation-based training is becoming an important part of obstetric training and is central to the Neonatal Resuscitation Program. Even more critical than specific policies or procedures, however, is establishing a culture of safety. Traditionally, health care has had a culture that blames and punishes individual practitioners when something goes wrong, placing caregivers in precarious situations (7). A culture of safety, however, while still emphasizing accountability, allows reporting of errors, injuries, and near misses in an environment “safe from blame, humiliation, and retaliation” (8).

High-reliability industries take a systems approach when analyzing errors. There is recognition that “errors and human behavior cannot be understood in isolation, but only in relation to the context in which people are working” (9). A number of system factors, such as the nature of the task being carried out, the make-up of the team, and the work environment, affect the jobs being done and must be taken into consideration in designing safe health care systems (10).

Communication gaps are the dominant root cause of adverse events and near misses in medicine. Statistics from The Joint Commission (JC) indicate that inadequate communication between health care providers or between health care providers and patients and families is the root cause of 60–70% of investigated sentinel events in medicine (11). The JC Sentinel Event number 30 investigated 47 perinatal deaths and reported that poor communication (involved in 72% of adverse events) was the most frequently cited root cause (12). In addition, 55% of the cases involved an organizational culture that prevented effective teamwork and communication (Fig. 12-1) (12).

**Definitions**

There is variation in the use of the following terms. The definitions listed are provided for clarification.

**Adverse event**: An event that results in unintended harm to the patient by an act of commission or omission rather than by the underlying disease or condition of the patient (8).

**Medical error**: The failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim (commission). This definition also includes failure of an unplanned action that should have been completed (omission) (8).

**Near misses**: An event or a situation that did not produce patient harm, but only because of intervening factors, such as patient health or timely intervention (13).

**Patient safety**: The prevention and mitigation of harm caused by errors of omission or commission that are associated with health care, and involving the establishment of operational systems and processes that minimize the likelihood of errors and maximize the likelihood of intercepting them when they occur (1).
Culture of Safety

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 an opportunity for a constructive, nonthreatening, and professional process. A key element of this is peer review, the focus of which should be the reporting of errors, near misses, and other safety concerns. Research into perinatal errors has expanded considerably, especially in descriptive epidemiology. Medical errors more frequently occur from the organization of health care delivery and the way that resources are provided to the delivery system than from individual human error.

Conclusions

• Changes to system design are crucial in the reduction of medical errors.
• Recognition of this factor can help to depersonalize error reporting and lead to establishment of a positive attitude toward creating a safety-based culture.

Identifying Medical Errors

The cornerstone of patient safety programs is error reporting. Analysis of errors can lead to systems improvement only if the errors are detected, reported, and then used to design better practices and systems. Reporting can be performed in a variety of ways but generally involves notifying a supervisory, oversight, or quality-improvement entity.

Conclusion

• Error reporting is the cornerstone of patient safety programs.

Root Cause Analysis as a Tool for Learning and Prevention

It is our duty as health care providers to learn from each adverse outcome with the goal of preventing similar events from occurring with subsequent patients and health care providers. In addition, it is our responsibility to ourselves and our patients to design systems to help individuals avoid errors and minimize the effect these errors have on our patients. The Accreditation Council for Graduate Medical Education recognized this responsibility when it stipulated that residents must do the following:
• Demonstrate the ability to investigate and evaluate their care of patients, to appraise and assimilate scientific evidence, and to continuously improve patient care based on constant self-evaluation and lifelong learning
• Systematically analyze practice using quality-improvement methods and implement changes with the goal of practice improvement
• Work in interprofessional teams to enhance patient safety and improve quality of patient care
• Participate in identifying system errors and implementing potential systems solutions (14)

The unexpected birth of a compromised neonate is one example of a situation in which obstetric and pediatric teams, including resident physicians, may learn to improve patient outcomes. A properly performed root cause analysis is a powerful tool through which teams can investigate an adverse event and try to prevent its recurrence. The Joint Commission requires that organizations perform a root cause analysis for every sentinel event, but root cause analysis also may be used to investigate near misses in which a patient was at risk of, but did not actually sustain, harm. During a root cause analysis, each component of patient care is evaluated, and its potential contribution to the adverse event is assessed. The root cause analysis process is designed to answer four basic questions: 1) What happened in this case? 2) What usually happens? 3) Why did this event occur? 4) What, if anything, can be done to prevent it from happening again (15)? If contributors to an adverse event are identified, corrective action plans can then be designed (16). The steps in performing a root cause analysis include the following:
• Establishment of a no-blame culture, in which the common goal of improving patient safety is explicit
• Identification of an event requiring further investigation
• Formation of a multidisciplinary team (include participation by both leadership of the organization and those most closely involved in the relevant processes and systems)
• Identification of all causes potentially associated with the undesirable outcome
• Development of targeted and measurable recommendations to prevent similar events in the future
• Effective communication to others in the organization about lessons learned from the root cause analysis
To comprehensively identify potential causes of the adverse event, many teams have found the Ishikawa diagram (also known as a fishbone diagram) to be a useful tool for analyzing adverse events. A fishbone diagram (Fig. 12-2) includes separate categories for every major contributing factor as well as subbranches within each of those categories. This method provides a prompt for considering each of a wide range of factors that potentially contributed to the adverse outcome and displays them in a simple schematic diagram (15). Once an in-depth evaluation of each category has been performed, the group identifies those factors that contributed to the adverse event (see Box 12-1). Problem solving and corrective actions are then aimed at rectifying these key factors. Individuals responsible for each corrective action are named, and follow-up assignments made. The benefits of using a fishbone diagram for a root cause analysis are that it encourages a team-based approach, explores multiple potential contributing factors to the adverse event, and tends to produce actionable areas for improvement. When using this tool, however, teams must be meticulous in capturing all potential contributing factors during the initial brainstorming phase, lest a major source of error elude analysis.

Root cause analysis can serve as a powerful tool to identify the contributing causes that underlie variations in performance associated with adverse events. Institutions can use root cause analysis both to explain how an adverse event occurred and to design systems to prevent its recurrence. Residency training programs are encouraged to use root cause analysis to teach their trainees the skills of quality improvement, teamwork, and patient safety. Ideally, root cause analysis should result in prevention, not punishment, and contribute to an organization’s efforts to build a culture of safety.

Conclusions

- Once errors are detected and reported, they can be subjected to root cause analysis and used to design better practices, surveillance mechanisms, and systems.
- A root cause analysis should be performed for every sentinel event, as well as for other selected adverse outcomes and near-miss cases. During a root cause analysis each component of patient care is evaluated, and its contribution to the adverse event is assessed. Problem solving and corrective actions should then be aimed at rectifying the key factors that have been identified.

Disclosure of Errors

Health care providers, as clinicians and advocates for patients, must act professionally. Honesty and integrity are core principles at the heart of professionalism (17). Parents overwhelmingly prefer to be told when an error occurs that may affect their child. A prospective survey of 431 parents found that 99% wanted disclosure if potential or actual harm occurred (18). Clinicians often find it challenging to openly discuss errors with patients and parents. There are natural feelings of fear, embarrassment, and shame. There also may be concern that disclosure will lead to disciplinary action as well as a lawsuit. Furthermore, in many cases involving adverse outcomes, it may be difficult to determine if an error actually occurred in the first place or, if it did, what effect it would have on the outcome. Yet there are a number of reasons why disclosure of
errors must occur. As noted previously, there is an ethical obligation to be honest with patients, and this is incorporated into a number of clinical codes of ethics (19). Simply put, when something goes wrong, patients have the right to know what happened. Additionally, since 2001 the JC has mandated open disclosure of unanticipated outcomes during patient care (20). In some states, there is a legal obligation to disclose errors. Pennsylvania, for example, requires hospitals to notify patients, or parents of minors, in writing within 7 days of a “serious event” (21).

From a safety perspective, an organizational commitment to open disclosure is an essential component of creating a culture of honesty and integrity, of examining and learning from mistakes rather than hiding them. For this reason, the National Quality Forum

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**BOX 12-1. Issues to be Considered During a Root Cause Analysis for an Adverse Obstetric Event**

These are examples of issues to be considered within the categories listed during a root cause analysis for an adverse obstetric event. Please note that these are simply stated as examples, and the lists provided are not meant to be exhaustive. Also note that some items may appear in more than one category.

**STAFF FACTORS**
- Were the obstetrician to nurse ratios appropriate?
- Were appropriately credentialed people available for monitoring and the delivery?
- What were the conditions on the floor at the time of the patient's labor and delivery?
- Was communication appropriate among the staff?

**PATIENT FACTORS**
- Were medical risk factors appropriately identified (antepartum and intrapartum)?
- Was assessment appropriate considering the risk factors?
- Was the monitoring appropriate during labor?

**TEAM AND SOCIAL FACTORS**
- Were the activities of the team appropriately coordinated during the labor and delivery?
- Was communication appropriate among the staff?
- Was the family's expectation for the delivery met (eg, was there a birth plan that didn't go as anticipated)?
- Was there adequate communication with the patient and her family?

**EDUCATION AND TRAINING**
- Were appropriately credentialed people available for monitoring labor and delivery?
- Were appropriately credentialed people available for assessment and resuscitation of the neonate?

**WORK ENVIRONMENT**
- Were staff ratios appropriate?
- Did the environment contribute to communication failures?
- Was the patient in the proper setting for appropriate monitoring (eg, triage or emergency room versus labor and delivery unit)?

**EQUIPMENT AND RESOURCES**
- Was the appropriate instrumentation for monitoring available?
- Was the appropriate instrumentation for infant resuscitation available?
- Were there issues with transportation of the patient?
- Were emergency consultation personnel available?
- Was there appropriate equipment available to handle an unanticipated emergency?

**ORGANIZATIONAL FACTORS**
- Was there appropriate access to antepartum information?
- Were laboratory results obtained in a timely fashion?
- Was patient transport available?
- Was an interpreter available?
- Was there sufficient documentation in the chart?

**PROCEDURES AND METHODS**
- Was there sufficient time to notify the neonatal team?
- Did the consults know where to go and how to get there?
- Did the obstetric team know how to manage the emergency situation?
- Was the proper equipment available for handling the emergency?
- Were all the proper people notified about the emergency?

After these have been analyzed, what are the correctable things that have come out of this, and what is your course of action to affect change? Finally, how will the effectiveness of the actions taken be measured and monitored?
considers “timely, transparent, and clear communication” with patients and families as a safe practice that should be “universally utilized . . . to reduce the risk of harm resulting from processes, systems, and environments of care” (22).

Conclusions
• An organizational commitment to open disclosure of medical errors is an essential component of examining and learning from mistakes.
• Disclosing adverse events to parents and families is an essential component of creating a culture of honesty and integrity.

Communication
Errors are often the result of inadequate or inaccurate communication with patients. These occur frequently and include difficulties in translation and medical interpretation. Investigators reported 31 medical interpretation errors per pediatric clinical encounter, with most having potential adverse consequences (23). Even English-speaking patients may have limited comprehension of what they are told. An assessment of health literacy has been advocated as a way to improve patient safety.

Communication errors also occur among health care providers, both within and between different services and disciplines. The potential for miscommunication in the perinatal setting is considerable. Pediatricians and neonatologists may not have an encounter with the obstetrician—or family—until the delivery. They may not be familiar with the problem, the plan of action, or the family’s wishes in the event of a serious anomaly. Predelivery consultation among families as well as physicians and other health care providers can alleviate many of these issues and help to establish treatment options and goals before the emotions of the birth of the infant take over.

Women with prenatally identified fetal malformations often are referred to high-risk centers where they are seen by multiple specialists. Care must be taken to avoid conflicting information, and a unified plan of care should be decided and placed in the medical record. Frequently, different individuals will be involved in the delivery and care of the infant after birth. Anticipation of a high-risk delivery should trigger communication of all services that might be potentially involved in the care of both the mother and infant. The obstetric team should notify anesthesiology of the potential need for maternal analgesia and anesthesia, as well as the neonatal team, which will be responsible for the initial stabilization of the infant. In specific situations, additional subspecialists, such as pediatric cardiologists or surgeons, might be necessary. Advance communication enables more time for preparation and also generates interservice communication and clarification of the care plan.

Neonatal transport places another strain on communication, as there may be no face-to-face contact between the mother and the neonatal intensive care unit (NICU) team, in which case information transfer depends to a large extent on the written medical record. The separation of the mother and infant adds an additional stress.

The importance of medical record documentation cannot be overemphasized. The medical record is the memorialization of medical care and is often the key piece of evidence used in litigation to determine the propriety of the care provided and to decipher the causes of injury. Medical records should be accurate, complete, and objective, and reflect the health care provider’s thought processes and assimilation of information (24).

Conclusions
• Errors are frequently the result of inadequate or inaccurate communication between members of the staff, or with patients, or both.
• Advance communication among families, physicians, and other health care providers enables more time for preparation and also generates interservice communication and clarification of the care plan.
• Medical records should be accurate, complete, and objective, and reflect the health care provider’s thought processes and assimilation of information.

Team Training
A team training program, based on crew resource management programs initiated and tested by the airline and defense industries, has been shown to enhance communication in those settings (25). Team training generally involves 4–8-hour seminars coupled with videos, lectures, and role-playing among a mix of individual attendees (ie, physicians, nurses, ancillary staff) within the obstetric team. Similar interventions have helped improve teamwork—but not necessarily outcomes—in various medical fields (26–29). Most powerfully, a retrospective “health services cohort” study demonstrated decreased surgical mortality in Veterans Health Administration centers that implemented structured team training programs (30). Examples of formalized medical team training
exercises include the Agency for Healthcare Research and Quality's TeamSTEPPS, the Veterans Health Administration's Medical Team Training, and MedTeams. Training staff in these settings can take months, and new hires need to be trained episodically over time. A more comprehensive approach that included crew resource management was associated with an improvement in obstetric outcomes in a composite index of maternal and neonatal outcomes but not in Apgar scores or NICU admissions (5).

**Conclusion**

- Team training generally involves 8-hour seminars coupled with videos, lectures, and role-playing among a mix of individual attendees (ie, physicians, nurses, ancillary staff) within the obstetric team. Similar interventions have helped improve teamwork—but not necessarily outcomes—in various medical fields.

**Simulation**

Pilots have been using aircraft simulators for more than a century, but simulation-based learning has only recently gained significant momentum in health care. Interdisciplinary simulation-based learning allows clinicians to acquire, maintain, and improve cognitive, technical, and behavioral skills (31). Additionally they can experience high-risk and challenging scenarios without placing real patients at risk. An important goal of simulation-based training is to improve teamwork and communication skills. As the JC has noted, “patient safety is a team activity. It's about teamwork—which involves the coordination, cooperation, and synchronization of tasks, events, and actions in support of patient needs” (32).

Initial areas of focus in obstetrics have centered on low-frequency but high-severity events, such as the management of shoulder dystocia (33–35), hemorrhage (36), and eclampsia (27). Simulation can be center based, occurring in dedicated space that may contain sophisticated mannequins, audiovisual equipment, and other technology that permits a true-to-life (high-fidelity) experience and facilitates extensive postsimulation debriefing. Alternatively, to cope with the logistical challenges associated with scheduling an obstetric team to be off-site in a center, some services have adopted an in situ approach, which makes use of times of low census and higher staff availability. These unannounced drills take place on a patient care unit and usually use more rudimentary equipment (37). Either approach may allow technical skills to improve to some degree, and both provide the opportunity to improve communication and dynamics between team members, especially those from different disciplines. Units may choose to focus on improving either skills and knowledge or teamwork, but any simulation drill likely enhances both simultaneously.

Simulation training has been shown to be an important educational intervention for rare events and emergencies (26), and although most studies have limited their scope to improved performance in subsequent simulations (38), some investigators have demonstrated improved clinical results for neonatal adverse outcomes (eg, Apgar scores and hypoxic–ischemic encephalopathy) (39) and events like shoulder dystocia (40). In a retrospective study at a single U.K. institution, a combination of classroom training in fetal heart rate monitoring interpretation, coupled with drills in obstetric emergencies, was implemented widely among staff. Compared with outcomes before staff were trained, Apgar scores of less than 6 decreased from 86.6 to 44.6 per 10,000 births (P<.001), and hypoxic–ischemic encephalopathy decreased from 27.3 to 13.6 per 10,000 births (P=.032) (39).

The Neonatal Resuscitation Program course for health care providers, revised in 2011, places an increased emphasis on teamwork and communication skills. There is recognition that technical knowledge alone is not sufficient. Health care providers must also be able to “communicate and coordinate with the other members of the team while working under the intense time pressure of neonatal resuscitation.” The Neonatal Resuscitation Textbook lists the following key behavioral skills: know your environment, allocate attention wisely, anticipate and plan, use all available information, assume the leadership role, use all available resources, communicate effectively, call for help when needed, delegate workload optimally, and maintain professional behavior (41).

The structure of the Neonatal Resuscitation Program course has been changed as well. The cognitive parts of the course are completed online, and most classroom time focuses on coordinated resuscitation performance via simulation (41). The Neonatal Resuscitation Program educational course is based on the American Heart Association Guidelines for Neonatal Resuscitation recommendation that simulation, briefing, and debriefing techniques be incorporated into the program (42). Some studies have demonstrated that team training in Neonatal Resuscitation Program results in improved teamwork behaviors and better workload management (43). The overall number of studies is small, however, and the Neonatal Resuscitation Program simulation recommendations are based
PATIENT SAFETY EFFORTS AND NEONATAL ENCEPHALOPATHY

on relatively limited data. The Eunice Kennedy Shriver National Institute of Child Health and Human Development workshop on patient safety has recognized that further study is needed in this area.

Conclusions

- Simulation training is being used increasingly not only to provide technical knowledge and improve technical aptitude but also to enhance teamwork and communication skills.
- It has been shown to be an important educational intervention for rare events and emergencies. Although most studies have limited their scope to improved performance in subsequent simulations, some investigators have demonstrated improved clinical results for neonatal adverse outcomes (e.g., Apgar scores and hypoxic–ischemic encephalopathy) and events like shoulder dystocia.

Fatigue

Because labor and the delivery of a depressed newborn can occur at any time of day or night, staff with requisite skill sets must be present to respond at all times. Disturbances in circadian rhythm, acute sleep deprivation, and chronic sleep deprivation create independent risks of impaired alertness and hazardous performance, and in combination the overall effects of these issues may be even greater than the sum of the parts (44). In recent years, measures have been taken by the Accreditation Council for Graduate Medical Education to curtail work hours for physician trainees, but no similar policies exist for attending physicians. This has created a paradox in which younger physicians are better protected from fatigue than their older counterparts.

Conclusion

- Long duty hours and sleep deprivation have the potential to contribute to medical error and to jeopardize patient safety.

Research Recommendations

- Research should be directed toward identifying the factors that contribute to adverse events before delivery and in the NICU, as well as to interventions designed to decrease harm to these patients.
- Patient safety research and literature needs to address neonates in addition to the adult population, which is the current focus of disproportionate attention.

- To improve the safety of the delivery room and NICU, it is essential to perform high-quality, innovative and prospective patient safety research geared toward the unique needs of the obstetric and neonatal populations. In addition to assessing the frequency of errors and untoward outcomes, intrapartum and NICU studies should address factors contributing to adverse events as well as interventions to decrease harm.
- Studies should evaluate the effect of human factors, fatigue, and systems issues—including physician and nurse workload—on performance and patient safety.
- The use of information technology, such as electronic medical records designed to enhance medical care and reduce errors, should be critically evaluated.

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An Acute Hypoxic–Ischemic Event and Neonatal Encephalopathy

Updated Perspective on Neonatal Encephalopathy and Intrapartum Hypoxia

In 2003, the American College of Obstetricians and Gynecologists Task Force on Neonatal Encephalopathy and Cerebral Palsy identified four essential criteria required to define an acute intrapartum hypoxic event as sufficient to cause cerebral palsy: 1) evidence of a metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH less than 7.0 and base deficit 12 mmol/L or greater), 2) early onset of severe or moderate neonatal encephalopathy in infants born at 34 weeks of gestation or greater, 3) cerebral palsy of the spastic quadriplegic or dyskinetic type, 4) exclusion of other identifiable etiologies, such as trauma, coagulation disorders, infectious conditions, or genetic disorders. These criteria were useful in clarifying previous uncertainties. It was useful, for example, to stress that neither spastic diplegic nor spastic hemiplegic cerebral palsy is likely to have its origin in birth hypoxia. It was equally useful to stress that moderate degrees of acidosis and low Apgar scores are relatively common in infants with normal subsequent neurologic outcome. A major goal of this report was to review these criteria and determine their usefulness in light of new knowledge gained since publication of the first report. This chapter represents the culmination of these efforts and provides a comprehensive multidimensional assessment tool to determine the likelihood that an acute hypoxic–ischemic event that occurred within close temporal proximity to labor and delivery contributed to neonatal encephalopathy.

The general understanding of the causes of neonatal encephalopathy and cerebral palsy in term infants is illustrated in Figure 13-1. Epidemiologic data indicate that acute intrapartum hypoxia–ischemia is uncommonly the sole cause of neonatal encephalopathy or spastic quadriplegic cerebral palsy (ie, the intrapartum hypoxia–ischemia etiologic pathway represented in column A of Figure 13-1 versus alternative pathways represented in columns B–E) and that most children with neonatal encephalopathy and neonatal encephalopathy-associated cerebral palsy do not have recognized hypoxia at birth. Although Figure 13-1 does not provide specific details regarding the many processes leading to neonatal encephalopathy and cerebral palsy, recent clinical and laboratory evidence as extensively reviewed in this update have added considerably to the knowledge of these processes. For example, it appears that third-trimester maternal bleeding or trauma in pregnancy are rarely associated with neonatal encephalopathy, whereas intrauterine infection, placental insufficiency with associated fetal growth restriction, and neonatal hypoglycemia may be important contributors and warrant further investigation. 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. Notable advances in neuroimaging, especially magnetic
resonance imaging (MRI), have claimed a vital role in our understanding of neonatal encephalopathy by elucidating patterns of neurologic injury. These studies have led to the recognition that the variability and injury susceptibility of specific neuronal cell types and systems in the developing brain are important factors in determining the final pattern of damage and functional disability (see also Chapter 10, “The Role of Neuroimaging”). Magnetic resonance imaging performed in the early neonatal period and interpreted appropriately can inform determination of—but not definitively specify—the etiology, time window of injury, and long-term prognosis after neonatal encephalopathy. Numerous developmental follow-up studies with psychometric evaluation of clinical and epidemiologic neonatal encephalopathy populations have revealed a broad array of abnormal developmental features in these children. Laboratory studies have advanced our understanding of fetal compensatory mechanisms in response to hypoxia–ischemia, the chain of molecular events that follow it, and the cofactors influencing fetal vulnerability to this disorder, such as infection, inflammation, and fetal growth restriction. Finally, development and routine implementation of therapeutic hypothermia for neonatal encephalopathy is a recent milestone in neonatal medicine.

In contrast, in the years since first publication of this guideline, new epidemiologic data on neonatal encephalopathy and hypoxic–ischemic encephalopathy (HIE) have been very limited; there have been no epidemiologic studies of the incidence of neonatal encephalopathy or HIE with updates from more recent births cohorts since the mid 1990s and very few reports on risk factors based on studies with larger sample sizes than the population-based Western Australia study. Despite the advantages of the three-tier fetal heart rate interpretation system proposed in 2008 by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the American College of Obstetricians and Gynecologists, and the Society for Maternal-Fetal Medicine, we still lack reliable and readily available assessment tools with clinical markers of fetal and neonatal status that are both sensitive and specific to an intrapartum insult and that are strongly predictive of long-term outcome, including umbilical arterial blood gas results (eg, cases have been reported of well-documented intrapartum events leading to severe neonatal encephalopathy and cerebral palsy.

**FIG. 13-1. 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 factor may lead to neonatal encephalopathy and subsequent cerebral palsy. B. Intrapartum brain injury may be the result of both distal and proximal risk factors that predispose the fetus to brain injury and cerebral palsy. C. Brain injury or anomaly may occur in the antepartum period as a result of distal and proximal risk factors. When brain injury or anomaly occurs at a time that is remote from the delivery process, neonatal encephalopathy may or may not be seen after birth. D. 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. (Note: Fig. 13-1 also appears in Chapter 1 as Fig. 1-1.)
The Utility of Identifying an Acute Intrapartum Hypoxic–Ischemic Event as a Contributory Factor to Neonatal Encephalopathy

In the first edition of this guideline, the task force outlined criteria deemed essential to establish a causal link between intrapartum hypoxic events and cerebral palsy. For the current edition, the task force determined that a broader perspective may be more fruitful. This conclusion reflects the sober recognition that our knowledge gaps still preclude a definitive test or set of markers that accurately identifies, with high sensitivity and specificity, an infant whose neonatal encephalopathy is attributable to an acute intrapartum event. For most neonates affected by neonatal encephalopathy, clinicians still lack the ability to determine whether the etiologic scenario depicted in Column A of Figure 1-1 is the true cause of the disorder. Nevertheless, there is strong justification for undertaking steps to assess the likelihood or probability that an acute hypoxic–ischemic event occurring within close temporal proximity to delivery was solely responsible for or contributed to neonatal encephalopathy. The information necessary for assessment of likelihood can be derived from a comprehensive evaluation of all potential contributing factors in cases of neonatal encephalopathy, including maternal medical history, obstetric antecedents, intrapartum factors (including fetal heart rate monitoring results), and placental pathology. Subsequent analysis of that information can produce a number of benefits (discussed as follows) that extend far beyond provision of a single probability estimate. This is the broader perspective championed in the current guideline. If a comprehensive etiologic evaluation is not possible, the term HIE should best be replaced by neonatal encephalopathy because neither hypoxia nor ischemia can be assumed to have been the unique initiating causal mechanism.

To set the framework for this perspective, we pose the following question: What is the purpose of identifying an acute intrapartum hypoxic–ischemic event as a contributory factor to neonatal encephalopathy? The answers highlight potential benefits for patients in terms of guiding treatment, judging prognosis, providing appropriate family counseling, improving clinical practice, as well as fostering advances in research to investigate the complex heterogeneous processes leading to neonatal encephalopathy.

Treatment

One of the aims of thorough assessment of the contributing events in neonatal encephalopathy is to identify neonates who are more likely to benefit from treatment. Different therapeutic interventions may be appropriate for different etiologic features or physiologic responses to harm. For example, oxygen deprivation as an instigator of neonatal encephalopathy would likely lead to different intervention strategies than cases caused by thrombosis or inflammation. More accurate and timely identification of the salient factors for intervention in each individual case will improve accuracy of the assignment of optimal treatment for a given patient and may improve the outcome of all the treated neonates. The fact that more than 40% of neonates undergoing hypothermia treatment still develop adverse neurologic outcomes underscores the research need to further understand the underlying processes in neonatal encephalopathy, which ideally will yield more effective clinical criteria for matching each patient with tailored treatment options. The current emphasis is on identification of the optimal criteria for the identification of cases in which there is a hypoxic or ischemic contribution to a neonatal encephalopathy of recent onset, which inevitably will be much less stringent than defining essential criteria.

Prognosis

Another aim of assessing the contributing events and medical profile of a neonate with neonatal encephalopathy is to compile a prognostic profile that sets reliable short-term and long-term expectations for the neonate’s clinical course, treatment needs, and outcome. Current prognostic indicators, such as the Sarnat classification system or electroencephalography to stratify the severity of neonatal encephalopathy, are useful but insufficient as stand-alone tests. It is likely that a battery of markers in conjunction with clinical findings and brain imaging will be most predictive, rather than any one feature alone. Thus, better understanding of the processes leading to neonatal encephalopathy and their associated outcomes may help develop more accurate and reliable tools for prognostic forecasting.
Family Counseling
Refinement of the eligibility protocols for specific interventions that improve efficacy of treatment, as well as development of better prognostic indicators, will enhance the quality of information provided to families about the care and expected outcome for their infant. More accurate information gathering regarding the contributors to the encephalopathy will also more quickly address family concerns over potential sources of harm.

Improving Clinical Practice and Systems
A comprehensive evaluation of contributing events in neonatal encephalopathy also should include assessment of the delivery of clinical care with the aim of identifying existing strengths, weaknesses, and opportunities for improvement (see Appendix A). Medical errors are frequently the result of inadequate or inaccurate communication, and a cornerstone of patient safety programs is error reporting. Root cause analysis can serve as a powerful tool to identify the contributing causes that underlie variations in performance associated with adverse events. Institutions can use root cause analysis both to explain why an adverse event occurred and to design systems to prevent or reduce the frequency of recurrence (see Chapter 12).

Research
Clinical practice and research have a direct relationship. Recognition of the limitations in current clinical assessment and data collection practices inform the research questions that need to be addressed and the corresponding data collection needs. In turn, results from laboratory, clinical, and epidemiologic research on the heterogeneous processes leading to neonatal encephalopathy and associated outcomes will have a significant effect on shaping the relevant data content needed for clinical assessment to determine the processes leading to neonatal encephalopathy in individual cases. As emphasized throughout this guideline, future research in this area requires detailed, in-depth data gathering on the complex causal mechanisms underlying neonatal encephalopathy and testing of novel hypotheses to provide new opportunities for intervention.

Assessment of an Acute Peripartum or Intrapartum Event Sufficient to Cause Neonatal Encephalopathy
To determine the likelihood that an acute hypoxic–ischemia event occurring within close temporal proximity to 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. The items to be included in the assessment are described as follows:

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 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 patient meets the case definition.

In confirmed cases of neonatal encephalopathy, the following assessment items 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. Appendix A and Appendix B provide examples of obstetric and neonatal data collecting guidelines for infants with 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
1. Low Apgar scores at 5 minutes and 10 minutes clearly confer an increased relative risk of cerebral palsy. The degree of Apgar abnor-
A sentinel hypoxic–ischemic event occurring immediately before or during labor and delivery.

1. A ruptured uterus
2. Severe abruptio placentae
3. Umbilical cord prolapse
4. 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

1. 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 standard deviation), or both is not consistent with an acute hypoxic–ischemic event.

2. 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 intrapartum timing of a hypoxic–ischemic event.
   c. 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. Magnetic resonance imaging and magnetic resonance spectroscopy are the most sensitive neuroimaging modalities to assist with the timing of cerebral injury. Magnetic resonance imaging—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 management 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 hypoxia–ischemia 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 less likely (see Fig. 13-1).

**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 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.

Magnetic resonance imaging 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. Magnetic resonance imaging 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 term-born 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 guideline was first published, considerable advances have been made in our 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 multidimensional assessment process for neonatal encephalopathy described in this chapter reflects the current state of scientific knowledge and acknowledges the limitations definitively distinguishing HIE from other forms of neonatal encephalopathy within the array of clinical tools currently at our disposal. The multidimensionality of the assessment process is key to recognizing that no one strategy to identify HIE at present is infallible and that no single strategy 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 our 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.
APPENDIX A

Data Collection Guideline for Infants Delivered at 35 Weeks of Gestation or More With Risk of Neonatal Encephalopathy *

1. In cases with delivery of a depressed newborn with Apgar scores of 5 or less at 5 minutes:
   - Obtain umbilical artery pH from a clamped section of umbilical cord
   - Submit placenta for pathological examination

2. Data Collection
   a. Predelivery Data
      - Maternal conditions:
        - Diabetes
        - Hypertension
        - Preeclampsia
        - Obesity
        - Vaginal bleeding
      - Fetal conditions:
        - Fetal growth restriction
        - Abnormal biophysical testing
        - Large for gestational age
        - Structural abnormality
      - Labor
        - Start of labor (time, date)
        - Transition to active phase (time, date)
        - 10 cm cervical dilatation (time, date)
        - Rupture of membranes time:
        - Amniotic fluid: Clear
        - Meconium-stained
        - Blood-stained
        - Fetal heart rate pattern on admission (first 30 minutes)
          - Contractions (number in 30 minutes)
          - Baseline: ________ beats per minute
          - Variability minimal or absent (minutes)
          - Decelerations (number in 30 minutes)

*Standardization of health care processes and reduced variation has been shown to improve outcomes and quality of care. This guideline for data collection reflects emerging clinical, scientific, and patient safety advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed. Although the components of a particular guideline may be adapted to local resources, standardization within an institution is strongly encouraged. The Data Collection Guideline for Infants Delivered at 35 Weeks of Gestation or More With Risk of Neonatal Encephalopathy should be completed by the health care provider.
• Fetal heart rate pattern in the 30 minutes before delivery
  ❑ Contractions (number in 30 minutes) __________
  ❑ Baseline: __________ beats per minute
  ❑ Variability minimal or absent (minutes) __________
  ❑ Decelerations (number in 30 minutes) __________
  ❑ Tachysystole (yes/no) __________
• Oxytocin
  ❑ Induction
  ❑ Augmentation
• Anesthesia/analgesia_____________________________
• Other abnormality: ______________________________

b. Delivery Data

❑ Delivery details
  Date ________ Time ________
  Birth weight ________ Length ________ Gestational age ________
• Delivery location:
  _____ Labor room _____ Delivery room _____ Operating room
• Delivery mode:
  _____ Vaginal spontaneous
  _____ Cesarean
  _____ Station at delivery (–5 to +5)
  _____ Vacuum _____ Forceps _____ Both
    _____ Application time
    _____ Procedure initiation time
    _____ Fetal position at application
    _____ Station at application (–5 to +5)
    _____ Number of tractions
    _____ Number of pop-offs
  Comment:
• Fetal presentation:
  _____ Vertex _____ Breech _____ Oblique/transverse

❑ Delivery team (actually participated in delivery)
  Name Time in room
  Obstetrician
  2nd obstetrician
  Anesthesiologist
  Resident or Fellow
  Other
  Other
  2nd obstetric nurse
  Other nurse
  Obstetric nurse
### Neonatal team

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Time in room</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatologist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd neonatologist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal resident nurse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resident or Fellow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
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</tr>
</tbody>
</table>

### Family

<table>
<thead>
<tr>
<th>Name</th>
<th>Time in room</th>
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</thead>
<tbody>
<tr>
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</tbody>
</table>

### c. Resuscitation Data

- **Apgar score**
  - 1 minute
  - 5 minutes
  - 10 minutes

- **Bag or mask**
  - Time

- **Intubation**
  - Time

- **Cardiopulmonary resuscitation**
  - Time

- **Epinephrine**
  - Time

### d. Newborn Investigations

- **Umbilical artery data**
  - pH
  - \( P_O_2 \)
  - \( P_C_O_2 \)
  - Base deficit
  - Lactate

- **Umbilical vein data**
  - pH
  - \( P_O_2 \)
  - \( P_C_O_2 \)
  - Base deficit
  - Lactate

- **Resuscitation gases:**
  - Arterial
  - Venous
  - Time
  - pH
  - \( P_O_2 \)
  - \( P_C_O_2 \)
  - Base deficit

- **Hemogram**
  - Hemoglobin
  - Hematocrit
  - White blood cells
  - Platelets
e. Maternal Investigations (if indicated)
   - Kleihauer–Betke stain
   - HbA1c
   - __________________________
   - __________________________
   - __________________________
   - __________________________
   - __________________________

f. Placental Investigations (if indicated)
   Weight (g) ________ Length x width (cm) _______
   - Membranes
     - Glistening
     - Cloudy
     - Meconium stained
   - Fetal surface
     - Clots
     - Infarcts
     - Missing cotyledons
   - Maternal surface
     - Infarcts
     - __________________________
     - __________________________
   - Umbilical cord
     - Short cord: Yes ___ No ___ Estimated length: ____________
     - Insertion:
       - Central
       - Eccentric
       - Marginal
       - Velamentous
     - Coiling:
       - Normal
       - Tight
       - Uncoiled
   - Umbilical vessels:
     - Two
     - Three
     - Four
   - Multifetal: Chorionicity __________________________

Bibliography


APPENDIX B

Data Collection Guideline for Neonatologists and Pediatricians Who Manage Infants With Neonatal Encephalopathy

Background

The pediatrician or neonatologist may encounter an encephalopathic neonate in the delivery room who may require resuscitation or a neonate in the nursery who is demonstrating symptoms of encephalopathy. In the former case, discussion with the obstetric attendant can aid in the collection of important material (such as cord blood gases, cultures, and preservation of the placenta which, will be helpful in establishing a diagnosis). In the latter case, clues to the diagnosis will guide by when the encephalopathy is recognized. A standard approach to any differential diagnosis may be followed, which includes maternal and family history, intrapartum events, birth and post birth information and laboratory and imaging studies (Box B-1).

BOX B-1. Potential Contributors to Early Neonatal Encephalopathy in the Term Infant

<table>
<thead>
<tr>
<th>Acute hypovolemic shock</th>
<th>Metabolic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute fetal maternal hemorrhage</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Ruptured velamentous cord insertion</td>
<td>Inborn errors of metabolism</td>
</tr>
<tr>
<td>Subgaleal hemorrhage</td>
<td>Thyroid disease</td>
</tr>
<tr>
<td>Cerebral tumors</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Epidural hemorrhage</td>
<td>Subdural hemorrhage</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>Vascular abnormalities</td>
</tr>
<tr>
<td>Hypoxic–ischemic cerebral injury</td>
<td>Aneurysm</td>
</tr>
<tr>
<td>Infection (primary or fetal inflammatory response)</td>
<td>Arteriovenous malformation</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>Vein of Galen malformation</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>Toxins</td>
</tr>
<tr>
<td>Intraparenchymal hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td></td>
</tr>
<tr>
<td>Arterial ischemic stroke</td>
<td></td>
</tr>
<tr>
<td>Cerebral sinovenous thrombosis</td>
<td></td>
</tr>
</tbody>
</table>

Use of the Worksheet:

Once an infant has been diagnosed with encephalopathy, consider use of the maternal data collection system found in Appendix A. Neonatal data may then be collected guided by the timing of when the encephalopathy appeared, the severity and manifestations (Sarnat Staging, Table B-1), and therapy necessary. A neonatal data collection worksheet can be used to complement the maternal data collection.
TABLE B-1. *Stages of Neonatal Encephalopathy*^ 

<table>
<thead>
<tr>
<th></th>
<th>Stage 1 (Mild)</th>
<th>Stage 2 (Moderate)</th>
<th>Stage 3 (Severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consciousness</td>
<td>Irritable or hyperalert</td>
<td>Lethargy</td>
<td>Coma</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Normal or hypertonia</td>
<td>Hypotonia</td>
<td>Flaccid</td>
</tr>
<tr>
<td>Tendon reflexes</td>
<td>Increased</td>
<td>Increased</td>
<td>Decreased or absent</td>
</tr>
<tr>
<td>Seizures</td>
<td>Absent</td>
<td>Frequent</td>
<td>± Seizures</td>
</tr>
</tbody>
</table>

*In this series severity of encephalopathy was the maximum state during the first 72 hours of life.


Neonatal Data Collection Guideline

Newborn history

Date and time of onset of encephalopathy

| __________________ |

Delivery room

➔ Resuscitation measures

• Ventilation

• Chest compression

• Drugs

• Postnatal blood gases (time)

• Other interventions

• Response to resuscitation measures

Nursery

➔ Timing of first symptoms

➔ Location of newborn when symptoms first noted

➔ Symptoms

➔ Initial treatment

General

➔ Examination:

• Anthropometric measurements

• Tone; changing tone over time

• Dysmorphic features

➔ Response to environment: feeding, temperature control

➔ Metabolic acidosis; serial blood gases and lactate levels

➔ Glucose homeostasis

Central nervous system

➔ Examination; head circumference; serial measurements over several days

➔ Studies

• Brain imaging (timing dependent on potential diagnosis)
  – Timing: 24–96 hours (earlier if suspecting hemorrhage); repeat in 7–10 days
  – Modality: ultrasonography, computed tomography, magnetic resonance imaging

• Electroencephalogram: Sequential

• Seizures:
  – Timing of onset
  – Manifestations
– Response to therapy
– Correlation with electroencephalogram

◆ **Organ System Manifestations:**

➔ **Lungs:**
- Onset of spontaneous respirations
- Need for assisted ventilation; how long?
- Meconium aspiration
- Pulmonary hypertension of the newborn

➔ **Heart**
- Two dimensional echocardiogram
- Blood pressure; need for inotropic support or volume support or both
- Tricuspid insufficiency murmur
- Troponin and cardiac enzyme levels: sequential studies over days

➔ **Liver**
- Increased enzymes: sequential studies over several days
- Jaundice or hyperbilirubinemia (fractionated)

➔ **Kidneys**
- Urine output (first day; subsequent days)
- Blood, protein in urine
- Blood urea nitrogen, Creatinine, electrolytes, calcium: sequential studies over several days

➔ **Hematologic markers**
- Complete blood count: sequential studies
- Changing hematocrit and hemoglobin values over time
- nRBCs, platelets: sequential studies over time
- Coagulation profile if bleeding suspected

➔ **Infection**
- Cultures of blood, CSF, urine
- Serial complete blood count, acute phase reactants
- Immunoglobulins: Nonbacterial infection evaluation

◆ **Workup for other causes of neonatal encephalopathy**

➔ **Metabolic workup**
- Amino acids; lactate, pyruvate levels; ammonia

➔ **Genetic evaluation**
- Genetics consult for dysmorphology
- Chromosomes; microarray, targeted genetic studies
- Genetic family tree and history

Timing of injurious events can be aided by serial clinical observations, imaging, and laboratory studies. The fetus/newborn maintains a certain baseline homeostasis of structure and function until a potentially damaging event or process. Clinical observations such as changing tone and urine output will respond in a time-ordered way to the event. Similarly, serial brain imaging, echocardiography and electroencephalography may show evolutionary changes subsequent to this event. Laboratory studies such as kidney and liver function tests will deteriorate over time and then usually return to baseline. This combination of observations and data may help time an event that may be related or causative of the encephalopathy.
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Glossary

**Acidemia:** Increased concentration of hydrogen ions in the blood.

**Adjusted relative risk:** The ratio of risk of disease or death among the exposed to that of the risk among the unexposed adjusted for a specific covariate (e.g., maternal age, weeks of gestation, size for gestational age).

**Asphyxia:** Marked impairment of gas exchange leading, if prolonged, to progressive hypoxemia, hypercapnia, and significant metabolic acidosis. The term asphyxia, which describes a process of varying severity and duration rather than an end point, should not be applied to birth events unless specific evidence of markedly impaired intrapartum or immediate postnatal gas exchange can be linked to neurologic illness in the neonate.

**Cerebral Palsy:** Chronic static neuromuscular disability characterized by aberrant control of movement or posture appearing early in life and not the result of recognized progressive disease.

**Chorioamnionitis (clinical):** A clinical presentation that may include maternal fever, maternal and fetal tachycardia, elevated white blood count, uterine tenderness, and foul-smelling vaginal effluent. The process can obviously evolve from mild subclinical to clinical disease.

**Chorioamnionitis (histologic):** Inflammation of the fetal membranes is a manifestation of an intrauterine infection and is frequently associated with prolonged membrane rupture and long labors. When mononuclear and polymorphonuclear leukocytes infiltrate the chorion, the resulting microscopic finding is designated chorioamnionitis.

**Dysmaturity syndrome:** A dysmature fetus is characterized by wasting of subcutaneous tissue, meconium staining, peeling or desquamating skin, long fingernails, and often an alert facial expression; some are said to have parchment-like skin.

**Fetal growth restriction:** Estimated fetal weight less than the 10th percentile. The term fetal growth restriction includes normal fetuses at the lower end of the growth spectrum, as well as those with specific clinical conditions in which the fetuses fail to achieve their inherent growth potential as a consequence of either pathologic extrinsic influences (such as maternal smoking) or intrinsic genetic defects (such as aneuploidy). Distinctions between normal and pathologic growth often cannot be made reliably in clinical practice, especially before birth. One study suggests that adverse perinatal outcome generally is confined to infants with birth weights below the fifth percentile and in most cases below the third percentile.

**Hypoxemia:** Decreased oxygen content in blood.

**Hypoxia:** Decreased level of oxygen in tissue.

**Hypoxia–ischemia:** Reduced amount of oxygen and inadequate volume of blood delivered to tissues; can cause brain injury if delivery of oxygen and glucose falls below critical levels. Also called postasphyxial encephalopathy, hypoxic–ischemic encephalopathy is a subtype of neonatal
encephalopathy for which the etiology is considered to be limitation of oxygen and blood flow near the time of birth.

**Injury:** Damage as a result of an insult. Alteration in normal homeostasis of limited duration and definable severity. Disruption of function that may be either transient or permanent.

**Insult:** Potential cause or risk factor of injury.

**Ischemia:** This word is derived from two Greek words: 1) ischein, “to suppress,” and 2) haima, “blood.” Thus, ischemia is the impairment of blood flow to tissues either because of constriction or frank obstruction of a blood vessel.

**Late preterm:** Infants born between 34 0/7 weeks and 36 6/7 weeks of gestation.

**Negative predictive value:** In screening and diagnostic tests, the probability that an individual with a negative test result does not have the condition is referred to as the predictive value of a negative test.

**Neonatal depression:** Clinical signs of neonatal depression include low Apgar score and its components and correlates, such as hypotonia; depressed reflexes, including cry, suck, and Moro’s embrace; decreased consciousness; difficulty in initiating and maintaining respiration; poor color; and bradycardia.

**Neonatal encephalopathy:** 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.

**Pathologic fetal acidemia:** A pH level associated with adverse neurologic sequelae; the threshold for pathologic acidemia varies among research protocols, but some investigators have suggested a pH of less than 7.

**Perinatal period:** From 20 weeks of gestation to 28 days of life.

**Peripartum:** Immediately preceding and after delivery, including labor, delivery, and the first 24 hours of life.

**Positive predictive value:** In screening and diagnostic tests, the probability that an individual with a positive test result is a true positive (ie, does have the condition) is referred to as the predictive value of a positive test.

**Postmature-dysmature neonate:** An undernourished newborn who exhibits wasting of subcutaneous tissue, meconium staining, and peeling of skin; approximately 10–20% of true postterm fetuses exhibit these findings at birth.

**Postterm pregnancy:** Gestation of 42 weeks or more (294 days or more from the first day of the last menstrual period). The term postdates can be simply interpreted as a pregnancy 1 or more days beyond the expected date of confinement and is not synonymous with postterm pregnancy.

**Relative risk:** The ratio of risk of disease or death among the exposed to that of the risk among the unexposed; this usage is synonymous with risk ratio. If the relative risk is higher than 1, there is a positive association between the exposure and the disease; if it is less than 1, there is a negative association.

**Sensitivity:** Sensitivity is the proportion of truly diseased individuals in the screened population who are identified as diseased by the screening test.

**Small for gestational age:** Infant with a birth weight at the lower extreme of the normal birth weight distribution, commonly defined as a birth weight below the 10th percentile for gestational age.

**Specificity:** Specificity is the proportion of truly nondiseased individuals who are so identified by the screening test.

**Term pregnancy:** From 37 weeks to 42 completed weeks of gestation since the first day of the last menstrual period.

**Thrombophilia:** A tendency or predisposition, either acquired or genetically inherited, to the occurrence of thrombosis, generally related to the presence or development of an aggregation of blood factors frequently causing vascular obstruction.
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![Graph showing prevalence of cerebral palsy by z score of weight for gestation for conventional and fetal standards.](image)

FIG. 10-5. **Watershed injury.** An infant delivered at 37 weeks of gestation by spontaneous vaginal delivery from a 23-year-old primigravida with a 30-hour labor complicated by intermittent maternal fever to 38.5°C. Magnetic resonance imaging (MRI) on day 3 of life with axial diffusion-weighted imaging (A) demonstrating high signal abnormalities in anterior and posterior watershed zones (arrows). These regions evolve into conventional MRI abnormalities on day 10 of life. Human neuropathology of watershed injury (B) between middle and anterior cerebral artery distribution (arrows) with vascular changes and infarction. (Image B reprinted with permission from Medscape Reference [http://emedicine.medscape.com/], 2013, available at http://emedicine.medscape.com/article/973501-overview.)
FIG. 10-6. **White-matter injury.** A 35-week preterm infant after “fetal distress,” low Apgar scores, and perinatal acidemia (pH 6.8, base deficit 19). Magnetic resonance imaging at day 7 of life demonstrated punctate periventricular white-matter lesions (A, arrows) on coronal T1-weighted imaging. Coagulative necrosis seen in the periventricular white matter (B, arrow) and associated gliosis seen throughout the white matter (C) in an infant born at term following a global hypoxic-ischemic insult.

FIG. 10-8. **Gross macroscopic appearance of the late stage of multicystic encephalomalacia,** which demonstrates widespread cystic changes in the cortex and white matter (arrows), ventricular enlargement that results from widespread atrophy (arrowheads), and dissolution of the deep nuclear gray matter (circled). (Reprinted from Neuropathology: an illustrated interactive course for medical students and residents. Asphyxia and hypoxic–ischemic encephalopathy in mature infants. Available at http://neuropathology-web.org/chapter3/chapter3bAsphyxia.html. Retrieved July 25, 2013.)

FIG. 10-9. **Time course of diffusion-weighted changes in neonatal encephalopathy treated with therapeutic hypothermia.** (A) The orange circles represent the mean diffusivity (MD) ratio in normothermic patients. The black circles represent the MD ratio in patients treated by hypothermia. Superposed on the figure are γ-variate functions that approximate the time course of the data. The orange line represents the time course for the normothermic cohort, and the black line approximates the time course for the hypothermic group. Notice the delay in time to pseudonormalization in the hypothermia cohort as compared with the normothermia group. (B) Only the hypothermic cohort is presented and is divided into two groups. The orange circles represent the mild and moderate injured group, and the black circles represent the severely injured group. The orange line is the γ-variate approximation for the mild and moderate injured group, and the black line represents the time course for the severely injured cohort. Notice that the MD ratio is lower on average in the severely injured group but there is no difference in the time of pseudonormalization in the two groups. (Reprinted from Bednarek N, Mathur A, Inder T, Wilkinson J, Neil J, Shimony J. Neurology. Impact of therapeutic hypothermia on MRI diffusion changes in neonatal encephalopathy. Neurology 2012 May 1;78(18):1420–7.)