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CLINICAL PEARL
Complications Associated with Premature Birth
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Parents of preterm infants and those at risk for preterm delivery face two major unknowns: Will this child survive? And, if he or she does, will major long-term disabilities ensue? Caregivers attempt to use the limited information available to guide parents as they make complicated decisions regarding the initiation, escalation, or withdrawal of intensive care for their children. An understanding of the early complications and long-term morbidities associated with premature birth provides the foundation for this guidance.

Complications in the Early Newborn Period
Respiratory distress syndrome. The earliest recognized complication associated with premature birth is respiratory distress syndrome (RDS). RDS is the result of insufficient surfactant production by the immature lung, leading to decreased lung compliance and inadequate gas exchange. Both the incidence and severity of this disorder are inversely related to the infant's gestational age. Within hours of delivery, affected infants develop symptoms of respiratory distress that include tachypnea, grunting, retractions, hypoxemia, hypercarbia, and acidosis. Administration of antenatal steroids, improved ventilatory strategies, and surfactant replacement therapy have improved survival rates, but RDS remains a leading cause of morbidity and mortality in premature infants.

Sepsis. Sepsis is a systemic inflammatory response, often uncontrolled, resulting from infection, such as bacterial infections with Staphylococcus or Streptococcus, or a blood stream infection with gram negative bacteria. Studies suggest that as many as 25 percent of very low-birth-weight infants (those weighing less than 1,500 grams) have one or more positive blood cultures over the course of their hospitalization [1]. This relatively high rate of infection is understandable, given that the preterm infant is an immune-compromised host; both the innate and adaptive immune systems are underdeveloped. Moreover, many of the procedures required to sustain these infants, such as central line placement, endotracheal intubation, and frequent blood draws, increase the risk of infection from invasive bacteria. In severe cases, sepsis progresses to multi-organ system failure and sometimes death, despite appropriate antimicrobial therapy. An uncontrolled inflammatory response can be more hazardous than the primary infection itself. Neonatal sepsis has been associated with poor neurodevelopmental and growth outcomes, particularly in infants with recurrent infection.

Necrotizing enterocolitis. The most serious gastrointestinal complication affecting preterm infants is necrotizing enterocolitis (NEC). The pathogenesis of NEC is complex and remains poorly understood despite decades of research. Immaturity of the gastrointestinal mucosa results in compromised barrier functions, immune defense, and abnormal motility. This intestinal immaturity together with abnormal bacterial colonization and ischemic insult are all theorized to contribute to the development of NEC [2]. The onset of disease may be insidious, with mild abdominal distention, lethargy, and feeding intolerance. Alternatively, it may begin abruptly with sudden development of intestinal perforation, hypotension, metabolic acidosis, and disseminated intravascular coagulopathy. Medical management consisting of antibiotic therapy and bowel rest is sufficient in the majority of cases. However, 20 to 40 percent of infants typically need intervention. Long-term morbidities include feeding intolerance, intestinal strictures, and short bowel syndrome. Preterm infants with a history of NEC—particularly those who require surgical management—are at increased risk for neurodevelopmental disabilities. Mortality rates for infants who develop NEC range from 15 to 30 percent [2, 3].

Intraventricular hemorrhage and periventricular leukomalacia. The most significant forms of perinatal brain injury observed in premature infants are intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL). IVH refers to bleeding within the ventricles of the brain, which, in severe cases, may extend into the surrounding parenchyma. The hemorrhage originates in the subependymal germinal matrix, a site of neuronal proliferation in the developing fetus, which typically begins to regress at 32 weeks' gestational age. The blood vessels supplying this tissue matrix are extremely fragile and may rupture with abrupt alterations in cerebral blood flow and pressure. The bleeding can destroy cerebral tissue and, in some cases, lead to post-hemorrhagic hydrocephalus. A recent study found that infants with severe IVH have a 28 to 37 percent mortality rate [4]. Surviving infants face a significant risk for long-term disabilities that include cognitive impairment, cerebral palsy, and recurrent seizures.

PVL is a form of cerebral white matter injury that has been highly correlated with the subsequent development of cerebral palsy. The key factors implicated in the development of PVL are cerebral ischemia and systemic inflammation following intrauterine or neonatal infection. These injurious processes result in the activation of brain microglia, which in turn release a variety of toxic mediators including cytokines, reactive oxygen species, and excitatory amino acids that damage the premyelinating oligodendrocytes [5]. PVL may be diagnosed in the early neonatal period by magnetic resonance imaging, which frequently reveals the presence of parenchymal cysts, areas of abnormal signal intensity, or reduced white and gray matter volumes. The associated neurocognitive and motor deficits, however, often do not manifest until well after discharge from the hospital.

Long-Term Complications

Bronchopulmonary dysplasia. Bronchopulmonary dysplasia (BPD) is a chronic lung disease of preterm infants typically defined by the presence of a supplemental

oxygen requirement at 36 weeks' gestational age and affects nearly 30 percent of extremely low-birth-weight infants [6]. Factors such as inflammation, barotrauma, and the production of reactive oxygen species are all believed to contribute to the pathogenesis of BPD by injuring small airways and interfering with alveolarization and the development of the pulmonary microvasculature. Therefore, preterm infants who require prolonged or aggressive ventilatory support and those with a history of antenatal or postnatal infection are at increased risk for developing BPD [7]. These individuals commonly experience recurrent pulmonary infections, increased airway reactivity, and poor postnatal growth.

Retinopathy of prematurity. Retinopathy of prematurity (ROP) is a major cause of severe visual impairment or blindness in infants born prematurely, with approximately 50,000 infants affected worldwide each year [8]. The disease is characterized by abnormal vascular proliferation in the immature retina, likely due to the presence of increased local reactive oxygen species and angiogenic growth factors. Extreme prematurity, growth restriction, male gender, hyperoxia, and septicemia are most consistently associated with the development of ROP [8]. Although changes in clinical practice, namely more judicious oxygen administration, have resulted in a decreased incidence of ROP in developed countries over the past several years, affected infants are still at risk for subsequent ophthalmologic complications such as strabismus, amblyopia, cataracts, and impaired visual acuity.

In sum, preterm infants, particularly those who experience one or more of the complications discussed above, are at risk for neurodevelopmental disabilities such as cerebral palsy, developmental delay, and mental retardation. Approximately 42 percent of very low-birth-weight infants have been found to have borderline IQ scores (70-84), and 7 percent had subnormal IQ scores (less than 70) when tested at 20 years of age, compared to 31 percent and 2 percent respectively in normal-birth-weight infants [9]. An additional 6 to 9 percent of these infants were classified as having cerebral palsy. Recent follow-up studies have also revealed that these infants may demonstrate more subtle impairments such as learning disabilities, impaired social skills, and behavioral problems, particularly attention-deficit-hyperactivity disorder [10].

Although we have data describing significant long-term morbidities and neurodevelopmental outcomes based upon birth weight and gestational age at delivery, the early identification of individuals at risk for these impairments remains an ongoing challenge for physicians. Recognizing and acknowledging our limited capability to predict which infants will be most severely affected is crucial for effective and honest communication with families.

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